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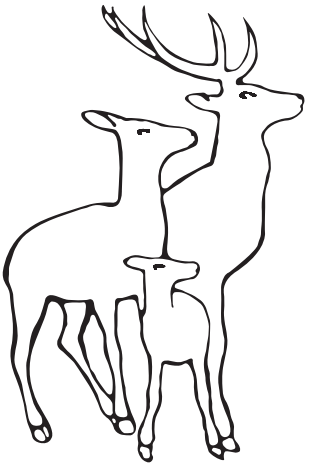

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Review

Neurocognitive abilities in individuals with Down syndrome-a narrative review

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ABSTRACT

Down syndrome (DS), or trisomy 21, is the most common genetic syndrome associated with intellectual disability. Despite the variability in expression, there is a distinct developmental phenotype characterized by deficits in learning/memory, executive functions, and language skills accompanying the psychomotor delay. The severity of intellectual impairment has the dominant effect on functioning, other influences such as parental and societal attitudes, supports available and social opportunities also play a role in the attainment of skills.

Key words: Down syndrome, cognition, learning.

Down syndrome (DS), or trisomy 21, is a common disorder associated with several complex clinical phenotypes. DS is estimated to occur in approximately 1 per 650–1000 live births.[1] A recent study from the Unites States of America showed a decrease in the prevalence owing to DS related elective terminations.[2] The features of DS were identified 150 years ago by Sir John Langdon Down who published his findings in London Hospital Clinical Lectures and Reports in 1866. After 66 years, P. J. Waardenburg suggested that DS was caused by a chromosomal aberration due to nondisjunction.[3] After almost a century later, an extra copy of chromosome 21 was identified as the etiology.[4] In the 20th century, almost all individuals with DS were separated from their families and institutionalized. They were also denied medical support which culminated in increased mortality in children with DS.[5] However, the advances in the medical and surgical treatment have led to improved life expectancies such as specialized surgical procedures of the congenital cardiac diseases, management of malignancies and endocrinopathies.[6] There has also been a change in the social circumstances for individuals with DS, as most are being reared at home.[7]

DS is diagnosed through karyotyping along with the phenotypic presentation. Maternally derived additional copy of an entire chromosome 21 due to non-disjunction is the most common cause of DS occurring in approximately 90–93% of the cases.[5] Translocation is the other pathological mechanism which causes DS in ~2–4% of the cases. Mosaicism is found in ~1.3–5% of cases.[8] In 95 % of the children, the condition is sporadic.[9]

The prenatal screening strategies have been developed ranging from amniocentesis to less invasive tests for different trimesters that incorporate various blood tests, nuchal translucency via ultrasonography.[9]

Substantial research has been carried out in the past several decades to unravel the molecular genetics of DS.[10] Although, some studies have suggested that duplication of an extended region on chromosome 21 (HSA21) is associated with DS features but it is yet to be established. It is also hypothesized that there is a critical region involved,[11] the DS consensus region that is responsible for severe DS phenotype.[10]

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DS is the most common known genetic cause of intellectual and developmental disabilities.[12] Although there is a global involvement encompassing motor, language, cognitive, self-care and personal-social dimensions[13], there is a disproportionate impairment in certain cognitive domains such as language and memory in comparison to other intellectual disabilities resulting in a characteristic neurocognitive phenotype.[6] However, there is heterogeneity amongst individuals in the cognitive abilities and skills phenotype due to genetics, cellular, neural, behavioral and environmental factors.[8] Research studies have shown that there is anomalous functional neural connectivity as compared to individuals with similar intellectual disabilities.[14] Also, mitochondrial dysfunction has been studied in correlation with the pathogenesis of DS and there is evidence to show increased oxidative stress in DS cells.[15] However, it is not known how oxidative stress causes clinical symptoms and there is a knowledge gap in the understanding of the molecular events leading to intellectual disability.[16]

Motor skills

There is a need for proficient motor skills in individuals with DS to perform day to day tasks.[17] Children with DS demonstrate challenges in terms of increased risk of motor delay and motor coordination capabilities which occur due to neuroanatomical and physiological changes because of muscle hypotonia, lax joints and slower reaction times causing alterations in postural control and muscle synergy.[13,18] This delay in motor skills may also hinder the child from the essential sensory stimulation that is needed for other aspects of learning.[19]

The gap in motor development emerges around 4 months of age and becomes more apparent as the age advances. Dissimilarities in the postural reactions have also been observed while comparing to neurotypical infants.[20] This happens as expectations for more coordinated motor tasks increase especially for skills requiring high levels of muscle co-activation against gravity. The sequence of attaining motor milestones is similar but qualitatively different which probably results from the compensatory mechanism. There is a wide range in the acquisition of motor milestones such that walking can be attained between 15 and 74 months while for the neurotypical children it is earlier than 18 months.[21] The percentage of children who were able to walk by 2 years of age has been reported between 25% to 44%, and by 3 years 78% to 82.[22]

There is a paucity of literature on the fine motor development in DS. It is heterogeneous and like gross motor skills has a broad range of acquisition. The achievement of early fine motor skills and writing skills is around the same age range as the typical children. However, with the increasing complexity of tasks, the difference increases between the children with DS and their typical peers.[23]

An interesting phenomenon in enhancing motor capabilities in individuals with DS is an improvement in tasks with practice as unfamiliarity of the motor tasks results in even worse motor coordination.[24] The existing body of literature, although limited, suggests that neuromuscular training which is characterized by stimuli provided by physical activities aims to enhance a myriad of neuromuscular components including muscular strength, physical coordination, and functional movements may be employed to promote general and maximal muscular strength development in children and youth with DS. However, there is a small impact on functional mobility performance owing to limitations in executive functioning.[25] Thus, rehabilitation contributes to the improvement of motor skills and ultimately the quality of life.[26]

Given this literature, general pediatricians may wish to consider co-morbid neurologic or developmental diagnosis if a child with DS presents with hypertonia, have asymmetric neurological findings or are significantly more motor delayed than most children with DS (for example not walking by 60-72 months).

Adaptive functioning

Adaptive behavior is essential to perform day to day activity independently and is comprised of conceptual, social, and practical adaptive skills.[27] The understanding of the adaptive behavior profile of DS is evolving.[28] So far, the adaptive behavior profile in DS is characterized by strengths in socialization and self- help[29] with difficulties in motor and communication skills.[30]

Progression in adaptive functioning is particularly seen in early childhood up to the age of 6 years; while in children and adolescents the gains in adaptive skills are not strongly correlated with age.[31]

Children with DS find it difficult to keep up with their typical peers in adaptive skills and deceleration is observed across all ages.[30] The domains continue to grow at a slower pace than typically developing children. Also, there is great variability in the attainment of skills in children with DS as compared to their typical peers such that adaptive scores are close together in neurotypical children in relation to their chronological age; while the scores have a larger spread in children with DS.[32]

Speech and language (Communication)

There is a characteristic profile of communication with strengths and challenges in individuals with DS.[33] Children with DS typically manifest significant delays in language development.[34] There are deficits in both receptive and expressive language skills which are more pronounced than cognitive development.[35] In general, expressive language is more affected than receptive language and/or language comprehension.[36] Hearing loss and anatomical and functional differences in the oro-motor apparatus have been associated with speech delay.[37]

Craniofacial differences including small oral cavity and narrow, vaulted palate, as well as hypotonia, contribute to the articulatory performance.[38]

The motor speech difficulties have historically included Childhood Apraxia of Speech (CAS) and Childhood Dysarthria. One can have either or both.[38]

The development of oral language is a complex process which requires cognitive, perceptual and language skills that begin to form in the prelinguistic stage.[39] Similar to typical children, children with DS use gestures and vocalizations in the prelinguistic stage. Children with DS show better performance using gestural communication than is expected for their developmental age thus placing them in "gestural advantage".[40] Delays in certain aspects of prelinguistic vocalizations especially canonical babbling (repeating consonants and vowels)[41,42] followed by delays to attain single words speech have been reported in the literature.[37] There is a range in the acquisition of the first words such that for some children the first words have emerged at around 9 months while for others they didn't come until 7 years of chronological age.[43]

The issues revolve around language production, syntax (sentence structure) and poor speech intelligibility.[44,45] Pragmatics (social use of language) is an area of relative strength for children with DS.[46]

Studies have suggested that early linguistic stimulation employing speech and language interventions specially designed for children with DS individualized with each child's characteristics can potentiate language development.[39]

Therefore, from the literature, pediatricians may consider comorbid developmental diagnosis if a child with DS has more impairments in the pragmatics than compared to their overall developmental level or if the clarity of the expressive communication is significantly unintelligible after short sentence utterances have been achieved.

Social-emotional/ behavioral development

Socialization is the strongest developmental

domain in children with DS.[47] It has been supported by literature that children with DS with the same level of developmental delay as children without DS demonstrated better socialization skills.[30] Also, different dimensions of social functioning such as social orientation, social engagement, and pro-social responsiveness are equally strong.[48,49]

Children with DS have been characterized by decreased emotional expression and environmental response.[50,51] Studies have shown that infants with DS displayed less intense emotions and increased latency to distress as compared to developmentally matched infants.[52]

Research on the recognition of emotional expressions by children with DS has been a work in progress.[53] Previous literature suggested that they have a better understanding of understanding emotions as expressed by facial expression as compared to other forms of intellectual disabilities.[54] Later studies looking into emotional processing in children with DS concluded that there were emotional perception deficits.[55]

A child with DS has been stereotyped to be affectionate, charming and friendly.[48] Thus, the co-occurrence of Autism Spectrum Disorder (ASD) with DS was considered to be a rare phenomenon in the past. However, recent research estimates have shown the prevalence of co-occurring ASD to be 5 to 18% in children with DS.[56-58] The published literature has not shown comprehensive or "gold standard" diagnostic assessments for diagnosing ASD in children with DS.[59] However, screening tools like Social communication questionnaire (SCQ) and Modified Checklist for Autism in Toddlers (M-CHAT)[56] have been used followed by Autism Diagnostic Interview-Revised (ADIR) and Autism Diagnostic Observation Schedule (ADOS).[60] Keeping in view that many of the symptoms that constitute the autism screening checklists are also present in intellectual disabilities, this may result in increased sensitivity with decreasing specificity.[61] A developmental approach to diagnose ASD has been recommended by various authors in children with intellectual disabilities where to diagnose an individual with ASD there should be significantly more impairment in social or communication domain than the overall intellectual capabilities.[62]

Several studies have contributed in creating the behavioral profile of children with DS with a dual diagnosis of ASD which includes increased behavioral disturbance, increased repetitive and stereotypical behavior, poorer social, language and adaptive skills and greater regression.[56] Another study demonstrated that individuals with a dual diagnosis of ASD-DS were less withdrawn than with idiopathic ASD.[57]

Maladaptive behaviors in DS occur in varying intensities across the lifespan. About one-third of individuals with DS have behavior challenges.[63] Behavior problems like inattention, stubbornness, non-compliance social- withdrawal and obsessive-compulsive behaviors have also been established in the profile.[64,65] In children with DS who have behavioral problems, vocabulary has been found to be a major contributor.[66] More externalizing behaviors have been observed in children with DS as compared to adolescents while both adolescents and adults have shown more propensity towards internalizing behaviors.[48]

Attention Deficit Hyperactivity Disorder (ADHD) has been reported in 9- 34% of children with DS.[67,68] Similar to ASD, making a dual-diagnosis of ADHD in a DS child is more difficult because some signs of ADHD and other comorbid disorders may be attributed to the child's intellectual disability.[69] Hyperactivity–impulsivity–inattention have been regarded as parts of the typical DS behavioral phenotype thus increasing the dilemma of diagnosing and treating ADHD in them even further.[70] The diagnosis is clinical and there are no standardized tests available to detect ADHD in children with DS. However, a neurodevelopmental assessment using clinical observation and

general rating tools like Aberrant Behavior Checklist (ABC), Child Behavior Checklists (CBCL), Conner's rating scale and/or Strengths and Difficulties Questionnaire (SDQ) etc. could be considered in all children with DS during clinical visits when there is a concern about inattention or impulsivity.[69] This may facilitate in implementing therapeutic interventions (both pharmacologic and behavioral) which decrease symptoms of hyperactivity and irritability.[70]

Cognition

The neurocognitive profile of DS is characterized by psychomotor delay with significant deficits in learning, memory, executive functions, and language abilities that define the intellectual disability.[21]

The intelligence quotient (IQ) in individuals with DS vary widely from below 20 to at least an IQ of 69 depending on the age, environment and the genotype.[71] A progressive declining trend has been demonstrated in individuals across childhood ranging between 60-70s in the preschool age group with a subsequent decrease to between 40-50s in kindergarten and further decline dropping to between 30-40 in school-aged children.[72] This declining cognitive growth rate correlates with declines observed in the rate of development of functional skills during childhood in DS.[73] However, the psychometric testing available does not account for the wide range of challenges experienced by this population.[16]

Few cognitive differences have been observed in infants with DS from neurotypical controls on standardized tests which may be due to a probable lack of sensitivity to detect them but, with increasing age, the gap becomes more obvious as the rate of intellectual development in DS slows considerably.[8] Deficits in verbal information processing are the most apparent which is also associated with verbal working memory have been reported in the literature which was historically known to be associated with the deficits in the auditory short-term memory.[74]

Executive functioning has also been found to be impaired in individuals with DS. Impairments in fluency, cognitive flexibility (shifting), planning, and inhibition were found in youth and middle-aged adults with DS when compared with adults with other developmental disabilities (DD).[75] Interestingly, there is also heterogeneity in performance even after acquiring skill with rigorous training. This is supported by studies that tested and retested children with DS and found the tasks which were successfully done during one test could not be replicated in the other instance. These deficits in memory can be explained by impairment in hippocampal function which is linked to the explicit memory.[76]

In contrast, visuospatial functioning and social relatedness are areas of relative strength.[77,78]

Academics

Academic skills in individuals with DS have garnered a lot of attention in the last few decades. From the perspective of quality of life, literacy, the ability of reading and writing as well as numeracy, the concept of the number are important in day to day life and facilitate the vocational opportunities as well as chances of independent living in individuals with DS.[79,80]

There is a spectrum of attainment of literacy skills in children with DS. When compared with mental age-matched children, the language was a stronger predictor of reading ability in contrast to cognition in the group with DS. There is evidence to suggest that there are strengths in word identification, possibly secondary to relative strengths in visual processing. However, there are challenges in verbal processing skills that lead to deficits in word attack skills.[79]

Individuals with DS can attain simple skills in numeracy but a study suggested that unlike reading this cannot be retained into adolescence and adulthood.[81] Research has also shown that children with DS can improve on these skills if appropriate strategies are used that employ

their stronger visual learning skills. Learning Numeracy has been suggested to be associated with real practical scenarios with concrete materials or computers.[82]

The learning process is said to be hindered by deficits in the working memory and executive functioning.[83,84] Another study that looked at the predictors of academic attainment elucidated that severity of learning disability, child's ability to sustain attention, mainstream education, mothers using a practical approach to problem-solving and fathers' feelings of having control over some parts of life positively impacted the achievement.[85] Children whose mothers were more supportive of their autonomy showed more persistence in performing challenging tasks. Interestingly, the relative social strength hinders collaborative learning as students with DS use avoidance and refusing tactics to save themselves from performing challenging tasks.[86,87] Researchers also observed higher levels of off-task behavior when children with DS were matched for mental age.[70] Deficits in goal-directed behavior have also been reported in the literature.[88]

Educational policies that emphasized inclusion and teaching academic skills, resulted in better attainment of skills and higher expectations of teachers. Also, a report on the practice of including children with DS in regular classrooms in England showed a difference in the phenotypic profile in older children and adolescents with DS.[89] They noted that children with DS attending school in special classrooms showed strength in socialization and activities of daily living while having marked deficits in adaptive communication.[76] In contrast, children who were in inclusive classrooms, these marked deficits were not demonstrated, and these children had much higher scores on speech, language, and academic skills. The learning targets, however, were individualized with additional in-class and some outside instruction when necessary.[89]

Take-home points

- The neurocognitive profile of DS is characterized by psychomotor delay and a generalized with significant deficits in learning, memory, executive functions, and language abilities that define the intellectual disability.
- Children with DS are typically delayed in all areas of development throughout their lives.
- The gap in the developmental skills widens during school-age childhood and adolescence compared to their same-age peers widens due to the slower pace of skill acquisition.
- Language is a stronger predictor of reading ability in contrast to cognition in the group with DS.
- The use of the combination of visual and phonological strategies in preschool children to augment the long-term learning has been supported by the literature.

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Review

Nationwide efforts for trauma-informed care implementation and workforce development in healthcare and related fields: a systematic review

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ABSTRACT

There is building evidence that Adverse Childhood Experiences without early and proper intervention leads to subsequent short- and long-term behavioral, social, physical and mental health problems. Practitioners, researchers, and healthcare systems have been implementing trauma-informed care (TIC) in a variety of health and human services settings, resulting in improvements in clinical care and prevention of illness by identifying high risk populations. This has led to positive health outcomes including improved compliance, better access to mental health services and reduced health care costs. A systematic review was conducted of studies that focused on TIC implementation in healthcare settings, statewide TIC implementation, impact of adverse childhood experiences on health outcomes, impact of TIC on health outcomes, and evaluation of TIC implementation. A search was conducted in March 2019 to identify studies in PubMed, Medline, and other online literature. We limited our search to articles published in English after 2000. This article aims to review the components of TIC phases of implementation in healthcare settings, success stories across the nation to help the readers understand the importance of a paradigm shift to improve healthcare delivery and health outcomes and to prevent illness starting from childhood with a family centered care perspective.

Key words: trauma-informed care implementation and interventions, adverse childhood experiences, childhood trauma, primary-level interventions.

What is Trauma-Informed Care?

Trauma-informed care (TIC) in healthcare systems is a multilevel, organizational framework to understand and respond to the impact of trauma on both survivors and healthcare providers. Trauma, defined in this context, describes physical and psychological responses to a distressing event or events. Such trauma can be in response to a wide range of stressors, including but not limited to damaging relationships, abuse, neglect, exposure to violence, poverty, homelessness, accident, war or natural disasters. These adverse experiences have been linked to health outcomes, and a large body of research has identified that when these events occur during childhood they have lasting and persistent effects on health.

The short- and long-term effects of adverse childhood experiences (ACEs) have been documented by a multitude of studies published over the last decades, as interest in health promotion and disease prevention has grown.[1-24] Household dysfunction-related ACEs—such as physical, sexual, and emotional abuse, emotional and physical neglect, and mental illness, substance abuse, criminal activity, domestic violence, and parental

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absence—and societal-related ACEs such as community violence, poverty, foster care and discrimination can have negative effects on a child in all health domains: behavioral, physical and physiological, cognitive, social, and mental health.[1-26] Health-risk behaviors are also associated with an increasing number of ACEs in a dose-response relationship for substance abuse, tobacco use, high-risk sexual behavioral, and overeating.[3,5,10,11,13,27] A higher number of ACEs has been associated with metabolic risk biomarkers including obesity, high blood pressure, high total cholesterol, low high-density lipoprotein cholesterol levels, and high glycated hemoglobin.[17]

Moreover, individuals exposed to multiple ACEs may lead a "trauma-organized" lifestyle where traumatic events and relationships create a personality, behavior, and lifestyle which may further predispose them to further traumatic situations mental and physical illness throughout life.[3,14,24,26,28-30] The leading causes of death among adults such as heart disease and stroke, chronic obstructive pulmonary disease, lung cancer, and liver disease are all associated with complex and multiple childhood trauma.[7,8,14] Furthermore, individuals, who report a high number of ACEs are more likely to die prematurely, by up to 20 years earlier than individuals who report fewer or no ACEs.[3,14,23] Individuals who report more ACEs are more likely to report poor or fair health, to have an overall lower sense of well-being, to have poorer access to medical/mental health services, to be less satisfied with their lives, and to have higher work related problems and rates of unemployment.[3,11,22,23,31,32]

Mental health is associated with exposure to multiple ACEs, including learning and behavioral problems, somatic disorders, hallucinations, anxiety and obsessive-compulsive disorders, substance use disorders, depression and subsequent suicide attempts during adulthood as well as posttraumatic stress disorder, which may not always respond to traditional treatment.[2,5,10-12,19-21,27,28,33-36] Previous studies have explored how ACEs create an environment of traumatic toxic stress that can lead to prolonged activation of the stress response system, excess cortisol circulation, and disruption of the neuroendocrine and immune systems. When the stress response system remains on high alert, it can lead to remodeling of neurological pathways particularly in the hippocampus, amygdala, and prefrontal cortex.[1,37-40] Lastly, many short- and long-term health problems in association with multiple ACEs increase healthcare utilization and costs in a dose-response curve pattern.[22,41]

Core features of trauma-informed systems include the integration of trauma-informed concepts and principles into policies, procedures, and practices, and building awareness, recognition, and implementation of screening, assessment and treatment services for trauma.[42-45] Thus, to provide TIC, there must be a commitment to these tasks throughout the organization with a resultant paradigm shift.[46,47] This shift, then, facilitates the identification of trauma and creates pathways to holistic family well-being assessment and intervention, the prevention of long-term negative health outcomes and a reduction in healthcare costs.[29,42-44,46,48,49]

TIC can also benefit medical professionals with a personal history of trauma or who have experienced work-related trauma.[50,51] Trauma-informed organizations that use trauma-sensitive practices can decrease trauma-related triggers and improve staff health, resiliency, and efficiency while enhancing the quality of care for patients and families.[52-55] TIC organizations strive to improve multiple practice domains: education of providers to change practice, early identification of children experiencing adversity, treatment through evidence supported and resiliency-focused services, and collaboration within and across agencies that serve children and families in the broader community.[34,56-58]

The Substance Abuse and Mental Health Services Administration (SAMHSA) outlines six broad principles to implement TIC (Table I).[59]

Table I. Broad principles of implementation of trauma-informed care.

1. Safety: Conscious organizational effort to promote physical and emotional safety for all members and clients of the organization.
2. Trustworthiness and Transparency: Organization makes decisions with transparency and engenders trust of staff and its clientele.
3. Peer support: Individuals with histories of trauma involved with the organization are engaged to be critical resources for support.
4. Collaboration and mutuality: All members of the organization can equally contribute to the healing of individuals impacted by ACEs.
5. Empowerment, voice and choice: Clients are provided with family- and patient-centered approaches while developing plans of action that empower clients.
6. Cultural, Historical and Gender Issues: Efforts are culturally sensitive and free of prejudices that arise from biases and stereotypes.

These principles include safety, organizational trustworthiness and transparency, peer support, organizational collaboration amongst its members, empowerment of clients, and culturally sensitive care. Understanding how TIC is defined and adopting these principles are typically the first steps for organizations and states interested in implementing trauma-informed approaches.

Methodology

The purpose of this article was to conduct a systematic review of research on how trauma-informed care is being implemented in healthcare settings nationally and its effect on the quality of healthcare delivery and on health and other outcomes. We then review efforts by states to implement TIC in multiple systems of care including healthcare, education, juvenile justice, and child welfare settings. Finally, we report on the evidence base for interventions to prevent childhood adversity and trauma before concluding the review with recommendations for future efforts.

A systematic review was conducted of studies that focused on TIC implementation in healthcare settings, statewide TIC implementation, impact of adverse childhood experiences on health outcomes, impact of TIC on health outcomes, and evaluation of TIC implementation. A search was conducted in March 2019 to identify studies in PubMed, Medline, and other online gray literature. Pubmed and Medline databases were searched using the following keywords: trauma-informed care implementation, adverse childhood experiences and trauma-informed care, trauma prevention, trauma-informed family centered healthcare, statewide trauma-informed care implementation.

We limited our search to articles published in English after 2000 that mentioned "trauma-informed" or "trauma-informed care" in the abstract, title, or key words. 792 articles and their references were screened if they met any of the following criteria:

- Definition of trauma-informed care, childhood trauma, and adverse childhood experiences
- Discussion of trauma-informed care implementations and interventions, and subsequent changes in practice
- Evaluations of the impact of trauma-informed care on child and family health outcomes
- Discussion of primary-level interventions to prevent childhood adversity and trauma
- Discussion of barriers and gaps to implementation of trauma-informed care

One hundred and forty-four articles met the inclusion criteria. The full texts of these articles

were obtained and classified according to the following categories: 59 articles discussed TIC and ACEs, 38 articles discussed the implementation of TIC in healthcare, 14 articles discussed changes in practice related to TIC, 19 articles discussed the impact of TIC on child and family health outcomes, 29 articles discussed statewide TIC efforts, 8 articles discussed primary prevention of childhood adversity and trauma, and 8 articles discussed barriers and gaps related to implementation of TIC.

Implementation of Trauma-Informed Care in Healthcare

Many healthcare organizations view TIC as a priority, and numerous studies have reported on the screening of patients for ACEs over the last decade although progress continues to be slow considering the vast healthcare network.[60-64] Healthcare organizations' commitment to TIC varies substantially and is influenced by different factors at the organizational and individual level.[65,66] Organizations and communities that have most successfully implemented TIC have reviewed and amended TIC procedures and policies, provided training to all staff and aligning staff hires with TIC training, followed recommended guidelines, and adopted refinements in TIC, such as service user involvement and ongoing staff training using system-level approaches.[67-72]

Healthcare systems remain an important setting for identifying children and families who have been exposed to trauma. Pediatricians and other childcare providers are integral to the process of implementing TIC, especially if they work in a trauma-informed system and are properly trained.[61,63,73-75] Within these systems, they ideally have the support and knowledge to recognize, assess and refer traumatized children and their families from inpatient, outpatient, or rehabilitation settings to much needed services within and outside the healthcare system.[61,74,76,77]

Most trauma-informed organizations begin by establishing a stakeholder group to look at the available policies, procedures, and practices to determine how they might better align with a TIC paradigm.[53,61,65] In some institutions, organizational leadership has implemented institution-wide training and education for their staff and administrators to ensure TIC principles are practiced across the organization.[66,67,69,72-74,78-80] Various curricula have been developed and piloted for healthcare professionals in different settings, which were designed to ultimately result in more effective patient-centered communication and intervention around ACEs.[81-84] Existing programs have also discussed self-awareness and self-care in order to mitigate the impact of trauma that healthcare providers may have experienced themselves.[85-88]

In other institutions, front-line providers have created 'grass-roots' training to increase TIC awareness among fellow workers and administrators in their departments, which subsequently led to an institutional paradigm shift.[50,61,67,81,83,89,90] When the leadership at all levels of an institution identify TIC as a priority, administrators may also change their hiring practices, staff training policies, and their work environments.[67] Consequently, each organization can create collaborative, safe, and patient-centered environments while proactively preventing secondary traumatic stress.[80]

Universal screening of trauma and resiliency, preferably embedded in routine intake procedures, has been adopted as an important component of TIC in healthcare and other settings, and assumes that most patients have experienced some childhood trauma and all patients possess some resiliency.[5,67,74,78,80-83,89-92] The assessment of ACEs during routine screening within healthcare settings has resulted in finding more cases in need of trauma-informed interventions. Consequently, some institutions are investigating how they might better integrate behavioral and mental healthcare services with primary care. Researchers stress the importance of the co-localization of behavioral health and primary care providers, supported with an adequate

number of social workers, to better address the needs of patients with a history of childhood trauma; these practices have led to substantial benefits for patients.[61-63,65-67,93-98] One prime example of this integrated behavioral health in primary care practice is the Montefiore Hospital Pediatric primary care clinics, which we will review in more detail in a later section.[95,96] Implementation of TIC has resulted in changes in healthcare practice.

Changes in Practice due to Trauma-Informed Care Implementation

Although there are numerous efforts to implement TIC in healthcare settings, the literature is sparse on whether it improves the quality of healthcare delivery. The first line of studies report on systems assessment and workforce development.[50,99,100] These efforts showed that training can result in a paradigm shift toward more TIC practices.[76] Many practitioners have gone further and reported on how adopting TIC, with its emphasis on patient empowerment and shared decision making, has improved provider-patient communication, which in turn, has led to improved patient satisfaction, medical information recall, compliance and decreased healthcare costs.[48,49,101,102] In a study that evaluated patients' perception of care delivery before and after primary care physicians completed a six-hour TIC course, providers in the study group were rated higher than providers in the control group on the Partnership Scale.[76]

Implementation of TIC can lead to the holistic care of the patient and their family, addressing their needs through the development of a therapeutic relationship, increased screening and/or by referral to specialists with subsequent improvement in the quality of healthcare delivered. Flynn et al.[75] reviewed multiple studies on the implementation of TIC in primary healthcare settings and found that most TIC programs quadrupled the proportion of trauma screening (from 12-21% for different variables to 46-88%) and improved physician knowledge, attitudes, and confidence to identify and work with traumatized patients. Briggs et al.[60] from the Montefiore Hospital Network screened children for trauma using the Healthy Steps model and referred them to behavioral health clinicians embedded in their primary care clinics. The percentage of families referred to services increased from 16% to 26%, and the percentage of families who complied with treatment increased from 20% to 63% with a warm hand-off.[60]

Glowa et al.[64] reported that in a family practice clinic, by screening for ACEs, practitioners gained new information about their patients. As a result, they discussed the impact of ACEs on their patients' health and the need for intervention almost three times more often with patients with four or more ACEs than with patients with fewer than four ACEs.[64] Kottenstette and colleagues[61] assessed children and families for trauma using the Family Well-being Assessment model in a child abuse clinic. They reported that recognition of referral for needed services among caregivers increased by close to tenfold (from 5.1% to 47.0%), which more than doubled the rate of referrals, mostly to mental health services.[61] The same model was implemented in the Emergency Department and the burn unit of the same institution, which increased the recognition of families and patients suffering from multiple trauma, dramatically.[62,63]

Impact of Trauma-Informed Care Interventions on Child and Family Health Outcomes

Despite the implementation of TIC spreading across healthcare and other family-serving systems, there are few published studies examining its impact on child and family outcomes. Some studies report on how the integration of multiple family serving systems statewide can impact children and families exposed to trauma. One notable multisystem intervention is the Hawaii Department of Health's Project Kealahou, which included the State's mental health, juvenile justice, education, and child welfare systems.[103] They provided services to girls at risk for truancy and

incarceration that included case management, peer support, group activities and therapy. The intervention resulted in improvements in the girls' competence, depression symptoms, and behavioral problems and a reduction in caregiver strain.[103]

The Massachusetts Child Trauma Project (MCTP), another multisystem, statewide project, aimed to improve the safety, permanency, and well-being of maltreated children by training child welfare workers and mental health providers on TIC, disseminating information on evidence-based treatment, and integrating the systems of care in their State. Barto et al.[104] examined provider and family outcomes at pre- and post-intervention. They found that not only the child protection capacity among providers increased, but also recidivism for substantiated maltreatment decreased by 12% for physical abuse, 14% for neglect and 15% for any maltreatment among children.[104] Bartlett et al.[105] found that children in the MCTP study had fewer posttraumatic symptoms and behavior problems at six-month follow-up. Azeem et al.[106] reported on how trauma-informed interventions changed practices in an inpatient child and adolescent psychiatric setting after hospital staff were trained using six core TIC strategies. They reported that episodes of seclusion/restraints in youth decreased from 93 episodes in the pre-intervention to 31 post-intervention.[106]

Providing TIC services to women is likely to benefit the wellbeing of children indirectly. For instance, providing interventions involving trauma-informed and trauma sensitive principles for women with mental health issues, substance use disorders, and histories of domestic violence was found to be associated with improved parenting capacity.[107,108] In a meta-analysis of a nine-site quasi-experimental intervention (N = 2,729 women), mental health and substance use agencies implemented trauma-informed interventions that included case management, integrated treatment for co-occurring disorders, counseling, training on parenting, and consumer involvement including peer support. They reported that post-traumatic symptoms, drug use severity, and mental health symptoms decreased.[107,108]

While the above studies show evidence of TIC implemented in larger systems of care leading to positive health outcomes for children and their caregivers, other studies reported on improvements in health outcomes as a result of TIC implementation directly in healthcare settings.[49,103-108] Machtinger et al.[52], for instance, developed a trauma-informed primary care (TIPC) framework for women which showed enhanced healing and healthier environments for themselves, their families including their children and the community. Other studies reported on how Integrated Behavioral Health (IBH) in pediatric clinics proved to be a sustainable and effective method to address and ameliorate pediatric behavior problems, many of which stem from trauma. As a result of this intervention, parents felt more empowered and less stressed-out.[60,97,98] Additionally, the Montefiore Hospital network's implementation of TIC in pediatric primary care along with IBH, which included social workers, behavioral health clinicians and child and adult psychiatrists, resulted in improved treatment compliance, better health outcomes, increased competence of primary care providers and even reduced healthcare costs.[95,96] This hospital successfully converted itself into an Accountable Care Organization, the offshoot of The Patient Protection and Affordable Care Act, allowing them to address modifiable social determinants of health, such as individual, family, and societal trauma.[77]

Flynn et al.[75], conducted a meta-analysis of studies focusing on ACEs and TIC implementation. Their analysis showed that it was difficult to compare study outcomes because they neither explored similar interventions nor used similar outcome measures. As a result, they reported that only half of the studies conducted in primary healthcare settings included patient outcomes. Furthermore, the studies reported mixed results related to child behavior, reported maltreatment, and referral.[75] However, Marie-

Mitchell and Kostolanski[103] in their review of 20 randomized controlled trials, reported that 17 of the studies they reviewed examined parent-child relationship outcomes and 15 examined child health outcomes They also reported that, due to varying ACE assessment tools, screening practices, scopes of intervention and a wide range of outcome measures, the results between studies were difficult to compare. Yet, it is noteworthy that generally, programs had a stronger impact on parent-reported parent-child relationship outcomes, and that medium and high intensity intervention programs were more likely to improve measured health outcomes.[109]

In summary, promising TIC interventions have started to emerge in mental health and pediatric and adult primary healthcare settings. There is a need to conduct multi-center prospective studies to assess and compare trauma-informed intervention modalities and treatments to better assess the impact of TIC on child and family health outcomes.

Statewide Efforts to Build Workforce Capacity and Integrate Systems Serving Families

Although healthcare settings are practical assessment and intervention entry points for children and families that are struggling with the impact of multi-trauma, the same population may also engage with school, child welfare, and juvenile justice systems.[79,100,103,105] States committed to multisystem TIC approaches demonstrate the importance of working across multiple systems when developing interventions for children and families who are often involved in more than one system.[57,67,72] This 'trauma-informed systems' approach promotes shared beliefs, values, and practice approaches among organizations, some of which are multilevel interventions that provide workforce training along with policy changes, while others offer targeted services, such as child welfare screenings across multiple agencies.[72,105,110,111] In fact, with the recognition that cross-system TIC implementation may improve health, social, and educational outcomes simultaneously, numerous states have started efforts to build capacity to deliver TIC across systems serving children and their families, including child welfare, education, health and mental health systems.[103,112]

States have focused their efforts in several areas: assessing whether and to what extent systems are trauma-informed, improving worker capacity through workforce training, disseminating information about trauma-informed practice, and integrating systems that serve families and children.[103,105] The assessment of a program is often an initial step to explore TIC readiness, available tools and gaps, and to develop training programs for workers and interventions for families and children in the child welfare and mental health systems. For instance, California, Oklahoma, and New Hampshire developed a process to evaluate how trauma responsive their child welfare systems were, with the goal of generating recommendations for statewide improvements. Bassuk et al.[100] developed and validated a brief assessment tool to measure the level of TIC in health and human services to determine training needs, evaluate their practice, and develop trauma-informed policies.

Trauma-informed workforce initiatives within the child welfare system range from trauma education training programs in Louisiana, Tennessee, and Arkansas to multisystem approaches in South Carolina.[110,113-115] Project Best, a statewide initiative in South Carolina, for example, relied on interprofessional collaboration to impact systems, resulting in improved trauma-informed practices and positive feedback about the community-based learning collaborative component.[110]

In a multifaceted, statewide program spanning child welfare, mental health, and juvenile justice in New Hampshire, the Partners for Change Project implemented case planning for youth who had been screened for trauma, multisystem collaboration, and evidence-based trauma treatments across systems, resulting in improvements in case planning, trauma

screening, mental health referrals, and overall system performance.[116] Because the child and family population in child welfare and juvenile justice system is known to have much higher healthcare needs, including physical, mental health and preventive care, implementing TIC in these systems could eventually have a significant impact on health care needs and outcomes of this vulnerable population.[79,99,104,117]

Healthcare and educational systems also interact frequently. It is well known that schools are overwhelmed with behaviorally challenged students, the majority of which receive healthcare; thus, TIC implementation in both systems may enhance health and educational outcomes simultaneously.[79,118-121] Massachusetts and Washington were among the first two states to provide guidelines for TIC implementation within schools.[122] Given the growing connection between trauma and the impact on student outcomes, school systems have made major strides in training their workforce.[118,119,123] A strong commitment from school leadership is paramount to successfully implementing training.[124,125] States have been legislating that schools train their personnel about trauma and ways to mitigate toxic stress (e.g., Nevada, Iowa, Delaware, Wisconsin), using models ranging from intensive two-day training to year-long training.[120,126,127] Both approaches have increased teachers' ability to respond to trauma, however, the year-long training was more effective.[121]

Wojciak and Smith[127] conducted a quasi-experimental study evaluating a year long, school wide, trauma-informed intervention with all school staff in an elementary school. Compared to the staff at control schools, staff participating in "We Can! Building Relationships and Resilience," reported significant increases in their understanding of the impact of trauma on student learning and behavior, their ability to work with students who have experienced trauma, and worker collegiality. In states like Washington and Massachusetts, principals have also reported reductions in office referrals and suspensions when trauma-informed practices were implemented in their schools.[128,129]

Primary Prevention of Childhood Adversity and Trauma

Programs that focus on population-level primary prevention that can reduce the incidence of ACEs are recognized as having the most potential for long-term impact. Poole et al. conducted a systematic review of programs that included a primary prevention campaign to prevent childhood trauma.[130] Programs included messages that focused on positive parenting, child development and expectations and asking for help. Although studies generally found positive results, Poole concluded that most studies did not measure changes in the risk factors targeted in the campaign: only one program, Triple-P, had rigorous, controlled evaluations to indicate the positive impact at the individual and population levels.[131-134] The challenge to the practice community when only one program is evidence-based is the lack of options or implementation strategies for diverse populations and varying levels of funding.

Strategies to reduce ACEs through environmental or policy approaches are promising but largely absent from the published evidence base. Great potential to reduce the burden of ACEs lies with policies that address the social determinants of health inequity, such as programs that reduce poverty, improve housing, or increase access to services such as healthcare and/or education.[135-137] Thus far, no published studies have examined ACEs as outcomes of these larger policy approaches.

The evidence-base for effective primary prevention strategies to reduce the burden of ACEs, although growing steadily, lags far behind community readiness to implement these strategies. There is critical need to grow the evidence base for programs that impact primary, secondary, or tertiary prevention of ACEs. Investment in program development, implementation, rigorous evaluation, and effective strategies for translation are an important federal research investment.

Barriers and Gaps Related to Implementation of Trauma-Informed Care

Despite ongoing efforts to implement TIC practices in healthcare and statewide efforts, there are still several barriers that have prevented wide-scale implementation of TIC. The need for comprehensive training, especially in trauma-sensitive approaches and language to increase provider comfort and competency to implement TIC has long been recognized. Studies investigating screening and identification of trauma victims consistently emphasizes this need, because most providers fear that asking about trauma will offend their clients.[138] Consequently, even with physical evidence of abuse, 88% of residents of a domestic violence shelter reported they were not asked about trauma or offered assistance by their dentists.[139]

Provider fear is, in fact, often unfounded because the majority of trauma survivors welcomes questions about their trauma and assistance to address it.[138,139] The need to be understood by their provider is a repetitive theme in this population.[62,140] Kottenstette et al.[61] and Fassel et al.[62] reported that their two-generational screening models for childhood trauma, family resiliency, and healthcare needs was well-received by clients; 98% and 75% of patients reported this model "could help their providers provide better healthcare" to them.

The same studies that report healthcare provider gaps in confidence and knowledge regarding addressing trauma in their patients also report a keen desire among providers for training in trauma sensitive methods to address clients' psychological distress effectively and confidently.[141,142] Barriers to asking about trauma may include the providers' discomfort with their own trauma history and the need for self-protection to avoid secondary trauma, compassion fatigue, and burn out.[138,139,143,144] Because one of the strengths of TIC is its focus on self-care and awareness of a provider's own needs, compassion satisfaction, and peer support, it may mitigate secondary traumatization and contribute to the providers' resilience.[59,144] Thus, implementation of TIC may enhance provider competencies, offer opportunities to strengthen the provider and patient relationship, and improve the identification of patients that require early and comprehensive interventions.

There is accumulating evidence that communities and systems of care including healthcare are energized to understand TIC, develop their workforce, implement trauma responsive practices, and evaluate outcomes for their clients. Statewide initiatives with strong collaborations among healthcare, mental health, child welfare, juvenile justice, and education systems have great potential to enhance well-being, decrease re-victimization, improve health, social, and educational outcomes and promote change at a societal level.[26,104]

To improve care for families and their children, healthcare systems should engage in and lead statewide initiatives to implement TIC across systems, like Hawaii, Massachusetts, Ohio, Wisconsin, Iowa and other states.[26,103] Through these collaborative efforts, different systems may learn from one another and, in addition, children and families served by these systems are likely to benefit from more synergistic comprehensive and family-centered approaches to care. Healthcare can borrow concepts like capacity building, trauma-informed systems, and assessment from statewide cross-system collaboration.

Healthcare systems moving toward accountable care designation also seems to hold the promise of a healthier population while being cost-effective. This life-course approach to disease prevention may offer opportunities at every age to build resilience as recommended by The American Academy of Pediatrics.[77] Policy makers should prioritize funding for Integrated Behavioral Health to help increase access to care in order to address difficulties early before escalation to improve health outcomes.[98]

Given the plasticity of the brain, all patients receiving healthcare have the potential to benefit from family- and patient-centered, trauma-informed, resiliency-focused care, which must to be implemented in all components of our healthcare systems.[66,67,69,72,79,80,145,146] Because the earlier the family-centered interventions are implemented, the higher the potential for better health outcomes, child-serving healthcare systems should work toward this paradigm shift now.[67,79,80]

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Original Article

Uncoupling protein gene UCP1-3826A/G, UCP2 Ins/Del and UCP3-55C/T polymorphisms in obese Turkish children

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ABSTRACT

Background. Mitochondrial uncoupling proteins (UCP) 1, 2 and 3 are members of the anion carrier protein family located in the inner mitochondrial membrane. There are various controversial reports on UCP genotypes and obesity in adults and children. This study aims to investigate the link between mostly studied UCP polymorphisms (*UCP1-3826A/G, UCP2 Insertion/Deletion (Ins/Del) polymorphism of exon 8,* and *UCP3-55C/T* Polymorphisms) and obesity in Turkish children. Furthermore, the relationships of UCP polymorphisms are also analyzed within the scope of metabolic parameters of obese children.

Methods. Molecular screening of the UCP1, UCP2, and UCP3 gene polymorphisms was carried out in 189 children aged 6 to 18 years, 102 of who had exogenous obesity (54 girls) and 87 of whom were healthy controls (48 girls). In the obese group, fasting lipids, glucose and insulin levels were measured. In 60 obese children, an oral glucose tolerance test (OGTT) was performed with 0, 30, 60, 90 and 120 minutes of sampling for plasma glucose and insulin levels.

Results. The frequency of UCP polymorphisms was similar in obese and non-obese children. In obese children, fasting lipids, glucose and insulin levels were not different among the UCP 1, 2 and 3 genotypes. While no relationship was found between the UCP 1 and 3 genotypes and glucose/insulin levels during OGTT, carriers of the Insertion allele with *UCP2 Ins/Del* polymorphism had significantly higher 30-minute insulin levels (p=0.018).

Conclusions. Polymorphisms of the *UCP1-3826A/G, UCP2 Ins/Del,* and *UCP3-55C/T* are not associated with obesity and related pathologies in Turkish children. However, the presence of the Ins allele of the UCP2 gene has been found to have an unfavorable influence on early insulin excursion after glucose loading.

Key words: UCP, polymorphism, obese, children, OGTT.

Obesity is caused by an imbalance between energy intake and output, which is influenced by numerous environmental, biological, and genetic factors. The consumption of high-calorie foods and having a sedentary lifestyle are reported as the main causes of an increasing rate of obesity; only a minority of obese people have a genetic defect. However, controversial results have been published about single nucleotide polymorphisms in obesity-related genes.[1-5]

Mitochondria are known as the primary organelle regulating metabolic and energy homeostasis and mitochondrial dysfunction is thought to play a key role in the pathogenesis of metabolic disorders in obesity. Mitochondrial uncoupling proteins (UCP) 1, 2 and 3 are the members of the anion carrier protein family located in the inner mitochondrial membrane. They act as a proton transporter, that uncouples oxidative metabolism from ATP synthesis

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and they dissipate energy through heat production.[6] Since the energy in this process is transferred to heat and not stored as fat in the body, polymorphisms in the UCP genes may contribute to variation in energy balance and potentially to the development of obesity.[7] This uncoupling effect subsequently leads to tissue-specific functions, such as thermogenesis and energy expenditure (UCP1), the regulation of free-fatty acids metabolism (UCP2 and UCP3), decrease in reactive oxygen species production by mitochondria (UCP1, UCP2, UCP3) and the regulation of insulin secretion by pancreatic beta-cells (UCP2), which are all associated with obesity and/or type 2 diabetes mellitus (T2DM) pathogenesis.[8]

Some well-known polymorphisms of the UCPs have been reported to be functional variants on gene expression because of their location within the genome. The polymorphisms located on the upstream region of the gene as *UCP1-3826 A/G* and UCP3-55C/T may associate with the quantity of the mRNA expression while UCP2 exon 8 Ins/Del polymorphism may associate with mRNA transcript stability.[6-11]

Given the location and proposed biological effects of the UCPs, it might be interesting to further evaluate the association among the *UCP1-3826A/G* (rs1800592), *UCP2 Ins/Del* and *UCP3-55C/T* (rs1800849) genotypes with childhood obesity and metabolic parameters.

Material and Methods

This study was approved by Baskent University Institutional Review Board (Project No: KA15/344), and supported by Başkent University Research Fund.

Written informed consent was obtained from the parents of the subjects. One hundred and two exogenously obese and 87 healthy age-matched controls were included in this study. In the obese group, fasting glucose, lipids and insulin levels were measured. All patients were clinically free of symptoms except for obesity and they were not taking any medication.

The heights of all subjects were measured by using a Harpenden wall-mounted stadiometer. Weight was measured with a calibrated electronic scale. Body mass index (BMI) was calculated by using the weight/height^2 (kg/m^2) formula. BMI -Z scores were calculated and children with a BMI-Z score greater than or equal to 2 were also accepted as obese.[12,13]

Serum low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglyceride levels were studied by using Roche diagnostics methods (GmbH, Germany).

A standard oral glucose tolerance test (OGTT) (1.75 g/kg or a maximum of 75 g of glucose) following a 3-day, high-carbohydrate diet (300 g/day) and a 12-hour overnight fast was performed in 60 obese children who accepted to be tested. For glucose and insulin assessments, their blood samples were taken at 0, 30, 60, 90 and 120 minutes, after glucose administration. The plasma glucose levels were measured with the glucose oxidase method and a modified Trinder color reaction was catalyzed by the peroxidase enzyme and their insulin levels were measured with an immunoradiometric assay kit.

Genomic DNA was isolated from leukocyte pellets by phenol/chloroform extraction, and ethanol precipitation.[14]

UCP1-3826A/G (rs1800592) and *UCP3-55C/T* (rs1800849) SNPs were determined by real-time PCR, using a panel of LightSNiP from TIB MolBiol (assays based on SimpleProbe®). The SimpleProbe® included in the LightSNP assay can detect single base mismatches, thus enabling the analysis of polymorphisms. At the end of the amplification, a melting curve analysis was performed according to the protocol (LightCycler 480, Roche). Polymorphic alleles were identified by the specific melting temperature (Tm) of the resulting amplicons.

For *UCP1-3826A/G* (rs1800592) individuals with -3826 A allele show a single melting peak at 57.94°C, while individuals with -3826 G allele also show a single melting peak but at 65.16°C

and individuals with both alleles (A/G) show two melting peaks at 57.94 and 65.16°C in this analysis (Fig. 1).

For *UCP3-55C/T* (rs1800849); individuals with two copies of the C allele show a single melting peak at 62.01°C, individuals with two copies of the T allele also show a single melting peak but at 67.31°C and individuals with both alleles (C/T) show two melting peaks at 62.01 and 67.31°C in this analysis (Fig. 2).

Ins/Del polymorphism of the UCP2 gene was also detected by electrophoretic separation of PCR products.[15] The presence of a 450-bp product indicated the Ins allele, whereas the presence of a 412-bp product indicated the Del allele. Each DNA sample revealed 1 of the 3 possible patterns after electrophoresis: a 412-bp band (genotype DelDel), a 450-bp band (genotype InsIns), or both bands (genotype InsDel).

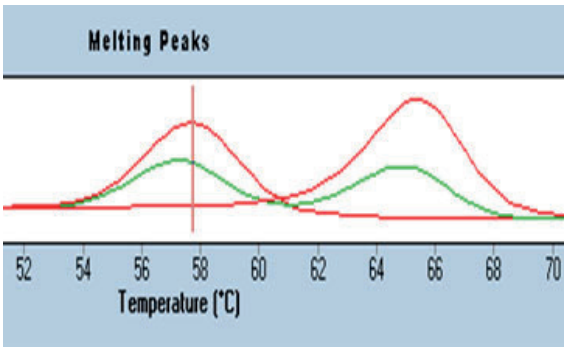

Fig. 1. Melting Curve Analysis UCP1 -3826A/G (rs1800592).

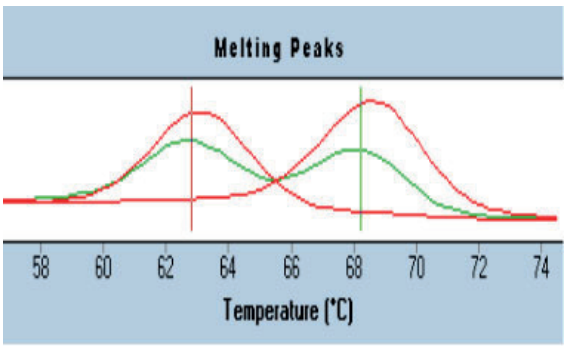

Fig. 2. Melting Curve Analysis UCP3 -55C/T (rs1800849).

Statistical analysis

Compliance with the normal distribution of continuous variables was checked with the Shapiro-Wilk test. The homogeneity of group variances was checked by Levene's test. If parametric test requirements were met, two independent group means would be compared by Student's t-test. If requirements were not met, the Mann Whitney U test would be used for the comparisons of groups' medians.

The allele and genotype frequencies were calculated for all investigated polymorphisms by direct counting. The distribution of genotypes for all polymorphisms was tested for conformity with Hardy-Weinberg equilibrium. To determine the relationships between genotypes and study groups, categorical variables were statistically evaluated by Pearson $\chi 2$ test and the Likelihood ratio test was used for small frequencies in some cells of the contingency tables. Relationships between alleles and study groups were analyzed by the Fisher Exact test. Data analyses were performed using the Statistical Package for the Social Sciences, version 19.0 (SPSS 19, Armonk, NY: IBM Corp). *p* values smaller than 0.05 were considered to be statistically significant.

Results

The frequencies of UCP1, UCP2, UCP3 genotypes were not different in the obese and control groups. The allele frequencies were also similar (Table I).

In obese children, gender, fasting lipids, glucose, and insulin levels were not different among the UCP 1, 2 and 3 genotypes (Table II). OGTT was performed in 60 obese children who approved of being tested.

Plasma glucose and insulin levels during OGTT were not different between G allele carriers and noncarriers in *UCP1-3826A/G* polymorphism and also between T allele carriers and noncarriers in *UCP3-55C/T* polymorphism genotypes. For *UCP2 Ins/Del* polymorphism, similarly, plasma

Table I. Genotype frequencies of the obese and control groups.

	Obese group (n=102) mean ±SD female/male 54/48	Control group (n=87) mean ±SD female/male 48/39	p
Age (year)	12.3 ± 2.8	11.9 ± 3.2	0.29
BMI-Z score	2.6 ± 0.5	-0.7 ± 0.8	<0.001
UCP1 -3826A/G			
AA	54 (53%)	57 (66%)	0.12
AG	40 (39%)	22 (25%)	
GG	8 (8%)	8 (9%)	
ALLELE FREQUENCY			
A	148 (73%)	136 (78%)	0.20
G	56 (27%)	38 (22%)	
UCP2 Ins/Del			
DD	72 (71%)	53 (61%)	0.11
DI	29 (28%)	29 (33%)	
II	1 (1%)	5 (6%)	
ALLELE FREQUENCY			
D	177 (87%)	150 (86%)	0.87
I	27 (13%)	24 (14%)	
UCP3 55C/T			
CC	75 (74%)	63 (72%)	0.86
CT	27 (26%)	24 (28%)	
TT	0 (0%)	0 (0%)	
ALLELE FREQUENCY			
C	177 (87%)	150 (86%)	0.87
T	27 (13%)	24 (14%)	

SD: standard deviation, BMI: body mass index

glucose and insulin levels during OGTT were not different between Ins allele carriers and noncarriers except for the 30th-minute insulin levels. The mean of the serum insulin level at the 30th-minute was significantly higher in the Ins allele carrier group (Table III).

Discussion

In this study, the genotype and allele frequencies of *UCP1-3826A/G*, UCP2 Ins/Del, and UCP3-55C/T polymorphisms were found similar in obese and non-obese Turkish children. Our study may indicate that the presence of the Ins allele of the UCP2 gene has an unfavorable influence on early insulin excursion after glucose loading.

UCP1 is expressed in brown adipose tissue and plays an important role in thermogenesis, regulation of energy metabolism, and reduction of reactive oxygen species production by mitochondria, which are important pathways in obesity and T2DM.[16]

UCP1-3826A/G polymorphism is one of the well-described polymorphisms for UCP1. In a study, it was reported that there is a positive correlation between UCP1 GG genotype and lower weight, while in two other studies it was mentioned that there is a causative effect in people carrying G allele and having a higher BMI, especially in women.[17-20] On the other hand, a report which supports an association between the -3826G allele and T2DM in adults[21] and a meta-analysis improves the lack of

Table II. Laboratory results of obese children in each polymorhism.

UCP1 -3826 A/G		Female/ Male	Age	HDL (mg/dl)	LDL (mg/dl)	Triglyceride (mg/dl)	Glucose (mg/dl)	Insulin μIU/ml
AA	Mean	30/24	12.9	42.6	98.5	118.9	86.7	20.1
	Std. Deviation		2.2	9.5	26.3	68.6	12.7	14.1
	Minimum		5.0	21.0	45.0	27.0	17.0	2.0
	Maximum		17.8	68.0	167.0	460.0	116.0	85.0
AG+GG	Mean	24/24	12.6	44.8	96.5	117.1	87.2	21.0
	Std. Deviation		2.6	9.8	23.8	60.0	6.6	16.7
	Minimum		5.0	26.0	50.0	40.0	73.0	6.0
	Maximum		17.3	72.0	159.0	304.0	100.0	87.0
p-value		0.57	0.80	0.34	0.70	0.89	0.81	0.76
UCP2 I/D		Female/ Male	Age	HDL (mg/dl)	LDL (mg/dl)	Triglyceride (mg/dl)	Glucose (mg/dl)	Insulin μIU/ml
DD	Mean	39/33	12.5	43.4	98.1	120.4	86.7	87.6
	Std. Deviation		2.8	9.7	26.8	66.1	11.3	7.3
	Minimum		5.0	21.0	45.0	27.0	77.0	74.0
	Maximum		17.8	72.0	167.0	460.0	116.0	101.0
II+ID	Mean	15/15	12.0	43.8	96.2	112.5	86.9	20.5
	Std. Deviation		2.8	9.6	20.1	60.9	10.3	15.4
	Minimum		5.5	26.0	51.0	41.0	17.0	2.0
	Maximum		17.3	64.0	128.0	304.0	116.0	87.0
p-value		0.34	0.78	0.85	0.72	0.57	0.70	0.65
UCP3 -55 C/T		Female/ Male	Age	HDL (mg/dl)	LDL (mg/dl)	Triglyceride (mg/dl)	Glucose (mg/dl)	Insulin μIU/ml
CC	Mean	38/37	11.9	43.3	96.8	114.5	86.1	19.8
	Std. Deviation		3.0	9.5	25.8	68.2	11.3	13.2
	Minimum		5.0	21.0	45.0	27.0	17.0	2.0
	Maximum		17.8	65.0	162.0	460.0	116.0	85.0
CT+TT	Mean	16/11	9.6	43.9	99.8	127.9	89.2	22.4
	Std. Deviation		2.1	10.2	22.8	52.8	6.4	19.9
	Minimum		8.3	30.0	54.0	40.0	73.0	7.0
	Maximum		16.3	72.0	167.0	264.0	100.0	87.0
p-value		0.44	0.67	0.76	0.60	0.36	0.18	0.45

HDL: high-density lipoprotein cholesterol, LDL: low-density lipoprotein cholesterol

the association of the relevant genotype and T2DM.[22] The result of our study shows that *UCP1-326A/G* genotype was not associated with obesity, metabolic disorders, gender and also glucose-insulin responses during OGTT.

UCP2 is widely expressed, especially in white adipose tissue, skeletal muscle, and pancreatic islets. The *UCP2 Ins/Del* polymorphism is a 45-bp insertion in exon 8 in the 3'-untranslated region of the UCP2 gene. It may affect UCP2 mRNA stability, post-transcriptional modification, or translation.[23] Although no significant association has been reported between UCP2 Ins/Del genotype and obese/non-obese adults and children in many reports, Yanovski et al.[24] have reported that children with Ins allele had a greater BMI. However, the metabolic parameters related to obesity were not included.[25,26]

Table III. Glucose and insulin levels during OGTT in UCP1. 2. 3 polymorphism genotypes.

	UCP1 3826A/G	Mean	Std. Deviation	Std. Error Mean	p	UCP2 Ins/Del of exon 8	Mean	Std. Deviation	Std. Error Mean	p	UCP3 55C/T	Mean	Std. Deviation	Std. Error Mean	p
	AA	86.7	12.7	1.7	0.81	DD	86.7	11.3	1.3	0.70	CC	86.1	11.3	1.3	0.18
Glucose 0	AG+GG	87.2	6.6	0.9		ID+II	87.6	7.3	1.3		CT+TT	89.2	6.4	1.2	
	AA	20.1	14.2	2.0	0.77	DD	20.9	15.3	1.8	0.66	CC	19.8	13.3	1.6	0.46
Insulin 0	AG+GG	21.0	16.7	2.5		ID+II	19.4	15.5	2.8		CT+TT	22.4	19.9	3.8	
	AA	142.2	25.8	4.4	0.78	DD	140.9	24.4	3.7	0.81	CC	139.0	27.7	4.2	0.46
Glucose 30	AG+GG	140.3	25.7	5.1		ID+II	142.7	28.6	6.7		CT+TT	145.5	18.3	4.6	
	AA	138.6	84.8	14.3	0.78	DD	120.6	74.1	11.4	0.01	CC	130.5	84.5	12.7	0.36
Insulin 30	AG+GG	132.8	72.2	14.4		ID+II	172.7	80.8	19.1		CT+TT	151.8	62.3	15.6	
	AA	140.9	27.9	4.7	0.44	DD	141.3	26.3	4.1	0.25	CC	138.3	26.5	3.9	0.84
Glucose 60	AG+GG	135.6	23.3	4.7		ID+II	132.7	24.9	5.9		CT+TT	139.9	25.4	6.4	
	AA	138.7	88.5	14.9	0.67	DD	136.3	78.2	12.1	0.39	CC	139.0	96.9	14.6	0.58
Insulin 60	AG+GG	149.5	106.4	21.3		ID+II	159.3	128.8	30.7		CT+TT	154.6	93.9	23.5	
	AA	132.9	36.2	6.1	0.45	DD	132.4	32.7	5.0	0.46	CC	129.4	32.2	4.9	0.62
Glucose 90	AG+GG	127.1	15.8	3.2		ID+II	126.2	19.9	4.7		CT+TT	133.7	20.2	5.1	
	AA	145.1	108.0	18.3	0.88	DD	138.6	105.1	16.2	0.63	CC	142.7	122.0	18.4	0.96
Insulin 90	AG+GG	140.5	119.9	23.9		ID+II	153.9	129.7	30.6		CT+TT	144.3	82.2	20.6	
	AA	122.3	25.6	4.3	0.11	DD	116.9	23.2	3.5	0.48	CC	116.9	24.1	3.6	0.43
Glucose 120	AG+GG	113.0	17.4	3.4		ID+II	121. 6	21.8	5.1		CT+TT	122.2	18.5	4.6	
	AA	137.1	103. 3	17.5	0.71	DD	131.6	109.3	16.7	0.28	CC	141.5	123.7	18.4	0.96
Insulin 120	AG+GG	148.4	129.3	25.4		ID+II	166.6	125.0	29.5		CT+TT	143.2	85.5	21.4	

All glucose levels were expressed as mg/dL and insulin levels were expressed as mU/mL

As for the UCP3, the gene is selectively expressed in human skeletal muscles, a major site of thermogenesis and substrate oxidation, which makes this gene an attractive candidate for studies of energy metabolism and body weight regulation. Recent evidence has suggested that UCP3 plays an important role in modulating the use of lipid and glucose as an energy substrate.[27] *UCP3-55C/T* polymorphism is the most well-documented one. Studies exploring the association of *UCP3-55C/T* genotype and BMI have provided conflicting results. Although no association was reported between *UCP3-55C/T* polymorphism and obesity, in some reports concerning adults, -55TT genotype of UCP3 was mentioned to have both higher BMI and lower BMI.[28-31] No significant association was reported between *UCP3-55C/T* polymorphism and childhood obesity in this study.

Gul et al.[32] studied *UCP1-3826A/G*, *UCP2 Ins/Del*, and *UCP3-55C/T* variants in 268 obese and 185 non-obese Turkish children and reported that the G allele was more frequent in obese subjects with hypertriglyceridemia. Although it has been reported that the polymorphisms of *UCP2 Ins/Del* and *UCP3-55C/T* do not influence the obesity risk, the Ins allele was associated with low HDL levels. In our study, we did not find any relation between UCP polymorphisms and lipid levels in Turkish children.

OGTT provides a dynamic view of glucose and insulin physiology and has been widely used for decades to diagnose diabetes.[33] The 30th-minute insulin levels in the test show the first-phase insulin secretion which can be an index of beta-cell function. In a recent study concerning adults,[34] it has been reported that, after glucose ingestion, individuals with insulin-resistance and normal glucose tolerance secreted even more insulin in the early phase (30th-minute measurement in OGTT). Therefore, we have investigated the association between UCP genotypes and post-challenge glucose-insulin levels during OGTT. Our results may indicate that the 30-minute post-challenge insulin levels were significantly higher in obese children who were Ins allele carriers in *UCP2 Ins/Del*. Csernus K. et al.[35] reported that in obese Hungarian children the *UCP2 Ins/Del* polymorphism was associated with a higher degree of obesity, insulin resistance (higher 0 and 120-minute insulin levels during OGTT), dyslipidemia and lower adjusted metabolic rate. The Ins allele of the *UCP2 Ins/Del* polymorphism was associated with worse indices of obesity, insulin resistance, and dyslipidemia. They did not measure insulin levels at 30, 60 and 90 minutes. Although we did not find any relation between the 120th-minute insulin levels with Ins allele carriers of the UCP2 gene, 30-minute post-challenge insulin levels were found to be higher.

In conclusion, based on our data from a single-center, we propose that *UCP2 Ins/Del* polymorphism has a significant role in glucose-insulin dynamics. Obese children who are Ins allele carriers of the UCP2 gene have a higher risk for exaggerated early-phase insulin response to glucose. Further studies with other genes are required to be carried out to understand the molecular mechanisms of obesity.

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Original Article

Healthy eating index in a nationally representative sample of children and adolescents by socio-demographic characteristics: the Weight disorders survey of the CASPIAN-IV Study

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ABSTRACT

Background. To date, the diet quality of Iranian students in relation to socio-demographic characteristics was not studied. The present study aimed to explore the association between the healthy eating index and socio-demographic characteristics among a nationally representative sample of Iranian children and adolescents.

Methods. This nationwide study was conducted in 5187 children and adolescents, aged 6-18 years. Data regarding socio-demographic variables, lifestyle factors, family and student dietary habits, and quality of life were gathered via validated questionnaires. The Alternate Healthy Eating Index-2010 (AHEI-2010) was used to calculate diet quality scores.

Results. The odds of high diet quality was 24% lower in adolescents (13-18years) compared to children aged 6-12 years (OR 0.76, CI 0.64-0.89, p= 0.001). Students in families with moderate (OR 1.30, CI 1.13-1.49, p <0.001) and high socioeconomic status (OR 1.36, CI 1.18-1.57, p <0.001) were 30% and 36% more likely to have a higher diet quality score, respectively. Lower mean AHEI-2010 scores (CI) were found for low socio-economic status (46.18-47.10), adolescents 47.40 (46.94-47.82), boys 47.51 (47.14-47.88) and South-East area 47.19 (46.54-49.15) (p<0.05) due to lower intake of fruits and vegetables and high intake of sodium and sugar-sweetened beverages.

Conclusions. The overall diet quality of Iranian children and adolescents was low with disparities across socio-demographic variables notably age and familial socio-economic status.

Key words: diet quality, socio-demographic, children, adolescents.

In recent years, there has been a change in food habits and dietary patterns of people from healthy to unhealthy and low nutritive content foods. These changes vary from one region to another[1] and may be responsible for the increased prevalence of cardio-metabolic disorders like overweight and obesity[2] especially in children and adolescents.[3-5] Some earlier studies suggest that early life nutrition significantly contributes to childhood overweight or obesity[6,7] which may track to adulthood resulting in lifelong obesity and its comorbidities battle like cardiovascular disease (CVD).[8] Healthy and proper nutrition is an essential factor for children's health and growth as well as their quality of life that tends to track into adulthood.[1] Findings showed that dietary patterns including a variety of fruits, vegetables, whole grains, low-fat dairy products, and lean

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meats reduce the risk of non-communicable diseases (NCDs) such as type 2 diabetes, some cancers, CVD, and osteoporosis.[9,10] According to the earlier investigations, the incidence of the aforementioned disease was higher in populations with low socioeconomic status.[1,2] Therefore there is a need to understand the dietary patterns of a population and provide a report of their nutritional status on a timely basis in order to identify sub-populations requiring intervention as well as getting an insight into how dietary patterns and diet quality may contribute to NCDs.[3,4] Diet quality which assesses quality and variety of the diet and shows the association between whole foods and health status, rather than just nutrients, is an effective tool to elucidate the relation between nutritional status and health.[5,6] The healthy eating index (HEI) is a measure of diet quality that can be used to evaluate nutrition interventions and education programs.[16] It has been reported that diet quality, as well as food choices, are influenced by a number of factors including socioeconomic, individual and environmental effects.[17,18] Although a number of recent studies demonstrate a positive association between socioeconomic status and indicators of diet quality,[19,20] few studies have assessed the association between socio-demographic and consumption patterns of some food groups.[4,7,8] To the best of our knowledge no study has assessed such association among Iranian children and adolescents. Therefore, we evaluated the association between healthy eating index as a diet quality indices and socio-demographic factors in a nationally representative sample of Iranian children and adolescents

Material and Methods

Study population

This nationwide cross-sectional study was conducted in the framework of the Childhood and Adolescence Surveillance and Prevention of Adult Non-communicable Disease" (CASPIAN-IV) study which included a large group of Iranian children and adolescents aged 6-18 years old, living in urban and rural areas of 31 provinces in Iran.[23] Participants were divided into two groups of age including children (6-12years old) and adolescents (13-18 years old). Detailed information about the study design, participants and data collection method has been published previously.[24]

Study protocols were reviewed and approved by the ethical committees of Isfahan University of Medical Sciences (189130/2011-2012). After a complete explanation of the study objectives and protocols, written informed consent was obtained from the parents and students.

All students were asked to fill in validated questionnaires and a group of health expertise supervised them. Data for socio-demographic, perinatal factors, lifestyle factors, as well as student's and familial history of chronic disease were collected.

Dietary intake assessment

A validated 168-items semi-quantitative food frequency questionnaire (sq-FFQ) was administered by participants to assess their dietary intake. The FFQ consisted of a list of foods with a standard serving size commonly consumed by Iranians. All students were asked for the amount and frequency of different food items during the last year based on daily, weekly, or monthly intake. The reported frequency for each food item was then converted to daily intake.[25] All dietary information was entered into the Iranian Food Consumption Program (IFCP), designed by Isfahan Cardiovascular Research Center (ICRC) and analyzed.[9] IFCP was designed based on the Iranian food composition table.[10] Energy and nutrient intakes were estimated using IFCP.

Anthropometric assessment

Weight and height were measured by a trained person under standard protocol as follows; weight was measured in minimal clothes and barefoot nearest to the 200g, height was measured without shoes to the nearest 0.1

cm. Body mass index (BMI) was calculated by dividing weight (kg) to height squared (m^2). Waist circumference (WC) was measured between the iliac crest and the lowest rib to the nearest 0.2 cm.

Socioeconomic status (SES) assessment

To determine the SES of participants, the previously approved methodology "Progress in the International Reading Literacy Study (PIRLS)" for Iran was used. Using principal component analysis (PCA), parents' education, parents' job, possessing a private car, school type (public/private), type of home (private/rented), and having a personal computer variable were summarized under one main component, categorized into four quartiles. Through an ascending grade, the first quartile was defined as the "lowest SES" and the fourth quartile as the "highest SES" groups.[11]

Calculating HEI scores

According to the recent studies, Alternate Healthy Eating Index-2010 (AHEI-2010) in comparison to Healthy Eating Index-2010 (HEI-2010) has a stronger link to chronic diseases and should thus forecast risks better.[12] Therefore, in the present study AHEI-2010 was used to calculate the scores. The AHEI-2010 is based on 11 components; for six components, the highest intake considered as desired including vegetables, fruits, whole grains, nuts, legumes, long-chain omega-3 fats (docosahexaenoic acid and eicosapentaenoic acid), and polyunsaturated fatty acids (PUFAs). For one component (alcohol) moderate intakes are supposed to be ideal while for the rest of the components lower intake posit to be desired including sodium, sugar-sweetened beverages (SSB), red and processed meat, and trans fats. Each component is given a score between 0 to 10. Total scores range from 0-110 by summing up the score of each component. A higher score represents a better diet quality.[26] In other words, AHEI-2010 makes no explicit division between adequacy and moderation.[12]

Statistical analysis

Continuous variables are showed as mean (95% CI) and categorical variables as a percent (95% CI). Study variables across socioeconomic status and socioeconomic status of the living area were assessed using ANOVA test and across gender and age categories were assessed by t-test. Considering the hierarchical structure of our data, a multilevel ordered logistic regression model (with two-level) was used to assess the association between quartile of the healthy eating index and socio-demographic characteristics, taking account the effect of a mix of individual-level (first level) and provincial level (second level) factors. Multilevel modeling adequately illustrates the unexplained variability of the nested structure, which is often hard to explain in the single-level approach.[27] The results of multilevel models were presented as odds ratios (OR) with 95% CI. A P-value of less than 0.05 was considered statistically significant in all analyses. All statistical analyses were conducted by Stata 11.2 (StataCorp LP, College Station, TX)

Results

A total of 5187 students were analyzed, 52.6% were boys and 72.4% lived in the urban area. Table I represents the socio-demographic characteristics of participants. Overall, 34% of children and adolescents lived in provinces with the highest socioeconomic status (central), and 15.6% of those lived in the southeast area with the lowest socioeconomic status.

Body composition and dietary intake of participants according to family socioeconomic status, socioeconomic status of living area, gender and age are presented in Tables II and III, respectively. Mean body weight, waist circumferences, and body mass index was significantly higher in students with high family socioeconomic status and those living in the central region (with the highest SES) than others (p-value <0.05).

Table I. Demographic characteristics of participants.

		Percent	95%CI
Age	6-12 years	61.7%	(60.4 63.3)
	13-18 years	38.3%	(36.6 39.6)
Gender	Boys	52.6%	(50.8 53.8)
	Girls	47.4%	(46.1 49.2)
Living area	Urban	72.4%	(69.8 72.6)
	Rural	27.5%	(27. 4 30.2)
Socio-economic status of living region	Lowest (Southeast)	15.9%	(17.1 19.4)
	Second Low (North-Northeast)	19.5%	(21.8 24.3)
	Second High SES (West)	30.6%	(32.4 35.3)
	Highest SES (Central)	34%	(23.6 26.2)
Family socio-economic status	Low	33.2%	(31.8 34.6)
	Moderate	33.4%	(32.0 .34.8)
	High	33.4%	(32.0 34.8)

Children and adolescents with high SES and those who lived in the central (with the highest SES) had significantly higher intakes of total calorie, carbohydrate, protein, fruit, vegetables, processed meat, and lower intake of total fat and PUFAs than others (p-value <0.05) (Tables II and III).

The mean healthy eating index (HEI) in participants who lived in the southeast (with the lowest SES) and those with low family SES was significantly lower than other students (p-value < 0.05) (Tables II and III)

Consumption of total fat, sodium, and vegetables was significantly higher among girls than boys (p-value < 0.05), while boys had a higher intake of SSB, nuts and legumes (Table IV).

Adolescents (students aged 13-18 years) consumed a significantly higher amount of sodium, whole grain, and SSB than children (students aged 6-12 years) (p-value < 0.05). The mean score (± SD) of HEI in boys (47.51 ± 9.22) was lower than girls (48.39 ± 8.99). Adolescents (47.40 ± 8.85) had lower HEI score compared to the children (48.25 ± 9.52) (p-value< 0.05) (Table IV).

Association between socio-demographic characteristics and HEI (at the provincial level) using multilevel ordinal logistic regression is shown in Table V. At an individual level, odds of higher HEI score in students aged 13-18 years, was 24% lower than students aged 6-12 years, (OR 0.76 < 95% CI: 0.64 to 0.89, P < 0.05). Students with high (OR 1.36 < 95% CI: 1.18 to 1.57, P < 0.05) and moderate (OR 1.30 < 95% CI: 1.13 to 1.49, P < 0.05) family SES were 36% and 30% more likely to have higher HEI score than students with low family SES, respectively. SES of living area at the provincial level was not significantly associated with HEI scores (p-value >0.05). Total diet quality scores based on socio-demographic variables categories are summarized in Figure 1. Based on this figure girls with high SES and living in north/north-east of Iran had better diet quality.

Discussion

The overall diet quality of Iranian children and adolescents based on a mean HEI score was less than half the maximum score. Such a score is due to the high consumption of sodium, SSB, processed meat, and a lower intake of whole grains, fruits, vegetables, nuts, and legumes. The results of the present study indicate an association between diet quality and socio-demographic characteristics. A higher score of diet quality was significantly associated with

Table II. Body composition and dietary intakes of children according to family socio-economic status.

Mean (95%CI)	Socio-economic status			P for trend
	Low	Moderate	High	
Body weight (kg)	38.48 (37.7 39.25)	41.09 (40.22 41.96)	46.47 (45.54 47.4)	<0.001*
Waist circumference (cm)	63.8 (63.27 64.42)	66 (65.43 66.67)	69.6 (68.95 70.29)	<0.001*
BMI (kg/m^2)	18 (17.81 18.28)	18.9 (18.60 19.15)	19.9 (19.64 20.16)	<0.001*
Total Energy intake (Kcal/day)	2445.1 (2401.6 2488.5)	2527.3 (2487.7 2566.8)	2598.4 (2558.5 2638.2)	<0.001*
Carbohydrate (% Kcal)	54.9 (54.5 55.36)	55.6 (55.20 55.96)	55.6 (55.22 55.96)	0.022*
Fat (% Kcal)	34.3 (33.91 34.69)	33.3 (32.94 33.62)	32.8 (32.48 33.13)	<0.001*
Protein (% Kcal)	12. 7 (12.53 12.83)	13.4 (13.28 13.54)	14.01 (13.87 14.15)	<0.001*
Fiber (gr/day)	26.93 (26.20 27.65)	28.51 (27.85 29.18)	29.51 (28.84 30.19)	<0.001*
Sodium (mg/day)	6150.40 (5720.2 6580.6)	6053.35 (5453.2 6653.5)	6033.02 (5442.1 6623.9)	0.77
Long chain omega 3 fatty acid	0.20 (0.18 0.23)	0.21 (0.18 0.23)	0.22 (0.20 0.24)	0.17
Poly unsaturated fatty acid (g/day)	18.74 (18.25 19.23)	17.76 (17.34 18.18)	17.46 (17.04 17.88)	<0.001*
Fruits (gr/day)	226.68 (214.84 238.51)	313.59 (298.70 328.49)	380.58 (363.88 397.28)	<0.001*
Vegetables (gr/day)	296.41 (286.70 306.12)	329.88 (319.70 340.06)	340.84 (330.28 351.39)	<0.001*
Whole grain (gr/day)	40.33 (37.43 43.23)	44.14 (41.05 47.24)	41.61 (38.86 44.36)	0.54
Nuts & legumes (gr/day)	49.81 (47.46 52.16)	51.08 (48.92 53.25)	50.15 (47.96 52.33)	0.84
Sugar-sweetened beverage (gr/day)	77.81 (72.44 83.18)	85.73 (79.94 91.53)	85.28 (79.95 90.61)	0.06
Processed meat (gr/day)	25.20 (23.78 26.62)	32.75 (30.97 34.52)	39.55 (37.47 41.63)	<0.001*
Healthy eating index (HEI)	46.63 (46.18 47.10)	48.53 (48.06 49.00)	48.67 (48.19 49.15)	<0.001*

*p-value < 0.05 considered as statistically significant

family SES while such an association was not observed for gender and socioeconomic status of living region. Children with high SES showed higher body weight, waist circumference, BMI, energy intake, protein, fiber, fruits, and vegetables intake coupled with lower fat and PUFAs intake. Furthermore, as age increased diet quality has decreased. In fact, a significant

Table III. Body composition and dietary intakes of children according to socio-economic status of living region.

Mean (95%CI)	Socio-economic status of living area				P for trend
	Lowest (Southeast)	Second Low (North/ Northeast)	Second High SES (West)	Highest SES (Central)	
Body weight (kg)	38.49 (37.36 39.62)	44.91 (43.85 45.98)	40.62 (39.82 41.42)	44.29 (43.21 45.37)	<0.001*
Waist circumference (cm)	62.75 (61.94 63.57)	69.06 (68.30 69.82)	66.21 (65.60 66.83)	67.63 (66.91 68.36)	<0.001*
Body mass index (kg/m^2)	17.43 (17.15 17.71)	19.64 (19.35 19.92)	19.01 (18.73 19.28)	19.39 (19.08 19.71)	<0.001*
Total Energy intake (Kcal/day)	2321.40 (2265.8 2377)	2531.31 (2482.1 2580.5)	2659.83 (2622.4 2697.2)	2579.73 (2544.5 2614.9)	<0.001*
Carbohydrate (% Kcal)	52.85 (52.31 53.39)	57.14 (56.71 57.56)	55.20 (54.82 55.57)	55.91 (55.57 56.25)	<0.001*
Fat (% Kcal)	35.92 (35.40 36.44)	31.94 (31.54 32.34)	33.92 (33.60 34.25)	32.84 (32.54 33.14)	<0.001*
Protein (% Kcal)	12.98 (12.76 13.20)	13.36 (13.21 13.1)	13.14 (13.01 13.27)	13.52 (13.40 13.65)	<0.001*
Fiber (gr/day)	22.02 (21.33 22.71)	28.62 (27.88 29.36)	32.40 (31.64 33.16)	29.48 (28.85 30.10)	<0.001*
Sodium (mg/day)	6085.59 (5737.9 6433.3)	6284.26 (5680.8 6887.8)	6095.83 (5680.8 6887.8)	5767.96 (5292.4 6243.5)	0.37
Long chain omega 3 fatty acid	0.32 (0.28 0.36)	0.22 (0.20 0.24)	0.18 (0.16 0.20)	0.15 (0.13 0.16)	<0.001*
Poly unsaturated fatty acid (gr/day)	19.48 (18.77 20.18)	17.23 (16.73 17.74)	18.88 (18.48 19.27)	17.79 (17.40 18.18)	0.003*
Fruits (gr/day)	178.42 (167.22 189.62)	320.26 (302.60 337.93)	295.36 (281.99 308.72)	379.30 (364.93 393.67)	<0.001*
Vegetables (gr/day)	275.07 (262.39 287.75)	328.96 (316.96 340.95)	336.00 (326.46 345.53)	332.18 (323.16 341.21)	<0.001*
Whole grain (gr/day)	19.59 (17.78 21.39)	80.35 (75.64 85.06)	34.80 (32.44 37.16)	39.18 (37.09 41.26)	0.053
Nuts & legumes (gr/day)	56.07 (53.21 58.93)	44.76 (42.05 47.47)	52.37 (50.27 54.48)	50.72 (48.74 52.70)	0.14
Sugar-sweetened beverage (gr/day)	78.52 (73.30 84.73)	81.06 (74.28 87.85)	86.52 (81.07 91.97)	76.51 (72.05 80.97)	0.97
Processed meat (gr/day)	24.05 (22.40 25.70)	30.18 (28.10 32.26)	35.06 (33.22 36.90)	38.36 (36.95 40.13)	<0.001*
Healthy eating index (HEI)	47.19 (46.54 47.85)	48.88 (48.31 49.45)	48.72 (48.29 49.15)	49.62 (49.01 50.23)	<0.001*

*p-value < 0.05 considered as statistically significant

inverse association was observed between age group and diet quality scores which is consistent with earlier studies.[3,13,14] In addition, the greatest disparity in diet quality in relation to socio-demographic variables was for SES of living area, followed by family SES, gender and

Table IV. Body composition and dietary intakes of children according to age and gender.

Mean (95%CI)	Gender		P-value	Age		P-value
	Girl	Boy		6-12 years	13-18 years	
Body weight (kg)	42.18 (41.47 42.88)	42.04 (41.31 42.78)	0.08	33.44 (33 33.88)	56.05 (55.31 56.70)	<0.001*
Waist circumference (cm)	65.81 (65.28 66.33)	67.19 (66.68 67.71)	0.015*	62.23 (61.85 62.63)	73.40 (72.84 73.93)	<0.001*
Body mass index (kg/m^2)	19.28 (19.06 19.50)	18.59 (18.41 18.78)	<0.001*	17.60 (17.44 17.77)	21.03 (20.81 21.25)	<0.001*
Total Energy intake (Kcal/day)	2525.1 (2492.8 2556.4)	2519.3 (2483.8 2550.7)	0.73	2519.34 (2489.9 2549.6)	25316 (2493.7 2569.2)	0.79
Carbohydrate (% Kcal)	345.37 (340.32 350.09)	315.29 (346.18 355.78)	0.12	346.2 (341.8 350.8)	353.10 (347.15 358.87)	0.07
Fat (% Kcal)	96.22 (94.67 97.78)	92.97 (91.37 94.48)	0.004*	83.97 (82.88 85.13)	83.70 (82.19 85.32)	0.12
Protein (% Kcal)	84.09 (82.83 85.34)	83.62 (82.30 84.90)	0.61	95.11 (93.70 96.52)	93.75 (91.97 95.45)	0.20
Fiber (gr/day)	27.81 (27.27 28.34)	28.70 (28.16 29.26)	0.17	27.96 (27.49 28.44)	28.77 (28.14 29.42)	0.13
Sodium (mg/day)	6491.9 (6049.1 7048.1)	5707.4 (5411.8 6110.7)	<0.001*	5649.41 (5308.2 6033.6)	6760.1 (6320.01 7438.8)	<0.001*
Long chain omega 3 fatty acid	0.21 (0.19 0.23)	0.22 (0.20 0.24)	0.45	021 (0.19 0.23)	0.22 (0.20 0.24)	0.26
Poly unsaturated fatty acid (gr/day)	18.24 (17.85 18.63)	17.76 (17.43 18.09)	0.120	17.90 (17.59 18.22)	18.22 (17.79 18.62)	0.56
Fruits (gr/day)	311.40 (298.61 324.43)	301.72 (290.74 314.3)	0.08	303.89 (293.80 314.84)	309.62 (295.32 323.85)	0.18
Vegetables (gr/day)	339.32 (331.52 347.46)	304.94 (296.98 312.86)	<0.001*	317.33 (310.03 325.11)	326.85 (317.78 336.90)	0.07
Whole grain (gr/day)	40.25 (38.13 42.50)	44.26 (41.84 46.87)	0.55	38.11 (36.21 40.22)	49.22 (46.38 52.46)	<0.001*
Nuts & legumes (gr/day)	48.80 (47.05 50.78)	51.76 (49.84 53.58)	<0.001*	50.25 (48.78 51.85)	50.21 (48.12 52.35)	0.038*
Sugar-sweetened beverage (gr/day)	79.64 (74.78 84.36)	86.80 (82.88 91.03)	<0.001*	82.48 (87.47 86.53)	85.23 (80.14 90.39)	0.008*
Processed meat (gr/day)	32.72 (31.18 34.27)	32.37 (30.84 33.82)	0.48	31.36 (30.12 32.62)	34.52 (32.64 36.30)	0.12
Healthy eating index (HEI)	48.39 (47.97 48.79)	47.51 (47.14 47.88)	<0.001*	48.25 (47.91 48.58)	47.40 (46.96 47.82)	0.003*

*p-value < 0.05 considered as statistically significant.

age. Results of the present study showed that people who are living in the south-east area had poorer diet quality due to lower intake of protein, fiber, fruits, vegetable and higher intake of fats. These results are in line with earlier studies that show a significant link between the socioeconomic status of the living region with diet quality in a way that those living in

Table V. Association between socio-demographic variables and HEI by multilevel ordinal logistic regression.

Socio-demographic variables			HEI (percent)				OR	P-value
			Q1	Q2	Q3	Q4	(95% CI)	
Individual-level	Age	6-12 years	58.4%	62.2%	63.2%	62.8%	1	0.001*
		13-18 years	41.6%	37.4%	36.8%	37.2%	0.76 (0.64 0.89)	
	Sex	Boy	57.3%	52.4%	50.3%	50.3%	1	0.07
		Girl	42.7%	47.6%	49.7%	49.7%	1.15 (0.99 1.32)	
	Family socio-economic status	Low	37.8%	34.9%	34.4%	26%	1	
		Moderate	31.3%	32.4%	34%	35.6%	1.30 (1.13 1.49)	<0.001*
		High	30.8%	32.7%	31.6%	38.2%	1.36 (1.18 1.57)	<0.001*
Provincial-level	Socio-economic status of living region	Lowest (Southeast)	19.4%	17.5%	13%	13.8%	1	
		Second Low (North/ Northeast)	20.2%	17.2%	19.2%	21.5%	1.19 (0.53 2.65)	0.68
		Second High SES (West)	31.1%	30.1%	31.5%	29.6%	0.90 (0.45 1.80)	0.76
		Highest SES (Central)	29.3%	35.2%	36.3%	35.1%	0.94 (0.44 2.02)	0.88
provincial level : Variance (95% CI)			0.26 (0.13 0.53)					

*p-value < 0.05 considered as statistically significant.
HEI: healthy eating index.

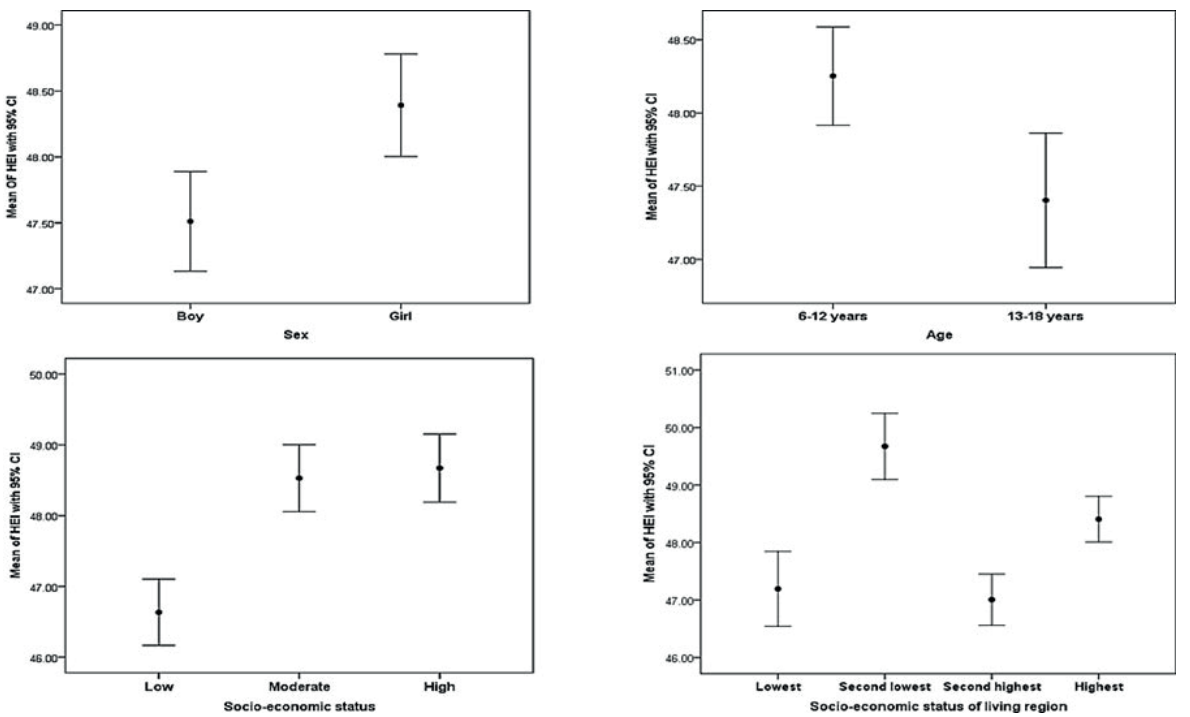

Fig. 1. HEI total mean scores and 95% CI by socio-demographic characteristics.

higher socioeconomic areas were more likely to have higher diet quality scores.[4,7] One of the SES factors which according to the literature plays a barrier role for having a healthier diet is the level of family income.[4,15] Recent meta-analysis and observational studies reported that healthier diet is more expensive than unhealthy ones.[4,16-20] Analysis of the present study showed that children and adolescents in families with high SES had higher body weight and BMI with better diet quality than those in the lower SES which is in line with earlier studies.[4,7] Better diet quality among these subjects was due to a higher intake of protein, fiber, fruits and vegetables and a lower intake of fat. The possible explanation for such an association is related to education and knowledge, two components of socioeconomic status.[22,23] In other word, studies justified that those in higher SES families had higher income, education and better knowledge about foods.[24-26]

In the present analysis, girls showed better diet quality than boys, a finding consistent with other researches.[15,27,28] Better diet quality among girls despite a higher intake of sodium and fats was owing to a higher score for vegetables and a lower score for SSB. Earlier investigations suggest that women are more likely to select healthier foods to maintain their body weight. A healthy diet is considered a feminine pursuit by men[29] that is why studies targeting men get better results in terms of healthy diet patterns.[30] The smallest disparities in diet quality of the analysis's socio-demographic variables were for age. Adolescents aged 13-18 years old compared to children aged 6-12years old showed higher body weight, BMI and lower diet quality due to consuming more sodium, and SSB and fewer amounts of nuts and legumes. Studies show that adolescents make poorer food choices than other age groups containing a higher amount of fat, sugar and processed foods.[22,31] In fact, the greatest concern is for adolescents who have the worst diet quality and tend to further decline in healthy eating patterns.[32] The strength of the present study that should be taken into account is a large nationally representative sample of Iranian children and adolescents and the use of FFQ to assess dietary intakes. The limitation of the study is a cross-sectional nature that does not allow establishing a causal relationship.

To sum up, the overall diet quality of Iranian children and adolescents were poor compared to the maximum score of HEI. Moreover, socio-demographic variables notably age and family income classes play a role in the quality of eating. It seems that Iranian girls aged 6-12 years old in families with high SES and living in the central area had better dietary patterns.

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Original Article

Determinants of outcomes in chronic pediatric peritoneal dialysis: a single center experience

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ABSTRACT

Background. In situations where it may take a long time to perform renal transplantation peritoneal dialysis may become a long-term maintenance treatment, especially in countries with low donor rates. Therefore, we aimed to evaluate peritonitis, catheter revision and survival rates in children on chronic peritoneal dialysis (CPD); and to define related factors in a single tertiary center from a WHO upper middle income country.

Methods. Between January 1998 and September 2018, data of pediatric patients receiving CPD with a follow-up longer than 3 months were retrospectively analyzed. Demographic, clinical and catheter-related data were collected. Patients were grouped as being operated before/after 2009 in order to evaluate the effects of 2 different periods on outcomes.

Results. A total of 229 catheters in 132 patients were included in the study. The female to male ratio was 60/72. The mean age at the time of dialysis was 8.9 ± 5.5 years. The median follow-up period was 22.5 months (IQR 8.25-50; range 3-139).

Peritonitis incidence in 1998-2008 and 2009-2018 periods was 0.13 episodes/patient-year and 0.09 episodes/patient-year, respectively. The overall revision rate was 1 per 46.7 patient-months. Peritonitis history was the only independent risk factor for access revision (p=0.003).

Peritoneal dialysis failure was observed in 25% (33/132) of patients. The need for catheter revision due to any cause, the presence of peritonitis, history of HD and infancy were independent risk factors for PD failure. The overall mortality rate was 15.2%(20/132). Having a history of temporary PD catheter placement and being infant were independent risk factors for mortality.

Conclusions. Access revision is still an important complication leading to PD failure despite the development of surgical techniques. Peritonitis is the most important cause of access revision and PD failure.

Key words: end stage renal disease, peritoneal dialysis, children, complication, outcome.

Incidence of end-stage renal disease (ESRD) and the need for renal replacement therapy (RRT) in children differs worldwide due to differences in etiology of kidney disease and the financial situation to treat affected children.[1,2] The incidence of ESRD in patients younger than 19 years worldwide was reported to be 4 to 18 per million of the age-related population (pmarp), with the prevalence of RRT ranging from 18 to 100 pmarp.[3] The prevalence and incidence of ESRD in Turkey in all ages were 870 and 138 per million population, respectively.[4] The CREDIT-C study which is a population-based survey demonstrated that the prevalence of chronic kidney disease (CKD) stages 3-5 in children aged 5-18 was 2,600 (95% CI 1,100-5,100) pmarp.[5]

Currently, the best choice for RRT in children is transplantation due to better survival

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and quality of life.[3] When this choice is not possible chronic peritoneal dialysis (CPD) or hemodialysis (HD) could be the only feasible option as a bridge therapy until transplantation with no difference in morbidity or mortality being reported between them.[6] CPD conserves the vascular pool required for long-term RRT and allows more individual liberty compared to HD. However, the practicability of this choice highly depends on the families' readiness and accommodation to take liability for ambulatory medical care. Also, despite the broad admissibility of CPD as the RRT modality of choice for children, it is impeded to a great degree by several complications like catheter revisions, infections and ultrafiltration insufficiency which may lead to dialysis failure.

With low organ donors rate in some countries, dialysis has become a final treatment destination rather than being a bridge to transplantation. More than one third of the patients on CPD are expected to shift to HD within 2 years and less than 40% of them are anticipated to continue beyond this point.[7] In this study, we aimed to evaluate peritonitis, catheter revision and survival rates; and to define related factors among pediatric patients on CPD in a single tertiary center from a WHO upper middle income country over the last 20 years.

Material and Methods

After obtaining ethical committee approval (GO19/1063)-Hacettepe University, we retrospectively analyzed the departmental records of pediatric patients with CPD in our center between 1998 and 2018. Patients equal to or younger than 20 years of age at the start of dialysis with a follow-up longer than 3 months were included in the study. We collected demographic data [age, gender, operation period (before or after 2009), etiology of ESRD, age at dialysis time and at last follow-up], clinical data including weight, height, BMI, presence of anorectal malformations, constipation, dialysis history before PD catheter replacement, time to first catheter use (break-in period), CPD program, exit-site or tunnel infection (ESI/TI) history, peritonitis attacks and culture results, time to first and second access revision and their causes, time to transplantation, PD failure and patient survival rates; and catheter related data [intra-abdominal (felt vs. curled) and extra-peritoneal (straight vs. swan-neck) configurations].

To better understand whether 2 different periods have effects on access revision, peritonitis or mortality rates, we labeled the patients being operated before/after 2009, the year which represents a midpoint of years and patients. BMI standard deviation scores (SDS) were calculated using CDC charts and according to the results patients were classified as underweight, normal or overweight. Depending on the International Society for Peritoneal Dialysis (ISPD) guidelines we put break-in periods as less or more than 14 days. Peritonitis was defined according to the recommendations of the ISPD.[8] Mechanical dysfunction was defined as catheter dysfunction caused by catheter migration, omental obstruction or occlusion by fibrin clots. Access revision occurs within 4 weeks of previous revision was considered as recurrent. PD failure is shifting to HD because of peritonitis, insufficient dialysis or mechanical dysfunction.

All patients received antibiotics peri-operatively at the time of induction of general anesthesia. Most of the time a first generation cephalosporin or an amino-penicillin was the choice. Postoperatively 10 ml/kg of a dilute solution of heparin and dialysate (0.5 unit/1 ml) was used to wash the catheter at the first 0-, 16- and 24-hours to prevent clot formation.

All statistical analyses were performed using Statistical Package for Social Sciences (SPSS) 22.0 for windows. Student's t test and Mann-Whitney U test were used to compare non-categorical variables; Chi-square test and Fisher's exact test were used to compare categorical variables. We used logistic regression modeling to find predictors for access revision. Survival analyzed using Kaplan-Meier curves. To define

factors predicting PD failure and mortality, Cox proportional modeling was used. Minimal statistical significance was defined as p values < 0.05.

Results

A total of 229 catheters in 132 patients were included in the study. Demographics and clinical characteristics are shown in Table I. There were 60 females and 72 males, with a mean age of 6.0 ± 4.9 years (range 1–240 months) at time of ESRD diagnosis and 8.9 ± 5.5 years at time of dialysis. 16 patients were infants (<1 year of age) with an average age of 5.5 ± 4.9 months. The median follow-up period was 22.5 months (IQR 8.25-50; range 3-139); 18.2% and 5.3% of patients were underweight and overweight, respectively. Rates of being underweight was not statistically different between infants and older age group (33.7% vs. 17.1%, p= 0.161). Congenital anomalies of kidney and urinary tract (CAKUT) were the etiology of ESRD in 59 patients (44.7%). Thirty-seven (28.0%) of patients had emergent need to dialysis due to electrolyte abnormalities, acidosis or edema; 64.9% (24/37) of these patients needed HD while the rest had a temporary PD catheter placed in intensive care unit conditions. Additional 13 patients were electively started on HD and transitioned to PD thereafter, resulting in 28.0% (37/132) of patients with history of HD. Constipation was documented in 13 (9.8%) patients.

Catheters with curled end and swan-neck configuration were the choice in 72 (54.5%) patients. The average break-in period was 16 days (IQR 8-20; range 1-150 days). PD program was known in 123 patients; all patients started with continuous ambulatory PD (CAPD) program and 28 patients shifted to automated PD (APD) program thereafter.

Peritonitis

Seventy-three (55.3%; 73/132) of patients had at least one attack of peritonitis with a 142 attacks at total, making the mean attack number of all patients as 1.07±1.47 episodes per patient.

Table I. Demographic and clinical patient characteristics.

Characteristic	Results
Gender, n (%)	
Female	60 (45.4)
Male	72 (54.6)
Age at ESRD diagnosis, years	6.0 ± 4.9
Age at the start of dialysis, years	8.9 ± 5.5
Patients <1 year of age, n (%)	16 (12.1)
Median follow-up period, months	22.5 (8.25-50.0)
Height, cm	116 ± 32 cm
BMI SD score	
Underweight	24 (18.2)
Normal	95 (72.0)
Overweight	7 (5.3)
Unknown	6 (4.5)
Operation period, n (%)	
Before 2009	67 (50.8)
After 2009	65 (49.2)
Diagnosis, n (%)	
CAKUT	59 (44.7)
Obstructive	20 (15)
Refluxive	14 (10.6)
Neurogenic	6 (4.5)
Renal hypo-/dysplasia	5 (3.8)
Cystic renal disease	14 (10.6)
Non-CAKUT	73 (55.3)
Glomerulopathy	47 (35.6)
Metabolic	18 (13.6)
Miscellaneous	8 (6.1)
History of HD, n (%)	37 (28.0)
Temporary PD catheter placement, n (%)	14 (10.6)
Constipation	13 (9.8)
Catheter configuration, n (%)	
Swan-neck, curled	72 (54.5)
Straight felt	10 (7.5)
Straight curled	25 (19.0)
Unknown	25 (19.0)
Break-in period, n (%)	
>14 days	57 (43.2)
<14 days	64 (48.5)
Unkown	11 (8.3)
PD program	
CAPD	95 (72.0)
APD	28 (21.2)
Unkown	9 (6.8)

ESRD: end-stage renal disease, BMI SD: body mass index standard deviation, CAKUT: congenital anomalies of kidney and urinary tract, HD: hemodialysis, PD: peritoneal dialysis, CAPD: continuous ambulatory peritoneal dialysis, APD: automated peritoneal dialysis.

Peritonitis incidence in 1998-2008 period was 0.13 episode/patient-year and decreased to 0.09 episode/patient-year in 2009-2018 period. Sixty-nine (69/142; 48.6%) and 22 (22/142; 15.5%) of peritoneal fluid cultures had gram positive and gram negative bacteria, respectively. The rest (35.9%) had negative culture results. Staphylococcus consisted 78.3% (54/69) of gram positive culprits while Pseudomonas consisted 31.8% (7/22) gram negative ones. 23.3% (17/73) of patients with peritonitis underwent access revision whether by removing the catheter (4/17) or replacing a new one in the same session (13/17). Among 73 patients with peritonitis, 39.7% (29/73) had access revision at some point of their follow-up due to mechanical dysfunction. Having ESI/TI was the only significant predictor for peritonitis at some point of follow-up (73.9% vs. 51.4% p= 0.048). Additionally, there was a direction heading towards significance between peritonitis and APD program and being operated before 2009 (Table II).

ESI/TIs were noticed in 17.4% (23/132) of patients and treated with oral antibiotics. Patients on APD program had higher exit-site or tunnel infection (ESI/TI) rate [35.7% (10/28) vs. 13.7% (13/95), p= 0.009]. Interestingly most of these patients had catheters with straight extra-peritoneal orientation compared to patients on CAPD program who had more swan-neck catheters [66.7% (12/18) vs. 26.2% (22/84), p=0.002]. Additionally, being operated before 2009 was another significant risk factor for ESI/TI [28.4% (19/67) vs. 6.2% (4/65), p= 0.001].

Revision Rate

Access revision rate was 51.5% (68/132). Second and third revision were needed in 36.8% (25/68) and 5.9% (4/68) of these patients, respectively, resulting in an average revision rate of 1 per 46.7 patient-months. While 75% (51/68) of first and 68% (17/25) of second revisions were due to mechanical failure, peritonitis was the reason in 25% (17/68) and 32% (8/25) of them, respectively. The rest were due to extravasations. Average time to first and second revisions was 9.7 ± 18.1 and 11.9 ± 18 months, respectively. 67.6% (46/68) had early revision (within 90 days). 28.0% (7/25) of second revisions were recurrent and all of these recurrent revisions occurred after revision due to mechanical failure. Demographic and clinical differences between patients with or without access revision are given in Table II. Including ESRD etiology, constipation and peritonitis in logistic regression analysis, the only independent predictor for access revision was peritonitis history (OR 2.8; 95% CI 1.3 to 5.9; p= 0.003).

PD Failure

During the observation period, 25.0% (33/132) of patients permanently shifted to HD after a median of 24 months (IQR 6.5-54); while 45.5% (15/33) of them shifted after peritonitis, 45.5% (15/33) of them shifted after mechanical failure. Inadequate dialysis was the reason in the other 3 (9.0%) patients. When we compared patients with PD failure (33/132) with patients who are still on PD (24/132), PD failure was significantly higher in patients operated before 2009 [80.8% (21/26) vs. 38.7% (12/31), p= 0.001] despite there was no significant difference in peritonitis or revision rates between patients operated before or after 2009. The need for catheter revision due to any cause (HR 3.65; 95% CI 1.19 to 11.17; p= 0.023), the presence of peritonitis (HR 3.46; 95% CI 1.11 to 10.78, p= 0.032), history of HD (HR 2.58; 95% CI 1.09 to 6.13, p= 0.032) and infancy (HR 5.2; 95% CI 1.02 to 26.70, p= 0.047) were independent risk factors for PD failure on multivariate analysis (Table III). There was no significant difference in PD failure between early or late revisions. PD technique survival rate at 1-, 5- and 10- year period was 75%, 35% and 10%, respectively (Fig. 1).

Forty-six (46/132, 34.8%) patients on PD had transplantation after a median of 26 months (IQR 15.75-66.25 months), and PD catheter was removed after an average of 6 ± 3 weeks. Out of 33 patients who shifted to HD 10 (10/132, 7.6%) patients had transplantation thereafter, making the median dialysis period before transplantation as 30 months (IQR 17-

Table II. Demographic and clinical characteristics and their relation to access revision and peritonitis.

Parameter		Access revision rate	*p*	Peritonitis rate	*p*
Gender	Male (72)	47.2% (34/72)	0.280	54.2% (39/72)	0.774
	Female (60)	56.7% (34/60)		56.7% (34/60)	
Date	<2009 (67)	52.2% (35/67)	0.866	62.7% (42/67)	0.083
	>2009 (65)	50.8% (33/65)		47.7% (31/65)	
Age	Infant (16)	56.3% (9/16)	0.686	56.3% (9/16)	0.935
	Others (116)	50.9% (59/119)		55.2% (64/116)	
ESRD etiology	CAKUT (59)	59.3% (35/59)	0.107	59.3% (35/59)	0.404
	Non-CAKUT (73)	45.2% (33/73)		52.1% (38/73)	
Constipation	Yes (13)	76.9% (10/13)	0.078	61.5% (8/13)	0.772
	No (119)	48.7% (58/119)		54.6% (65/119)	
BMI	Underweight (24)	62.5% (15/24)	0.234	50% (12/24)	0.602
	Others (102)	49% (50/102)		55.9% (57/102)	
History of HD	Yes (40)	56.8%	0.452	48.6%	0.337
	No (92)	49.5%		57.9%	
Temporary PD catheter placement	Yes (14)	35.7% (5/14)	0.264	57.1% (8/14)	0.884
	No (118)	53.4% (63/118)		55.1% (65/118)	
Break-in period (days)	>14 (57)	47.4% (27/57)	0.645	56.1% (32/57)	0.499
	<14 (64)	51.6% (33/64)		50% (32/64)	
Catheter configuration (Curled Swan-neck)	Yes (72)	52.8% (38/72)	0.493	51.4% (37/72)	0.784
	No (35)	45.7% (16/35)		48.6% (17/35)	
PD program	CAPD (95)	54.7% (52/95)	0.296	52.6% (50/95)	0.154
	APD (28)	42.9% (12/28)		67.9% (19/28)	
ESI/TI	Yes (23)	52.2% (12/23)	0.945	73.9% (17/23)	**0.048**
	No (109)	51.4% (56/109)		51.4% (56/109)	
Peritonitis	Yes (73)	63% (46/73)	**0.003**		
	No (59)	37.2% (22/59)			

ESRD: end-stage renal disease, CAKUT: congenital anomalies of kidney and urinary tract, BMI: body mass index, HD: hemodialysis, PD: peritoneal dialysis, CAPD: continuous ambulatory peritoneal dialysis, APD: automated peritoneal dialysis, ESI/TI: exit-site infection/tunnel infection.

Table III. Cox proportional hazard modeling of factors affecting peritoneal dialysis failure.

Variable	Hazard ratio (95% confidence interval)	*P*
Operation period (before 2009)	1.56 (0.69-3.49)	0.282
History of hemodialysis	2.58 (1.09-6.13)	0.032
Age < 1 year	5.2 (1.02-26.70)	0.047
Presence of peritonitis	3.46 (1.11-10.78)	0.032
Presence of revision	3.65 (1.19-11.17)	0.023

66.5 months); 18.2% (24/132) of patients still having PD with a median of 15 months (IQR 8-50.75 months); 6.9% (9/132) of patients lost to follow up. The median dialysis period before transplantation shortened with time [before 2009 median 37 months (IQR13.25-74.5) while after 2009 median 26 months (IQR 18-54.5), p= 0.3].

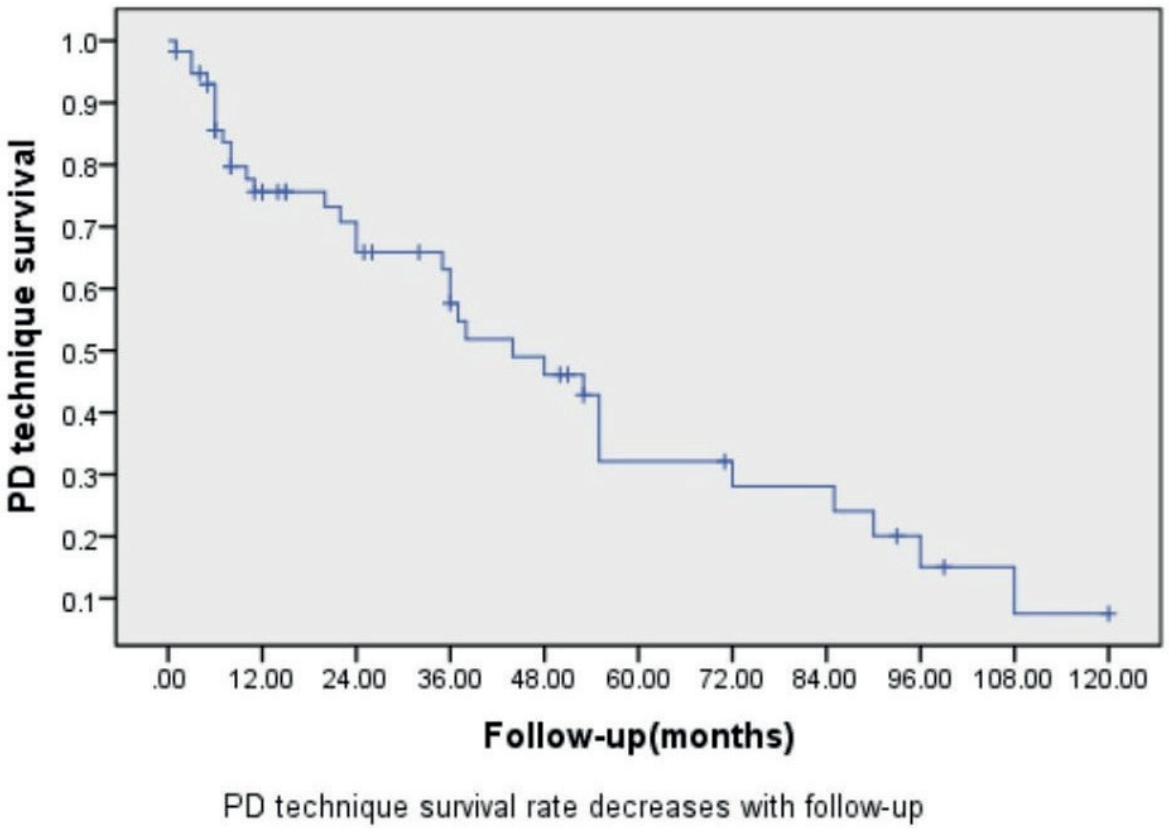

Fig. 1. PD technique survival rate during follow-up period.

Mortality

Twenty (20/132; 15.2%) patients died after a median PD period of 13.5 months (IQR 2.5-43.5); seven of them were infants. Thirty percent (6/20) of them were dialysis-related (four peritonitis, one hypertensive encephalopathy, one cardiac tamponade). Pneumonia was the cause in two patients. Data related to the etiology in the rest was not available. In multivariate analysis, having a history of temporary PD catheter placement (HR 2.98; 95% CI 1.06 to 8.37, p= 0.038) and infancy (HR 4.05; 95% CI, 1.58 to 10.35, p= 0.003) were independent risk factors for mortality. Patient survival rate at 1-, 5- and 10-years was 92%, 76% and 55% respectively.

Discussion

When transplantation is not possible, peritoneal dialysis is the preferable choice in children requiring RRT due to its simplicity and utility of conserving residual renal function. But unfortunately, this modality is associated with complications like access revision, peritonitis and ultrafiltration insufficiency which may lead to technical failure. Rigoni et al.[9] reported 0.4 year period for patients on PD to receive call to transplantation, this period is much longer in Turkey compared to the literature which indicates that PD has become a long-term maintenance treatment. This emphasizes the need to minimize complications and technique failure rates.

Different studies reported that ESRD etiology may have an effect on access revision, mortality and transplantation rates.[10] According to TUPEPD study group's report[11] related to 1989-2002 period, CAKUT and non-CAKUT were the etiology in 42.3% and 46.4% of Turkish children with ESRD–the rest were with unknown etiology-, with glomerulonephritis and vesico-ureteral reflux disease (VUR) being the cause in

28.8% and 18.1% of the cases. In this study, we observed similar rates with different subgroup distribution in the CAKUT arm - lower VUR and higher obstructive anomalies-. It was postulated that these diseases may require complex urologic intervention which can lead to infectious and mechanical complications. Additionally, patients with CAKUT have better residual renal function and are less likely to develop oligo-anuria.[12] In conjunction with literature data, although it did not reach to statistical significance, we noticed a tendency of patients with CAKUT to have higher revision rates (59.3% vs. 45.2%, p= 0.107) and longer time-to-transplantation period (34.5 months (IQR 16.5-75.2) vs. 28 months (IQR 17-61), p= 0.38) without any difference in mortality.

PD failure is still a major complication that precludes the continuation of peritoneal dialysis. Sampimon et al.[13] studied 224 patients managed by PD and reported 21% rate of PD failure after 2-year period. We observed a 25% PD failure rate, with access revision and peritonitis being the major risk factors. Also, being operated before 2009 increased PD failure risk which could be related to the chronic exposure to dialysate and the peritoneal membrane injury initiated during peritonitis. A study conducted from the IPPN registry[10] reported a lower access revision rate at a younger age; however, access survival in infants (< 1year) and PD technique survival in patients younger than 3 months of age were poorer. Similarly, we observed a higher PD failure risk in infants (<12 months of age). We think that this observation could be explained by the fact that infants do not have a very well developed abdominal wall.

Access revision is considered a bothering stressful situation for surgeons to deal with, especially when the cause is mechanical. The rate of such complications is variable between different studies and ranges between 13-34%. The major cause is also variable as these studies are related to different eras.[10,14] This difference is mostly related to the adherence to better antibiotic prophylaxis guidelines, thereby lowering infection requiring revision. In our study, the only significant predictor for catheter revision was a history of peritonitis. Being a single-center experience over 20 year-period -with near one-third of our patients being operated before 2004- may explain these results. There are scarce data related to the second recurrent revision rate in pediatric PD. The IPPN analysis[10] reported 16% second recurrent revision rate, and almost all of them occurred after a revision for mechanical dysfunction. In this study, 28.0% of second revisions were recurrent. All of them occurred after a revision for mechanical dysfunction.

Peritonitis stays the main complication of PD and a primary cause for technical failure despite the reported decrease in its rates since the late 1980s.[15] Its' incidence in pediatric patients ranges between 0.21-0.71 episode/patient-year, and gram positive bacteria -especially Staphylococcus – are the culprit most of the time.[16] In this study, we postulate that our lower peritonitis incidence and the decrease noticed between two periods may be related to increased adherence to early management policy and increased education in parents and patients. Additionally, as ESI/TI seems to be a pathway to develop subsequent peritonitis, any patient with ESI suspicion was started on povidone dressing, and if pus is present oral antibiotics were prescribed. Peritoneal fluid culture results are similar to the ones reported in the literature.[15,16]

Exit-site infection is the pathway to develop subsequent tunnel infection and peritonitis that leads to elevated rates of catheter loss, morbidity, and mortality. Swartz et al.[17] reported a 17% rate of ESI for an annualized rate of 0.25 ESIs per year of PD. PD program whether plays a role in ESI or not is still debatable.[18] In this study, being on an APD program besides being operated before 2009 were risk factors for ESI. Most of the patients on an APD program had PD catheter with straight extra-peritoneal orientation.

The impact of PD catheter configuration on complication rates are still arguable.[10,19] In our patients there was no significant difference in complication rates between diverse catheter configurations.

Although both the International Society for Peritoneal Dialysis (ISPD) and European guidelines recommend a break-in period of 10-15 days to prevent leaks and catheter complications, the effect of break-in period on PD outcome is still questionable.[20] In this study, break-in period had no significant impact on access revision or patient survival. In our center, all patients begin with low fill volume and short dwell times which may explain these results.

Constipation in PD patients is a risk factor for peritonitis and catheter malfunction or migration.[21] In this study many patients' records were deficient in data related to their bowel movements. But we noticed that patients with constipation had a strong tendency to have catheter revisions, mostly due to mechanical failure.

Its reported that the mortality of dialyzed children is declining, and mortality as a direct outcome of PD is rare.[22] In the early days of RRT, younger age at the start of dialysis was associated with poor outcome.[23] These results improved in recent years because of the greater attention paid to dialysis technology, nutrition and infection prevention and management.[24] Body mass index (BMI) whether low or high is related to increased mortality in children with ESRD.[25] We observed a 15.2% all-cause mortality rate. Being an infant and having a history of temporary PD catheter placement were associated with increased mortality. These results can be explained by the "obesity paradox" effect as 33.7% of infants were underweight[26], and by the observation that most of the temporary PD catheters were placed in the intensive care unit which implies the severity of disease status.

The present study comes with limitations. Data related to omentectomy whether performed or not was not available. All patients had open procedure therefore we could not compare it with other surgical procedures. Also, as routine nasal cultures were not taken, no data were available to check the relationship between the infection rates and nasal carriage. Still, this study clearly identifies the complications of chronic PD and related risk factors in a relatively large sample size and long follow up period. Additionally, it states the expected period of PD before transplantation in a WHO upper middle-income country with low donor rates which will help physicians and patients in decision making process.

As a conclusion, access revision is still a bothering complication leading to PD failure despite the development of surgical techniques. Peritonitis-which is caused primarily by ESI- is the most significant reason for access revision and PD failure. Mortality is higher in patients who need temporary PD catheters. The infant age group carries higher risk in terms of both PD failure and mortality. According to these results, better strategies should be adopted to lower peritonitis rates in PD patients.

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Original Article

Off-label drug use in pediatric patients: a comparative analysis with nationwide routine prescription data

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ABSTRACT

Background. Children constitute a special population for off-label drug use (OLDU), yet limited drug-focused data exist regarding pediatric OLDU in clinical practice. This study aimed to investigate pediatric OLDU practice and compare it with pediatric drug utilization patterns of routine prescribing data.

Methods. This cross-sectional study examined all approved pediatric OLDU applications, compared with electronic prescription data on national Prescription Information System of Turkish Medicines and Medical Devices Agency in 2015. OLDU applications and prescriptions were analyzed for demographic characteristics, healthcare/socioeconomic indices as well as details of drugs and diagnoses.

Results. We found 7,896 OLDU applications and 7,029,512 prescriptions for the pediatric population in 2015. OLDU applications and prescriptions were mostly practiced for "2-11-year-old" children (52.7% vs. 63.4%, respectively; $p<0.01$). OLDU applications and prescriptions were detected to have a positive correlation with socio-economic development index ($r = 0.45$, $p<0.0001$ and r: 0.40, $p = 0.0002$; respectively) and the physician density ($r = 0.66$, $p<0.0001$ and r: 0.43, $p<0.0001$; respectively). In addition, OLDU was also positively correlated with the number of hospital beds per province ($r = 0.39$, $p = 0.0003$). Antineoplastic/immunomodulating agents were the most commonly applied drug category in OLDU (47.0%), compared with respiratory system drugs (36.6%) in routine prescribing. Eculizumab (6.5%), mycophenolate (5.6%), and canakinumab (4.4%) were the top drugs used as off-label. OLDU applications and routine prescription data revealed the most frequent diagnosis as "I27-other pulmonary heart diseases" (7.4%) and "J06-acute upper respiratory infections" (12.6%), respectively.

Conclusions. This is the first nationwide study to show indication- and drug-centered aspects of pediatric OLDU and prescribing practice. Though OLDU applications is overall consistent with routine clinical practice in terms of demographics and institutional capacity, substantial variations exist regarding main drug classes and diseases. Our findings are expected to shed light on interventions focused on improving "indicated" pediatric use of drugs currently applied as off-label.

Key words: off-label drug use, children, prescribing, antineoplastic, immunomodulating.

New drug development is a long-term and costly path that requires pre-clinical and clinical efficacy and safety studies. Incorporating all potential indications and target age groups that could benefit from the investigational new drug poses additional burden, further increasing the expenditure and duration.[1] Therefore, restricting approved indications and age groups of potential novel drug is attempted by conducting clinical trials on somehow standardized populations of healthy/patient volunteers beside ethical, legal, or economic concerns. This pragmatical approach, however, results in limited data of drug use in special groups, such as fragile elderly or children.[2,3]

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Use of drugs for other than their approved indications, doses, way of administration, age group, or special populations etc. is defined as "off-label drug use (OLDU)".[4,5] It is more common in several branches of clinical practice, including oncology (85%), gynecology and obstetrics (25%), and pediatrics (3% to 90%).[6-10] An important reason for increased rate of OLDU in pediatrics is that children are usually excluded from clinical phase studies due to above-mentioned reasons.[2,11,12] In order to make pediatric pharmacotherapy more labelled, further clinical studies need to be performed with designs overcoming potential difficulties pertaining to children. This could be preceded by comprehensive assessments of routine drug utilization patterns. In addition, age group-specific indications require being reviewed through the evidence arising from systematic evaluation of OLDU experiences in children.

The literature on OLDU seems to be based on rather general off-label use or is focused on special patient subsets, lacking descriptions of a nationwide pediatric OLDU practice compared to routine prescription data.[8-10,13-15] This study aimed to investigate pediatric OLDU practice and compare it with pediatric drug utilization patterns in routine prescribed data.

Material and Methods

This cross-sectional study examined approved pediatric OLDU applications and electronic prescription data registered on national Prescription Information System (PIS). OLDU applications were made to Turkish Medicines and Medical Devices Agency (TMMDA) of the Ministry of Health. The agency reviews the applications and records main medical data and its final status on its electronic medium.[4] PIS, used for examining routine prescription data, mediates several analyses and assessments about electronic prescriptions submitted to the national prescription database.[16] In this study, all pediatric OLDU applications with the final status of "approved" during year 2015 were analyzed. Routine prescribing was evaluated by the prescriptions in PIS, which were delivered by pediatricians or subspecialists of pediatrics for 18-year-old children. In 2015, the universe of our study, i.e. children, constituted 29.0% of the total population of 78.7 million inhabitants in Turkey.[17]

OLDU applications/prescriptions were examined with respect to patients' demographics, drugs' Anatomical Therapeutic Chemical (ATC) classification, and International Statistical Classification of Diseases (ICD) category. The latter also included applications/prescriptions with multiple diagnoses. Pediatric population were stratified as three groups: infants (<2 years old), children (2-11 years old), and adolescents (≥12 years old). These groups were compared in terms of the number of applications/prescriptions, sex, and the mean age. Furthermore, OLDU applications and prescriptions were analyzed with respect to several regional healthcare utilization parameters (number of hospital beds, number of physicians per 100,000 inhabitants, percentage of child population, number of health service applications to secondary/tertiary centers) and socio-economic development index (SEDI). While data on regional healthcare utilization was obtained from Health Statistics Yearbook 2015 of Turkish Ministry of Health and Turkish Statistics Institute[17,18], SEDI has 61 items indicating various domains (demographics, employment, health, finance, and quality of life, etc.) that were used for scoring and ranking the provinces, as rigorously calculated by the Turkish Ministry of Development.[19]

The drugs at OLDU applications were compared by age groups at the ATC-1 level. Furthermore, the top 15 most commonly applied drugs were examined at ATC-5 level. These drugs were also assessed as to whether they fell into a biotechnological or licensed category.

The top three commonly encountered diagnoses in OLDU applications were examined with their top three applied drugs and the applying physicians' specialty. Beside this indication-focused approach, a drug-focused approach was

also undertaken to show diagnostic distribution: most frequent three diagnoses and total number of different diagnoses were determined for each of the top ten drugs in OLDU applications. This analysis was performed using applications with only a single diagnosis.

Statistical analysis

Statistical analyses were made through SPSS 25.0 software. Categorical and continuous variables were expressed as number/percentage and mean/standard deviation, respectively. The comparisons between groups were analyzed via chi-square for categorical and t-test for continuous variables. The associations of number of OLDU applications and prescriptions to regional healthcare utilization parameters and SEDI was tested using Spearman's rank correlation. An overall 5% type-I error level was used to infer statistical significance.

The data were collected after the study was approved by the Ethics Committee of Institute of Health Science of Marmara University (Approval Date/No: 11.09.2017/171).

Results

A total of 7,896 pediatric OLDU applications were detected in the one-year study period, during which the number of prescriptions in PIS generated for pediatric population was 7,029,512 as routine prescribing. The majority of applications/prescriptions in OLDU and routine PIS practice were for the "children" subgroup (52.7% vs 63.4%, respectively; p<0.01); followed by adolescents in OLDU (36.1%) and infants in PIS practice (24.9%). All comparisons between the age groups in terms of percentage of applications/prescriptions significantly differed from each other (p<0.01, Fig. 1). The mean age of the "age groups" was significantly higher in OLDU applications than that in PIS (p<0.01 for all age groups). The applications/prescriptions were more likely to be generated for boys over girls in all age groups in both OLDU and PIS database with a tendency to be balanced with increasing age: girls constituted 45.5% and 45.0% in infants and 48.4% and 49.4% among adolescence in OLDU and PIS database, respectively.

The number of OLDU applications and prescriptions were found to be positively correlated with SEDI (r = 0.45, p <0.0001 and r = 0.40, p = 0.0002; respectively), the number of physicians per 100,000 inhabitants (r = 0.66, p <0.0001 and r = 0.43, p <0.0001; respectively). In addition, OLDU applications were also positively correlated with the number of hospital beds per province (r = 0.39, p = 0.0003).

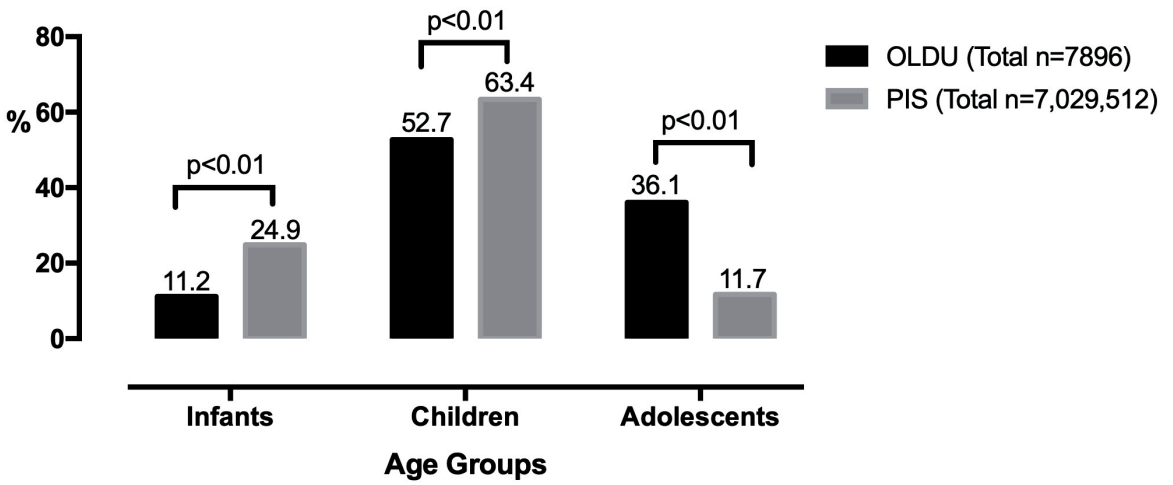

Fig. 1. Comparison of OLDU applications and routine prescribing data on PIS based on the age. groups (OLDU, off-label drug use; PIS, Prescription Information System).

The number of health service applications or the percentage of child population was not correlated with OLDU applications or routine prescriptions (p >0.05 for each).

OLDU applications showed the most common drug group at ATC-1 level as "antineoplastic and immunomodulating agents" (47.0%), followed by "blood and blood forming organs" (7.7%) and "alimentary tract and metabolism" (7.7%). On the other hand, the most commonly prescribed drug group in routine practice belonged to "respiratory system" (36.6%), "anti-infectives for systemic use" (22.9%) and "alimentary tract and metabolism" (13.4%), (Fig. 2).

The distribution of drug categories in OLDU applications revealed significant differences between infants, children and adolescents (p <0.05), except "blood and blood forming organs" and "systemic hormonal preparations, excluding sex hormones and insulins" ATC-1 categories (Table I).

A total of 336 different drugs were detected in OLDU applications. The most commonly applied drug was eculizumab (6.5%), followed by mycophenolate (5.6%) and canakinumab (4.4%). The most commonly applied off-label drug by age groups was determined as sapropterin (16.6%) in infants, eculizumab (6.7%) in children, and mycophenolate (8.0) in adolescents. The top 15 drugs in OLDU applications were found to constitute 50.0% (n = 3937). While eight of these (53.3%) were biotechnological drugs overall, stratification by age group showed three (20.0%) in infants and eight (53.3%) in both children and adolescents. In addition, only two (13.3%) of these top 15 drugs were found to be unlicensed in Turkey (Table II).

The distribution of diagnoses in OLDU applications revealed 548 different diagnoses with the most frequent group as "I27-other pulmonary heart diseases" (7.4%), as compared to that in PIS-based routine prescribing as "J06-acute upper respiratory infections"

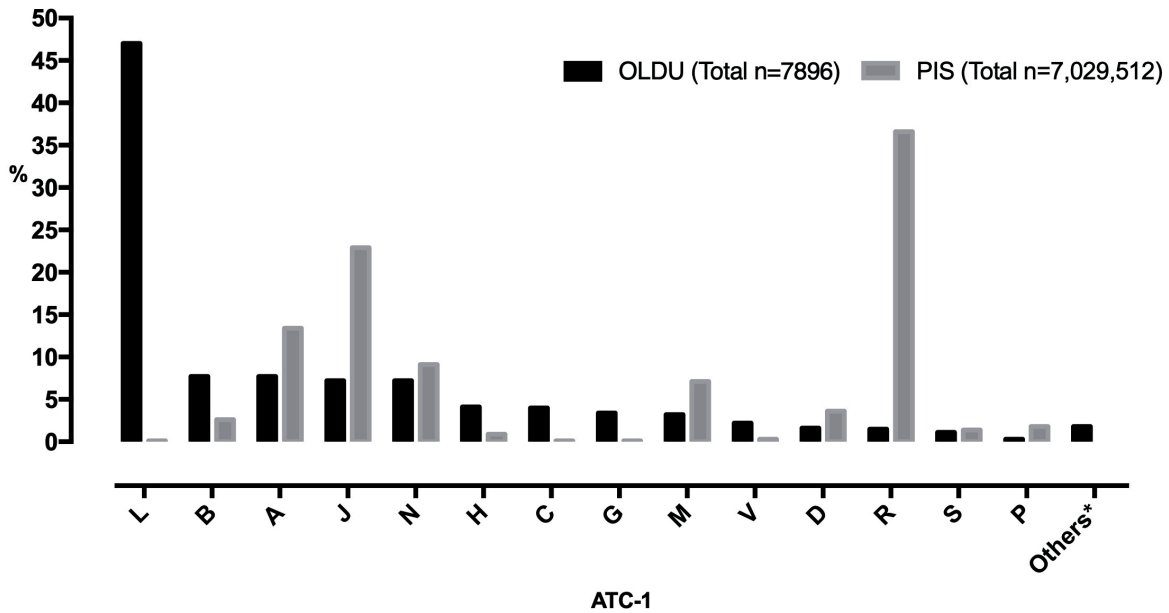

Fig. 2. Distribution of the drugs at OLDU applications and routine prescribing data on PIS by ATC-1 category.

(OLDU, off-label drug use; PIS, Prescription Information System; A, Alimentary tract and metabolism; B, Blood and blood forming organs; C, Cardiovascular system; D, Dermatological; G, Genitourinary system and sex hormones; H, Systemic hormonal preparations, excl. sex hormones and insulins; J, Anti-infectives for systemic use; L, Antineoplastic and immunomodulating agents; M, Musculoskeletal system; N, Nervous system; P, Antiparasitic products, insecticides and repellents; R, Respiratory system; S, Sensory organs; V, Various; *, Products with no ATC code).

Table I. Comparison of drugs at ATC-1 level in OLDU applications based on age groups.

ATC-1 codes	Infants n (%)	Children n (%)	Adolescents n (%)	P-value
L-Antineoplastic and immunomodulating agents	248 (28.2)	1894 (45.5)*	1566 (54.9)#	<0.05
B-Blood and blood forming organs	66 (7.5)	325 (7.8)	220 (7.8)	>0.05
A-Alimentary tract and metabolism	188 (21.3)	338 (8.1)*	84 (2.9)#	<0.05
J-Anti-infectives for systemic use	80 (9.1)	301 (7.2)	189 (6.7)	<0.05
N-Nervous system	24 (2.7)	382 (9.2)*	160 (5.6)#	<0.05
H-Systemic hormonal preparations, excl. sex hormones and insulins	23 (2.6)	182 (4.4)	121 (4.2)	>0.05
C-Cardiovascular system	61 (6.9)	151 (3.6)*	102 (3.6)*	<0.05
G-Genitourinary system and sex hormones	41 (4.6)	103 (2.5)§	122 (4.3)	<0.05
M-Musculoskeletal system	6 (0.7)	148 (3.6)*	98 (3.4)*	<0.05
V-Various	40 (4.5)	88 (2.1)*	42 (1.5)*	<0.05
D-Dermatologicals	18 (2.0)	82 (2.0)	28 (1.0)#	<0.05
R-Respiratory system	31 (3.5)	43 (1.0)*	45 (1.6)#	<0.05
S-Sensory organs	23 (2.6)	27 (0.6)*	38 (1.3)#	<0.05
P-Antiparasitic products, insecticides and repellents	11 (1.2)	8 (0.2)*	7 (0.2)*	<0.05
Products with no ATC code	23 (2.6)	91 (2.2)	28 (1.0)#	<0.05
Total	883 (100.0)	4163 (100.0)	2850 (100.0)	

*p<0.05 vs. infants; #p<0.05 vs. both infants and children; §p<0.05 vs. both infants and adolescents
OLDU: off-label drug use.

Table II. Distribution of drugs at ATC-5 level in OLDU applications based on age groups.

Rank	All age groups, (%)	Infants, (%)	Children, (%)	Adolescents, (%)
1	Eculizumab*, (6.5)	Sapropterin, (16.6)	Eculizumab*, (6.7)	Mycophenolate, (8.0)
2	Mycophenolate, (5.6)	Eculizumab*, (11.3)	Mycophenolate, (5.0)	Rituximab*, (6.1)
3	Canakinumab*, (4.4)	Sirolimus, (4.0)	Iloprost, (4.5)	Canakinumab*, (5.6)
4	Iloprost, (4.3)	Valganciclovir, (3.3)	Sirolimus, (4.3)	Eculizumab*, (4.7)
5	Rituximab*, (4.1)	Dextromethorphan, (2.9)	Canakinumab*, (4.2)	Iloprost, (4.5)
6	Sirolimus, (3.8)	Sildenafil, (2.8)	Lacosamide, (3.9)	IVIG*, (3.3)
7	Sapropterin, (3.4)	Bosentan, (2.7)	Adalimumab*, (3.3)	Anakinra*#, (3.3)
8	Lacosamide, (2.9)	Iloprost, (2.6)	Rituximab*, (3.2)	Sirolimus, (3.1)
9	IVIG*, (2.8)	Ranibizumab*, (2.4)	Somatropin*, (3.1)	Adalimumab*, (2.6)
10	Anakinra*#, (2.7)	Propranolol, (2.3)	Sapropterin, (2.8)	Somatropin*, (2.3)
11	Adalimumab*, (2.7)	Calcium folinate, (2.3)	IVIG*, (2.7)	Infliximab*, (2.1)
12	Somatropin*, (2.6)	Isotretinoin, (1.9)	Anakinra*#, (2.6)	Lacosamide, (1.9)
13	Sildenafil, (1.4)	Imatinib, (1.8)	Elosulfase alfa*#, (2.0)	Tacrolimus, (1.7)
14	Tacrolimus, (1.4)	IVIG*, (1.7)	Botulinum toxin, (1.4)	Botulinum toxin, (1.6)
15	Elosulfase alfa*#, (1.4)	Foscarnet#, (1.6)	Tacrolimus, (1.4)	Testosterone, (1.6)
Others n, (%)	3959, (50.0)	578, (39.8)	2029, (48.9)	1353, (47.6)
Total n, (%)	7896, (100.0)	883, (100.0)	4163, (100.0)	2850, (100.0)

*Biotechnological drugs; # Unlicensed drugs in Turkey.
OLDU: off-label drug use, IVIG: intravenous immunoglobulin.

(12.6%). Among the top 15 diagnoses of OLDU applications, three belonged to "E-endocrine, nutritional and metabolic diseases" (22.2%) and other three belonged to "D-diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism" (18.8%) main ICD categories. On the other hand, ten out of 15 top diagnosis belonged to "J-diseases of respiratory system" (82.4%) category in routine prescribing (Table III).

The most commonly applied diagnosis for pediatric OLDU was epilepsy (G40), for which the most commonly requested off-label drug was lacosamide (42.4%) by mostly pediatric neurologists (92.4%). The second most common

Table III. Distribution of diagnoses in OLDU applications and routine prescribing on PIS.

Rank	OLDU applications		PIS prescriptions	
	Diagnosis	n (%)	Diagnosis	n (%)
1	I27_Other pulmonary heart diseases	592 (7.4)	J06_Acute upper respiratory infections of multiple and unspecified sites	1,105,753 (12.6)
2	G40_Epilepsy	537 (6.7)	J02_Acute pharyngitis	887,111 (10.1)
3	D59_Acquired haemolytic anaemia	496 (6.2)	J03_Acute tonsillitis	832,465 (9.5)
4	N04_Nephrotic syndrome	390 (4.9)	J20_Acute bronchitis	408,156 (4.6)
5	E85_Amyloidosis	388 (4.8)	J00_Acute nasopharyngitis [common cold]	406,688 (4.6)
6	E70_Disorders of aromatic amino-acid metabolism	349 (4.3)	K52_Other noninfective gastroenteritis and colitis	297,534 (3.4)
7	M08_Juvenile arthritis	319 (4.0)	J21_Acute bronchiolitis	291,426 (3.3)
8	E23_Hypofunction and other disorders of pituitary gland,	221 (2.8)	J45_Asthma	254,218 (2.9)
9	D69_Purpura and other haemorrhagic conditions	166 (2.1)	J39_Other diseases of upper respiratory tract	240,556 (2.7)
10	T86_Failure and rejection of transplanted organs and tissues	164 (2.0)	J30_Vasomotor and allergic rhinitis	232,309 (2.6)
11	C91_Lymphoid leukaemia	146 (1.8)	J01_Acute sinusitis	218,139 (2.5)
12	D18_Haemangioma and lymphangioma, any site	146 (1.8)	L30_Other dermatitis	216,021 (2.5)
13	B25_Cytomegaloviral disease	142 (1.8)	R10_Abdominal and pelvic pain	202,737 (2.3)
14	C74_Malignant neoplasm of adrenal gland	139 (1.7)	D64_Other anaemias	173,984 (2.0)
15	G80_Cerebral palsy	112 (1.4)	Z00_General examination and investigation of persons without complaint and reported diagnosis	153,660 (1.7)
	Others	3718 (46.3)	Others	2,886,872 (32.8)
	Total	8025 (100.0)	Total	8,807,629 (100.0)

OLDU: off-label drug use, PIS: Prescription Information System.

diagnosis was "other secondary pulmonary hypertension (I27.2)" where more than half (56.2%) included iloprost for OLDU near always by pediatric cardiologists (99.6%). "Hemolytic uremic syndrome (HUS) (D59.3)" was the third indication, for which eculizumab constituted near all applications (99.1%) by mostly pediatric rheumatologists/nephrologists (93.1%), (Table IV).

Drug-centered analysis for diagnoses in OLDU applications showed eculizumab to be mostly requested for HUS (86.4%), mycophenolate for nephrotic syndrome (35.8%), and canakinumab for amyloidosis (66.2%), (Table V).

Discussion

This study examined an exclusive practice of drug use in pediatrics, as off-label, and we described close to eight thousand OLDU applications all over the country, compared to routine prescribing from several aspects. It appears that OLDU shared several characteristics of routine prescribing practice such as sex, health/socio-economic indicators, or partially age group distribution, however it substantially differed in terms of drug and disease spectrum.

A major contribution to OLDU applications came from the children (2 to 11-year-old) group in routine prescribing. Though lower than the latter, the percentage of this age group in all pediatric OLDU applications (52.7%) seemed to comparably reflect the share of this age group (49.6%) within the pediatric population in 2015.[20] The distinguishing feature of OLDU in terms of age distribution was that adolescents dominated infants, which was the inverse in routine prescribing. This brings the possibility of delayed recognition of conditions that could require OLDU in early periods of life. In fact, OLDU practice was reported to be more frequent at younger ages, including newborns.[14,21] However, the distribution of OLDU applications by age groups in our study appears to be very similar to that of the corresponding age groups reported in the normal population.[20] Therefore, the difference between OLDU and routine prescription in terms of age groups is likely to result from the nature of the latter. While OLDU is a physician-driven practice, the key trigger in routine prescribing is patients' health-seeking behavior, which may account for increased representation of infants. In fact, health-seeking behavior in parents of <1-year-old children was reported to be about seven-fold of that in parents of 1 to 5-year old children.[22]

OLDU applications or routine prescribing were reported to be influenced by several factors, including regional variations, inhabitant's distribution, and institutional

Table IV. Distribution of mostly encountered diagnoses in OLDU applications with requested drugs and applying physician specialties.

Drugs		Epilepsy (G40), n (%)	Other secondary pulmonary hypertension (I27.2), n (%)	Haemolytic-uremic syndrome (D59.3), n (%)
Most commonly applied drugs	1	Lacosamide, 228 (42.4)	Iloprost, 267 (56.2)	Eculizumab, 445 (99.1)
	2	Zonisamide, 57 (10.6)	Sildenafil, 77 (16.2)	Mycophenolate, 2 (0.4)
	3	IVIG 43 (8.0)	Bosentan, 68 (14.3)	Rituximab, 1 (0.2)
Major applying specialty		Paediatric neurology, 496 (92.4)	Paediatric cardiology, 473 (99.6)	Paediatric rheumatology & nephrology, 418 (93.1)

OLDU: off-label drug use, IVIG: intravenous immunoglobulin.

Table V. Distribution of top ten drugs used as off-label with their frequent diagnoses and diagnostic variation.

Drug, (n)	Most frequent diagnosis, n (%)	Second most frequent diagnosis, n (%)	Third most frequent diagnosis, n (%)	Total number of different diagnoses, n
Eculizumab, (515)	Haemolytic-uremic syndrome, 445 (86.4)	Unspecified nephritic syndrome: diffuse mesangiocapillary glomerulonephritis, 27 (5.2)	Paroxysmal nocturnal haemoglobinuria, 19 (3.7)	10
Mycophenolate, (439)	Nephrotic syndrome, 157 (35.8)	Systemic lupus erythematosus, 42 (9.6)	Idiopathic thrombocytopenic purpura, 38 (8.7)	42
Canakinumab, (347)	Amyloidosis, 230 (66.3)	Juvenile arthritis with systemic onset, 83 (24.0)	Juvenile rheumatoid arthritis, 12 (3.5)	8
Iloprost, (336)	Other secondary pulmonary hypertension, 267 (79.5)	Primary pulmonary hypertension, 64 (19.0)	Dilated cardiomyopathy, 3 (0.9)	5
Rituximab, (318)	Nephrotic syndrome, 74 (23.3)	Idiopathic thrombocytopenic purpura, 28 (8.8)	Systemic lupus erythematosus, 18 (5.7)	57
Sirolimus, (303)	Haemangioma, any site, 55 (18.2)	Other congenital malformations of circulatory system, 48 (15.2)	Lymphangioma, any site, 45 (14.9)	37
Sapropterin, (266)	Classical phenylketonuria, 198 (74.4)	Other hyperphenylalaninaemias, 65 (24.4)	Disorders of aromatic amino-acid metabolism, 2 (0.8)	4
Lacosamide, (228)	Epilepsy, 227 (99.6)	Other generalized epilepsy and epileptic syndromes, 1 (0.4)	-	2
IVIG, (221)	Epilepsy, 43 (19.5)	Immunodeficiency with predominantly antibody defects, 31 (14.0)	Kidney transplant failure and rejection, 26 (11.8)	49
Anakinra, (217)	Amyloidosis, 130 (59.9)	Juvenile arthritis with systemic onset, 62 (28.6)	Juvenile rheumatoid arthritis, 15 (6.9)	10

OLDU: off-label drug use, IVIG: intravenous immunoglobulin.

infrastructure.[23-25] OLDU practice was reported as more common in the provinces with high numbers of physicians and secondary/tertiary institutions.[24] On the other hand, prescribing studies reported association of drug utilization to some regional characteristics such as socio-economic indicators, number of physicians, or percentage of young population.[23,25] These seem to be consistent with our findings, showing positive correlation of OLDU applications and routine prescriptions to regional healthcare utilization and socio-economic indicators. The mere difference between OLDU and prescribing practice was the positive association between OLDU and the number of hospital beds. This might be attributed to the fact that OLDU is more likely to be applied from secondary/tertiary healthcare institutions, as a recent nationwide study in Turkey reported that 81% of all applications for OLDU were submitted from university hospitals.[26]

Our study showed comparably lower rates of off-label biotechnological drugs in infants. While efficacy/safety data on biotechnological drugs is already scarce in the overall pediatric population, this difference between the age

groups might be explained by increased recognizability of some diseases with increasing age. For instance, several chronic inflammatory conditions such as juvenile idiopathic arthritis, inflammatory bowel diseases, or endemic familial Mediterranean fever was reported to be more prevalent with increasing age in children.[27,28] This was further supported by our findings that showed higher off-label use for canakinumab, adalimumab, rituximab, anakinra, and infliximab -typical biologicals for the abovementioned conditions- in children and adolescent age groups compared to that in infants.

Routine prescribing demonstrated predominance of respiratory diseases along with drugs of respiratory system and systemic anti-infectives, consistent with the literature.[29-32] On the contrary, near half of the drugs (47.0%) applied for pediatric OLDU was antineoplastic/immunomodulating agents. The most frequently applied drug, eculizumab, is a monoclonal complement C5 antibody,[33] and the first novel anti-complement therapy in HUS characterized by complement alternative pathway dysregulation.[34] A recent study in France reported close to 80% of off-label eculizumab use was due to hemolytic anemias including HUS.[35] In our study, it was also the third most common diagnosis among OLDU applications and responsible for >85% of off-label eculizumab use. Meanwhile, the drug acquired approval towards the end of this study period in October 2015 and started to be used as labelled.[36]

Mycophenolate, the second most common reason for our pediatric OLDU applications, is an immunosuppressive approved in post-transplant patients in many countries including Turkey.[37,38] In our study, being among the top two applied drugs particularly in children and adolescent groups, mycophenolate was used for nephrotic syndrome over one-third of applications. A systematic review regarding off-label use of mycophenolate reported that nephrotic syndrome constituted ten out of 41 studies with beneficial effects.[39] Off-label use in this indication might be attributed to its comparably lesser toxicity over other currently used immunosuppressive agents like cyclosporin A or cyclophosphamide.[40,41] Furthermore, the fact that its off-label use was requested for 42 different diagnoses including systemic lupus and thrombocytopenic purpura in our study indicates the need for mycophenolate as an alternative immunosuppressive drug in children. Rituximab was one of such drugs that were applied for a variety of diagnoses (57 out of the 548 different diagnoses in total) in our study, particularly in adolescent and child groups. It was reported to have promising results in children with immunosuppressive-refractory nephrotic syndrome or those suffering from serious adverse effects,[42] which may explain its preference as a therapeutic alternative for different conditions. In fact, a Spanish study performed in adults reported off-label use of rituximab in 17 different autoimmune conditions, 55% of which were systemic lupus erythematosus.[43] In addition, reports from several recent studies on rituximab's efficacy on nephrotic syndrome[44,45] suggest that off-label experience in pediatrics could constitute a base for such use in adults.

The only nervous system drug among the top ten OLDU applications was lacosamide, approved by the FDA for partial epilepsy in ≥16-year-old children in 2008 and ≥4-year-old in 2017.[46] In Turkey, it is still only approved for ≥16 years of age and above.[47] Epilepsy was the second most frequent diagnosis in our study, consistent with reports stating the disease as a common condition requiring OLDU.[48] While lacosamide was among the most frequently requested drugs in child and adolescent groups (sixth and twelfth rank, respectively), it was beyond the 15th rank in infants. This might suggest that physicians are unlikely to prefer unapproved antiepileptics in younger patients even in the OLDU context. In addition, though a study reported its efficacy for refractory focal epilepsy,[49] two studies in different European countries reported lower prescription rates of newer antiepileptics in infants than that in older children.[50-51]

The main indication for OLDU practice in our study was "other pulmonary heart disease", encompassing primary and secondary pulmonary hypertension. Beside digoxin, calcium antagonists, anticoagulants, and oxygen therapy, the disease could also be managed with prostanoids, endothelin receptor antagonists, and phosphodiesterase inhibitors.[52,53] Consistent with these, iloprost, sildenafil, and bosentan were the most commonly applied drugs for secondary pulmonary hypertension in our study. Moreover, a previous OLDU study in Turkey reported that these drug groups were most commonly requested for pulmonary hypertension in pediatric populations.[26] It could be suggested that these drugs were subject to OLDU applications as they had limited clinical trial data on pediatric use.[52] Among these agents, bosentan had been approval in pulmonary hypertensive ≥3-year-old children in US,[54] and the summary product of bosentan in Turkey with a statement of limited experience in <2 years of age.[55] These might explain higher off-label use of bosentan in infants. On the other hand, sildenafil use was common in this age group whereas iloprost was found to dominate child and adolescent groups. In fact, the latter is approved for pulmonary hypertension in Turkey with a warning that stated it had no clinical data on pediatric use.[56] Contrarily, sildenafil is only approved for erectile dysfunction.[57] This difference of indication might partly explain preference of iloprost over sildenafil in older age groups. Another factor could be the warning on sildenafil's FDA-approved pulmonary hypertension label that recommends against chronic use in pediatric cases due to increased mortality concerns.[58]

Our findings should be interpreted in the light of several limitations. First, we did not have information on medication history regarding the diagnoses that required OLDU or currently used drugs for accompanying diseases. Diminished efficacy or adverse effects due to concomitant medication might have forced physicians toward OLDU practice. In addition, we did not collect data on how many OLDU applications were made for a particular indication regarding same/different drugs with no further information about OLDU switches for the same indication. Another limitation was the lack of data on duration and posology of off-label drugs. Finally, this study only included OLDU requests that were approved by the health authority, excluding rejected applications and any other OLDU practiced with the physicians' own discretion.

In conclusion, this study is the first to show indication- and drug-centered aspects of pediatric OLDU at national level, exposing its similar and distinguishing features from routine prescribing practice. Though OLDU applications is overall consistent with routine clinical practice in terms of demographics and institutional capacity, substantial variations exist regarding main drug classes and diseases. Pediatric OLDU practice seems to converge on particular classes of drugs for certain indications that are rather encountered during childhood and usually required alternative pharmacotherapeutic options. Besides, pediatric OLDU appears to differ from that in adults in terms of indications and drugs. Our findings are expected to shed light on interventions focusing on increasing "indicated" use of off-label drugs and contribute to their rational use within the pediatric OLDU context, if inevitable.

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Original Article

Comparative study of various therapeutic modalities for Guillain Barré syndrome in Assiut University Children Hospital

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ABSTRACT

Background. Our study aimed to compare the outcome of different therapeutic modalities for the management of children with Guillain-Barré syndrome (GBS) and to identify the associating risk factors that may affect the course and prognosis of the disease.

Methods. Our retrospective study compared the outcomes of different therapeutic regimens for patients with GBS who were admitted to Assiut University Children Hospital, Assiut, Egypt, from 2014 to 2016.

Results. The study included 50 patients diagnosed with GBS. Upper respiratory tract infection was the most prevalent preceding factor (66%). Acute inflammatory demyelinating polyneuropathy (AIDP) was the most prevalent type (80%). Regarding therapeutic modalities, 45 patients started with IVIG treatment, and five patients started plasmapheresis. Seventeen patients showed no improvement after two weeks of IVIG and received plasmapheresis as a sequential therapy. We found no patients who received plasmapheresis, followed by IVIG. Patients treated with plasmapheresis alone showed a significantly shorter duration of hospitalization and better outcomes in comparison to those treated with IVIG alone or with both modalities.

Conclusions. AIDP was the most common variety of GBS in our study. GBS patients who were treated with plasmapheresis had a better outcome with a short duration of hospitalization.

Key words: Guillain-Barré syndrome, intravenous immunoglobulin, plasmapheresis, outcome.

Guillain-Barre syndrome (GBS) is an inflammatory polyneuropathy characterized by acute onset, rapid progressive, ascending symmetric muscular weakness, pain, and paresthesia.[1,2] The disease can take half a day to over four weeks to reach maximum severity and then stabilizes. Weakness varying from abnormal gait to total paralysis, cranial nerve palsies, respiratory compromise, and autonomic instability can be observed.[1,2] The incidence of GBS in the pediatric age group is 0.8 patients per 100.000. However, the prevalence depends on the geographic region. The etiopathogenesis of GBS has been hypothesized to involve a direct immune-mediated mechanism against the peripheral nerve components, including the myelin sheath and the axon.[2] GBS is a heterogeneous disease with various subtypes. Recognition of these subtypes is of clinical importance since each subtype differs in pathogenesis and prognosis: these include acute inflammatory demyelinating polyneuropathy (AIDP), acute motor axonal neuropathy (AMAN), and unclassified.[3] Miller Fisher syndrome (MFS) is a clinical variant of GBS characterized by acute onset ophthalmoplegia, ataxia, and areflexia.[4]

The diagnostic criteria of GBS depend on findings such as rapidly progressive and

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relatively symmetrical weakness, muscle paralysis, reduced reflexes, the absence of concomitant fever and exclusion of another possible cause.[4] Cerebrospinal fluid analysis (CSF) and nerve conduction velocity (NCV) studies are supportive investigations commonly performed in the diagnosis of GBS. Testing for antiganglioside antibodies is performed when available. Blood tests are generally performed to exclude the possibility of other causes for weakness.[4] Characteristic CSF findings are an elevated protein level usually >0.55 g/L and fewer than ten white blood cells per cubic millimeter (i.e., albumino-cytological dissociation). This combination distinguishes GBS from other conditions (such as lymphoma and poliomyelitis) in which both the protein and the cell count are elevated. Elevated CSF protein levels are found in approximately 50% of patients in the first three days after onset of weakness, and up to 80% after the first week.[5] Electromyography (EMG) and NCV are performed when needed to exclude other causes of acute muscle weakness and to distinguish the different types of GBS.[4] Plasmapheresis, and intravenous immunoglobulin (IVIG) are the two main treatments for GBS. Plasmapheresis attempts to reduce the body's attack on the nervous system by filtering antibodies out of the bloodstream. Similarly, the administration of IVIG neutralizes pathogenic antibodies and suppresses inflammation through multifactorial mechanisms. The immunomodulatory effect of IVIG is mediated through increasing glycosylation of the Fc portion of serum immunoglobulins which inhibits complement deposition.[5] Our study aimed to compare the outcome of different therapeutic modalities for the management of children with GBS and to identify the associating risk factors that may affect the course and prognosis of the disease.

Material and Methods

The Ethics Committee of Assiut University, Assiut, Egypt, approved the study. All methods and procedures used in this study were approved by the Institutional Review Board (IRB number 12-2014).

This retrospective study included all children with GBS where complete, valid records were available in our center. We studied the outcome of different therapeutic regimens for GBS patients who were admitted to Assiut University Children Hospital, Faculty of Medicine, Assiut, Egypt, from June 2014 to June 2016. The diagnosis of acute GBS was based on Brighton criteria.[6] We excluded any patient with incomplete data and referred patients with previous treatment trials. We studied all data of GBS, children including history considering age, gender, the season of affliction, antecedent infection, vaccination, neurological deficit, and naïve/recurrent. The clinical data included full neurological examination and laboratory investigations that included CSF examination, NCV, EMG, complete blood count, serum electrolytes (Na, K, Ca, and Mg), blood chemistry (urea and creatinine), coagulation profile, monitoring of blood gases for patients who developed clinical features of respiratory distress, monitoring while the patient is on plasmapheresis of vital signs, blood pressure, oxygen saturation, and any complications. The severity of the condition was assessed into three categories; Group I (mild GBS): patients with involvement of upper limbs (UL) and lower limbs (LL) only and throughout >48 hours, Group II (moderate GBS): patients with involvement of UL and LL throughout <48 hours with no bulbar or autonomic manifestation, or, the involvement of UL and LL throughout >48 hours with bulbar or autonomic manifestation, and Group III (severe GBS): patients with respiratory muscle involvement at presentation, or UL and LL over <48 hours with autonomic manifestation and/or bulbar involvement.[7] For the treatment of GBS, IVIG or plasmapheresis were used in our center, IVIG in a dose of 0.4 g/kg/day for five days, and plasmapheresis according to the protocol of the North American Trial where total 200-250 ml/kg is exchanged over 7-10 days.[8] Patients who received IVIG with no improvement within two weeks received additional plasmapheresis.

Indicators of improvement included: duration of hospital stay, improvement of movement, weaning of mechanical ventilation, and associated complications.

Statistical analysis

We used SPSS (version 21, Inc., Chicago, IL, USA) for analysis of patients' data. Categorical data are presented as proportions and continuous data as means ± SD (standard deviations). P-value <0.05 was considered significant. We used the chi-square test to compare the proportions of categorical variables. Finally, a multi-factor logistic regression analysis was done to recognize the statistically significant risk factors that affect the outcome of GBS patients.

Results

Demographic and clinical data of the patients are presented in Table I. Spring was the highest season of presentation (46%). Upper respiratory tract infections were the antecedent infection in the majority of patients (66%), followed by gastrointestinal infection (34%). Regarding clinical presentations (Table I), limb weakness was present in all patients (100%), bulbar manifestations in 72%, respiratory muscle affection in 44%, and facial palsy and ataxia in 2% each. According to electrophysiological studies, AIDP was the most prevalent type (80%). Axonal type (AMAN) was detected in 18% and MFS in 2% of patients. Regarding treatment modalities, 45 patients started with IVIG treatment, and five patients started with plasmapheresis. Seventeen/45 patients showed no improvement after two weeks of IVIG and received plasmapheresis as a sequential therapy. No patients received IVIG after plasmapheresis. All patients who received plasmapheresis alone started the treatment within one week of disease. About two-thirds of IVIG group (31/45) started the therapy within one week of the disease, and 14 patients began the IVIG after seven days of the clinical manifestations. In our study, the severity of GBS according to Sejvar et al.[6] was: mild GBS (n=14), moderate GBS (n=14), and severe GBS (n=22) (Tables I, II).

The documented side effects in IVIG included mild infusion reactions, namely, headache (three patients), myalgia (two patients), paresthesia (one patient), and anaphylaxis with hypotension in (one patient). The most important side effects in plasmapheresis group were hypotension (one patient) and arrhythmias (one patient). In patients who received both treatment modalities; sepsis and disseminated intravascular coagulation (one patient) and prolonged fever (five patients) were observed. Regarding outcome, although all patients treated with plasmapheresis alone had severe GBS, they showed a significantly shorter hospital stay and better recovery.

Patients treated with both IVIG and plasmapheresis showed a higher percentage of complications, need for mechanical ventilation, longer hospital stay and higher incidence of deaths in comparison to the other patients.

Regarding risk factors affecting the outcome, the nature of preceding infections was significantly effective: gastrointestinal infections were associated with a longer hospital stay in comparison to respiratory infections. The severe form of GBS was significantly associated with a higher frequency of need for ICU ($p<0.001$), mechanical ventilation ($p<0.001$), the incidence of complications ($p=0.02$), and deaths (0.029). The axonal type was significantly associated with a higher risk of longer hospital stay, need for mechanical ventilation, and ICU admission and death rate (Table III).

Discussion

GBS is the most important cause of acute flaccid paralysis in children and infants. The mean age and distribution of gender in our series are similar to others.[9] In our study; males were affected more than females (56% vs 44%) with male to female ratio of 1.27:1. In contrast, other studies reported female predominance or equal distribution.[10] The higher frequency of GBS in

Table I. Demographic, electrophysiological criteria and clinical data of all studied patients.

Parameters		N (%)
Age: <5 years/>5 years		24 (48)/26 (52)
Gender: male/female		28 (56)/22 (44)
Residence: rural/urban		33 (66)/17 (34)
First attack/relapse		48 (96)/2 (4)
Seasonal variation	Spring	32 (46)
	Summer	11 (22)
	Winter	9 (18)
	Autumn	7 (14)
Antecedent infection	Upper respiratory tract infection	33 (66)
	Gastroenteritis	17 (34)
Clinical data	Flaccid paralysis	50 (100)
	Bulbar manifestations	36 (72)
	Difficulty in respiration	22 (44)
	Gasping respiration	16 (32)
	Autonomic manifestations	10 (20)
	Facial palsy	1 (2)
	Ataxia	1 (2)
Subtypes	AIDP	40 (80)
	AMAN	9 (18)
	MFS	1 (2)
Treatment groups	IVIG	28 (56)
	Plasmapheresis	5 (10)
	Both IVIG and plasmapheresis	17 (34)

AIDP: acute inflammatory demyelinating polyneuropathy, AMAN: acute motor axonal neuropathy, IVIG: intravenous immunoglobulin, MFS: Miller Fisher syndrome.

females may be related to the age of patients (prepubertal) and type of GBS (AIDP).[10]

In our study, 66% of patients were from rural areas that are consistent with other reports.[11] The higher incidence of GBS among rural children could be explained by a higher rate of gastroenteritis and respiratory infections. Although GBS occurred throughout the year, with peaks reported at different seasons, most of the researchers noted a seasonal variation in their studies.[11] Seasonal variations may depend on the seasonality of the precipitating infection, for instance by the higher frequency of viral infections in Spring in Egypt.9 This explanation is supported by the fact that 66% of our patients had a history of preceding viral infections. Dhadke et al.[12] reported respiratory infections as the most common preceding infections in their study, followed by gastroenteritis. In agreement with our findings, a previous study showed that preceding infections were present among 66.5% of patients of GBS.[13]

In this study, 4% of patients had recurrent GBS attacks. Koul et al.[14] reported a recurrence rate of 9.8% among their patients. GBS may recur in up to 10% of patients after several months to several years of the initial attack. The risk factors for recurrent GBS include young age, having MFS and patients with a shorter initial episode.[14,15]

In the present study, AIDP was the most common type, like in other studies from Africa, Europe and North America.[9,16,17] On the other hand, AMAN pattern was the predominant GBS type in Japan, China, and South America.[16,17]

Table II. Relation between the type of therapy and outcome of the studied groups.

Complications		IVIG (N = 28)	Plasmapheresis (N = 5)	IVIG + Plasmapheresis (N = 17)	p-value
Complications: Yes/No, N (%)		10 (35.7)/18 (64.3)	2 (40.0)/3 (60.0)	15 (88.2)/2 (11.8)	0.002
Need for mechanical ventilation: Yes/No, (N/%)		4 (14.3)/24 (85.7)	5 (100.0)/0 (0.0)	17 (100.0)/0 (0.0)	<0.001
Duration of hospital stay: ≤14 days/>14 days, N (%)		16 (57.1)/12 (42.9)	5 (100.0)/0 (0.0)	0 (0.0)/17 (100)	0.002
Outcome: Improved/Died, N (%)		26 (92.9)/2 (7.1)	5 (100.0)/0 (0.0)	12 (70.6)/5 (29.4)	0.072
Residual neurological deficit, N (%)		4 (14.3)	0 (0.0)	3 (17.6)	0.05
Severity of GBS	Mild	14 (50.0)	0 (0.0)	0 (0.0)	<0.001
	Moderate	9 (32.1)	0 (0.0)	5 (29.4)	
	Severe	5 (17.9)	5 (100.0)	12 (70.6)	
Pathological type	Demyelinating	22 (78.6)	4 (80.0)	14 (82.4)	--
	Axonal	5 (17.9)	1 (20.0)	3 (17.6)	--
	Miller Fisher	1 (3.6)	--	--	--

These variations in the types of GBS may be related to genetic factors with no clear evidence clarifying this difference.[9] Routine electrodiagnostic studies are uncomfortable and can be technologically difficult in children; they should be avoided when the diagnosis of GBS is clear. In addition, they should be undertaken only by experts in pediatric electrophysiological studies.[9,16,17]

In our study, we classified patients according to type of therapy into three groups: IVIG alone, plasmapheresis alone and IVIG followed by plasmapheresis after no improvement observed in two weeks. No patients received IVIG after plasmapheresis. The group treated with plasmapheresis alone showed a shorter duration of hospital stay, mechanical ventilation <14 days, and a better outcome, when compared to other groups. All patients of this group received plasmapheresis early within one week of presentation. Our data are in line with previous reports that showed a better outcome of GBS children who received plasmapheresis when compared to other modalities.[9,16] In contrast to our results, some studies found that IVIG treatment was either better or equivalent to plasmapheresis.[18,19]

IVIG combined with plasmapheresis was associated with a higher frequency of complications, prolonged hospital stay, need for mechanical ventilation, and mortality. This may be due to the higher severity of GBS in this group (70.6%, Table II) in addition to the delayed starting of management after one week of the manifestations. Oczko-Walker et al.[20] showed that treatment with IVIG followed by plasmapheresis was not better than IVIG alone. Their patients who received both treatments had a worse GBS disability scale at discharge and had longer hospitalization.[20] The researchers reasoned such results to a more severe disease course in patients receiving treatment, and/or, plasmapheresis washing out IVIG and eliminating its therapeutic effect.[20] The choice to use IVIG or plasmapheresis should be based on several factors, including the accessibility of treatment, the experience of the team, and the patient's condition and comorbidities.

The present study showed no significant effect of age, gender, or residence on the outcome. However, there was statistically significant effect as regards to severity of GBS on admission (need for ICU admission, p <0.001), need for mechanical ventilation (p <0.001), and the higher incidence of complications among

Table III. Risk factors affecting the outcome of the studied patients.

Variable		Hospital stay duration		Need for ICU admission		Need for mechanical ventilation		Complications		Death	
		<14 days	>14 days	Yes	No	Yes	No	Yes	No	Yes	No
Age	<5 years	12 (50)	12 (46.2)	12 (46.2)	12 (50)	12 (46.2)	12 (50)	14 (51.9)	10 (43.5)	4 (57.1)	20 (46.5)
	>5 years	12 (50)	14 (53.8)	14 (53.8)	12 (50)	14 (53.8)	12 (50)	13 (48.1)	13 (56.5)	3 (42.9)	23 (53.5)
	P	0.786		0.786		0.786		0.555		0.697	
Gender	Male	16 (66.7)	12 (46.2)	12 (46.2)	16 (66.7)	12 (46.2)	16 (66.7)	13 (48.1)	15 (65.2)	4 (57.1)	24 (55.8)
	Female	8 (33.3)	14 (53.8)	14 (53.8)	8 (33.3)	14 (53.8)	8 (33.3)	14 (51.9)	8 (34.8)	3 (42.9)	19 (44.2)
	P	0.144		0.144		0.144		0.226		1.000	
Residence	Urban	6 (25)	11 (42.3)	9 (34.6)	8 (33.3)	9 (34.6)	8 (33.3)	7 (25.9)	10 (43.5)	3 (42.9)	14 (32.6)
	Rural	18 (75)	15 (57.7)	17 (65.4)	16 (66.7)	17 (65.4)	16 (66.7)	20 (74.1)	13 (56.5)	4 (57.1)	29 (67.4)
	P	0.197		0.924		0.924		0.192		0.677	
Preceding infection	Gastrointestinal	3 (12.5)	14 (53.8)	12 (46.2)	5 (20.8)	12 (46.2)	5 (20.8)	11 (40.7)	6 (26.1)	4 (57.1)	13 (30.2)
	Respiratory	21 (87.5)	12 (46.2)	14 (53.8)	19 (79.2)	14 (53.8)	19 (79.2)	16 (59.3)	17 (73.9)	3 (42.9)	30 (69.8)
	P	0.002		0.059		0.059		0.276		0.210	
Severity	Moderate	4 (16.7)	10 (38.5)	5 (19.2)	9 (37.5)	5 (19.2)	9 (37.5)	4 (14.8)	10 (43.5)	0 (0.0)	14 (32.6)
	Severe	6 (25)	16 (61.5)	21 (80.8)	1 (4.2)	21 (80.8)	1 (4.2)	15 (55.6)	7 (30.4)	7 (100)	15 (34.9)
	P	1.000		<0.001		<0.001		0.020		0.029	
Pathological type	Demyelinating	23 (95.8)	17 (65.4)	16 (61.5)	24 (100)	16 (61.5)	24 (100)	18 (66.7)	22 (95.7)	3 (42.9)	37 (86)
	Axonal	0 (0.0)	9 (34.6)	9 (34.6)	0 (0.0)	9 (34.6)	0 (0.0)	9 (33.3)	0 (0.0)	4 (57.1)	5 (11.6)
	Miller Fisher	1 (4.2)	0 (0.0)	1 (3.8)	0 (0.0)	1 (3.8)	0 (0.0)	0 (0.0)	1 (4.3)	0 (0.0)	1 (2.3)
	P	0.004		0.003		0.003		0.006		0.014	
Occurrence	First attack	23 (95.8)	25 (96.2)	26 (100)	22 (91.7)	26 (100)	22 (91.7)	25 (92.6)	23 (100)	7 (100)	41 (95.3)
	Recurrent	1 (4.2)	1 (3.8)	0 (0.0)	2 (8.3)	0 (0.0)	2 (8.3)	2 (7.4)	0 (0.0)	0 (0.0)	2 (4.7)

severe patients (p = 0.02), and death (p = 0.029) on outcome of patients with GBS. Our data agreed with previous reports.[9,21]

In our study preceding gastroenteritis, GBS of axonal type were associated with negative outcome indicators such as longer hospital stay, need for ICU admission, need for mechanical ventilation, incidence of complications and mortality. Our results match previous research in Turkey where time to recovery was longer in patients with preceding acute gastroenteritis compared to upper respiratory tract infection.[22]

Our study is retrospective: therefore, some data were not available. Besides, the sample size was small, preventing the application of some comparative statistics. Despite these limitations, it adds epidemiologic and clinical data from this region to a disorder where most information is contributed from East Asia.

Acute inflammatory demyelinating polyneuropathy (AIDP) was the most common variety of GBS in our study. GBS patients who were treated with plasmapheresis had a better outcome with a short duration of hospitalization.

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Original Article

Sensory profile, ferritin and zinc levels in preschool-aged children with symptoms of attention deficit hyperactivity disorder

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ABSTRACT

Background. Attention Deficit Hyperactivity Disorder (ADHD) is one of the most common neurodevelopmental disorders and has a big impact on the well-being of children. The disorder can lead to noticeable functional limitations for children and bio-ecological factors also contribute to symptoms of ADHD. We aimed to investigate the associations between ADHD symptoms and some related bio-ecological factors including serum ferritin, zinc levels and sensory processing in preschool-aged children.

Methods. Twenty-two children who had been referred to the division of Developmental Pediatrics because of ADHD symptoms and 22 participants from the general pediatric outpatient clinics were included in the study. The symptoms of ADHD were evaluated with Conners' Parent Rating Scale-Revised Short form. Complete blood count, serum ferritin and zinc levels were also evaluated. A blind occupational therapist implemented sensory processing measurements. The characteristics of each participant such as prematurity, perinatal complications, developmental practices and sociodemographic data were also considered.

Results. Sensory processing measurement analysis revealed that all Sensory Profile scores were significantly lower in the children with ADHD symptoms compared to the control group indicating that the child shows the behavior more than desired. The low level of zinc (p=0.026, OR=6.153, 95% CI= 1.247-30.362) and the presence of perinatal complications (p=0.045, OR=10.864, 95% CI=1.059-111.499) increased the risk of ADHD symptoms. We could not find an association for ferritin levels in our study.

Conclusions. The evaluation of zinc level and sensory profile parallel to other strategies can be recommended during the management of ADHD symptoms in preschool children.

Key words: attention deficit hyperactivity disorder, ferritin, sensory profile, zinc.

Attention Deficit Hyperactivity Disorder (ADHD) is one of the most common neurodevelopmental disorders and has a big impact on the well-being of children.[1] In a recent national study ADHD has been reported as the most common mental disorder in children, with an overall prevalence of 19.5% without impairment, and 12.4% with impairment.[2] The disorder can lead to low quality of life and noticeable functional limitations for children and families.[3] The presentation of the disorder is heterogeneous and the exact etiology remains unclear.[4] Genetic polymorphism of dopamine transporter and receptors play an important role in the pathophysiology of the disorder.[5,6] Bio-ecological factors also contribute to symptoms of ADHD.[7-9] Iron and zinc metabolism are important factors that have commonly been investigated related to ADHD symptoms.[10-17] Iron is necessary for normal myelination and neurotransmitter function in early brain development and is stored safely in

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the body as ferritin.[11] A number of studies have indicated that children with ADHD have lower serum ferritin levels than children developing normally.[12] Furthermore, low serum ferritin levels have been associated with symptom severity of ADHD.[13] Likewise zinc levels and their association with symptom severity of ADHD have been investigated previously in school aged children.[14] Zinc is a dopamine transporter with inhibitor properties that are related to stimulant medication therapies.[15] It has been shown that there might be different information processing in patients with zinc deficient ADHD and zinc supplementation might decrease the symptom severity of ADHD.[16,17] Furthermore there are few studies investigating the association between ADHD symptoms and both iron and zinc metabolism but to our knowledge ,there is no study investigating this association in preschool-aged children.[10] It is noteworthy due to the importance of both zinc and iron in the dopamine pathway during this critical period.

In addition, children of these ages face multiple stimuli from their environments and may have difficulties processing them. A significant overlap has been shown for ADHD and sensory processing disorders in the literature.[18] Sensory integration has been considered as a framework to handle and process sensory inputs from the environment.[19] Sensory processing is defined as the ability to integrate multiple sensory information received from an individual's environment and to create adaptive responses to the sensory environment in order to provide meaningful participation in the activities of daily living. Although a relationship has been suggested between ADHD and sensory processing disorders in the literature, there is little data investigating the co-occurrence of these problems.[20-23] It has been reported that in one of six children with ADHD there were sensory symptoms sufficient to adversely affect participation in daily life.[21] Some researchers have noted that children with sensory processing deficits have more inattention, impulsivity, over-arousal and distractibility than children with normal sensory processing.[20] In only one study with a sample of preschoolers was it shown that children with higher sensory deficits have displayed increased hyperactivity behavior.[22] Other studies were mostly in school children and they found that children with ADHD had more sensory processing problems than those without ADHD.[20,23] Although these limited studies have indicated an association between ADHD and sensory problems, further studies are needed to evaluate the potential impact of sensory processing for children with ADHD symptoms.[20]

In this study, we aimed to investigate the associations between ADHD symptoms and some related bio-ecological factors including serum ferritin, zinc levels and sensory processing in preschool-aged children. Since many environmental factors have been related to ADHD symptoms in this age group such as prematurity, perinatal complications, developmental practices, sociodemographic characteristics, these possible factors were also addressed. Little data exists about these problems in early childhood. We hypothesized that behavioral symptoms of ADHD are related to low serum ferritin and zinc levels, and sensory deficits are higher in children with ADHD symptoms. This is the first study to research all these bio-ecological factors in the same sample group, and particularly in preschool-aged children who are in a special sensitive period for brain development.

Material and Methods

Procedures and Participants

This cross-sectional study was conducted by the Division of Developmental Pediatrics, Department of Pediatrics between September 2016 and February 2017. After receiving ethical approval (GO 16/566), from the Ethical Committee of Hacettepe University Faculty of Medicine, 22 children who had been referred to the developmental pediatrics division because of ADHD symptoms, were included

in the study. The comparison group included 22 participants who had been admitted to the general pediatric outpatient clinics for well-child visits and similar in age and gender to the children with ADHD symptoms. Each child was examined by a pediatrician and screened for eligibility for the study. Inclusion criteria for the study were having normal development. After receiving written consent from the parent/guardian of each participant they were referred to the division of developmental pediatrics. The general development and behavioral symptoms of each child were evaluated by the developmental pediatrician with the Denver II- Developmental Screening Test[24] and Conners' Parent Rating Scale-Revised Short form.[25] Symptoms of ADHD were evaluated by Conners' and children without developmental delay with Denver II were included in the study.

Blood sampling was conducted for the analysis of complete blood count, serum zinc and serum ferritin levels. The complete blood count was performed with the Coulter hematology analyzer. Serum ferritin and zinc levels were analyzed by D-mode spectrophotometric analysis. Serum levels of ferritin and zinc were categorized as low and normal according to laboratory cut-offs. All assessments were implemented at the first appointment. A blind occupational therapist implemented sensory processing measurements in a few days.

Evaluation tools

The questionnaire for prematurity, perinatal complications, developmental practices and sociodemographic characteristics was prepared by the study team. Developmental practices were playing with the child (regular or not), reading to the child (regular or not) and screen viewing of the child (mean time/day). The meaning of 'regular' was accepted as at least once a day here. The questionnaire also encompassed mothers' social support dichotomizing as 'have' or 'not'. The number of children in the family and preschool education was also queried. Mothers were asked about perinatal complications whether they had a problem during pregnancy or delivery and, whether the baby had any postnatal medical problems (e.g., low birth weight, severe jaundice, seizures, difficulty breathing, or hernia) and was transferred to the intensive care unit. When the mothers answered yes for at least one of these questions the patient was accepted as having perinatal complications.

Hollingshead Redlich Scale which was based on the profession and training of both parents was used to determine social economic status.[26]

Denver-II- Developmental Screening Test is used to evaluate the developmental screening of 0 to 6-year-old children.[27] Multiple translations have been conducted and all demonstrated cross-cultural reliability and validity. The original test was revised in 1990, forming the Denver II- Developmental Screening Test and the Turkish version was used in this study.[24]

Conners' Parent Rating Scale-Revised Short form evaluates the behavior of children as assessed by their parents. The scale includes 4 domains including oppositional behavior, inattentiveness, hyperactivity and ADHD index. Higher scores indicate higher symptom severity. The Turkish translation has good reliability and validity, Cronbach alpha and split-half reliability coefficients of the subscales were between 0.73 and 0.86 and 0.72 and 0.85, respectively. Test-retest reliability coefficients of the subscales were between 0.56 and 0.72.[25]

The Sensory Profile (SP) is an occupational therapist guided caregiver questionnaire that determine how children between 3 and 10 years process sensory information in everyday situations with 125 items in which parents report the frequency of their child's response to items.[28] The frequency is determined according to a Likert scale (1 = always: when the child responds in the manner 100% of the time and 5 =never). The rating ''always'' received the lowest score for each item because more frequent use of the behavior is undesirable. The cross-cultural adaptation of the questionnaire was carried out

and Cronbach's alpha ranged from 0.63 to 0.97 with excellent test-/re-test reliability.[29]

Sensory Integration and Praxis Test (SIPT) is a standardized test battery which evaluates sensory processing disorders in children aged between 4 years and 8 years and 11 months.[30] The test has high interrater reliability (r^3.90) and discriminates between typical and atypical samples (p<.01). The battery can be applied by a certified therapist and test-/re-test reliability is high. The score is evaluated by calculating the Z scores in a computer environment and interpreting the results by deducing the sensory profile of the child.[31]

Data analysis

Parametric tests were used for data with normal distributions whereas non-parametric tests were used otherwise. The normality for numerical variables was checked by using Kolmogorov-Smirnov test. Descriptive statistics were expressed as mean ± standard deviation or median (min-max) according to the assumption of normal distribution. For categorical variables, count and percentages were used for description. Independent samples t-test was performed to compare the means of two groups for normal distribution data. Non-normal data were analyzed by using Mann-Whitney U-test. Pearson Chi-square test, Yates' Chi-square test or Fisher Exact tests were used to examine the difference between groups for categorical variables.

The relationship between symptoms of ADHD and sensory processing measurements was analyzed using the Spearman correlation coefficient.

Logistic regression analysis was performed to determine important risk factors for symptoms of ADHD. Factors determined by p<0.20 significance level in univariate analysis were included in the model. Using the logistic models, odds ratios (OR) and their respective 95% confidence intervals (CI) were calculated. The backward stepwise elimination method was used to select significant factors. The power analysis of the study was made with NCSS 2007 in PASS programme to compare the groups according to Conners' scores and obtained 93% of power. Statistical analysis was performed using SPSS 21 software and p<0.05 was accepted as significant.

Results

Forty-four participants were included in the study, 22 of them were children with ADHD symptoms. The mean ages of the case (children with ADHD symptoms) and control (children without ADHD symptoms) groups were 55.3 ± 7.5 months and 54.0 ± 8.1 months, respectively with a range of 48-72 months. There were no differences in sociodemographic characteristics between the case and control groups (p>0.05), however perinatal complications including pregnancy, delivery and neonatal complications were higher in the case group than in the control group (p= 0.039). Detailed sociodemographic data of both groups are shown in Table I. The mean scores of all Conners' subscales; Oppositional (8.2 ± 4.3 by comparison 3.5 ± 3.2), Cognitive Problems-Inattention (6.8 ± 4.6 by comparison 1.0 ± 1.4), Hyperactivity (8.9 ± 4.2 by comparison 1.9 ± 2.9), ADHD index scales (18.6 ± 7.3 by comparison 3.7 ± 3.9) were significantly higher in the case group than in the control group (p<0.001 for all comparisons).

Complete blood analyses were usually in the normal range and similar in the case and control groups (p= 0.463). Children with low zinc levels were higher in the case group (n= 9, %40.9) than in the control group (n= 3, %13.6) (p= 0.042). Mostly children in the case (n= 14, 63.6%) and the control (n= 13, 59.1%) group had normal ferritin levels, and there was no significant difference between the groups (p= 0.757).

Sensory processing measurement analysis revealed that all SP scores were significantly lower in the case group compared to the control group indicating that the child shows the behavior more than desired (Table II).

Table I. Sociodemographic characteristics of the case (children with ADHD symptoms) and control (children without ADHD symptoms) groups.

Sociodemographic characteristic N (%)	Case n=22	Control n=22	p
Age (mean ±SD) (month)	55.3 ± 7.5	54.0 ± 8.1	0.455
Male	18 (81.8)	13(59.1)	0.186
Preterm	7(31.8)	3(13.6)	0.150
Perinatal complications	6(27.3)	1(4.5)	0.039
Maternal age (mean± SD)	33.2 ± 4.4	30.8 ± 5.2	0.105
Maternal education (under high school)	10(45.4)	10(45.5)	0.221
Maternal employment (housewife)	18(81.8)	19(86.4)	1.000
Paternal age (mean± SD)	35.8 ± 4.04	34.9 ± 5.6	0.565
Paternal education (under high school)	8(36.4)	7(31.8)	0.267
Paternal employment (regular)	19(86.4)	16(72.7)	0.457
Married	21(95.5)	22(100)	1.000
Social support (have)	8(38.1)	11(50)	0.632
Reading book to the child (regularly)	7(31.8)	5(22.7)	0.747
Screen viewing of the child (mean ±SD)(hours)	4.11 ± 2.58	3.77 ± 2.72	0.570
Playing with the child (regularly)	7(31.8)	7(31.8)	0.252
Preschool education	12(54.5)	7(31.8)	0.223
Number of children (median)(range)	2(1-4)	2(1-3)	0.478
SES(mean± SD)	3.09 ± 1.15	3.09 ± 0.81	0.806

ADHD: attention deficit hyperactivity disorder, SD: standard deviations, SES: social economic status.

Table II. Sensory profile test results of the groups.

Sensory profile test* (mean±SD)	Case group** (with ADHD symptoms)	Control group** (without ADHD symptoms)
Auditory processing	20.634 ± 4.945	31.436 ± 5.043
Visual processing	27.832 ± 4.843	34.435 ± 5.265
Vestibular processing	39.376 ± 5.769	48.459 ± 3.634
Touch processing	61.471 ± 12.738	79.376 ± 6.487
Multisensory processing	19.482 ± 2.487	28.582 ± 3.256
Oral processing	42.634 ± 7.698	50.671 ± 6.112
Sensory Processing related to tone endurance/tone	34.132 ± 5.231	43.532 ± 4.523
Modulation related to body position and movement	32.271 ± 5.482	42.612 ± 4.287
Modulation of movement affecting activity level	18.375 ± 3.571	24.438 ± 4.217
Modulation of sensory input affecting emotion	12.459 ± 2.641	16.437 ± 2.653
Modulation of visual input affecting emotion	10.582 ± 2.781	14.659 ± 2.398
Emotional social responses	50.247 ± 9.621	69.351 ± 9.430
Behavioral outcomes of sensory processing	16.471 ± 3.874	22.472 ± 2.738
Items indicating threshold of response	10.217 ± 3.211	12.935 ± 2.261

*Higher scores indicate better scores according to Likert scale, **: p<0. 05 for all comparisons of Sensory Profile Test scores between the case (with ADHD symptoms) and control (without ADHD symptoms) groups, SD: Standard Deviation

Similarly, some of the SIPT sub scores of the case group were significantly lower than in the control group (Table III). There was no clinically significant association between SP, SIPT and ADHD index scores in correlation analysis (p>0.05). Also, there was no association between low ferritin levels and SP and SIPT in either group (p>0.05). However low zinc levels were associated with the 'Modulation of movement affecting the activity level (p= 0.033) of SP and the 'Manual form perception' (p= 0.001) of SPIT in the case group.

Step-wise logistic regression analyses were also implemented to identify the risk factors associated with the symptoms of ADHD. In multivariate analysis, factors determined by p <0.20 significance level in univariate analysis (child gender, maternal age, perinatal complications, zinc and prematurity) were included in the model. Finally, low zinc level (p= 0.026, OR= 6.153, 95% CI=1.247-30.362) and the presence of perinatal complications (p= 0.045, OR= 10.864, 95% CI=1.059-111.499) increased the risk of the symptoms of the disorder.

Discussion

In this study, we identified higher sensory deficits in children with symptoms of ADHD and, among all possible related factors low zinc levels and perinatal complications were found to be associated with symptoms of ADHD. To the best of our knowledge, this is the first report discussing these bio-ecological factors in the same-sample group and also in preschool children.

Sensory processing measurements of all participants were evaluated in the study. Sensory Profile scores of the children with ADHD symptoms were lower than the control group. A theoretical overlap has been noted between ADHD and sensory processing disorder in the literature.[18] However to our knowledge there is only one study with a sample of preschoolers

Table III. Sensory integration and praxis test (SIPT) scores of the groups.

SIPT tests (mean±SD)	Case group (with ADHD symptoms)	Control group (without ADHD symptoms)
Space visualization	-0.92 ± 0.91*	-0.59 ± 0.78*
Figure-ground perception	-0.59 ± 1.21	-0.29 ± 1.01
Standing and walking balance	-1.74 ± 1.32*	-1.32 ± 1.24*
Design copy	-1.88 ± 1.59*	-1.39 ± 1.49*
Postural praxis	-1.52 ± 1.39*	-1.21 ± 1.42*
Bilateral motor coordination	-1.12 ± 1.12	-1.81 ± 1.04
Praxis on verbal command	-1.46 ± 1.87	-1.93 ± 1.76
Constructional praxis	-1.15 ± 1.39	-1.66 ± 1.42
Post-rotary nystagmus	-0.72 ± 1.27*	-0.26 ± 1.32*
Motor accuracy	-0.73 ± 1.29*	-0.31 ± 1.28*
Sequencing praxis	-1.23 ± 1.14	-0.88 ± 1.02
Oral praxis	-1.59 ± 1.51	-1.11 ± 1.23
Manual form perception	-1.24 ± 1.59	-0.81 ± 1.52
Kinesthesia	-1.43 ± 1.71	-1.12 ± 1.64
Finder identification	-0.99 ± 1.21	-0.61 ± 1.19
Graphestesia	-1.44 ± 1.29	-1.12 ± 1.21
Localization of tactile stimuli	-0.59 ± 1.93	-0.53 ± 1.62

SIPT: Sensory Integration and Praxis Test, *: p<0. 05 for the scores of SIPT between the case (with ADHD symptoms) and control (without ADHD symptoms) groups, SD: Standard Deviation

and it has demonstrated that children with more sensory deficits have displayed increased hyperactivity behavior.[22] Other limited studies in school-aged children have also reported that children with ADHD symptoms had more sensory processing problems than those without ADHD symptoms.[20,21,23] Ultimately they were all consistent with the findings of this study. Ferritin and zinc levels were also assessed in relation to the SP and SIPT scores which we did not come across in current literature. There was an association between low zinc levels and certain subgroups of SP and SIPT in the children with ADHD symptoms. However, further studies are needed to understand the underlying mechanism in this field.

An important factor associated with symptoms of ADHD in our study was low zinc levels. Researchers have begun to look at all possibilities in the field of nutrition to better understand and address mental health issues. Noticeable evidence for the role of micronutrients in mental health has come from those studies focusing on the role of zinc in common disorders such as ADHD. Lower zinc concentrations have been found in children with ADHD in several studies with the suggestion that zinc levels might be related to the severity of symptoms.[16] A review with numerous controlled studies has reported cross-sectional evidence of lower zinc tissue concentrations in children with ADHD than in control subjects and compared with population norms.[32] Consistent with these studies, it was found that low-level zinc increased the risk of having ADHD symptoms.

Ferritin is another widely investigated factor in this field. Lower serum ferritin levels in children with ADHD comparing to children with normal development and, the associations between low ferritin levels and symptom severity have been reported previously.[10-13] Similarly, a recent meta-analysis has indicated that children with ADHD have lower serum ferritin levels than children developing typically.[7] Although these reports, we could not find an association for ferritin levels in our study. However, the previous studies were mostly in school-aged children. There need to be further studies with larger samples in preschool-aged children.

Another factor associated with symptoms of ADHD was perinatal complications among the results. Prematurity was higher in children with ADHD symptoms, but there was no significant difference between the groups. Despite a clear demonstration of the association between prematurity and ADHD, there remains insufficient evidence to support a definite causal relationship.[33-35] It might be biologically plausible that as there is less time for neural development, prematurity is a risk factor of ADHD; however it is more likely that the underlying mechanism operates through a variety of factors such as increased incidence of obstetric complications which may lead to neural insult.[36] Consistent with literature our regression analysis revealed an association between perinatal complications and symptoms of ADHD. There has been a considerable amount of investigation researching the association of perinatal complications including pregnancy, labour/delivery and neonatal complications with ADHD. It has been reported that perinatal complications might contribute to symptoms of ADHD, because of the immaturity of the central nervous system and the vulnerability of functional abnormalities in neurological pathways.[37]

Behavioral symptoms of ADHD were evaluated in this study, it was not a diagnostic process. The small sample size was an important limitation of the study. However, the power analysis of the study has demonstrated that the sample was large enough to enable to compare the groups according to Conners' scores. Sensorial evaluations were made by a blind occupational therapist which we believe is an important strength of the study. It was noteworthy to implement all these measurements in the same-sample to contribute to literature related to preschool children with ADHD symptoms.

In conclusion, several bio-ecological factors have been investigated related to ADHD symptoms in this study. Our results demonstrate that low

zinc levels and perinatal complications were related to symptoms of ADHD and, sensory deficits were determined more in children with ADHD symptoms. We could not find an association with ferritin levels in our study sample. The evaluation of zinc level and sensory profile parallel to other strategies can be recommended during the management of ADHD symptoms in preschool children.

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Original Article

Serum levels of VEGF and bFGF in infantile hemangiomas treated with propranolol

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ABSTRACT

Background. Infantile hemangiomas (IH) represent the most common type of benign tumors of infancy. Vascular endothelial growth factor (VEGF) and basic fibroblastic growth factor (bFGF) have a central role in the pathogenesis of infantile hemangiomas.

Methods. In this prospective study, we aimed to investigate the relationship between serum VEGF and bFGF levels and clinical characteristics and the serological changes in VEGF and bFGF levels associated with propranolol treatment in infants diagnosed with IH. Blood samples were taken from 34 patients with IH and 10 controls. Serum VEGF and bFGF levels were studied by ELISA.

Results. At initial diagnosis, median serum bFGF levels were 11.1 ng/ml (4.8-16.6) in patients with IH (n=34) and 2.6 ng/ml (1.7-4.7) in controls ($p < 0.001$), and, median serum VEGF levels for same groups were 58.5 ng/ml (25.3-190.2) and 11.4 ng/ml (8.2-19.8) ($p < 0.001$), respectively. Serum VEGF and bFGF levels were not correlated. In 18 infants who were treated with propranolol with serial measurements, median serum bFGF levels were 10.7 ng/ml, 9.8 ng/ml and 10.5 ng/ml ($p = 0.8$), and median serum VEGF levels were 68.6 ng/ml, 63.5 ng/ml and 45.1 ng/ml ($p < 0.001$) at initial diagnosis, at first and third months, respectively. Median regression rates of the hemangiomas at the first and third months were -%47.3 and -%58.3 ($p < 0.001$), respectively.

Conclusions. Serum bFGF levels didn't change in time. Serum VEGF levels seemed to follow the natural course of IH and might be a marker for follow-up. The contribution of propranolol treatment should also be considered.

Key words: basic fibroblastic growth factor (bFBF), infantile hemangioma, propranolol, treatment, vascular endothelial growth factor (VEGF).

Infantile hemangiomas (IH) represent the most common type of benign tumors of infancy with an estimated prevalence of 1-10%.[1] An impaired balance between proangiogenic and antiangiogenic factors in a background of hypoxia has been implicated in the pathogenesis of IH.[2,3] Numerous stimulants and inhibitors have been discovered in humans; vascular endothelial growth factor (VEGF) and basic fibroblastic growth factor (bFGF) appear to be essential for vasculogenesis and angiogenesis.[4] Although bFGF acts synergistically with VEGF, variable results have been reported in studies regarding serum bFGF levels in IH.[5,6] Propranolol being a nonselective beta-blocker has become the first choice of therapy for IH.[7-9] The mechanism of action of propranolol on IH remains elusive.[6]

In this prospective study, we aimed to investigate the relationship between serum VEGF and bFGF levels and clinical characteristics as well as the serological changes in VEGF and bFGF levels associated with propranolol treatment in infants with IH.

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Material and Methods

Between September 2013 and September 2014, 34 newly diagnosed cases of IH and 10 age-matched healthy controls were enrolled in the study. All patients had cutaneous hemangiomas at proliferation phase and none had received any previous treatment or underwent any local interventions for the hemangiomas. Proliferation phase of IH was defined as rapid growth during the first 6 months of life.[2] This growing may continue until 12 months.

This study was approved by the Non-interventional Clinical Research Ethics Board of Hacettepe University (GO 13/431). All the parents gave written informed consent for the study.

Physical examination findings were normal except for the cutaneous hemangiomas and routine laboratory tests were within normal limits for all cases. Twenty-two of 34 cases were followed regularly, 18 were administered oral propranolol treatment and 4 were followed with no treatment. All the hemangioma lesions were evaluated visually and the lesion sizes were measured by two researchers independently.

Peripheral venous blood samples of 34 cases were collected at the time of initial diagnosis. Additional blood samples were collected at the first and third months after diagnosis in 22/34 cases whom were followed-up regularly. Single peripheral venous blood samples were collected from the children in the age- and sex-matched control group. The serum samples obtained after centrifugation were stored at -20°C until analysis. The remaining 12 patients were followed without treatment. Treatment indications for our cases were in accordance with the recommendations derived from the relevant medical literature such as life threatening complications, functional impairment or ulceration.[7]

Eighteen infants who received propranolol treatment had routine hematological examinations, hepatic and renal function tests and also, electrocardiogram and echocardiography to rule out any cardiac disease before treatment. They were hospitalized for two days and propranolol was administered initially at a dose of 0.5 mg/kg orally and the dose was increased to 2 mg/kg gradually in two days under monitoring.

All frozen serum samples were thawed to room temperature and analyzed for VEGF and bFGF serum levels using a quantitative enzyme-linked immunosorbent assay (ELISA) method using human VEGF/bFGF 96 ELISA kits according to the manufacturer's instructions (Molecular Devices, England). Standard curves were created. The units of measurement for serum VEGF and bFGF were pg/ml.

The relationship between serum VEGF and bFGF levels and clinical course of the IH in the follow up were analyzed for 18 infants treated with propranolol. Clinical course and response to treatment of hemangiomas were assessed clinically and pictures were taken periodically. Two investigators independently evaluated the changes in the hemangiomas visually and also the sizes were measured in two maximal dimensions perpendicular to each other in cm. Multiplication of 2 dimensions was calculated and their averages were recorded.

For each case, the follow-up percent changes were assessed both visually and by measurement by both researchers (designated as a) and the follow-up percent changes in the lesion sizes measured as described above (designated as b) were calculated. For evaluation of response of hemangiomas, patients were grouped according to the degree of treatment response in percentages [(a + b)/2] as follows: group 1 for <30% improvement or poor response, group 2 as 30% to <70% improvement or good response and group 3 as >70% improvement or excellent response. The response evaluation methodology was based on the system defined by Achauer et al.[10] with modifications.

Statistical analysis

In the statistical analyses, the mean values in the subgroups were compared using t-test,

and the median values between unrelated pairs of variables were compared using the Mann-Whitney U test or Kruskal-Wallis tests. Correlations between sets of data was analyzed with the Pearson test and linear regression analysis. The median percent of regression rates of the hemangiomas and median values of serum VEGF and bFGF at different time points were compared using the Friedman test. In every instance, a p-value < 0.05 was considered statistically significant.

Results

Thirty-four patients with IH and 10 healthy controls were included in the study. Median age of 34 patients with IH (Female/Male, 29/5) was 5.5 months (0.8-37 months) and that of the control group (Female/Male, 5/5) was 4.9 months (2.1-23 months). Twenty patients were younger than 6 months (58%) and 31 (91%) patients were younger than 1 year. Twenty-four (70%) patients had single cutaneous IH, 8 had two lesions and the remaining two had 3 lesions (total 46 lesions in 34 patients). The localizations of lesions were as follows: 36 (78%) in the head and neck, 7 (15%) on the trunk and remaining 3 on the extremities. The greatest diameter of the hemangioma lesions ranged between 1 and 8 cm (median 3 cm) and the total lesion sizes (multiplication of 2 diameters) ranged between 1 – 25 cm^2 (median 6 cm^2); 62% of the lesions were >4 cm^2.

At the time of initial diagnosis; median serum VEGF levels were 58.5 ng/ml (25.3-190.2) in 34 IH patients and 11.4 ng/ml (8.2-19.8) in the control group ($p < 0.001$); median serum bFGF levels were 11.1 ng/ml (4.8-16.6) in 34 IH patients and 2.6 ng/ml (1.7-4.7) in the control group. Initial serum VEGF and bFGF levels were not correlated but both were significantly higher in IH cases than controls ($p <0.001$). There were no significant differences in serum levels of VEGF and bFGF between patients younger than 6 months (n= 20) and older than 6 months (n= 14), and also between males and females. No correlation was found between total tumor size and serum levels of bFGF or VEGF. Median regression rates by appearance and size after 1 and 3 months were -47.3% and -58.3% ($p <0.001$), respectively.

In 18 infants treated with propranolol, there were no major treatment-related adverse effects. Efficacy for propranolol treatment was evaluated as follows: excellent response in 5 patients (27%), good response in 11 patients (61%) and poor response in 2 (11%) patients.

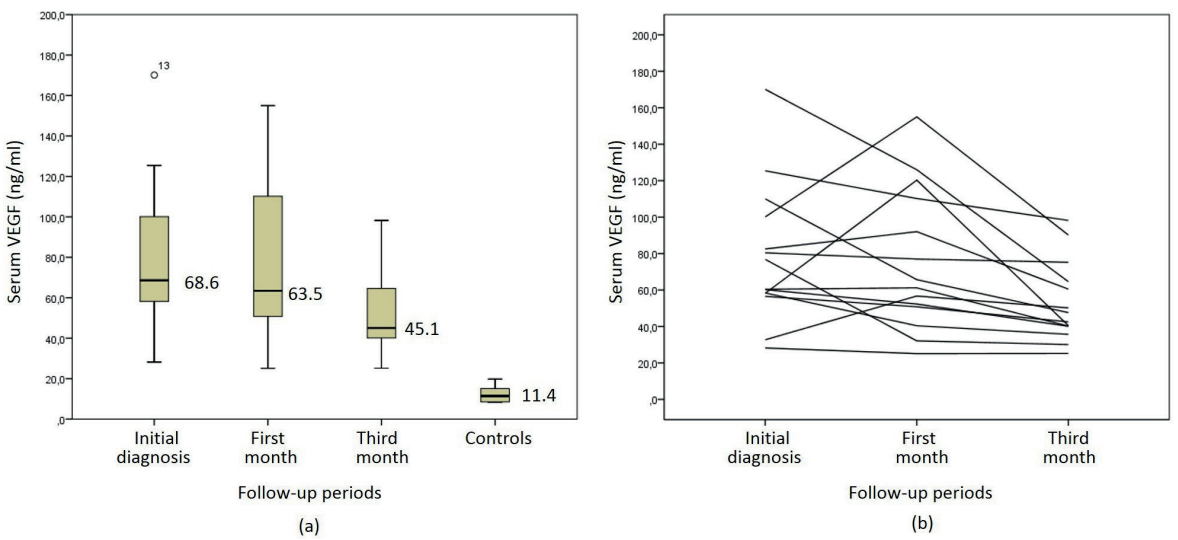

Fig. 1 a-b. Serial serum VEGF levels in 14 infantile hemangioma cases who were treated with propranolol and had serial measurements.

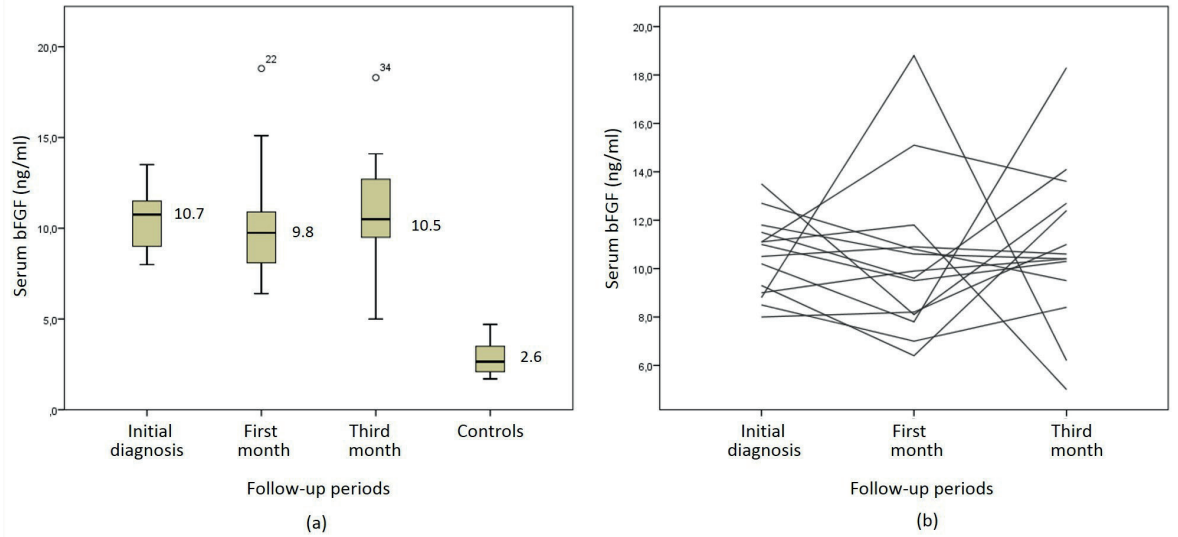

Fig. 2 a-b. Serial serum bFGF levels in 14 infantile hemangioma cases who were treated with propranolol and had serial measurements.

The total response rate was 89%. No infants were withdrawn from treatment because of side effects. Follow up analysis was performed for 18 cases who received propranolol and had serial measurements at three-time points. In those 18 infants, at initial diagnosis, the first and third months median serum levels of bFGF were 11.1 ng/ml, 9.8 ng/ml and 10.5 ng/ml (p= 0.8) and median serum levels of VEGF were 68.6 ng/ml, 63.5 ng/ml and 45.1 ng/ml (p <0.001), respectively (Figs. 1 and 2). Both VEGF and bFGF were significantly higher than the control group at all the time points. The decrease in serum VEGF levels was most significant in the third month of follow-up.

Discussion

Both VEGF and bFGF are important proangiogenic growth factors that can stimulate both endothelial cell proliferation and differentiation and promote vasculogenesis.[11] Excessive expression of VEGF and bFGF in hemangioma tissue has been confirmed in various studies, which parallels the proliferating phase of hemangioma growth.[5,12-14] Although increased serum levels of VEGF in infants with IH compared to vascular malformations and healthy controls have been documented in many studies[13,15-20], data examining the role of serum bFGF in IH were reported much less.[5,6,13,21-23] Przewratil et al.[5,13] reported that serum bFGF levels were not elevated in patients with hemangiomas but were high locally around the lesion and they hypothesized that bFGF has a strong local activity and serum levels may not reflect its activity in tissues.

In our study, almost all of the hemangioma lesions were in the proliferation phase because 31 (91%) patients were younger than 1 year. Our patients had significantly elevated serum VEGF and bFGF levels at the initial presentation compared with the control group which supports the hypothesis of increased activity of these cytokines. The results for elevated serum VEGF levels are parallel many similar studies.[13,15-20] On the other hand, elevated serum bFGF levels contradict with that of Przewratil et al.[5,13] but are comparable to findings reported in more recent studies.[6,20,22] In agreement with our findings for bFGF, elevated levels of bFGF were also found in the urine of patients with IH.[16,23]

Currently, oral propranolol is the preferred first-line treatment for IH and response rates to treatment with propranolol are high, ranging

from 80% to 100%. Based on case reports and series oral propranolol appears to have a favorable safety profile in children.[24-26]

Plasma VEGF levels significantly decreased in the following months after starting propranolol in our study. These results are consistent with the results in similar studies investigating the effects of propranolol on serum cytokines.[6,17-19,22] The decrease in serum VEGF levels was much more significant after 12 weeks of propranolol treatment. Chen et al.[18] reported that very high serum VEGF levels decreased significantly after one month compared to three months of treatment with propranolol. In a recent study, Przewratil et al.[27] found no significant decrease in serum VEGF levels after propranolol treatment. They stated that their results were difficult to explain and did not support the theory of antiangiogenic properties of propranolol. Depending on our results, we propose that the measurement of serum VEGF may be a useful tool for predicting the course of IH and monitoring the efficacy of treatment with propranolol especially for deep-seated lesions.

The mechanisms of action of propranolol in IH remain unclear. Early effects of propranolol are proposed to be vasoconstriction, intermediate effects involve the inhibition of angiogenesis resulting from the blocking of proangiogenic cytokines such as VEGF and bFGF and long-term effects are characterized by induction of apoptosis in IH endothelial cells which result in tumor regression.[28,29] Léauté-Labréze and colleagues[30] also postulated that propranolol may decrease expression of bFGF and VEGF.

Wu et al.[6] reported that serum concentrations of VEGF, bFGF, and MMP-9 decreased significantly in the treatment group 8 weeks after medication. They concluded that the mechanism underlying the effects of propranolol may be associated with the downregulation of VEGF, bFGF and MMP-9 expression. Also, Babiak-Choroszczak et al.[22] reported a decrease in serum VEGF and bFGF levels in the course of propranolol treatment of IH.

In hemangioma derived stem cells, Zhang et al.[12] showed that propranolol is capable of down-regulating the expression of VEGF mRNA and decreasing VEGF protein levels. They also found that propranolol can downregulate the expression of bFGF, although not as pronounced as that observed for VEGF expression.[12]

Our results did not confirm the effect of propranolol treatment on bFGF levels, since the expression of bFGF remained elevated during propranolol therapy in contrast to VEGF levels. This finding might indicate different effects of bFGF in the pathogenesis and course of IH.

Initial serum VEGF and bFGF levels were not correlated in our study. Our results are consistent with a recent study by El Raggal et al.[20] In our study, no correlation was found between the serum cytokine levels and patient ages. Our results are consistent with other reports confirming a lack of gender and age differences in serum VEGF and bFGF levels in IH.[17,19] No such correlation was found in the control group as well.Another finding of this study was the lack of correlation between the serum VEGF and bFGF levels and the size of the lesions.

Propranolol has revolutionized the treatment of IHs while the exact mechanism of action is poorly understood.[7,8,26] Propranolol may be exerting its effect primarily through the inhibition of VEGF. Other mechanisms might also be dominant in inhibition of IH growth by propranolol beyond effects on bFGF. We may speculate that initially high serum bFGF levels may reflect the bFGF activity in IH pathogenesis, but may not be useful for monitoring the treatment response and effectiveness of propranolol during follow-up.

This study has some limitations. We studied only a small cohort of patients. Additionally, the study included limited measurement values as an objective outcome assessment. These findings require further study and a large cohort of patients and the control group.

In conclusion, serum VEGF and bFGF levels were significantly elevated in IH. Serum bFGF levels didn't change over time. The results of our study add significant information regarding serum levels of both VEGF and bFGF during propranolol treatment which may help predict the mechanism of action of propranolol. Measurement of VEGF may be a useful tool for predicting the course of IH and monitoring the efficacy of propranolol.

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Original Article

Fecal calprotectin levels in *Helicobacter pylori* gastritis in children

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ABSTRACT

Background. Fecal calprotectin is an important inflammatory marker in intestinal diseases and is not routinely used in the upper gastrointestinal system disorders. The aim of this study was to show whether there is a relationship between fecal calprotectin levels and *Helicobacter pylori (H pylori)* gastritis in children and to determine the association of fecal calprotectin levels with gastric biopsy results in terms of chronic inflammation and neutrophil activity.

Methods. Patients with the complaints of the upper gastrointestinal system (epigastric pain, heartburn, nausea and vomiting) who were planned to undergo endoscopy were enrolled prospectively. The presence of *H pylori* was defined according to the gastric antrum biopsy results. Fecal calprotectin level was tested in the stool sample of the patients. The fecal calprotectin levels, upper gastrointestinal endoscopy and gastric biopsy results of 89 patients were evaluated.

Results. *H pylori* was found to be positive in the gastric biopsies of 51 (57.3%) patients. In the *H pylori* positive group mean fecal calprotectin level was 74.8 ± 67 μg/g, and in the *H pylori* negative group mean fecal calprotectin level was 52.7 ± 46 μg/g and the difference was significant (p= 0.039). We also found a significant relationship between fecal calprotectin levels and gastric neutrophil activity grades (p= 0.034).

Conclusions. Mean fecal calprotectin levels were found to be higher in *H pylori* positive subjects in our study. Fecal calprotectin levels were correlated with gastric neutrophil activity grades. Fecal calprotectin represents gastric neutrophilic inflammation. When interpreting a high fecal calprotectin level, *H pylori* infection should be kept in mind.

Key words: fecal calprotectin, gastritis, gastric biopsy, Helicobacter pylori, child, pediatric.

Helicobacter pylori (H pylori) is the major cause of chronic gastritis and peptic ulcer disease, and classified as a group 1 carcinogen by the World Health Organisation.[1] *H pylori* infection is usually acquired during childhood via fecal-oral or oral-oral routes.[2] Most of the infected children are asymptomatic. Pediatric prevalence of the infection is 10% in developed countries, whereas it is more than 50% in developing countries and the prevalence increases with age.[3,4] In a group of children who had upper gastrointestinal system symptoms and underwent endoscopy, the incidence of *H pylori* was reported as 51.8%.[5] The most accurate diagnostic method for detecting *H pylori* is showing the microorganism in the gastric endoscopic biopsies.[6]

H pylori infection usually presents as antral gastritis or gastric and duodenal ulcers in children. Chronic gastritis is found in almost every child infected with *H pylori*; whereas peptic ulcer develops in only 10%.[7,8] Alterations in the infected gastric mucosa may result in

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atrophy, metaplasia and cancer in years.[9]

There is an evolution of the inflammatory response to *H pylori* as the infection persists over time. In the early stages of *H pylori* infection, polymorphonuclear cell infiltration in the gastric mucosa is the major histopathological finding in adults, whereas lymphocytes predominate with the progression of the disease.[10] In children, although the lymphocytic response to *H pylori* appears to be the predominant component, active chronic gastric inflammation with neutrophils is also detected.[10,11]

In gastric biopsies of almost all cases with *H pylori*, neutrophils are detected; neutrophil activity is a common feature of *H pylori* gastritis.[12] Neutrophils are usually located in the lamina propria, within the epithelium and the foveolar lumen. The extent of mucosal injury and the intensity of *H pylori* infection is associated with the density of intraepithelial neutrophils.[12-14]

Calprotectin, a calcium and zinc binding protein which is mainly released from the neutrophils, increases in many inflammatory processes as a sign of the neutrophil chemotaxis.[15] Fecal calprotectin is an objective, non-invasive marker of the intestinal inflammation, commonly used in the diagnosis and follow-up of inflammatory bowel diseases.[16] However there are very few studies that investigate the relationship between fecal calprotectin levels and the upper gastrointestinal system diseases in adults and children.[17,18]

The aim of this study was to show whether fecal calprotectin levels increase in *H pylori* infection, and to determine the relationship between gastric neutrophil activity and fecal calprotectin levels in pediatric patients.

Material and Methods

Study Population

Children with complaints of the upper gastrointestinal system, such as epigastric pain, pyrosis, heart burn, nausea, vomiting, and halitosis, who applied to the Pediatric Gastroenterology Departments of Baskent University, Faculty of Medicine and Dr. Sami Ulus Maternity, Children's Health and Diseases, Training and Research Hospital were evaluated between November 2013 and May 2014.

Children who were older than five years of age, who had not used proton pump inhibitors or antibiotics within the last 15 days, and who were planned to undergo upper gastrointestinal endoscopic examination were enrolled as the study group. Children with chronic liver, kidney, rheumatological diseases and celiac disease patients were excluded.

We also excluded patients who had endoscopic mucosal lesions such as esophagitis, gastric ulcer, gastric polyps, duodenal ulcers in order to prevent their possible effects on fecal calprotectin levels. Fecal calprotectin test was performed in 89 patients who fulfill all these criteria mentioned above.

Direct microscopic examination of the stool to exclude parasites, and fecal calprotectin measurement were performed within two days of the endoscopy.

Only patients older than five years of age were enrolled in the study due to the requirement of being able to define the symptoms and answer the questions related to their gastrointestinal complaints. Besides, fecal calprotectin values are known to be higher in infants, and the cut-off value of fecal calprotectin showing inflammation has not been studied well enough in patients younger than 5 years of age.[19] Previous studies have demonstrated that the fecal calprotectin levels do not differentiate between the age groups after the age of four, and 50 μg/g level may be used as a cut-off value for mucosal inflammation.[20]

Histopathological examination of the gastric mucosa was used as a diagnostic method to show the presence of *H pylori*. Gastric antral biopsies were evaluated according to The Sydney Histopathologic Classification[12],

by two pathologists who were blinded to the fecal calprotectin results of the patients. Hematoxylen-Eosin and Giemsa dyes were used for the examination of the specimens. According to the endoscopic gastric antral biopsy results, the subjects were divided into two groups, *H pylori* positive and negative groups. Fecal calprotectin levels were compared between *H pylori* positive and negative groups. Chronic inflammation, neutrophil activity and *H pylori* intensity grades were also compared with fecal calprotectin levels.

This study was conducted with the approval of the Ethical Committee of Baskent University Faculty of Medicine on 02/10/2013 *(Project number: KA 13/196)*. Informed consent were taken from families. Baskent University Research Foundation supported the study.

Fecal Calprotectin Measurement

Stool specimens were taken within two days of the endoscopic procedure. Quantum Blue Calprotectin ® BÜHLMANN rapid test was used for fecal calprotectin measurement. Quantitative results are available with this rapid test, and the results are comparable with ELISA test. Fecal calprotectin level is measured between 30-300 mcg/g and the cut-off value is 50 mcg/g. With this cut-off value the sensitivity and the specificity of the test for differentiating organic and functional disorders, are 84.4% and 94.5 respectively.

The quantitative rapid test uses lateral flow technology, calprotectin reader analyzes the signal intensity from the test and control line to give a quantitative value.[21] Stool extract is diluted with buffering solution, and centrifugated; supernatant part is used for analysis.

Statistical Analysis

Preliminary statistical analysis showed that the number of the subjects needed to compare the *H pylori* positive and negative groups, were a minimum of 38 patients for each group.

The results of 38 patients in *H pylori* negative group, and 51 patients in *H pylori* positive group were evaluated with SPSS for Windows 11.5.

For the analysis of the categorical data of *H pylori* positive and negative groups, χ^2 test and Fisher-Exact tests were used. Student t test was performed for normally distributed data, and Mann-Whitney U test for non-normally distributed data. Spearman Rank Correlation analysis and Kruskal-Wallis tests were used for the relations with fecal calprotectin.

Frequencies and percentages were used as descriptive values in the categorical data. Arithmetical mean ± standard deviation was used for the normally distributed data, and median and interquartile range (IQR) were used for the non-normally distributed data.

Statistical significance was accepted as 0.05.

Results

The fecal calprotectin levels of 89 patients (70 (78.7%) girls, and 19 (21.3%) boys) who underwent upper gastrointestinal endoscopy were evaluated. *H pylori* infection was found in the gastric biopsies of 51 (57.3%) patients, whereas in 38 (42.7%) patients *H pylori* was negative. The mean age was 12.8 ± 3 years in the *H pylori* positive group, and 13.11 ± 2.4 years in the *H pylori* negative group ($p > 0.05$).

The main presenting symptoms were epigastric pain in 55 (61.8%) patients, abdominal pain in 13 (14.6%) patients, heartburn (pyrosis) in 12 (13.5%) patients, and nausea in seven (7.9%) patients. Halitosis in one, and epigastric fullness in another patient were recorded as chief symptoms (Table I).

When we performed detailed symptom inquiry, 71 (79.8%) patients denoted epigastric pain, and 46 (52%) patients expressed pyrosis. There was not a difference in epigastric pain and pyrosis frequency in terms of *H pylori* status ($p > 0.05$). Nausea and/or vomiting were stated in 29 (34.5%) patients and this symptom was more

Table I. Main symptoms of the patients at presentation.

	Hp presence		Total
	Hp (-)	Hp (+)	
Epigastric pain (n)	23	32	55
%	60.5%	62.7%	61.8%
Heartburn(pyrosis) (n)	4	8	12
%	0.5%	15.7%	13.5%
Stomachache (n)	5	8	13
%	13.2%	15.7%	14.6%
Nausea (n)	5	2	7
%	13.2%	%3.9	%7.9
Halitosis (n)	0	1	1
%	0%	2.0%	1.1%
Fullness (n)	1	0	1
%	2.6%	0%	1.1%
Total	38	51	89

frequent (20 vs. 9) in *H pylori* positive patients ($p < 0.05$).

When the endoscopic diagnoses were evaluated, 36 (40%) subjects were found to have normal upper endoscopic findings, 24 (27%) had antral nodular gastritis, 21 (24%) had erythematous gastritis, 6 (7%) had antral superficial gastritis, 2 (2%) had erosive gastritis.

In 51 *H pylori* positive patients, 21 (41%) had antral nodular gastritis. Twenty one out of 24 (87.5%) patients with antral nodular gastritis were found to be positive for *H pylori*. The relationship between antral nodular gastritis and *H pylori* was statistically significant ($p < 0.001$) (Table II).

Mean fecal calprotectin level of all patients was 65.9 ± 60.3 mcg/g (min: 10, max: 300 mcg/g). Mean fecal calprotectin levels of *H pylori* positive and negative groups were 74.8 ± 67 μg/g, and 52.7 ± 46 μg/g, respectively. The difference between the two groups was statistically significant ($p = 0.039$) (Table III).

The cut-off value for fecal calprotectin for this study was calculated as 30.49 μg/g with ROC (receiver operating character) analysis. According to this cut-off value, for the detection

Table II. Endoscopic diagnoses and *H pylori*.

	Hp (-)	Hp (+)	Total
Normal (n)	18	18	36
%	47.7%	35.3%	40.4%
Antral nodular gastritis (n)	3	21	24
%	7.9%	41.2%	27%
Antral superficial gastritis (n)	6	0	6
%	15.8%	0%	6.7%
Erosive gastritis (n)	2	0	2
%	5.3%	0%	2.2%
Erythematous gastritis (n)	9	12	21
%	23.7%	23.5%	23.6%
Total	38	51	89

Table III. The relationship between fecal calprotectin and Hp infection (*p= 0.039).

Fecal calprotectin (μg/g)	Hp (-) n=38	Hp (+) n=51
Mean*	52.7	74.8
Standard deviation	46.8	67.6
Median	29.9	40
Minimum	29.9	29.9
Maximum	222	300
Interquartile Range (IQR)	27.6	86

of *H pylori*, the sensitivity and the specificity of fecal calprotectin testing were 60.8% and 63.2% respectively.

The possibility of fecal calprotectin level being more than 30.49 μg/g in *H pylori* positive patients was 2.657 times higher than *H pylori* negative patients (Odds ratio 2.657, CI: 95%, 1.117-6.319).

However, the recommended cut-off value to determine the presence of intestinal inflammation is accepted as 50 μg/g in Quantum Blue Calprotectin ® BÜHLMANN rapid test. When we use this cut-off level, the sensitivity and the specificity of fecal calprotectin to detect *H pylori* were 39.2% and 73.7% respectively.

We evaluated gastric biopsy results in terms of chronic inflammation, neutrophil activity, *H pylori* intensity, intestinal metaplasia and atrophy according to the updated Syndey Classification.[12]

Out of 38 *H pylori* negative children, 7 (18%) cases had normal findings in their gastric biopsies. Mean fecal calprotectin level in those with normal gastric biopsies was 53.8 ± 31.04 μg/g. Remaining 31(82%) patients reported as having gastritis in their gastric biopsies, despite not having *H pylori*. Mean fecal calprotectin in that group was 52.4 (± 50.09) μg/g. The difference in mean fecal calprotectin levels between those two groups was not significant.

All 51 *H pylori* positive patients had some degree of chronic inflammation as mild in 18, moderate in 24 or severe in 9 cases. Chronic inflammation of the gastric antral mucosa was seen in 30/38 (79%) of *H pylori* negative patients as mild in 26, moderate in 4 cases. Severity of chronic inflammation was higher in *H pylori* positive group (p <0.001) than the *H pylori* negative group.

Gastric neutrophil activity was seen in 40/51 (78%) *H pylori* positive patients (mild 17, moderate 19, and severe in 4 cases). Neutrophil activity was seen only in 12 out of 38 (32%) *H pylori* negative patients. When we compared two groups, gastric neutrophil activity grades were higher in *H pylori* positive group (p <0.001).

There was no relationship between fecal calprotectin levels and chronic inflammation grades (p= 0.093), however, we found a significant relationship between fecal calprotectin levels and gastric neutrophil activity grades (p= 0.034) (Table IV).

H pylori intensity was mild in 22 (43%), moderate in 17 (33%), and severe in 12 (%24) patients with *H pylori* infection. When the relationship between fecal calprotectin levels and *H pylori* intensity in gastric biopsy samples were evaluated; although *H pylori* intensity grade and fecal calprotectin median levels are proportional, this relationship was not statistically significant (p= 0.197) (Table IV).

Intestinal metaplasia was not seen in any of the subjects. Gastric atrophy was seen in 12 (13%) children (3 *H pylori* negative and 9 *H pylori* positive).

Discussion

H pylori is one of the world's most common infectious diseases and half of the world's population is infected with it. *H pylori* is usually

Table IV. The relationship between fecal calprotectin levels and the grades of chronic inflammation, neutrophil activity, and Hp intensity.

	0 (none)	1(mild)	2 (moderate)	3 (severe)	P value
A. Chronic inflammation Fecal calprotectin (μg/g)					0.093
Mean	74	48	81	89	
Median	50.4	29	44	29.9	
Minimum	29	29	10	29	
Maximum	222	220	300	243	
B.Neutrophil activity Fecal calprotectin (μg/g)					0.034
Mean	54	58	74.8	164	
Median	30	29.9	43	178.5	
Minimum	29	29	10	58	
Maximum	300	222	243	242	
C. Hp intensity Fecal calprotectin (μg/g)					0.197
Mean	52.7	60	86	86	
Median	29.9	32	43	44	
Minimum	29.9	29.9	30	29.9	
Maximum	222	141	300	242	

acquired during childhood, infection rates remain higher in some groups of children, dependent on factors such as low socioeconomic status and bad sanitary conditions.[22]

Epigastric pain, nausea/vomiting, regurgitation, pyrosis, abdominal pain are the symptoms of *H pylori* infection in children, whereas the infection may also be asymptomatic. In our study group consisting of 89 patients with upper gastrointestinal symptoms, 51 (57%) of the subjects were found to have *H pylori* infection. Although we excluded the duodenal and gastric ulcer patients, *H pylori* prevalence is still high when compared with the literature.[18,23]

In a study in China, 1634 children underwent upper endoscopic evaluation due to gastrointestinal system symptoms, and *H pylori* prevalence was found to be 32.1%. Active inflammation in gastric biopsies was shown in 26.9% of *H pylori* positive patients, whereas it was only 4.1% in *H pylori* negative patients.[24] In our study, we found higher rates of active gastric inflammation apart from *H pylori* status, and significant difference in terms of gastric neutrophil activity between *H pylori* positives (78%) and negatives (32%). These different results could be explained by other environmental factors and ethnic differences.

Studies searching about the utilization of fecal calprotectin in the diagnosis of gastritis are very limited. Montalto et al.[17] evaluated fecal calprotectin levels in histologically diagnosed 61 adult gastritis patients and 74 healthy adults. Subjects with chronic gastritis were divided into three groups having mild, moderate and severe gastritis. Fecal calprotectin levels did not differ between those three groups and healthy controls. Also, there were not any differences between the groups, related with *H pylori* presence and chronic proton pump usage.

In a recent study in pediatric functional abdominal pain-related gastrointestinal disorders, the fecal calprotectin levels of 17 *H pylori* positive and 39 *H pylori* negative patients were found to be similar. In this study, median fecal calprotectin levels did not also differ between cases of patients and healthy controls.[18] In contrary to that study, our *H pylori*

positive subjects had higher fecal calprotectin mean levels than *H pylori* negative subjects. Nevertheless, our sample size of patients with *H pylori* gastritis was larger and gastric neutrophilic activity was high.

Flagstadt et al.[25], demonstrated low levels of fecal calprotectin in children with functional gastrointestinal disorders (FGID); fecal calprotectin levels did not differ significantly between FGID entities. However, this study was performed after excluding any organic disease such as *H pylori* gastritis.

In a patient group with 56 cases and quiescent Crohn disease, it was shown that fecal calprotectin levels did not change significantly with *H pylori* eradication.[26] There were only six *H pylori* positive patients which lead them to avoid coming to a clear conclusion.

When we compared fecal calprotectin levels with chronic inflammation, neutrophil activity, and *H pylori* intensity grades of gastric biopsies according to the updated Sydney Classification[12], a significant relationship to fecal calprotectin was only shown between grades of neutrophil activity. *H. pylori* gastritis is characterized by the infiltration of the lamina propria between the surface epithelium, the foveolae and gland necks by plasma cells, lymphocytes, macrophages and neutrophil granulocytes. The existence and degree of neutrophils inside the epithelium or in the lamina propria determine the activity of gastritis.[13] Since fecal calprotectin is a marker of neutrophilic inflammation, our result showing the significant relationship between fecal calprotectin and gastric neutrophil activity might be stated as an expected finding.

Summerton et al.[27] evaluated fecal calprotectin levels in 26 patients with gastritis or duodenitis, and found normal results. Fecal calprotectin levels are expected to be higher with increasing neutrophil degree, which is a sign of activity. Contrary to previous studies we found that activity degree is related with fecal calprotectin levels. The lower fecal calprotectin levels in upper gastrointestinal diseases in previous studies might be explained by less severe inflammation and a smaller area of inflammation when compared to inflammatory bowel diseases.[17]

This study compares fecal calprotectin levels between *H pylori* positive and negative patients, as well as in different degrees of inflammation, activity and *H pylori* density in childhood gastritis. Mean fecal calprotectin levels were found to be significantly higher in *H pylori* positive subjects in our study. We also found a relationship between neutrophil activity grades and fecal calprotectin. However, these data are not sufficient to make a statement about the certain increase of fecal calprotectin levels in childhood *H pylori* gastritis.

Fecal calprotectin is a non-invasive marker showing the neutrophilic inflammation. Further studies are needed to confirm our results and provide the routine usage of fecal calprotectin in patients with upper GI symptoms and in the diagnosis of *H pylori*.

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Original Article

Life-stage factors associated with overweight severity in adolescents

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ABSTRACT

Background. Investigating life-stage factors associated with overweight may be useful in the prevention of excessive BMI increase. The main aim of this study was to investigate the influence of the route of delivery, birth weight and overweight onset on overweight severity in a sample of overweight adolescents followed at a Pediatric Obesity Clinic.

Methods. Clinical data from 412 adolescents with overweight (BMI ≥ p85), aged 10-18 were retrospectively collected and analyzed.

Results. Adolescents born by cesarean section (CS) showed a lower age of overweight onset, compared to other methods of delivery (*d*= 0.33, *p*= .009). Birth weight was positively associated with BMI z-score (*r*=.164, *p*= 002) and waist circumference (WC) (*r*=.191, *p*=.001). The overweight onset was negatively associated with BMI z-score (*r*= -.277, *p* <.001), WC (*r*= -.270, *p* <.001) and body fat mass (*r*= -.199, *p*=.001). Overweight duration was the best predictor of BMI z-score, explaining in 75% its variation (F=1,317)=26.94, *p* <.001), which increased to 99% when birth weight was included in the model (F(2,316)=18.47, *p* <.001).

Conclusions. This study suggests that lifestyle may interrupt the burden of CS on BMI z-score throughout growth. Moreover, increased birth weight may anticipate overweight onset, and consequently overweight duration in the presence of inadequate lifestyle behaviors.

Key words: adolescent, birth weight, way of delivery, overweight, overweight severity.

Obesity is a major chronic disease and public health concern around the world. Over a third of the world population has obesity.[1] A secular trend of the increasing prevalence of obesity has been estimated with 38% of the world's adult population developing overweight and another 20% obesity, by 2030.[2]

Besides the way of delivery, with an acknowledged association between cesarean section (CS) and obesity, the three critical periods for the development of childhood obesity include fetal life, the period of adiposity rebound (4-6 years old), and adolescence.[3-5]

According to the developmental origins of health and disease hypothesis, adverse conditions throughout early development, either in the uterus or during the early postnatal years or both, may lead to metabolic changes that increase obesity risk later on.[6] In that line, the prenatal period is referred to as a 'critical period' where adverse events may have a lifelong effect on body composition and contribute to the development of obesity.[7] Based on the International Study of Childhood Obesity, Lifestyle and the Environment (ISCOLE) which covered urban and sub-urban regions in twelve countries, high birth weight (defined as birth weight ≥3500 g) was associated with increased

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odds of obesity.[8] Gillman et al.[9] showed that high birth weight was a risk for overweight in adolescence. Other studies have shown that birth weight is linear and proportionally correlated to body mass index (BMI).[10] Frisancho et al.[11] showed that the relative risk for high BMI in adolescence was 1.9-times higher for children who were born as small for gestational age (SGA), 2.2-times for appropriate weight for gestational age (AGA), and 5.7-fold for large for gestational age (LGA). On the other hand, other authors have reported a relationship between SGA and adulthood obesity.[12] The supporting evidence explaining these results is based on the "J-shaped" (association of low birth weight with increased body fat mass (BFM)) as well as on the "U-shaped" curve hypothesis (association of both low and high birth weight with BFM).[13]

The lack of consensus suggests further more complex associations between birth weight and obesity. The period of adiposity rebound corresponds to the second rise in the BMI curve occurring between the ages of 4 and 6, when the BMI begins to increase again, after a rise in infancy and a subsequent decline.[14] This is another critical period for the development of childhood obesity that can track to early adulthood.[15] According to Geserick et al.[16] children who become overweight during this period have higher odds of being obese at adolescence. Adolescence may be considered as the last critical period for the development of obesity.[17]

Although the prevalence of obesity has come to a plateau in many European countries, the severity of obesity seems to increase, especially among adolescents.[18] Due to the increased obesity severity and its related comorbidities, several authors have suggested that waist circumference (WC) and waist-height ratio (WHtR) should be routinely assessed and used as measures of central adiposity.[19,20]

It is crucial to identify early life-stage factors associated with overweight in order to prevent excessive BMI increase till reaching adulthood. In fact, it has been shown that adolescent obesity is associated with increased risk of obesity during adulthood with 70.5% of severely obese adolescents remaining obese as adults.[21]

Although several studies have analyzed the relationship between some perinatal factors, such as the way of delivery, birth weight or overweight onset and BMI in children, to the best of our knowledge, the interaction between these factors in adolescents with overweight has never been investigated so far.

The main aim of this study was to investigate the influence of the way of delivery, birth weight for gestational age and overweight onset on adolescent overweight severity. We have hypothesized that: (i) CS is a predictor of increased BMI and waist circumference during adolescence; (ii) birth weight for gestational age is positively associated with BMI and WC during adolescence; (iii) overweight onset during the period of adiposity rebound is a predictor of BMI and WC severity during adolescence.

Material and Methods

Participants

Clinical files from adolescents with overweight (BMI ≥ p85), aged 10-18, with a first appointment between October 2014 and December 2018 at the Pediatric Obesity Clinic, Hospital de Santa Maria, Lisbon, Portugal, were searched and data collected retrospectively.

This study was approved by the research ethics committee of the Faculty of Medicine of the University of Lisbon, Portugal (271/2016), and is in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Signed informed assent/consent was signed by all the participants and respective caregivers.

Measures and instruments

Birth weight, gestational age and way of delivery

Birth weight, gestational age and way of delivery were collected using the individual health

booklet, and birth weight for gestational age was categorized according to INTERGROWTH 21st.[22]

Birth weights ranging from percentile 11 to 89 for gestational age were considered as AGA, at percentile 10 or under as SGA and at percentile 90 or above as LGA. The z-score of birth weight for gestational age was also computed according to INTERGROWTH 21st.[22]

Overweight onset and overweight duration

Overweight onset, considered as the time where BMI started to exceeded percentile 85 based on the World Health Organization charts, was assessed using the individual health booklet.

Overweight duration was calculated as the difference between current age and overweight onset. Both variables were registered in years.

Anthropometric and body composition assessment

Height was assessed with a height stadiometer (SECA 217, Hamburg, Germany) in the Frankfurt plan, without shoes, with the participants back to the stadiometer, and after an expiratory phase. Height was registered to the nearest 0.1 cm.

Bodyweight and body composition were measured with a bioelectrical impedance scale (InBody 230, Seoul, Korea) to the nearest 0.1 kg, with the subjects wearing as few clothes as possible, and without shoes or socks. % of BFM and % of skeletal muscle mass (SMM) were calculated dividing the total BFM and SMM (kg) by body weight, respectively.

BMI was calculated dividing the body weight in kilograms by the square of height in meters [BMI= weight (kg)/height^2 (m)]. The BMI z-score was calculated according to World Health Organization [BMI z-score= $[(BMI/M(t))^{L(t)}-1]/L(t)S(t)$].

WC was assessed using a flexible anthropometric tape (SECA 203, Hamburg, Germany). WC was measured at the iliac crest level, with the subjects standing and at the end of a regular expiration (Cameron method).

WHtR was calculated dividing the WC in centimeters by the height in centimeters [WHtR= WC (cm)/Height (cm)].

Clinical assessments

Pubertal status was assessed and categorized according to Tanner stages.

Statistical analysis

Data was analyzed using the IBM SPSS statistics (IBM SPSS statistics, version 21.0, IBM, New York, USA).

Chi-square and Independent sample t-test were used in order to analyze gender differences. Because statistically significant differences between girls and boys were found, all the analyses were performed controlling for sex.

The associations between gestational age, birth weight, overweight onset, and all the anthropometric and body composition variables were analyzed using partial correlations, controlling for age, sex and way of delivery. BMI z-score prediction (dependent variable) was computed using multiple linear regressions (stepwise method). A p value of <.05 was considered statistically significant.

Results

Clinical data from 412 overweight adolescents (87.1% Caucasian) were analyzed.

Boys (n=192, mean age 13.9 ± 2.0) showed higher height (d= 0.53, p <.001), BMI z-score (d= 0.21, p=.040), WC (d= 0.21, p=.048) and SMM (d= 0.40, p <.001), compared to girls (n= 220, mean age 14.4 ± 2.2). On the other hand, girls showed higher BFM (d= 0.53, p <.001) compared to boys (Table I).

Statistically significant differences between girls and boys were also found in the number of CS, with a higher number of CS among boys (46.6% vs. 29.5%, p=.001) (Table I). Adolescents born by CS showed a lower age of overweight onset, compared to those born with other methods of delivery (d= 0.33, p=.009).

Table I. Sample characteristics.

	Girls		Boys			Total	
	n	Mean±SD	*n*	Mean ±SD	*p*	*n*	Mean ±SD
Age (years)	220	14.4 ± 2.2	192	13.9 ± 2.0	.017	412	14.2 ± 2.1
Height (cm)	220	158.9 ± 7.5	192	163.7 ± 10.6	<.001	412	161.1 ± 9.4
Weight (kg)	220	82.9 ± 18.6	192	86.5 ± 24.2	.098	412	84.5 ± 21.5
BMI (kg/m^2)	220	32.59 ± 6.02	192	31.78 ± 6.36	.186	412	32.21 ± 6.19
BMI z-score	220	2.68 ± 1.02	192	2.89 ± 0.99	.040	412	2.78 ± 1.01
WC (cm)	189	101.5 ± 12.9	152	104.4 ± 14.5	.048	341	102.8 ± 13.7
WHtR	189	0.63 ± 0.07	152	0.63 ± 0.07	.681	341	0.63 ± 0.07
BFM (%)	193	44.1 ± 5.7	180	40.7 ± 7.2	<.001	373	42.5 ± 6.7
SMM (%)	175	31.8 ± 6.1	158	34.5 ± 7.2	<.001	333	33.1 ± 6.8
Overweight onset (years)	163	6.2 ± 4.3	161	5.3 ± 3.65	.042	324	5.7 ± 4.03
Birth weight (g)	214	3261 ± 554	191	3287 ± 659	.664	405	3273 ± 605
Gestational age (weeks)	220	38.8 ± 1.8	192	38.1 ± 2.6	.001	412	38.4 ± 2.2
Birth weight z-score	214	0.40 ± 1.29	191	0.51 ± 1.24	.365	405	0.45 ± 1.27
Race	*n*	%	*n*	%	*p*	*n*	%
Caucasian	192	87.3	167	87.0		359	87.1
Black	27	12.3	24	12.5	.993*	51	12.4
Asian	1	0.5	1	0.5		2	0.5
Delivery							
Eutocic	114	60.0	84	47.2		198	53.8
Cesarian section	56	29.5	83	46.6	.001*	139	37.8
Other	20	10.5	11	6.2		31	8.4
Birth weight category							
SGA	28	13.1	9	4.7		37	9.1
AGA	131	61.2	137	71.7	.008*	268	66.2
LGA	55	25.7	45	23.4		100	24.7
Tanners' stage							
1	1	12.5	7	87.5		8	2.2
2	25	31.6	54	68.4		79	21.4
3	18	39.1	28	60.9	<.001*	46	12.4
4	29	43.3	38	56.7		67	18.1
5	124	72.9	46	27.1		170	45.9

AGA: appropriate weight for gestational age, BFM: body fat mass, BMI: body mass index, CS: cesarean section, LGA: large for gestational age, SGA: small for gestational age, SMM: skeletal muscle mass, WC: waist circumference, WHtR: waist-to-height ratio.
* Chi-square test.

From the 412 adolescents, 37 were born SGA and 100 LGA. According to birth weight for gestational age, LGA participants showed a higher BMI z-score during adolescence compared to AGA (d= 0.32, p=.023). No statistically significant differences were found between SGA and AGA or between SGA and LGA.

No associations were found between birth weight for gestational age and overweight onset.

When controlling for sex, age and way of delivery, birth weight showed to be positively correlated with BMI z-score (r=.164, p=.002), WC (r=.191, p=.001) and WHtR (r=.126, p=.028); birth

weight z-score was positively correlated with BMI z-score (r=.144, p=.006) and WC (r=.153, p=.007); overweight onset was negatively correlated with BMI z-score (r= -.277, p <.001), WC (r= -.270, p <.001), WHtR (r= -.227, p <.001), and BFM (r= -.199, p=.001); overweight duration showed to be positively correlated with BMI z-score (r= -.261, p <.001), WC (r= -.260, p <.001), WHtR (r= -.213, p <.001), and BFM (r= -.176, p=.003). Gestational age was positively correlated with birth weight (r= .472, p <.001), and negatively correlated with birth weight z-score (r= -.234, p <.001) (Table II).

According to multiple linear regressions (stepwise method), overweight duration was the best predictor of BMI z-score during adolescence, explaining in 75% its variation (F(1,317)= 26.94, p <.001). Including birth weight in the model, the interaction between these variables was able to explain 99% of BMI z-score variation (F(2,316)= 18.47, p <.001).

Overweight onset during the period of adiposity rebound was not associated with BMI and WC severity.

Table II. Partial correlations between life-stage factors and adolescent anthropometric/body composition measures.

	Gestational age	Born weight	Born weight zs	Overweight onset	Overweight duration	WC	WHtR	%BFM	%SMM	BMI zs
Gestational age	1									
Born weight	.472†	1								
Born weight zs	-.234†	.731†	1							
Overweight onset	-.026	-.014	.007	1						
Overweight duration	.019	.005	-.013	-1†	1					
WC	.057	.191†	.153§	-.271†	.260†	1				
WHtR	.027	.126*	.098	-.227†	.213†	.926†	1			
%BFM	.073	.086	.028	-.199†	.176§	.597†	.673†	1		
%SMM	-.045	-.008	.038	.013	-.005	-.316†	-.369†	-.465†	1	
BMI zs	.022	.164§	.144§	-.277†	.261†	.812†	.822†	.673†	-.349†	1

*p<0.05; §p<0.01; †p<0.001
BFM: body fat mass, BMI: body mass index, SMM: skeletal muscle mass, WC: waist circumference, WHtR: waist-to-height ratio, ZS: – z-score.
* Partial correlations controlling for sex, age and way of delivery.

Discussion

Adolescent overweight dramatically progresses into adulthood. It is crucial to investigate life-stage factors associated with overweight in order to prevent excessive BMI increase throughout this critical period for the development of obesity.[17,23,24]

The main aim of this study was to investigate the influence of perinatal factors (i.e. way of delivery, birth weight) and overweight onset on overweight severity in a sample of overweight adolescents followed at a Pediatric Obesity Clinic, in order to identify the factors associated with BMI severity in this population. Identifying these factors may allow the improvement of both preventive and timely weight management interventions.

Literature shows a strong association between CS and increased BMI and WC, in the offspring

and later in life.[25,26] According to our findings, CS was not associated with BMI z-score during adolescence. One possible explanation for the lack of association may be the specific characteristics of the sample studied. In fact, the majority of the studies that reported an association between CS and BMI z-score studied the general population.[25] The absence in our sample of other weight categories, besides overweight, most probably impaired this association. Another possible explanation could be the adoption of healthy lifestyle behaviors at a certain point in time. Although the way of delivery may influence overweight onset, dietary and physical activity behaviors are concurrent and modifiable factors that may influence BMI z-score at any time.[27] Indeed, in this study, CS showed to be only associated with overweight onset. Adolescents born by CS have shown decreased age (-1.4 ± 0.47 years) of overweight onset, compared to other ways of delivery. According to the literature, the link between CS and increased BMI relies on the *hygiene hypothesis*. In other words, infants born by CS are mainly exposed to maternal skin microbiota and to external environmental bacterial communities at birth. CS impairs the exposure of the newborn to maternal vaginal bacteria, which is known to be the major source of the newborn's intestinal bacteria. The decreased intestinal bifidobacteria and bacteroids (known to be negatively associated with dietary nutrient absorption) in the newborn delivered by CS compared to vaginal, may lead to early overweight onset. Although data on intrapartum indications for CS is missing, it should be noted that the main intrapartum indications for this procedure are not known as risk factors for obesity.[28]

In line with several other studies, our findings show a positive association between birth weight/birth weight z-score and BMI z-score, WC and WHtR. Interestingly, birth weight by itself showed higher association levels with BMI z-score, WC and WHtR during adolescence, compared to the birth weight z-score. Although not further explored, other authors have reported similar results.[6,7,29,30] In this study, birth weight was the second-best predictor of adolescent BMI z-score. In addition, gestational age was positively correlated with birth weight and negatively associated with birth weight z-score, with a higher correlation level within the former. These results suggest that the use of a z-score, adjusting for gestational age may have affected and biased the association between the variables under study.[25] A similar finding regarding the use of birth weight z-score was reported by Delbaere et al.[31]

Conversely to our hypothesis and to the results reported by other authors,[5,32] overweight onset during the period of adiposity rebound was not associated with BMI and WC severity. Instead, overweight onset, as a continuum variable, was negatively correlated with BMI z-score, WC, WHtR and BFM. The negative correlation between overweight onset and WC/WHtR was as relevant as the one between overweight onset and BMI z-score. The association between WC and impaired metabolic profiles in adolescents with overweight has already been widely described.[33,34]

Regression analyses showed that overweight duration and not overweight onset was the best predictor of adolescent BMI z-score. Prolonged inadequate dietary and physical activity behaviors may lead to excessive weight gain and in turn, to harmful metabolic adaptations and adipose tissue dysfunction as early as in childhood.[35] Adipose tissue dysfunction, is characterized by changes in adiponectin and leptin levels as well as in insulin sensitivity.[35] However, it is not completely understood whether these metabolic changes are a consequence or a trigger of an adipose tissue increased proliferative capacity which may be potentiated by overweight duration.[35] As overweight duration may lead to short and long-run psychological consequences, such as body dissatisfaction, low self-esteem, poor health-related quality of life and even depression it may negatively affect behavior change thus perpetuating the cycle.[36,37]

The retrospective nature of this study has not allowed for dietary and physical activity data collection. Another limitation is the cross-sectional design, not allowing for causal inferences. Nevertheless, to the best of our knowledge, no other study has investigated the interaction between the method of delivery, birth weight and overweight onset on overweight severity in a sample of adolescents with overweight. The fact that this study brings further knowledge to the study of BMI severity during adolescence is its main strength.

In summary, this study showed a positive association between CS and early overweight onset, which reinforces the need for a careful assessment of the risk-benefit balance to conduct a CS on an individual basis. Overweight onset and particularly overweight duration were associated with BMI z-scores severity. Nevertheless, CS was not a perinatal predictor of adolescent BMI z-score, which suggests that life-style may interrupt the burden of CS on BMI z-score throughout growth. On the other hand, birth weight was the perinatal factor best associated with BMI z-score. This finding, in addition to the fact that overweight duration was found to be the best predictor of BMI z-score severity, led us to conjecture that increased birth weight may anticipate overweight onset, and consequently overweight duration in the presence of inadequate lifestyle behaviors.

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Original Article

Clinical evaluation of the effectiveness of interferential current therapy in the treatment of children with pelvic floor dyssynergia-type constipation: a randomized controlled study

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ABSTRACT

Background. Despite several treatment modalities being described for pelvic floor dyssynergia-type constipation, the clinical evaluation of interferential current therapy (IFC) has not been examined. We aimed to examine the clinical effects of IFC therapy in the treatment of children with pelvic floor dyssynergia-type constipation.

Methods. Between May 2018 and July 2019, this randomized controlled study included sixty-two children (46 boys and 16 girls) with pelvic floor dyssynergia-type constipation; their ages ranged between 7 and 15 years. The children were randomly divided into either the IFC group (n = 31) who received an active IFC therapy to stimulate the pelvic floor and external anal sphincter muscles, three times per week for four successive weeks, or the control group (n = 31) who received sham IFC stimulation. Stool-incontinence frequency per week, stool type, pelvic floor excursion, and myogenic activity of external anal sphincter were evaluated at the baseline, post-treatment, and three months after treatment termination.

Results. The baseline evaluation showed non-significant differences between the IFC and control groups ($p>0.05$). The post-treatment results showed a statistically significant difference between both groups regarding all variables, favoring the IFC group ($p<0.05$). Further, the favorable effect of IFC on all variables continued at the follow-up, three months later.

Conclusions. IFC therapy appears to improve stool-incontinence frequency, stool type, pelvic floor excursion, and myogenic activities of the external anal sphincter in children with pelvic floor dyssynergia-type constipation. These results suggest that adding IFC therapy to the medical treatment could improve the main features of pelvic floor dyssynergia-type constipation.

Key words: interferential current therapy, constipation, pelvic floor dyssynergia, electromyography.

Constipation is a frequent complaint in children, with an estimated worldwide prevalence varying from 0.3% to 8%.[1] Constipation is a symptom that is generally associated with infrequent defecation, abdominal pain, and fecal incontinence, causing significant distresses to children and their families, and impacting the health-care cost.[2]

Constipation can be categorized as primary or secondary. Primary constipation is also referred to as functional constipation, where no organic reasons are established. It accounts for 90% of children with constipation, and can be further classified into slow-transit, normal-transit and obstructed defecation.[3] While, secondary constipation is a consequence of other health problems such as diabetes mellitus,

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an underactive thyroid, hyperparathyroidism, drug, or other organic disorders such as Hirschsprung disease, or due to anatomical disorders.[4,5]

Pelvic-floor dyssynergia (PFD) is a form of obstructed defecation (primary constipation), which has also been identified as dyssynergic defecation, anismus, puborectalis paradoxes or spastic pelvic floor. PFD is described as a disorder in the capability to discharge feces from the rectum, induced by paradoxical contraction or failure to coordinate the abdominal muscles contraction and relax the pelvic floor musculatures during trying to defecate, leading to inadequate propulsive force, paradoxical anal sphincter contraction or insufficient loosening of the anal sphincter.[6,7]

There are several treatment options for PFD such as regimented eating plan, improved toileting behaviors, laxatives, behavioral therapy, surgery, and physical therapy modalities like biofeedback training of pelvic floor muscles and electrical stimulation (ES).[8,9] Although comprehensive medical and behavioral therapy for PFD, long-standing follow-up trials have shown that more than 50% of children still complain from constipation 5 years later.[10] Over the past years, different procedures of ES of the neuromuscular system have been utilized as an optional therapy for pelvic floor disorders such as urinary and fecal incontinences and overactive bladder with high improvement rates.[11,12]

Interferential current (IFC) is a kind of ES utilizing medium-frequency currents, creating low skin resistance and permitting profound tissue penetration.[13] IFC has previously been applied to improve the strength of the pelvic musculature in involuntary urination induced by overactive bladder and nocturnal enuresis.[14,15] Recently, it has been discovered to be efficient in a few clinical trials in treating chronic transit constipation in adults[16] and children.[17] It is a non-invasive, cost-efficient, and comfortable physical therapy modality that can be used safely at home.[18]

Despite some prior studies examining the effect of IFC therapy on constipation, to our knowledge, the therapeutic effectiveness of IFC has not been evaluated to treat children with pelvic floor dyssynergia-type constipation. Thus, the aim of this study was to evaluate the clinical effects of IFC therapy in the treatment of children with pelvic floor dyssynergia-type constipation by assessing the stool-incontinence frequency, stool type, pelvic floor muscles excursion, and myogenic activities of the external anal sphincter.

Material and Methods

This was a randomized placebo-controlled, double-blind, two-parallel group study conducted between May 2018 and July 2019. The Cairo University Hospitals Ethics Committee approved the study protocol (PT-018-031) at 25/2/2018. Research procedures were carried out according to ethical guidelines of the Helsinki Declaration 1964. After a full explanation of the experimental procedures, written consent was obtained from children's parents before commencement of the study.

Children included in this study were referred from the pediatric gastroenterologist to the outpatient clinic of the physical therapy department, New Kasr El-Aini Teaching Hospital. A total of 62 children (46 boys and 16 girls), aged 7-15 years, and diagnosed by a pediatric gastroenterologist with idiopathic constipation as PFD, were enrolled in the present study. Children were considered to have pelvic floor dyssynergia-type constipation if they had all of the succeeding criteria: inappropriate contraction of the pelvic floor muscles (i.e., anal sphincter or puborectalis) or less than 20% relaxation of basal resting sphincter pressure by manometry; past history of too much strain during excretion; lack of secondary reasons of constipation; lack of surgically repairable sources of PFD, like rectal prolapse; and lack of colorectal diseases representing constipation, like colorectal cancer. Children with Down syndrome, Hirschsprung disease, endocrine &

metabolic disorders such as hypothyroidism, diabetes mellitus, and neurologic & psychiatric disorders such as spina bifida, cerebral palsy, epilepsy, autism were excluded from the study.

Before commencing the study, the sample size was estimated that 27 children would be required in each group to achieve success rate differences of at least 30 % in the proportion recording acceptable power of 80%. To achieve a significant change in the myogenic activities of external anal sphincter with a standard deviation of 0.5 and a margin of error of 0.05 is 70% with 27 children in each group for two-sided equality. Therefore, the present study included a total of 66 children to account for the dropout rate of 20% because one child did not meet the inclusion criteria of the study and three children declined to participate in the study.

Enrolled children were randomized by a blinded investigator, who was not in control of the present study at any time utilizing SPSS software version 25 (IBM Corp., Armonk, NY, USA) to obtain two equal-sized groups, following a simple random allocation method. They were randomized into the IFC group (active stimulation, 31 children) or the control group (sham stimulation, 31 children). The CONSORT flow diagram of the study is presented in Figure 1.

All children underwent an initial assessment which included; lumber, pelvic, and hip range of motion, lower limbs and pelvic floor muscle strength, and generalized posture screening. In addition, a pelvic floor evaluation was performed in the form of resting muscle tone, presence or absence of anal reflex, pelvic floor muscle contraction, relaxation, and lump.[19,20]

The treatment procedures (IFC or control groups) were blinded; neither the children nor their parents were aware of the study groups. Children in both groups followed the same treatment procedures. A rechargeable battery-operated, three-in-one electrical stimulator (NexWave, Zynex Medical, Inc., USA) that delivers IFC, transcutaneous electrical nerve stimulation (TENS) or neuromuscular electrical stimulation (NMES) was used for the application of IFC therapy to the study groups.

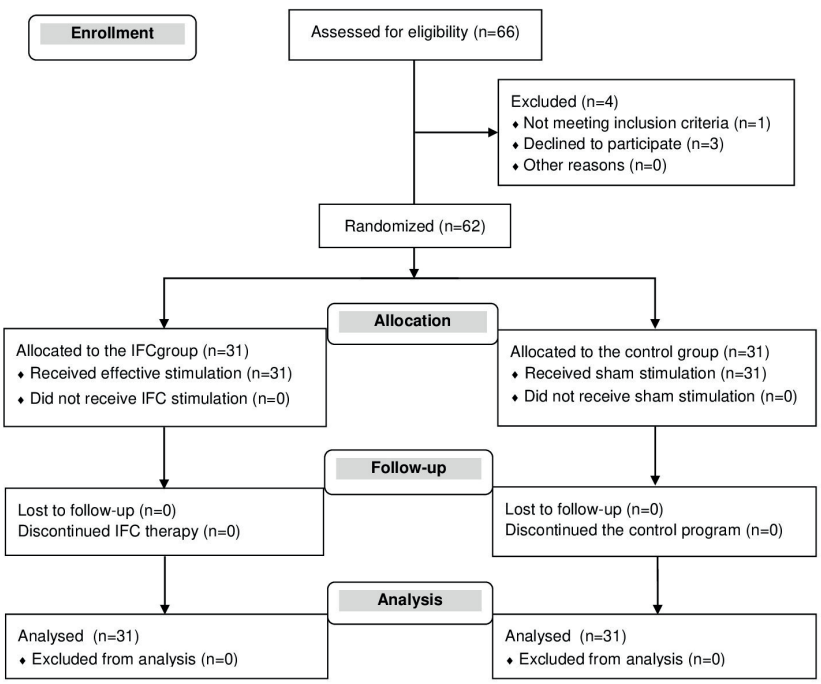

Fig. 1. The CONSORT flow diagram of the study (IFC: interferential current therapy).

In the IFC group (active stimulation)

The stimulator was adjusted to the IFC mode (symmetrical biphasic waveform). While each child was comfortably positioned on his/her back, two self-adhesive, 2.5×3.5 cm electrodes were attached to the skin over the symphysis pubis and on the opposite side over the ischial tuberosity (channel 1; delivered a frequency of 4000 Hz), and two other electrodes were put in a cross path on the skin over the other symphysis pubis and on the contralateral ischial tuberosity (channel 2, delivered a frequency of 4001-4128 Hz, drags every 15 sec). The currents produced from both channels crossed diagonally and were concentrated on the pelvic floor muscles and external anal sphincter. The currents were increased gradually until each child felt a strong comfortable sensation. The IFC stimulation was applied for a duration of 30 min/session, 3 sessions per week for 4 consecutive weeks (12 sessions). Children were instructed to immediately report any itching, burning, or other adverse effects during the treatment.

Control group (sham stimulation)

The same device and electrodes placement applied in the IFC group were used without stimulation for 30 min/session, 3 sessions per week for 4 consecutive weeks (12 sessions).

Children in both groups were instructed to try to move bowels for 5 min, two times per day, half-hour prior to eating time, regardless of their urge to stool. Also, each child was instructed to facilitate his/her pushing attempt by utilizing diaphragmatic breathing exercises and postural corrections as home exercises program for 15 min, 3 times per day.[21] During defecation, the child should be in a comfortable squat position on the toilet by putting footstool as high as from 20 to 30 cm with both feet 45-60 cm apart to assist in enhancing the angle of the rectum within the pelvis and making it easier to pass stool. All children were required to follow a balanced dietary regimen with enough calorie intake. They were instructed to have diets that were rich in vegetables & fruits, and have frequent meals. The dietary regimen secured a consumption of about 25 grams of natural dietary fibers every day for each child.[22]

The clinical evaluations of this study were the stool-incontinence frequency per week, stool type, pelvic floor muscles excursion, and myogenic activities of the external anal sphincter. These outcome measures were assessed at the baseline, post-treatment, and were followed after three months of the treatment termination.

The stool-incontinence frequency was defined as the total number of defecations in one week. The findings of the stool incontinence frequency were categorized as excellent (perfect control), good (more than 50% decline in stool frequency), fair (not deteriorating but less than 50% advancement), and poor (more frequent stool incontinence). Both excellent and good findings were classified as desirable, while fair or poor findings were classified as being undesirable. This categorization was established mainly on a recommendation from experts that a ≥ 50% decrease in stool incontinence frequency is a clinically significant result.[23]

The type of stool was reported per week, using the Bristol stool chart which was reported by parents. According to the Bristol Stool Chart, seven types of stool are reportable; types 1 and 2 indicate constipation, types 3 and 4 mean best stools because stools are easy to pass, and types from 5 to 7 indicate diarrhea.[24]

The pelvic floor muscles excursion was used to assess the coordination and relaxation of the pelvic floor muscles and external anal sphincter. Children were positioned in crook-lying and asked to contract their pelvic floor musculatures and squeeze their external anal sphincter, loosen them and then bearing down and loosen again. The caudal lengthening and external sphincter loosening throughout the tried were visually inspected during the tried bulge. The range of pelvic floor muscles excursion was categorized as: absent (0%), poor (1%-25%), fair (26%-50%), good (51%-75%), and excellent (76%- 100%).[20]

According to this test, poor and fair indicate PFD, while good and excellent mean clinical improvement.

The myogenic activities of pelvic floor musculatures and external anal sphincter were measured by electromyography Neuroscreen plus system® (EMG, Jaeger-Toennies, Hochberg, Germany) to explore muscular contradictory through assessing amplitude per turn (A/T) in mV. Children were positioned in crook-lying, skin was cleaned with alcohol to decrease skin resistance while capturing the EMG signals, surface EMG electrodes were applied as follow: the active electrode placed on the anal skin over the external anal sphincter and the reference electrode was placed at an electrically neutral area like the thigh. Each child was informed to repeatedly contract the external anal sphincter for 10-sec flowed by relaxation for 10-sec, repeated for 10 times without bearing down to relax the pelvic floor musculatures. EMG activities (A/T in mV) were measured during relaxation of the pelvic floor musculatures and external anal sphincter, in an attempt to defecate.[25] A continuous increase in myogenic activity of external anal sphincter and failure to relax the pelvic floor muscles is attributed to PFD.[26]

Statistical analysis

Data were demonstrated and analyzed in the form of means ± standard deviations. The descriptive analysis measured the differences of the mean values of the continuous variables (myogenic activities of external anal sphincter and stool incontinence frequency) between the two groups of the study using unpaired t-test while the intragroup changes were assessed using the repeated-measure ANOVA test. Categorical variables (pelvic floor excursion and stool type) were analyzed using Fisher's exact test. Statistical analysis was performed using SPSS software version 25 (IBM Corp., Armonk, NY, USA) and was assessed with the Kolmogorov-Smirnov test for normality. The significance level was set at $p < 0.05$.

Results

As revealed in Table I, baseline characteristics showed non-significant differences between both groups in gender, age, body mass index (BMI), stool-incontinence frequency per week, stool type, pelvic floor muscles excursion, and myogenic activities of the external anal sphincter ($p > 0.05$). The findings of the mean values of the amplitude per turn (A/T) in mV and the stool-incontinence frequency per week showed statistically significant differences in the IFC group ($p < 0.001$). On the other hand, the mean values of both measures in the control group revealed that there were statistically non-significant differences ($p > 0.05$) as described in Table II. The comparison between the mean values of both measures immediately after treatment and after 3-month follow-up period disclosed that there were statistically significant differences ($p < 0.001$) in favor of the IFC group (Table III).

There were statistically significant differences in numbers and percentage of children in the pelvic floor muscles excursion in the IFC group ($p < 0.05$) while, there were statistically non-significant differences in the control group ($p > 0.05$) as described in Table II. There were statistically significant differences in all numbers and percentage of children immediately after treatment, and after 3-month follow-up period in the IFC group compared to the control group ($p < 0.05$) in favor of the IFC group (Table III).

There were statistically significant differences in the number and percentage of children in stool type per week in the IFC group ($p < 0.05$) with non-significant changes in the control group ($p > 0.05$) immediately after treatment and after 3-month follow-up period (Table II). There were statistically significant differences in all numbers and percentage of children immediately after treatment, and after 3-month follow-up period in the IFC group compared to the control group ($p < 0.05$) in favor of the IFC group (Table III).

Table I. Baseline characteristics of the participants.

Measures	IFC group (n=31)	Control group (n=31)	P-value
Male/female, n/n	24/7	22/9	0.920
Age (years)	12.5 ± 4.23	13.2 ± 4.51	0.531
Body mass index (kg/m^2)	24.33 ± 2.72	25.21 ± 2.84	0.217
A/T (mV)	0.31 ± 0.14	0.33 ± 0.18	0.627
Stool frequency/week	2.3 ± 0.5	2.4 ± 0.6	0.478
PFE*, n (%)			
Excellent	0 (0)	0 (0)	0.781
Good	0 (0)	0 (0)	
Fair	23 (74.2)	21 (67.7)	
Poor	8 (25.8)	10 (32.3)	
Stool type**, n (%)			
1-2	31 (100.0)	31 (100.0)	1.000
3-4	0 (0)	0 (0)	
5-7	0 (0)	0 (0)	

A/T (mV): amplitude per turn in millivolt, IFC: interferential current, PFE: pelvic floor excursion.
*: The range of pelvic floor muscles excursion was categorized as: absent (0%), poor (1-25%), fair (26-50%), good (51-75%), and excellent (76-100%).
**: Stool types according to the Bristol Stool Chart: type 1 and 2 indicate constipation, type 3 and 4 indicate best stools because stools are easy to pass, and types from 5 to 7 indicate diarrhea.

Table II. Changes of mean values within each group before, after intervention and 3-month follow-up.

Measures	IFC group (n=31)			P-value	Control group (n=31)			P-value
	Before	After	Follow-up		Before	After	Follow-up	
A/T (mV)	0.31 ± 0.14	0.08 ± 0.01	0.11 ± 0.03	<0.0001	0.33 ± 0.18	0.29 ± 0.16	0.30 ± 0.19	0.653
Stool frequency/week	2.3 ± 0.5	5.2 ± 0.31	4.9 ± 0.37	<0.0001	2.4 ± 0.6	2.6 ± 0.5	2.5 ± 0.6	0.387
PFE*, n (%)								
Excellent	0 (0)	3 (9.7)	1 (3.2)	<0.0001	0 (0)	0 (0)	0 (0)	0.242
Good	0 (0)	24 (77.4)	22 (71.0)		0 (0)	3 (9.7)	1 (3.2)	
Fair	23 (74.2)	3 (9.7)	5 (16.1)		21 (67.7)	23 (74.2)	22 (71.0)	
Poor	8 (25.8)	1 (3.2)	3 (9.7)		10 (32.3)	5 (16.1)	8 (25.8)	
Stool type**, n (%)								
1-2	31 (100.0)	4 (12.9)	6 (19.4)	<0.0001	31 (100.0)	29 (93.5)	26 (83.9)	0.436
3-4	0 (0)	27 (87.1)	25 (80.6)		0 (0)	2 (6.5)	5 (16.1)	
5-7	0 (0)	0 (0)	0 (0)		0 (0)	0 (0)	0 (0)	

A/T (mV): amplitude per turn in millivolt, IFC: interferential current, PFE: pelvic floor excursion.
*: The range of pelvic floor muscles excursion was categorized as: absent (0%), poor (1-25%), fair (26-50%), good (51-75%), and excellent (76-100%).
**: Stool types according to the Bristol Stool Chart: type 1 and 2 indicate constipation, type 3 and 4 indicate best stools because stools are easy to pass, and types from 5 to 7 indicate diarrhea.

Discussion

The present study was designed to assess the effects of 4-week IFC therapy in the treatment of children with pelvic floor dyssynergia-type constipation. It was hypothesized that IFC therapy could provide a good prognosis and decrease the symptoms of pelvic floor dyssynergia-type constipation with improvement continued up to three months later. The results of the study confirmed our

Table III. Changes of mean values between groups after intervention and 3-month follow-up.

Measures	After intervention		P-value	3-month follow-up		P-value
	IFC group (n=31)	Control group (n=31)		IFC group (n=31)	Control group (n=31)	
A/T (mV)	0.08 ± 0.01	0.29 ± 0.16	<0.0001	0.11 ± 0.03	0.30 ± 0.19	<0.0001
Stool frequency/week	5.2 ± 0.31	2.6 ± 0.5	<0.0001	4.9 ± 0.37	2.5 ± 0.6	<0.0001
PFE*, n (%)						
Excellent	3 (9.7)	0 (0)	<0.0001	1 (3.2)	0 (0)	0.007
Good	24 (77.4)	3 (9.7)		22 (71.0)	1 (3.2)	
Fair	3 (9.7)	23 (74.2)		5 (16.1)	22 (71.0)	
Poor	1 (3.2)	5 (16.1)		3 (9.7)	8 (25.8)	
Stool type**, n (%)						
1-2	4 (12.9)	29 (93.5)	<0.001	6 (19.4)	26 (83.9)	0.005
3-4	27 (87.1)	2 (6.5)		25 (80.6)	5 (16.1)	
5-7	0 (0)	0 (0)		0 (0)	0 (0)	

A/T (mV): amplitude per turn in millivolt, IFC: interferential current, PFE: pelvic floor excursion.
*: The range of pelvic floor muscles excursion was categorized as: absent (0%), poor (1-25%), fair (26-50%), good (51-75%), and excellent (76-100%).
**: Stool types according to the Bristol Stool Chart: type 1 and 2 indicate constipation, type 3 and 4 indicate best stools because stools are easy to pass, and types from 5 to 7 indicate diarrhea.

hypothesis regarding that IFC therapy provided a significant improvement in the

stool-incontinence frequency per week, stool type, pelvic floor muscles excursion, and myogenic activities of the external anal sphincter without detecting any adverse or side effects.

The results of the study confirmed our concept that IFC therapy may improve the performance of pelvic floor musculatures and the external anal sphincter by reducing the hyper myogenic activity of these muscles which was assessed by EMG regarding the reference values. Simultaneously the stool-incontinence frequency per week was increased up to normal values, also the stool type was changed from types 1 and 2 constipations to types 3 and 4 normal defecations. The results of the visual assessment of the pelvic floor excursion after the application IFC therapy showed an increase in the numbers and percentage of children with excellent and good responses than of those with fair and poor responses. The improvements of the study outcomes were continued up to three months later after completing 4-weeks of IFC therapy.

Regarding the control group (sham IFC therapy with the prescribed home routine recommendations), there was no improvement in all outcome measures. Clarifying that both sham IFC stimulation and home recommendations were not enough to improve pelvic floor dyssynergia-type constipation in children.

In consistence with the results of the present study, previous studies confirmed that IFC therapy is efficacious in the treatment of transient constipation.[17,18,27] In the present study, the pelvic floor dyssynergia was assessed by various, easy, non-invasive, and inexpensive methods.

Initially, IFC therapy was used to control pain and reduce the instability of bladder detrusor.[28] The clinical applications of IFC were advanced by Nemec who stated that the intersecting of dual current paths produces maximal stimulation in the tissues.[29] Other suggestions could be recommended to enlighten the detected results of the present study. An improvement of the pelvic floor dyssynergia could also be provided through stimulating various nerve roots

through the self-adhesive surface electrodes that are located over symphysis pubic and over the ischial tuberosity. Consequently, the sympathetic and parasympathetic efferent fibers can target directly or indirectly through stimulating afferent fibers. Definitely, the sympathetic stimulation is identified to reduce motor activities. But also, this may cause a direct inhibition or blockade of sympathetic nerve fibers.[30] Moreover, the rhythmic contraction and stimulation of pelvic floor muscles and external anal sphincter can lead to coordination of defecation reflexes.[31]

The underlying mechanism of IFC therapy be may explained by the intersection of two medium-frequency currents which creates a third therapeutic current at the point of intersection. The advantages of utilizing medium frequency current are lowering skin impedance to electrical currents, more deep stimulation with a comfortable tingling sensation. Additionally, the proper placements of electrodes transfer the ES precisely on the target crossover region with the least adverse effects to the nearby regions.[32]

The principle of neuromodulation for applying IFC therapy was accepted for treatment of constipation caused by unknown reason and irritable bowel syndrome.[33,34] IFC therapy is supposed to stimulate somatosensory nervous plexus in the pelvic area with improvement in the voluntary and involuntary processes of defecation; apparent decrease in pain and flatulence with enhancement of bowel-movement.[33,35] IFC therapy has been used previously to treat idiopathic constipation in pediatrics and adults.[34,36] Chase et al.[37] reported that not just evacuation difficulties were decreased, but also a considerable drop in defecation periods in bathroom was noted.

In this study, different clinical evaluation methods were applied to evaluate the effects of IFC therapy in children with pelvic floor dyssynergia- type constipation. The objective evaluation of the myogenic activity of pelvic floor muscles and external anal sphincter was measured by EMG and the subjective evaluation of prognosis of the pelvic floor excursion examination in addition to the parents' evaluation of the stool-incontinence frequency per week, stool type was used to determine the prognosis of constipation in children with PFD.

There are several strengths to the present study. It is the first study to evaluate the impacts of IFC therapy in the treatment of children with pelvic floor dyssynergia- type constipation. The study findings showed that IFC therapy is an effective, save, non-invasive modality without any side or adverse effects for managing pelvic floor dyssynergia in children during the study intervention and 3-month follow-up. Comparatively, IFC therapy is a low-cost, and applicable simply so that it may be considered as a practicable therapeutic modality and recommendable to be used in the treatment of pelvic floor dyssynergia- type constipation.

The limitations of the study were the lack of long follow-up duration after 6-12 months, besides the results of the type of stool were collected by children's parents that may have a certain degree of bias. Finally, we could not be sure that all the children followed the home recommendations. Further studies should be done with longer follow-up periods to explore the efficacy and optimal duration for usage of IFC therapy.

Using IFC therapy may provide improvements of stool-incontinence frequency per week, stool type, pelvic floor muscles excursion, and myogenic activities of the external anal sphincter. Due to the convenient application of IFC therapy, it can be used in the treatment of children with pelvic floor dyssynergia-type constipation.

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Original Article

Emotion regulation in adolescents with acne vulgaris: correlates of medication adherence, clinical dimensions and psychopathology symptoms: a cross-sectional study

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ABSTRACT

Background. Acne vulgaris causes profound negative physical, psychological and social effects on self-image and a negative impact on the quality of life. Most research so far has been limited to adults, and little is known about the emotion regulation, medication adherence, clinical dimensions and psychopathology symptoms in young people with acne vulgaris.

Methods. A cross-sectional analytical study was conducted in a center in western Turkey. Ninety-six adolescents with acne vulgaris and 100 controls participated in the study. All participants completed self-report questionnaires including the Strength and Difficulties Questionnaire (SDQ), Difficulties in emotion regulation scale (DERS) and Morisky medication adherence scale-8 (MMAS-8). Acne severity was assessed with The Global Acne Grading Score (GAGS).

Results. Acne vulgaris patients showed poorer SDQ and DERS scores reflecting the emotional regulation problems and psychopathological symptoms compared to healthy controls. The percentages of high, medium and low adherence were 6%, 36% and 58% for oral medication; and 17.39%, 56.52% and 26.09% for topical medication, respectively. There were significant correlations between all SDQ subscale scores and the scores for the impulsivity subscale and total scores of DERS. A statistically significant positive correlation was found between MMAS-8 and the choice of topical/oral medication. Likewise, GAGS were correlated with three specific SDQ domains: emotional symptoms, prosocial behavior and total scores, and with three specific DERS domains: clarity, strategy and total scores.

Conclusions. Maladaptive emotion regulation strategies of patients with acne vulgaris may be associated with higher psychopathological symptoms and lower beliefs in treatment efficacy. It is important to include emotional regulation interventions to improve medication adherence and quality of health care in young acne patients.

Key words: acne vulgaris, adolescent, Difficulties in emotion Regulation Scale, medication adherence, psychopathological profile.

Acne vulgaris is a chronic inflammatory skin condition that primarily affects adolescents. It is characterized by comedones, papules, pustules, nodules, atrophic or hypertrophic scars, preferentially affecting the face and trunk.[1] The estimated worldwide prevalence of acne among young people in Europe has been reported to range from 42.2% to 73.5%.[2]

Acne vulgaris is now considered a chronic condition that not only negatively affects the physical status of an individual, but also imposes a threat to the psychological and social health of those affected.[3] Published literature has documented that acne is associated with anger, anxiety, depression; and patients with acne have difficulties in their social and functional aspects of life.[6,7] Considering the well-

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known psychosocial impact of acne vulgaris in adult patients, it can be predicted that acne vulgaris may also cause a negative impact on the psychosocial and social development of adolescents.[5]

Adolescence is a critical stage of life in the development of personal identity, which is a time marked by the interplay of biological, social and physiological factors. Observations from various sources indicate that physical appearance and body image are very important in adolescence.[4] As a disfiguring and highly visible condition, acne may cause emotional dysregulation in this group of patients. Moreover, excessive manipulation of the skin by emotionally stressed individuals can also complicate the course of acne with facial scarring that in turn leads to a vicious cycle of psychological problems.[8] Poor treatment adherence is the other common problem among acne patients which may lead to worse outcomes and greater health-care use.

According to the accumulated evidence, psychopathology can be described as a set of failures in emotional regulation. Deficits in such skills may contribute to the development and maintenance of mental disorders such as anxiety, mood disorders, depression, panic disorders, social phobia, posttraumatic stress disorder, eating disorders, substance disorders, somatoform disorders and psychotic disorders. Moreover, emotional dysregulation is accepted as the most important facet of personality disorders. Several studies emphasize that focusing on enhancing emotion regulation skills may be a promising transdiagnostic target in the treatment and prevention of mental disorders. Since the period of adolescence represents a vital opportunity to intervene to prevent the detrimental effects of poor mental health being carried through to adulthood, knowledge of the prevalence of emotion regulation difficulties in adolescents with acne vulgaris is crucial to appropriately plan emotional regulation strategies in a global health perspective and to have psychologically healthy generations.[9]

In this study, we hypothesized that acne vulgaris causes significant emotional impairment in adolescents which may also be associated with medication adherence and psychopathology symptoms. With this purpose, we analysed sociodemographic and clinical findings, emotional and behavioral aspects of psychosocial functioning and the degree of treatment adherence in a sample of Turkish adolescents with acne vulgaris.

Methods

Ethics

The study was performed in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of The Dokuz Eylul University (Date: 08.05.2019, Number: 2019/12-34). All patients and their legal guardians signed informed consent forms prior to participation in this study.

Study design

The sample size of this cross-sectional, case–control study was calculated using the OpenEpi Programme, Version 3.01. Precision (α) was set at 0.05 with a 95% confidence interval (CI), and power 80%. The estimated sample size per group came to 92. Ninety-six adolescents with acne vulgaris and 100 age- and gender-matched control subjects who were consecutively admitted to the outpatient clinics of The Dermatology Department of Dokuz Eylul University Hospital, Izmir, Turkey between January 2019 and March 2019 were enrolled in the study. The controls were subjects referred during the study period for complaints other than acne vulgaris including benign nevi on the trunk, plantar corns, calluses or warts. Apart from acne vulgaris, neither patients nor control participants had any other chronic inflammatory disorder. Inclusion criteria were as follows: aged 12–17 years and having a diagnosis of acne vulgaris. Exclusion criteria were as follows: the presence of a major central nervous system disease, cognitive

impairment, psychiatric comorbidity, presence of an additional dermatological disease affecting appearance, chronic disease or malignancy, and use of systemic medications (e.g., retinoids) that may cause psychiatric diseases. After signing the informed consent, all cases and controls were evaluated for acne by a dermatologist (I.T.K.). Thereafter, a child and adolescent psychiatrist (S.T.) conducted the psychiatric evaluation according to The Kiddie Schedule for Affective Disorder-Lifetime Version (K-SADS), which is a semi-structured interview to measure current and past symptoms of mood, anxiety, psychotic, and disruptive behavior disorders in children aged 6-18 years. K-SADS was applied to all of the participants and their psychiatric diagnoses were determined according to the DSM-V criteria. Sociodemographic findings such as age, gender, education, family type, socioeconomic level, home conditions, the status of parents, background and family history were registered in a sociodemographic data form. Acne severity, emotional regulation and clinical psychopathological profile symptom tests were performed at baseline. All acne patients received topical or oral medications. Evaluations were performed at baseline and after 4, 8 and 12 weeks of treatment. Medication adherence and treatment outcomes were assessed at week 12 (end of treatment) using a five-point scale; 0: worsening or unchanged, 1: mild improvement, 2: moderate improvement, 3: good improvement and 4: excellent improvement.

Instruments

Strengths and Difficulties Questionnaire (SDQ)

The SDQ is a screening tool developed to assess behaviors, emotions, and relationships in young children and adolescents.[12] It consists of 25 items that are grouped into five scales (Hyperactivity-inattention, Conduct disorder, Emotional problems, Peer problems, and Prosocial skills) of five items each. Of the 25 items, 14 are generally thought of as difficulties, 10 as strengths, and 1 as a neutral question. It is one of the most widely used brief screening instruments of its kind and it is used in both community and clinical samples. Higher scores on the four subscales and the total score reflect more serious problems, while higher scores on the prosocial behavior subscale mean better social behavior such as being kind to others. The total difficulties score is obtained from the first four subscales (excepting the prosocial scale). A reliability and validity study of the SDQ in the Turkish language has been performed.[13]

Difficulties in Emotion Regulation Scale (DERS)

The DERS comprises 36 items and is designed to measure difficulties in emotion regulation across six dimensions. These dimensions include non-acceptance of emotional responses (Non-acceptance), lack of emotional awareness (Awareness), difficulties engaging in goal-directed behaviors (Goals), limited access to emotion regulation strategies (Strategies) and lack of emotional clarity (Clarity).[10] Participants are asked to rate their agreement with the statements on a 5-point Likert scale ranging from 1 (almost never) to 5 (almost always). Higher scores indicated greater difficulties in regulating emotions. The Turkish version of DERS for adolescents was conducted by Sarıtas and Gencoz in 2011, and was found to be a valid and reliable instrument for clinical population.[11]

Morisky Medication Adherence Scale (MMAS-8)

The scale consists of eight questions, first seven items having a dichotomous answer (yes/no) that indicates adherent or non-adherent behavior.[14] For item 8, a patient can choose an answer on a 5-point Likert scale, expressing how often happens that a patient does not take his medications. MMAS-8 scores can range from 0 to 8 points. Cut-off values for categorizing patients as having a high, medium or low adherence rate were chosen based upon association with acne. The original MMAS-8 was translated to Turkish language and has been validated in the Turkish population in previous studies.[15]

Global acne grading system (GAGS)

This system divides the face, chest, and upper back into 6 areas: the forehead, right cheek, left

cheek, nose, chin, and torso (chest and upper back combined). Each acne lesion is described and scored as a comedo (1 point), papule (2 points), pustule (3 points), or nodule (4 points); the absence of an acne lesion in an area results in a score of 0 points. The local score for each anatomic area is determined by multiplying the score of the most severe lesion by an area factor (1 to 3), and the local scores of the 6 areas are then added together to obtain the total score. Acne severity is graded as none (total score, 0 points), mild (total score, 1–18 points), moderate (total score, 19–30 points), severe (total score, 31–38 points), and very severe (total score 39-44 points).[16]

Statistical analysis

Differences in all study variables were analyzed using the Statistical Package for the Social Sciences (IBM, NY), version 22 for Windows. Before the statistical analysis were performed, it was checked whether the data met the assumptions of the parametric tests, the normal distribution and the homogeneity of variance by using the Shapiro–Wilk test. Descriptive statistics for the obtained data were given as number, percentage and mean ± standard deviation. Variables that don't show normal distribution were evaluated by appropriate analysis. In the interpretation of the variables, descriptive statistical techniques and quantitative data analysis were used. Chi-square analysis was used to compare categorical variables between groups. The Pearson Correlation Test was used to determine the direction and level of correlation between the variables, and the results were indicated by "r" (correlation coefficient) and p value (significance level). P <0.05 was considered statistically significant.

Results

Over a period of six months, 96 acne patients and 100 controls were enrolled in the study. The acne group was made up of 46 (47.92%) males and 50 (52.08%) females with an average age of 15.22 ± 1.43 years; and the control group was made up of 43 (43%) males and 57 (57%) women with an average age of 15.01 ± 1.49. No statistically significant differences were determined between patients and controls regarding sociodemographic findings such as age, gender, education level and economic status (p >0.05).

The comparisons of behavioral problem areas between the acne vulgaris and healthy groups using the SDQ and DERS subscales are presented in Table I. Individuals in the acne vulgaris group assigned significantly higher scores to subscale items of SDQ including emotional problems, conduct problems, hyperactivity, peer relationship problems and total difficulty scores than the individuals of the control group. Prosocial behavior subscale scores in SDQ were also interestingly found to be higher in the patient group. All subscale scores and overall scale scores of DERS (except the awareness subscale) were also found significantly higher in the acne vulgaris group compared to healthy controls (p<0.001).

In the patient group, 50 patients received topical medications including antibiotics, benzoyl peroxide, retinoic acid and salicylic acid either single or in combination. The remaining 46 patients received doxycycline 100 mg/day in systemic therapy. Treatment outcomes at week 12 were excellent in 26 (56.5%), good in 12 (26.1%), moderate in 6 (13.04%) and mild in 2 (4.3%) patients in the systemic medication group; excellent in 10 (20%), good in 12 (24%), moderate in 19 (38%), mild in 8 (16%) and worse in 1 (2%) patients in the topical medication group. Patients' adherence levels were evaluated after a follow-up of 12 weeks. The percentages of high, medium and low adherence were 6%, 36% and 58% for oral medication, and 17.39%, 56.52% and 26.09% for topical medication, respectively (Table II). The overall adherence status was significantly better for topical medication than for oral medication.

Table III shows the correlations between SDQ scores, DERS scores, topical/oral medication, GAGS and MMAS-8 scores for the acne vulgaris

Table I. Strengths and Difficulties Questionnaire (SDQ), Difficulties in Emotion Regulation Scale (DERS) and Global Acne Grading System (GAGS) scores of the patients and controls.

Scales, (mean ± sd)	Acne Vulgaris (n= 96)	Controls (n= 100)	t	p
SDQ				
Emotional symptoms	4.65 ± 2.51	2.99 ± 1.44	5.703	** < 0.001
Conduct problems	4.21 ± 2.34	3.22 ± 1.63	3.447	**p < 0.01
Hyperactivity	5.41 ± 1.98	4.53 ± 1.45	3.546	**p < 0.01
Peer problems	3.71 ± 1.64	2.99 ± 1.36	3.350	**p < 0.01
Prosocial behavior	4.86 ± 2.90	2.43 ± 1.42	7.528	**p < 0.01
Total	17.97 ± 5.52	13.68 ± 3.33	6.620	**p < 0.01
DERS				
Goal	14.18 ± 3.97	13.34 ± 4.38	1.399	**p < 0.01
Strategy	15.92 ± 5.76	12.75 ± 3.30	4.751	**p < 0.01
Impulsivity	13.54 ± 4.74	11.10 ± 3.81	3.983	**p < 0.01
Awareness	15.49 ± 3.35	14.54 ± 3.59	1.913	0.057
Clarity	11.71 ± 3.38	9.88 ± 2.90	4.067	**p < 0.01
Non-acceptance	10.47 ± 3.05	9.11 ± 2.30	3.530	**p < 0.01
Total	81.71 ± 15.04	70.93 ± 12.13	5.534	**p < 0.01
GAGS	15.78 ± 6.42			

*p<0.05, **p<0.01. p values from Pearson correlation test.

Table II. Treatment-related features in patients with acne vulgaris.

Features	n (%)
Frequency of hospital visits (per the past half year)	
At least once	72 (75)
Less than once or unknown	24 (25)
Oral medication	
Experience of drug effectiveness	34 (73.91)
Experience of adverse events	12 (26.09)
Topical medication	
Experience of drug effectiveness	40 (80)
Experience of adverse events	10 (20)
Overall satisfaction with treatment	
Satisfied	59 (61.46)
Unsatisfied	37 (38.54)
Medication adherence for oral medication	
High	3 (6%)
Medium	18 (36%)
Low	29 (58%)
Medication adherence for topical medication	
High	8 (17.39%)
Medium	26 (56.52%)
Low	12 (26.09%)

Table III. Two-tailed Spearman's rank-order correlations between Strengths and Difficulties Questionnaire, Difficulties in Emotion Regulation Scale, Morisky Medication Adherence Scale and Global Acne Grading System for the Acne Vulgaris sample.

Variables	Topical/ Oral	SDQ-1	SDQ-2	SDQ-3	SDQ-4	SDQ-5	SDQ-Total	DERS-1	DERS-2	DERS-3	DERS-4	DERS-5	DERS-6	DERS-Total	MMAS-8
SDQ-1 (Emotional symptoms)	-0.039														
SDQ-2 (Conduct problems)	-0.131	0.103													
SDQ-3 (Hyperactivity)	-0.071	0.382**	0.354**												
SDQ-4 (Peer problems)	0.057	0.361**	0.089	0.194**											
SDQ-5 (Pro-social behavior)	-0.013	0.553**	0.441**	0.448**	0.366**										
SDQ-Total	-0.082	0.722**	0.612**	0.729**	0.566**	0.697**									
DERS-1 (Goal)	-0.059	0.091	0.038	0.077	-0.019	0.053	0.072								
DERS-2 (Strategy)	-0.019	0.285**	0.094	0.158*	0.110	0.158*	0.254**	0.438**							
DERS-3 (Impulsivity)	0.031	0.285**	0.187**	0.248**	0.170*	0.276**	0.340**	0.424**	0.470**						
DERS-4 (Awareness)	0.053	0.084	0.191**	0.064	0.115	0.114	0.174*	-0.002	0.080	0.008					
DERS-5 (Clarity)	0.034	0.209**	0.120	0.125	0.051	0.200**	0.204**	0.122	0.440**	0.343**	0.364**				
DERS-6 (Non-acceptance)	-0.038	0.093	0.037	0.026	0.124	0.075	0.104	0.408**	0.521**	0.442**	-0.163*	0.143*		,	
DERS-Total	-0.008	0.298**	0.168*	0.205**	0.171*	0.249**	0.324**	0.631**	0.780**	0.715**	0.321**	0.639**	0.586**		
MMAS-8	0.325**	-0.042	-0.146	-0.149	-0.046	-0.136	-0.148	0.057**	0.083**	-0.012	-0.058	0.164	0.062	0.079	
GAG-Score	0.121	0.142*	0.110	0.091	0.054	0.204**	0.160*	0.086	0.186**	0.103	0.152	0.179*	0.068	0.175*	0.089

n, number; SD, standard deviation; SDQ, Strengths and Difficulties Questionnaire; DERS, Difficulties in Emotion Regulation Scale, GAG, global acne grading system; MMAS-8, Morisky Medication Adherence Scale.

**.Correlation is significant at the 0.01 level (2-tailed).

*.Correlation is significant at the 0.05 level (2-tailed).

sample. There were significant correlations between all SDQ subscale scores and the scores for the impulsivity subscale and total scores of DERS. On the other hand, the DERS and SDQ subscale scores correlated with each other except some subscale scores. A statistically significant positive correlation was found between MMAS-8 and the choice of topical/oral medication. Likewise, GAGS was correlated with three specific DERS domains: clarity, strategy and total scores; and with three specific SDQ domains: emotional symptoms, prosocial behavior and total scores.

Discussion

Although acne vulgaris has long been regarded as an adolescent skin condition without significant sequelae, it is now considered a chronic disease with negative psychological and sociological impacts on those affected.[17] Considering the high prevalence of the condition, the profound impact of the disease on patients' well-being cannot be overemphasized. Although health-related quality of life and emotional state have been widely studied in the field of acne patients, no previous study comprised a detailed clinical psychiatric evaluation in adolescents. In this study, we investigated the psychopathology symptoms and related clinical dimensions, emotion regulation and medication adherence in young people with acne vulgaris. To our knowledge, we demonstrated for the first time significantly higher impairment on the SDQ and DERS scores that could explain a set of inabilities in adolescents with acne vulgaris in their social interactions compared with age and sex-matched control subjects.

Emotion regulation refers to the process of how, which, and when negative and positive emotions are expressed and experienced and may include strategies such as suppression and/re-appraisal of stressful conditions.[18] Emotions help inform others about one's internal states that are essential for relationships and are the crucial determinants of social and psychological well-being. In our study, all dimensions of emotion regulation difficulties were found to be significantly elevated among adolescents with acne vulgaris compared to the controls. These parameters were also found to be correlated with the examined psychopathological symptoms of the SDQ, such as the emotional symptoms, peer problems, hyperactivity-inattention and conduct problems, and with the severity of acne vulgaris. It has been well known that, emotion regulation deficits are predictive of increased risk for mental health disorders, and a failure to meet any of these dimensions may result with the development and maintenance of different psychopathologies, such as anxiety, depression, addictive behaviors, eating disorders, deliberate self-harm and suicidal ideation.[19] Previous studies have shown that 18-44% of acne patients have clinically evident depression and anxiety leading to a decrement in productivity and performance in work or school.[20] Furthermore, acne vulgaris has been shown to contribute to suicidal thoughts and behavior in 6-7.2% of patients, which is much higher than that seen in other skin disorders.[21,22] Our findings are in accordance with the results of previous studies indicating that acne vulgaris negatively influences social interactions by challenging interpersonal relationships and limiting opportunities to engage in social interactions.

As a facial and disfiguring chronic disease, severe acne may be responsible for a significant source of emotional distress and may cause feelings of shame, humiliation and social stigmatization in patients. On the other hand, a paucity of high-quality research data indicates that stress can cause or exacerbate acne lesions by itself, which creates a classic "chicken and egg" dilemma. Stress has often been associated as a result of the physical changes experienced by the patient suffering from acne, and the body's response to stress by inducing the secretion of some neuropeptides and hormones, such as cortisol, catecholamines, corticotropin releasing hormone and substance P, which contribute to the development and severity of acne, eventually leading to a vicious circle.[23] In this study, acne severity was found to be directly

correlated with the total scores of the SDQ and DERS, supporting the relationship between acne and stress. Correlational patterns were also found between the emotional symptoms and the hyperactivity, peer problems areas of the SDQ subscale; and the strategy, impulsivity, clarity and total areas of the DERS subscale indicating that individuals with acne vulgaris tend to express their unstable emotions by suppressed and disagreeable behaviors.

Determination of factors related to medication adherence in acne is critical because identification of these factors associated with adherent and non-adherent behavior is important for positive patient outcomes. The limited number of research on improving the medical adherence for individuals with acne vulgaris shows that the accompanying psychiatric comorbidity is one of the strongest predictors of poor compliance with the treatment.[24] This correlational pattern between medication adherence and the goal and strategy subscales of the DERS was also detected in young acne patients in our study. The inability to behave in accordance with goals in the presence of negative affect or to access to emotion regulation strategies that are perceived to be effective for feeling better in these group of patients with acne vulgaris may be contributing to the lower beliefs about drug efficacy, treatment refusal, under treatment and dissatisfaction. A full understanding and management of these factors are critical steps in the process of developing effective therapeutic strategies.[25]

This study has certain limitations. First, consecutive sampling may cause sampling bias. Second, our samples came from a general hospital and may not represent the general population. Third, our study was a single centre study, so further large-scale multicenter studies are necessary to better understand the physiological burden associated with the disease.

In conclusion, acne vulgaris has a negative impact on adolescents. It is necessary to know that dermatological diseases affecting patients during their childhood or adolescence will have a significant effect on the formation of their personality. Considering that difficulties in school, family life and personal relationships during these ages may cause long-term sequelae such as psychiatric morbidities, integration of assessment of clinical dimensions and psychopathology symptoms in the treatment process, and emotional regulation interventions might be beneficial for prevention of invisible effects of acne. The patient's psychological distress is also correlated with the severity of the disease, which can be modified by effective treatments. Therefore, it is important to take care of young people and their opinions about their skin condition.

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Original Article

Pediatric Bell's palsy: prognostic factors and treatment outcomes

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ABSTRACT

Background. Idiopathic facial paralysis or Bell's palsy is the most common type of peripheral facial paralysis. Children with Bell's palsy is an uneasy situation for the family and physician with questions about the etiology, treatment options and the healing process. Here, we aimed to compare the epidemiologic features and prognostic factors of patients with Bell's palsy aged <18 years.

Methods. Records of patients with Bell's palsy who were admitted to our clinic between January 2008 and December 2017 were evaluated.

Results. Forty-seven patients with Bell's palsy were included to this study. The patients' ages varied between 7 and 17 (14.7±2.5) years. At the end of at least 6 months of follow-up, 32 (68.1%) of the patients presented with House Brackmann (HB) grade 1 facial paralysis, while 12 (25.5%) of them had grade 2 and 3 (6.4%) of them had grade 3 facial paralysis. Mean neutrophil-to-lymphocyte ratio (NLR) in patients with advanced grades (grade 4, 5, 6) was higher, compared to that of patients with grade 2 and 3 (4.10 ± 1.06 vs 1.34 ± 1.02 ($p < 0.001$).

Conclusions. In our study, the response rate to treatment was high. In differential diagnosis, congenital anomalies, malignancy, trauma, middle ear infection and surgery should be considered. In addition, NLR at admission can be considered as a prognostic factor.

Key words: Bell palsy, children, inflammation, neutrophils, neutrophil-to-lymphocyte ratio, prognosis.

Acute idiopathic peripheral facial paralysis (PFP) or Bell's palsy (BP), can be seen in all age groups.[1] In general, its frequency is considered to be 20-30/100,000.[1] It is also the most common cause of unilateral facial paralysis and constitutes 60-75% of paralysis of the facial nerve.[2,3] Nine percent of the patients have a previous history of paralysis.[1] Bilateral paralysis is observed in 0.3 % of the patients.[1] Although the incidence of BP in childhood is not known clearly, Peitersen reported that it is seen in 14% of the patients under 15 years of age, among 2500 BP patients.[4] BP prognosis is usually good and over 85% of patients have a significant improvement in 3-4 weeks.[4]

Genetic factors, infection and autoimmune diseases that cause vascular ischemia and inflammation, temporal bone fractures, neoplastic lesions can be observed in the ethiology.[4] Speech and social communication may be affected due to the weakness of facial muscles; most importantly, eye and vision may deteriorate due to decreased corneal reflex.[5]

Bell's palsy in children is an uneasy situation for the family and physician with questions about the etiology, treatment options and the healing

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process.[6] In these patients, history taking and neuro-clinical examination should be performed carefully; and audiological evaluation, biochemical analysis and radiological imaging methods should be followed if possible.[6] These evaluations are important to reveal the possible cause of paralysis.[6] Although there is no universally accepted treatment modality for the treatment of BP in children, corticosteroids, antiviral agents and decompression surgery seem to be the best alternatives at the moment.[6] Corticosteroids are the most commonly used agents.[6] In particular, initiation of corticosteroid therapy in the first week of the disease improves muscle function and decreases complication rates.[6] Although antiviral agents are useful in the herpes zoster facial paralysis, its usefulness is limited in idiopathic facial paralysis.[6,7] Surgical treatment may be considered in cases where there is no clinical improvement or no regeneration is observed with electrophysiological tests, although with controversial results.[6,7]

Bell's palsy is the most common cause of PFP in childhood, and proper management of BP is essential for pediatricians, otolaryngologists and general practitioners since it can be a devastating situation for the family.[6,7] In this study, epidemiological characteristics, treatment responses and possible prognostic factors of pediatric patients diagnosed with BP were investigated.

Material and Methods

Study design and patients

We evaluated the records of patients aged <18 years who received treatment for PFP at our clinic between January 2008 and December 2017, with a minimum follow-up period of 6 months. The institutional University of Health Sciences, İzmir Bozyaka Training and Research Hospital review board approved this retrospective study (04/17.10.2018).

Age, sex, duration from the onset to the treatment, previous history of facial palsy, such as pain and skin eruption around the affected ear, hyperacusis, upper respiratory tract infection history, family history of facial paralysis, neurootologic examination and laboratory tests (complete blood count, serum biochemistry panel, serologic tests for herpes simplex virus-1 [HSV], varicella zoster virus [VZV], mumps virus and Mycoplasma pneumoniae), radiologic tests such as brain magnetic resonance and/or computed tomography, and treatment results of all patients were evaluated. Peripheral facial paralysis without an apparent specific etiology was considered as BP. During the first consultation and evaluation of treatment outcomes, the House-Brackmann (HB) facial nerve grading system was used to identify the degree of paralysis (Table I).[8] In patients diagnosed with progressive facial paralysis, only the last grade of facial paralysis was taken into consideration. Moreover, all patients were

Table I. House Brackman facial palsy grading system.

Grade	Appearance	Forehead	Eye	Mouth
1	Normal	Normal	Normal	Normal
2	Slight weakness Normal resting tone	Moderate to good Movement	Complete closure Minimal effort	Slight asymmetry Slight weakness
3	Non-disfiguring weakness Normal resting tone	Slight to moderate Movement	Complete closure Maximal effort	Maximal effort
4	Disfiguring weakness Normal resting tone	None	Incomplete closure	Asymmetric with maximal effort
5	Minimal movement Asymmetric resting tone	None	Incomplete closure	Slight movement
6	Asymmetric	None	None	None

assessed by an ophthalmologist and physical therapist for designing a suitable physical therapy program that included facial muscle training. All patients underwent an initial blood test prior to treatment, and the neutrophil-to-lymphocyte ratio (NLR), thrombocyte-to-lymphocyte ratio (TLR) and mean platelet volume (MPV) levels of all patients were examined. At the 6th month follow-up, HB grade 1 was considered as "complete" recovery and HB grade 2 as "almost complete" recovery. If the patients had a facial paralysis HB grade 3 or over at the last follow up visit, they were considered as "partial" recovery if they showed an improvement in terms of HB grading; and "no recovery" if there was no improvement.

Treatment protocols

At our clinic, the treatment for patients with BP includes oral or intravenous methyl prednisolone (1 mg/kg/day) at tapered doses for 14 days. Further, antiviral therapy was included for the treatment of patients with a positive recent upper respiratory tract infection history or positive serologic test results for aforementioned viruses.

Statistical analysis

Descriptive statistics (arithmetic mean, median, minimum, maximum, standard deviation, and standard error) were first calculated on the basis of the obtained data. Spearman's rho correlation analysis, Kruskal–Wallis test, and Mann–Whitney *U*-test were performed in accordance with the data distribution. $p<0.05$ was considered statistically significant. The Statistical Package for the Social Sciences (SPSS) software was used for statistical analysis.

Results

Patient characteristics

Of the 51 patients with PFP, 4 (7.8%) patients with different etiologic factors were excluded. Of these excluded patients, two was secondary to acute otitis media, one had acoustic neuroma and one patient had osteopetrosis. The remaining 47 patients with PFP were included to the study with the diagnosis of BP.

Period from the onset of the disease to hospital admission ranged from 1 to 10 days (mean, 3.48 ± 0.21) days. Three (6.3%) patients were diagnosed with progressive facial paralysis while five (10.6%) patients had a positive family history. Nine (19.1%) patients had a history of upper respiratory tract infection, accordingly received antiviral therapy.

Three (6.3%) cases of recurrent facial paralysis were observed. The patients' ages ranged from 7 to 17 (mean, 14.7 ± 2.5) years. Twenty-three (48.9%) of the patients were boys and 24 (51.1%) of them were girls. The follow-up period ranged from 6 to 108 months (mean, 61.23 ± 31.83). Paralysis was observed on the right side in 23 of the patients (48.9%); meanwhile, 51.1% (n = 24) of the patients experienced paralysis on the left side.

HSV-1 DNA was detected in two of nine patients with a history of upper respiratory tract infection and mycoplasma Ig M serology was positive in one patient.

When facial paralysis was investigated in terms of seasonal distribution, 17 (36.2 %), 12 (25.5%), 12 (25.5%), and 6 (12.8%) patients presented with paralysis during the spring, winter, summer, and fall, respectively.

Patients' initial and last facial paralysis grades are summarized in Table II. Overall, 93.6% of the children had complete or almost complete recovery, with the rest of them showed partial improvement. No association was found between gender, side of the paralysis and season of the paralysis and pre-treatment and post-treatment grades ($p>0.05$). Cranial and/or temporal magnetic resonance examination of 6 patients who did not exhibit complete recovery after 3 weeks of treatment revealed no pathologic lesion.

Table II. Clinical grades of patients (N = 47) according to House Brackman facial palsy grading system.

Clinical grades	Frequency (N)	Percent
Initial		
2	1	2.1
3	21	44.7
4	12	25.5
5	10	21.3
6	3	6.4
Follow-up		
1	32	68.1
2	12	25.5
3	3	6.4

Laboratory results

The mean NLR, TLR and MPV at initial admission were 2.69 ± 1.57, 147.33 ± 76.38, and 9.01 ± 1.71 fL, respectively. Mean NLR in patients with advanced grades (grade 4, 5, 6) was higher (4.10 ± 1.06), compared to that of patients with grade 2 and grade 3 (1.34 ± 1.02); p <0.001 (Fig. 1). No statistically significant difference was found for TLR and MPV (p = 0.146, p = 648, respectively).

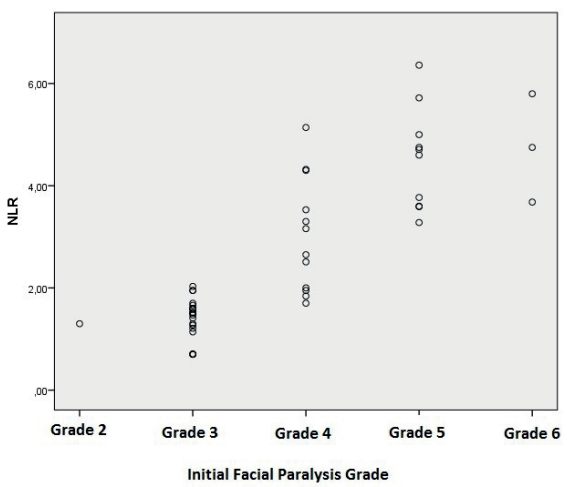

Fig. 1. Neutrophil/lymphocyte ratio (NLR) according to initial facial paralysis grade (House Brackmann). Patients with advanced grades (grade 4, 5, 6) had higher (4.10 ± 1.06) NLR, compared to that of patients with grade 2 and grade 3 (1.34 ± 1.02); p<0.001

Discussion

BP is the most common cause of unilateral facial paralysis and accounts for 60–70% of all facial nerve paralysis cases.[9] Likewise, BP is the most common cause of PFP in childhood, and proper management is essential for the medical professionals since parents of the patients are usually panicky and demanding.[9]

The prognosis of BP is extremely good, more than 85% of all patients exhibit complete/near complete recovery in 3 to 4 weeks.[9] Treatment is usually based on steroids and antiviral agents and surgical treatment is generally kept for rare cases where no regeneration based on electro physiologic tests or if no clinical recovery is observed.[9]

Cha et al.[9] reported that BP was the most common condition in childhood facial paralysis (66.7 %) and cases were mostly (62.5%) presenting with HB grade 5 facial paralysis. At the end of the 6-month follow-up, facial paralysis regressed to HB grade 1 or 2 in 91.6% of the patients. Similarly, May et al.[10] reported 170 patients under 18 years of age with PFP, and BP was the most common cause (42%), followed by trauma (21%), infection (13%), congenital causes (8%) and malignancy (2%). In other studies, the incidence of PFP secondary to acute otitis media was reported between 4% and 37% and the incidence of tumor-induced PFP was between 2% and 12%.[11-13]

BP was the cause of peripheral facial paralysis in 93.1% of the patients in the present study. This higher BP rate in patients with peripheral facial paralysis compared to previous studies may be attributed to easier access of the families to healthcare services, hence early diagnosis and proper management of acute otitis media and other possible causes in children in recent years.

Although recurrent facial paralysis is rare in children, the incidence of recurrent PFP has been reported in 3-15% of studies.[11-14] In our study, 3 patients (6.3%) had recurrent BP with two patients had two facial paralysis attacks and one patient had three facial paralysis attacks.

The family history of all these three patients was positive. In the literature, the family history of BP varies between 8.5% and 10.3%,[15,16] which was also positive in five (10.6%) patients in our series. It is essential to have a detailed family history in patients with PFP, since the recurrence of paralysis is significantly higher in patients with family history.

Facial paralysis usually onsets suddenly, but it can be seen progressively in some cases.[16] Kasse et al.[17] reported the rate of sudden onset facial paralysis as 72.5% while it was progressive in 27.5% of the patients in their study with 1521 BP patients in all age groups. They reported that the progressive course was associated with significantly worse prognosis.[17] In our study population, progressive facial paralysis was detected in three (6.3%) patients and complete recovery was observed in the 6th month in all these patients. Although patient numbers are limited, pediatric patients with progressive paralysis seem to heal better.

We did not observe any bilateral cases in our series, accordingly bilateral BP is very rare in the literature.[1,17,18] Most studies did not show any gender differences among children with PFP[18-21] as in our study, in which no gender difference was found both in incidence and treatment responses. It has been suggested that, there might be a seasonal distribution of the paralysis with different results. While Peitersen et al.[4] did not indicate a seasonal difference, Devriese et al.[18] reported that BP was more common in winter. We did not find a significant difference in seasonal distribution of pediatric patients with PFP ($p>0.05$).

Dhiravibulya[19] reported a complete recovery (HB grade 1) rate (61.7%) and a nearly complete recovery rate (HB grade 2) (38.2%) in 39 pediatric patients at the end of 7 months. Chen and Wong reported that all cases except for one (3.1%) patient were fully cured (complete-HB grade 1; almost complete-HB grade 2) and complete recovery rate in the first 3 weeks was 68.8% in their study.[20] In our study, complete recovery was achieved in 32 patients (68.1%), almost complete recovery was achieved in 12 patients (25.5%) at the end of 6 months of follow-up, which are similar to the previous studies. These high recovery rates emphasize the importance of proper treatment, since sequalae of PFP might be psychologically catastrophic to children and their parents, even though it is not a life threatening disease.

Epstein-Barr virus, cytomegalovirus, mumps virus, rubella virus, varicella zoster virus, coxsackie virus, M. pneumoniae and herpes simplex virus can play a role in the etiology of PFP.[20,21] Kang et al.[22] found that the combined treatment with acyclovir and prednisolone in advanced grade (HB grade 5, 6) patients was higher than that of prednisolone alone. In our study, HSV-1 DNA was detected in 2 of 9 patients with a history of upper respiratory tract infection and M. pneumoniae Ig M serology was positive in 1 patient. Patients with herpes simplex were treated with acyclovir plus steroid treatment, patient with mycoplasma for 10 days with standard steroid plus clarithromycin treatment in patients with after the treatment, complete improvement was observed in all 3 patients.

Corticosteroids are still the most commonly used agents in the treatment of PFP.[23,24] Sullivan et al. reported a high recovery rate of 90% with prednisolone monotherapy in BP.[23] It is a difficult clinical decision to discontinue a childhood case without treatment even in low grade paralysis that could be usually followed-up without any treatment in adults, and it should be taken into consideration that lack of treatment will have a lasting effect on the life of the child.[25] Although steroid related side effects can be used as a data against steroid use, none of the patients in our study had any apparent adverse effects of steroid therapy in therapeutic doses.[25] We therefore suggest steroid therapy to all pediatric patients with BP. An MRI scan should also be performed if there is no response to proper treatment for more than 3 weeks, in cases with recurrent PFP, in children with additional neurological abnormalities and when there is a suspicion of malignancy.[26]

In our study, three patients with progressive facial paralysis showed no pathology in cranial MRI and CT examinations; however, a 16-year-old boy with HB grade 3 PFP who had no improvement after 2 weeks of treatment was found to have osteopetrosis in the cranial CT and MRI examinations. No improvement in 6th month control was observed in this patient. A 15-year-old boy with HB grade 4 left PFP who had not recovered after 3 weeks of standard treatment was found to have a soft tissue consistent with Schwannoma, measured approximately 5x3mm in the left internal acoustic canal in the MRI. Complete recovery was achieved in the follow-up controls. No increase in lesion size was observed in the control MRI's that were performed annually.

Complications such as synkinesis, or keratitis can be seen after BP.[27] We observed synkinesis in 2 patients (4.2%) and hemifacial spasm in 1 patient (2.1%). Although these are rare complications, patients have to be followed up closely for a couple of years even if complete recovery is achieved.

Several recent studies have utilized the NLR and TLR as inflammation markers.[28,29] Reasonably, a high NLR was reported among patients with BP.[28,29] Ozler et al.[30] reported considerably high levels of NLR in patients who did not recover from facial paralysis within 3 months of treatment follow-up. Moreover, a correlation was found between the grades of facial paralysis and NLR upon admission.[30] We observed significantly high rates of NLR in patients with a high onset grade of facial paralysis; however, no significant correlation was observed between the MPV, TLR, and FBG levels and facial paralysis degree. We also found that higher NLR rates were associated with poor prognosis. NLR can be suggested as an inflammatory marker that may predict the prognosis of facial paralysis in children, even in the early periods of the paralysis.

BP in children is a relatively rare situation compared to adults and causes significant concerns in doctors and parents due to functional and aesthetic concerns. In differential diagnosis, congenital anomalies, malignancy, trauma, middle ear infection and surgery should be considered. High NLR can be used as poor prognostic marker in BP. Steroid treatment to all patients and antiviral agents in selected cases promise excellent results.

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Original Article

The effect of warts on quality of life in Turkish pediatric patients

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ABSTRACT

Background. The negative effect of genital and extragenital warts on adult patient quality of life (QoL) is well known; however, the literature lacks data on the effect of extragenital warts on Turkish pediatric patient QoL. The aim of this study was to determine the effect of extragenital warts that persist for ≥6 months on Turkish pediatric patient QoL, as well as to determine the relationship between patient demographic and clinical characteristics, and QoL.

Methods. The Pediatric Quality of Life Inventory Version 4.0 (PedsQL™ 4.0) was administered to 85 children and their parents (patient group), and 85 age- and gender-matched children without any skin disease and their parents (control group). Children's Dermatology Life Quality Index (CDLQI) was administered to the patients. Higher CDLQI and PedsQL™ are indicative of lower QoL.

Results. Median wart duration and median age at the time of wart onset was 12 months (range 6-84) and 10 years (range 1-16), respectively. In the patient group mean (±Standard deviation [SD]) CDLQI score was 5.20 ± 5.97, and warts had the greatest negative effect on CDLQI symptoms and feelings scores. Mean (±SD) PedsQL™ total score was higher in the affected patients than that for the controls (23.42 ± 12.33 versus 15.81 ± 7.37, P<0.001), and school, social and emotional functionality subscales exhibited the greatest differences between these groups. Mean (±SD) PedsQL™ total score for the patients' parents was higher than that for the controls' parents (25.94 ± 12.49 versus 17.81 ± 6.87, P<0.001), and social and emotional functionality subscales exhibited the greatest difference between these groups.

Conclusions. The findings show that Turkish children with warts that persist for ≥6 months had lower QoL than the controls.

Key words: dermatology, infectious diseases, quality of life.

Warts are common benign skin and mucosa lesions caused by human papillomavirus that can occur anywhere on the body. The disease is more common in children than in adults.[1] The prevalence of cutaneous warts in children varies from 3.3% in the US[2] to 24% in Australia[3] and 33% in Netherlands.[4]

Since both genital and extragenital warts can adversely affect patient quality of life (QoL), it is important for clinicians to understand the effect of warts on patient QoL and improve clinician awareness of the negative effects of skin diseases on QoL.

Most relevant research has focused on QoL in adults with genital warts.[5-8] The persistence and recurrence of genital warts, treatment resistance, and the duration of treatment may have profound negative effects on patient QoL. The effect of skin diseases, including warts, on QoL in children has been reported to be impaired in cross-validation or validation of QoL questionnaire studies with limited number of wart patients.[9-12] This study aimed to determine the effect of extragenital warts on QoL in Turkish pediatric patients, as well as

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to determine the relationship between patient demographic and clinical characteristics, and QoL.

Material and Methods

Study design and patient selection

The Pediatric Quality of Life Inventory Version 4.0 (PedsQL™ 4.0) Generic Core Scales was administered to 85 children aged 8-17 years with warts and their parents (patient group), and 85 age- and gender-matched children without any skin disease and their parents (control group) in this case-control study. Although patients were matched for age and gender, the parents of patients were not matched. In addition, the Children's Dermatology Life Quality Index (CDLQI) was administered only to the patients. All patients had warts that persisted for ≥6 months, were aged 8-17 years, and did not have any learning or intellectual disability. The control group included healthy siblings of any patient aged 8-17 years who were examined for another dermatological disease other than warts. The patients and controls were divided into 2 age subgroups (8-12 and 13-17 years). Demographic data, disease duration, age at the time of disease onset, lesion number and localization, and previous and current treatments were noted. The study protocol was approved by the Hacettepe University Ethics Committee (G-14/258, June 4, 2014), and written informed consent was obtained from all the children's parents. All study procedures were performed in accordance with the ethical principles of the 1964 Declaration of Helsinki.

Data collection and measurements

The 10-item CDLQI was used to measure the effects of warts on QoL in children. The CDLQI is a commonly used dermatology-specific tool used to evaluate the effect of skin disorders on QoL in children and has been used in many studies.[13,14] The CDLQI includes the following subscales: symptoms and feelings (items 1-2), leisure (items 4-6), school or holidays (item 7), personal relationships (items 3 and 8), sleep (item 9), and treatment (item 10). The patient group were instructed to answer the CDLQI items by their selves according to how their warts affected them during the preceding week. The CDLQI total score was calculated by summing the scores of each of the 10 items; the minimum score is 0, versus a maximum score of 30. CDLQI total scores were then assigned to 5 score bands, as previously reported: 0-1, no negative effect on QoL, 2-5, a small negative effect on QoL, 6-10, a moderate negative effect on QoL, 11-20, a large negative effect on QoL, and 21-30, an extremely large negative effect on QoL.[15] Permission to use the CDLQI was obtained from Professor Andrew Y. Finlay.

The PedsQL™ 4.0 Generic Core Scales is used to assess QoL in children aged 2-18 years and includes 23 items and 4 subscales; physical health (8 items), emotional functionality (5 items), social functionality (5 items), and school functionality (5 items).[16] The patients, controls, and their parents were instructed to provide answers to the items based on how much the warts affected the patients during the preceding month. The total PedsQL™ score is calculated by summing the subscale scores; the minimum score is 0, versus a maximum score of 92. Higher PedsQL™ scores indicate poorer QoL. Permission was obtained from J.W. Varni to use the PedsQL™ in this study.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows v.21.0 (IBM Corp., Armonk, NY). Descriptive statistics were used to describe the participants' demographic characteristics. The Shapiro-Wilk test was used to determine the normality of the distribution of numeric variables. Data is expressed as mean ± standard deviation (SD) or median (range) as appropriate. The Mann-Whitney U test was used to compare PedsQL™ scores between patients and controls, as well as between their parents. Additionally, the Mann-Whitney U test was used to identify differences in CDLQI scores according to age at the time of disease

onset and disease duration, and to identify differences in PedsQL™ scores according to lesion localization, gender, and the presence of previous therapies. Spearman's correlation coefficient was used to determine the correlation between CDLQI and PedsQL™ scores, and number of lesions, whereas the Kruskal-Wallis test was used to identify differences in CDLQI and PedsQL™ scores, according to treatment modalities. The level of statistical significance was set at $p < 0.05$.

Results

The study included 85 patients (44 females and 41 males) and their parents (n= 85) and 85 healthy controls (44 females and 41 males) and their parents (n= 85). Warts were most commonly located on the hands (42.4%), followed by the face (41.2%) and feet (32.9%). Table I summarizes the demographic and clinical characteristics of the patients.

Table I. Demographic and clinical characteristics of the participants, and CDLQI total and subscale scores.

Data	Patients (n = 85)
Age in years, median (range)	12 (8-17)
8-12 years, n (%)	49 (57.6%)
13-17 years, n (%)	36 (42.4%)
Gender, n (%)	
Male	41 (48.2%)
Female	44 (51.8%)
Disease duration in months, median (range)	12 (6-84)
Age at the time of disease onset in years, median (range)	10 (1-16)
Number of lesions, median (range)	3 (1-50)
Lesion site, n (%)	
Hands	36 (42.4%)
Face	35 (41.2%)
Arms	5 (5.9%)
Legs	4 (4.7%)
Feet	28 (32.9%)
Previous treatments, n (%)	
Cryotherapy with liquid nitrogen	41 (48.2%)
Topical salicylic acid	14 (16.5%)
Other therapies (TCA, tea tree oil, and topical tretinoin cream)	6 (7.1%)
No treatment	24 (28.2%)
Family history of warts, n (%)	
Yes	32 (37.6%)
No	53 (62.4%)
CDLQI Total score, mean ± SD	5.20 ± 5.97
Symptoms and feelings	1.66 ± 1.53
Leisure	1.27 ± 2.17
School or holidays	0.47 ± 0.87
Personal relationships	0.79 ± 1.39
Sleep	0.39 ± 0.77
Treatment	0.59 ± 0.93

IR: interquartile range, TCA: trichloroacetic acid, n: number, %: percentage, CDLQI: Children's Dermatology Life Quality Index.

CDLQI score

Among the patients, the mean (±SD) CDLQI score was 5.20 ± 5.97. In 32.9% (n= 28) of patients the negative effect on QoL was categorized as a small, whereas warts had extremely large effect on QoL in 5.9% (n= 5) of the patients (Fig. 1).

CDLQI subscale analysis showed that warts had the greatest negative effect on CDLQI symptoms and feelings scores, with a mean (±SD) score of 1.66 ± 1.53, whereas school or holidays, leisure, personal relationships, sleep, and treatment subscales were not affected by warts in any of the patients (Table I). There was not a significant correlation between CDLQI score, and age, age subgroup, age at the time of disease onset, lesion site, disease duration, treatment option, or previous treatments; however, there was a weak positive correlation between the number of lesions and CDLQI score (r=0.26, P=0.02).

PedsQL™ 4.0 Generic Core Scales

The mean (±SD) PedsQL™ total score was higher in the children in the patient group than in those in the control group (23.42 ± 12.33 versus 15.81 ± 7.37, P<0.001). The mean (±SD) school functionality subscale score (6.20 ± 3.19 versus 4.11 ± 2.67, P<0.001), social functionality subscale score (4.38 ± 3.63 versus 1.69 ± 1.67, P <0.001), and emotional functionality subscale scores (5.56 ± 3.98 versus 4.05 ± 2.69, P= 0.029) exhibited the greatest difference between the children in the patient and control groups (Table II and Fig. 2).

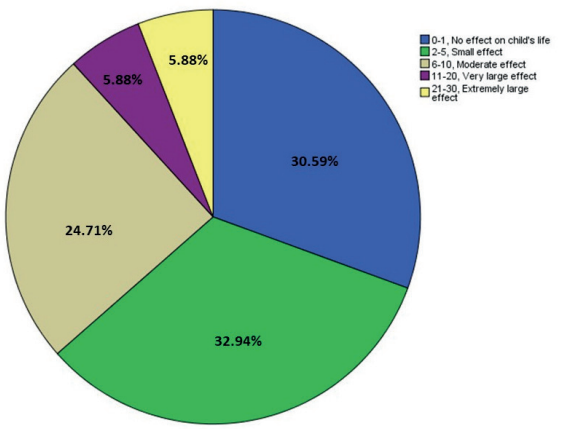

Fig. 1. Distribution of the patients according to CDLQI score.

The mean PedsQL™ total score in the patients' parents was higher than in the controls' parents (25.94 ± 12.49 versus 17.81 ± 6.87, P<0.001). The mean social functionality and emotional subscale scores exhibited the greatest difference between the parents of the patients and controls (5.07 ± 3.68 versus 2.19 ± 2.22, P<0.001 and 6.54 ± 4.05 versus 4.09 ± 2.58, P<0.001, Table II and Fig. 2). There was not a significant correlation between PedsQL™ score (patients, parents, and controls), and age, age group, and gender. There was not a significant correlation between PedsQL™ total score (patients), and lesion number, disease duration, age of disease onset, treatment option, or previous treatments. The localization of warts did not significantly affect the PedsQL™ total scores of the patients. However, the presence of warts on legs significantly decreased PedsQL™ social functionality subscale score, and the presence of warts on feet significantly decreased PedsQL™ school functionality subscale score (P=0.04 and P=0.04, respectively).

Discussion

The literature includes several studies on the effect of anogenital warts on QoL in adults.[5,6,17]; however, few studies have investigated the role of extragenital warts on patient QoL. Salah[18] administered the Dermatology Life Quality Index to adults with genital warts and adults with extragenital warts to compare the effect of warts on QoL, and observed that extragenital warts had a greater negative effect on patient QoL than genital warts.

Chronic skin diseases in children, including atopic dermatitis, psoriasis, acne, and vitiligo, can negatively affect QoL due to their associated social, psychological, and physical burden.[19-22] Lewis-Jones and Finlay[9] administered the CDLQI to 233 children with psoriasis, eczema, molluscum contagiosum, acne, moles, scabies, and alopecia, as well as 34 children with warts,

Table II. Comparison of PedsQLTM total and subscale scores in patients, controls, and their parents.

PedsQL™ scales	Children		P	Parents		P
	Patients (n = 85)	Controls (n = 85)		Patients (n = 85)	Controls (n = 85)	
Physical health	7.26 ± 5.18	5.98 ± 3.53	0.209	8.80 ± 6.13	6.92 ± 3.98	0.059
Emotional functionality	5.56 ± 3.98	4.05 ± 2.69	0.029	6.54 ± 4.05	4.09 ± 2.58	<0.001
Social functionality	4.38 ± 3.63	1.69 ± 1.67	<0.001	5.07 ± 3.68	2.19 ± 2.22	<0.001
School functionality	6.20 ± 3.19	4.11 ± 2.67	<0.001	5.53 ± 3.37	4.61 ± 2.67	0.098
PedsQL™ total score	23.42 ± 12.33	15.81 ± 7.37	<0.001	25.94 ± 12.49	17.81 ± 6.87	<0.001

P < 0.05 is shown as bold.
n: number; PedsQL™: Pediatric Quality of Life Inventory.

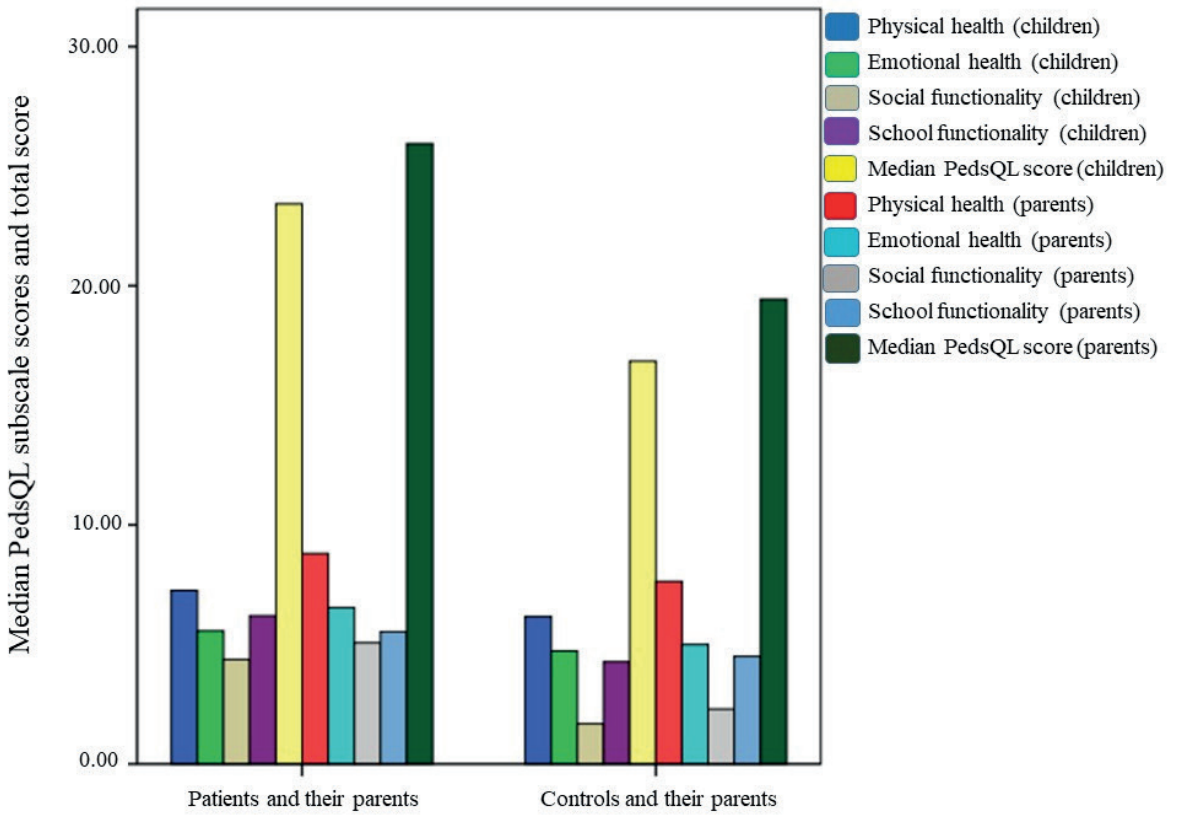

Fig. 2. PedsQL™ total and subscale score in the patients, controls, and their parents.

all aged 4-16 years. Their findings showed that the mean CDLQI score in the children with warts was significantly higher than in those in the control group (3.3 versus 0.38). Balci et al.[10] examined the validity of the Turkish version of the CDLQI in a study that included 154 children with skin diseases and 58 children with health problems unrelated to skin. Among the 154 children included, 21 had warts. They reported that warts had a mild to moderate negative effect on the CDLQI score. Beattie et al.[11] studied 379 children with chronic skin diseases and their parents, including 24 patients with warts, and compared them to 161 children with other chronic diseases, such as cerebral palsy, renal disease, diabetes, and cystic fibrosis. The mean CDLQI score in the patients with warts was 2.87. In the present study the mean CDLQI score in the children with warts was 5.20, which is higher than that in the earlier studies, this

may be explained by the fact that patients that have warts greater than 6 months are more likely to seek medical attention and more likely frustrated.[9-11]

This study is the first to use PedsQL™ to determine the effect of warts on QoL in children. The PedsQL™ Version 4.0 Generic Core Scales is widely used for measuring patient and parental perceptions of health-related QoL in pediatric patients with acute and chronic diseases. It is a brief, practical, developmentally appropriate, reliable, and valid scale designed to measure physical, emotional, social, and school functioning, and is available in multiple languages. The fact that PedsQL™ is not commonly used in QoL studies related to dermatological diseases and the present study is the first to use this scale to investigate children with warts is a particular strong suit of the present study. Varni et al.[23] showed that pediatric patients with moderate-to-severe plaque psoriasis had significantly lower physical, emotional, social, and school functioning, as compared to healthy children, based on PedsQL™ scores. In the present study, mean PedsQL™ total score for the patient group was higher than that for the control group. Additionally, the decreased PedsQL™ social functionality subscale score in patients with warts on legs, and the decreased PedsQL™ school functionality subscale score in patients with warts on feet may be explained by the fact that these areas are covered by clothing.

The present study has a few limitations, including its small study sample. As the study was conducted at a single research center, the findings lack generalizability. Another limitation is that the patient group only comprises those who were already motivated to seek treatment which may lead a possible sampling bias in this study because the warts are already symptomatic or affecting QoL enough to seek treatment.

In conclusion, this study shows that warts persisting for ≥6 months had a small negative effect on QoL in pediatric wart patients, as compared to the controls. Warts had the greatest negative effect on PedsQL™ school, social, and emotional functionality scores, and CDLQI symptoms and feelings scores, based on patient scores. According to the parents' PedsQL™ scores, warts primarily had a negative effect on children's social and emotional functioning. Clinicians should be aware of the negative effect of warts on pediatric patient QoL and treat kids that are severely affected more aggressively than watch and wait. QoL screening should be included in the routine evaluation of childhood warts and the findings should be incorporated into the therapeutic decision-making process. In addition to the effects of wart treatment on QoL, the degree of discomfort children of different ages is willing to undergo to eliminate warts should also be investigated in future studies.

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Original Article

Evaluation of blood pressure responses to treadmill exercise test in normotensive children of hypertensive parents

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ABSTRACT

Background. Hypertension is a progressive disease with a prehypertensive phase. The most important feature of this period is the abnormal cardiovascular reactivity to various stressors. In our study, we focused on normotensive children of hypertensive parents, a special group that is at risk.

Methods. We evaluated the children according to age, studying whether they showed higher cardiovascular reactivity at different steps of an exercise test and during a recovery period than their counterparts with a negative history. A total of 110 normotensive children who were between the ages of 6 and 18 years were enrolled into the study. Sixty-two children whose parent(s) had a history of hypertension formed the study group while 48 without this history formed the control group. An exercise test was performed according to the Bruce protocol. Maximal systolic blood pressures and systolic blood pressures were taken while the participants were at rest; during phases 2 and 3; and also in the first, third, and sixth minutes of the recovery period.

Results. Measurements were significantly higher in the study group ($p < 0.05$). In the group of children between the ages of 6 and 10 years, cardiovascular responses were similar. Children older than 10 years, however, had significantly higher blood pressure levels than those in the control group. The children who were at risk of hypertension showed more exaggerated cardiovascular responses during the exercise test and recovery period. This response was particularly evident for those children 10 years of age and older.

Conclusions. Our study indicates that treadmill exercise is a safe and effective investigational method which can be used to identify children who are at risk for development of hypertension before this condition becomes clinically evident.

Key words: cardiovascular physiological processes, exercise test, blood pressure, risk factors.

Primary or essential hypertension (HT) is a condition of elevated blood pressure (BP) with no identifiable underlying cause.[1] Although genetic predisposition, environmental factors and role of the life style are considered in the etiopathogenesis of primary HT, the pathophysiological process is highly complex and not completely understood.[2] In many studies, it is found that genetic predisposition especially positive family history is a significant risk factor in the development of HT.[3,4]

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Although cardiac stress test is not easily available as a routine clinical tool used for diagnosing HT, it is a relatively cheap cardiovascular stimulation modality and frequently used for evaluating many clinical conditions. During the test, cardiovascular response is evaluated by monitoring electrocardiographic (ECG) traces and BP. A physiological response to the exercise is characterized by increased cardiac output, which is obtained by increasing heart rate and stroke volume, mediated by sympathetic system, in order to supply increased metabolic need of muscles. The BP response, secondary to the increased cardiac output, is compensated, albeit partially, by minimal decrease in peripheral vascular resistance.[5]

It is suggested that onset of the HT is associated with a pre-hypertensive course, which is primarily characterized with abnormal cardiovascular reaction to various stressors.[6] It is also reported that patients with positive family history of HT usually have hyperactive sympathetic nervous system, and that hyperactive reactions lead to peripheral vasoconstriction, increased heart rate and ultimately, increase in peripheral vascular resistance.[7] Moreover, it was found that there is a significant correlation between exaggerated BP reaction to the exercise test and increased peripheral vascular resistance caused by vascular endothelial dysfunction and arterial stiffness.[8] Exaggerated response to cardiac stress test is also observed in hypertensive people and normotensive people with hypertensive parents.[9,10]

Evaluating BP response during exercise enables healthcare providers to identify children at risk for HT; this cannot be determined while they are at rest.[11] However, the range of normal BP response that occurs during exercise in children and adolescents hasn't been clearly established. Most previous studies of BP levels during exercise have only involved investigations of the adult population, and their authors highlighted different stages of exercise testing and suggested various methodologies.[11,12] For example, recent adult studies have been focused on the recovery period of the test, which has proven prognostic value.[13,14] On the other hand, studies of this type conducted on children are scarce and most of them have only involved examination of maximal systolic and diastolic BP readings during exercise.[15,16] Therefore, pediatric cardiac stress test studies are not only limited in number but they also lack methodological quality.

Since it is known that pathophysiological processes of HT begin in childhood, we think there might be a relationship between a child's age, their stage of development, and these processes. Therefore, in our study, we focused on normotensive children of hypertensive parents (NCHP), a special at-risk group, to see if NCHP have higher cardiovascular reactivity in different steps of exercise testing and during a recovery period, as compared to their counterparts whose parents do not have HT.

Material and Methods

This was a cross-sectional study conducted with 110 normotensive children (BP <90th percentile according to age, gender and height), aged between 6-18 years, undergoing treadmill exercise testing according to Bruce protocol. Sixty-two children with parental history of HT formed NCHP group while age- and gender-matched 48 healthy children without parental history formed the control group (normotensive children of normotensive parents, NCNP). All subjects drafted from children who presented with silent murmur or non-specific chest pain. BP was measured with digital sphyngomanometer after the child rested for 10 minutes. Each measurement was repeated thrice, and the mean value was recorded. The family history of HT was defined as at least one parent who was diagnosed by a physician and requiring regular antihypertensive therapy. Normotensive parents were selected from those who had no history of HT and whose BPs were checked during the last 12 months by a physician. But the parents whose blood pressures were not checked at that time, their BPs were measured at our clinic. Children with chronic systemic disease, anemia or who were on medications that could interfere with the behavior of arterial BP and children with body mass index >85th percentile (with regards to age and gender) were not included. Families who refused cardiac stress test and children who would not possibly comply with the exercise test were also excluded. Children and their families were duly informed about the study and cardiac stress test and informed consent were taken. Participants were assigned to 1 of 3 groups according to age: 6 to 10 years (prepubertal); 11 to 14 years (pubertal); and 15 to 18 years (postpubertal).

The study was approved by the Ethics Committee

of the School of Medicine, Eskişehir Osmangazi University (Letter No. 28.04.2011/05). Informed consent was obtained from all individual participants included in the study.

Treadmill test (cardiac stress testing)

At treadmill test laboratory, ECG electrodes were placed according to Mason-Likar technique and a proper sized Orbit-K™ BP cuff was fitted on the right arm of children and then they were allowed to rest for at least 10 minutes.[17] Resting (basal) ECG, BP and heart rate were measured and recorded. The stress test was performed with General Electric Marquette Case Exercise Testing System (CASE Value v6.6 package) and GE T2100 treadmill (GE Healthcare Company, Wauwatosa, WI, USA). All participants did the treadmill exercise test using Bruce Protocol, a safe and standard stress protocol. The Bruce Protocol is a multi-phase protocol, where inclination and velocity of the band are increased at each phase, and it is comprised of three-minute periods, where the patient is allowed to reach steady state, before workload is increased for the next phase. The test launched and ECG, BP and heart rate were recorded at second minutes of each three-minute stages during the test. The second part of the test was the recovery period or slowing down period and directly follows the exercise termination wherein the speed will decrease successively for a few minutes. Heart rate, ECG and BP were recorded at first, third and sixth minutes of this period. In our laboratory, BP is automatically measured by SunTech Tango + Stress BP monitor (SunTech Medical, Inc. Morrisville, NC, USA) with oscillation technique. The device is specifically developed for exercise testing and Korotkoff sounds, sensed by microphones equipped on orbit-K cuff, are analyzed by the developer company's patented Dimensional K-Sound Analysis "DKA".

Submaximal exercise (sub), implies the phase when a subject cannot yet reach the maximal exercise capacity in the exercise test and it is assigned as a pre-determined point or the duration the subject cannot exceed 85% of the maximal target heart rate.[18] In our study, submaximal exercise response was identified as the end of second phase, since all children achieved this phase and had not yet reached 85% of the maximal heart rate.[6,18,19]

Statistical analysis

The statistical program IBM SPSS v20 for Windows was used to perform the statistical analysis. Normality of the distribution for all the variables was assessed with the Shapiro-Wilk test. Various variables which were normally distributed between the two study groups were compared using t-test, multiple comparisons of the variables were made by ANOVA test. Tukey's and Tamhane's post-hoc analysis was used to identify significant group differences that were indicated by ANOVA. For parameters without normal distribution, Mann-Whitney U test was used to compare two groups, while multiple comparisons were made with Kruskal-Wallis test. For analysis of cross tables, chi-square test was used. Pearson's correlation coefficients were computed to evaluate strength and direction of relationship of the measured variables showing normal distribution. A p-value of 0.05 or less was considered statistically significant. All data were expressed as mean ± standard deviation (SD).

Results

Anthropometric data and clinical characteristics of NCHP and NCNP are given in Table I. Distribution of subjects by age groups is given in Table II. No statistically significant difference was found between groups in terms of age, gender, height, weight and BMI ($p>0.05$). Also there were no statistically significant differences between groups for exercise test duration and MET (metabolic equivalent, a MET is a ratio of working metabolic rate relative to resting metabolic rate. Average oxygen consumption in resting and sitting position is 3.5 ml/kg/min and this is expressed as "1 MET") values. Maternal HT was noted in 37 children in the

Table I. Comparison of baseline characteristics and exercise times between normotensive children of hypertensive parents and normotensive children of normotensive parents.

	NCHP (n = 62)	NCNP (n = 48)	p
Gender (female /male), n (%)/n (%)	28 (45) / 34 (55)	22 (46)/ 26 (54)	0.94
Age (years)	12.11 ± 3.35	11.50 ± 3.40	0.94
Weight (kg)	43.0 ± 14.6	38.9 ± 14.6	0.15
Height (cm)	153.1 ± 16.6	148.2 ± 20.3	0.17
Body mass index (kg/m^2)	17.67 ± 2.80	17.03 ± 2.31	0.21
Endurance time (min)	12.48 ± 1.83	12.72 ± 1.76	0.48
MET (metabolic equivalent)	14.99 ± 2.36	15.03 ± 2.12	0.92

Values are shown as mean ± standard deviation or numbers (%).
MET (metabolic equivalent): A MET is a ratio of working metabolic rate relative to resting metabolic rate. Average oxygen consumption in resting and sitting position is 3.5 ml/kg/min and this is expressed as "1 MET", NCHP: normotensive children of hypertensive parents, NCNP: normotensive children of normotensive parents.

Table II. Distribution of children by age groups.

Age groups	NCHP, n (%)	NCNP, n (%)
6-10 ages	22 (35.5)	18 (37.5)
11-14 ages	22 (35.5)	16 (33.3)
15-18 ages	18 (29.0)	14 (29.2)
Total	62 (100.0)	48 (100.0)

NCHP: normotensive children of hypertensive parents, NCNP: normotensive children of normotensive parents.

NCHP group (59.6%), while 25 fathers (40.4%) were hypertensive in the same group. None of the children had a history of HT in both parents.

Resting systolic blood pressure (SBP) records were significantly higher in the NCHP group than in the NCNP group (p = 0.001). However, no inter-group difference was found for diastolic blood pressure (DBP) or heart rate (HR). During the test, phase-2 SBP, phase-3 SBP, and phase-4 DBP readings of NCHP were significantly higher than those of the NCNP group (p = 0.001, p = 0.009, and p = 0.04, respectively). SBP readings measured at the first, third, and sixth minutes of recovery were significantly higher in the NCHP group in comparison to those of the control group (p = 0.02, p = 0.001, and p = 0.001, respectively). No statistically significant difference was found between the groups in terms of heart rate and DBP during the recovery period (p >0.05). Changes in SBP, DBP, and heart rate readings of both groups are shown in Figure 1.

Maximal and submaximal (phase-2) BP and HR values and their changes according to the resting values are summarized in Table III . Maximal SBP responses were significantly higher in the NCHP group than in the NCNP group (p = 0.007). No difference was found between the two groups in terms of changes in HR and BP readings relative to resting values (p >0.05).

When exercise data were compared by gender, test durations (13.23 vs. 11.82 min) and MET values (15.91 vs. 13.92) were found to be significantly higher in male subjects. In the NCHP group, resting HR and phase-2 HR (sub-HR) measurements were higher in females than males (p=0.04 and p=0.01) (Fig. 2a). Moreover, maximal SBP (p = 0.03) (Fig. 2b), Δmax-SBP (p = 0.01), Δmax-DBP (p = 0.02), and Δsub-SBP (p = 0.04) readings were significantly higher in male subjects than in those of the females (data not shown). But in the NCNP group, no difference was found between the genders in all variables, excluding higher MET values and longer test durations of the males.

Table III. Maximal and submaximal (phase 2) blood pressure and heart rate values and their changes according to resting values.

Parameters	NCHP	NCNP	p
sub-SBP	142.1 ± 16.1	132.4 ± 11.3	0.001
sub-DBP	65.5 ± 10.7	63.0 ± 8.5	0.188
Δsub-SBP	29.3 ± 14.7	26.4 ± 11.4	0.25
Δsub-DBPα	2.5 [-8.0; 9.0]	1.0[-4.0 ± (+6.5)]	0.79
max-SBP	162.3 ± 21.1	152.7 ± 13.6	0.007
max-DBP	69.2 ± 10.4	65.8 ± 7.8	0.061
Δmax-SBP	49.7 ± 18.9	46.7 ± 14.5	0.054
Δmax-DBP	4.66 ± 11.03	4.7 ± 9.2	0.36
sub-HR	140.6 ± 17.7	137.4 ± 14.4	0.31
Δsub-HR	39.1 ± 15.1	38.2 ± 14.2	0.75
max-HR	194.3 ± 10.8	192.3 ± 11.8	0.33
Δmax-HR	92.9 ± 18.0	93.1 ± 20.0	0.95

Values are shown as mean ± standard deviation or median [25th percentile; 75th percentile].
DBP: diastolic blood pressure, HR: heart rate, max: maximal, NCHP: normotensive children of hypertensive parents, NCNP: normotensive children of normotensive parents, SBP: systolic blood pressure, sub: submaximal (phase 2), Δsub: submaximal-resting value, Δmax: maximal-resting value.

When data were compared by age, no statistically significant difference was found in any group among the NCNP and NCHP groups in terms of exercise duration and MET values (p >0.05). No statistically significant difference was found between subgroups of those who were 6 to 10 years of age in terms of exercise test data points (p >0.05). For the subgroups of children ages 11 to 14, resting-DBP (p = 0.04) , phase-1 SBP (p = 0.04), phase-2 SBP (p = 0.017), phase-3 DBP (p = 0.016), phase-4 DBP (p = 0.03), max-DBP (p = 0.006), R1-DBP (p = 0.04) and R3-SBP (p = 0.04) readings were significantly higher in the NCHP group than in the NCNP group. For the subgroup with children ages 15 to 18, resting SBP (p = 0.006), phase-1 SBP (p = 0.038), phase-2 SBP (p= 0.006), phase-3 SBP (p = 0.002), phase-4 SBP (p = 0.009), max SBP (p = 0.002), R1 SBP (p = 0.024), R3 SBP (p = 0.004), and R6 SBP (p = 0.001) measurements were significantly higher in the NCHP group in comparison to those of the NCNP group (Fig. 3).

Changes observed in SBP and DBP readings by age subgroups during the exercise test and recovery period are shown in Figure 3 (A-B-C).

For paternal or maternal HT we found all the test results to be statistically similar (p >0.05). When age and anthropometric data of children in the study group were correlated with data obtained during the exercise test and recovery period, resting SBP, maximal SBP, HR at the first minute, and SBP at the sixth minute of the recovery period showed strong correlations with age, height, weight, and BMI .

We observed no problem or complication, such as severe arrhythmia, dyspnea and excessive hypertensive response (>250/125 mmHg), which would, otherwise, require terminating the test.

Discussion

Pre-stress test data

In this study, the resting SBP levels of NCHP were significantly higher than those of the control group. We believe that this finding can be related to increased sympathetic stimuli secondary to mental stress, although no physical stress was observed in that group. It is suggested that the onset of HT is associated with a pre-hypertensive course, primarily

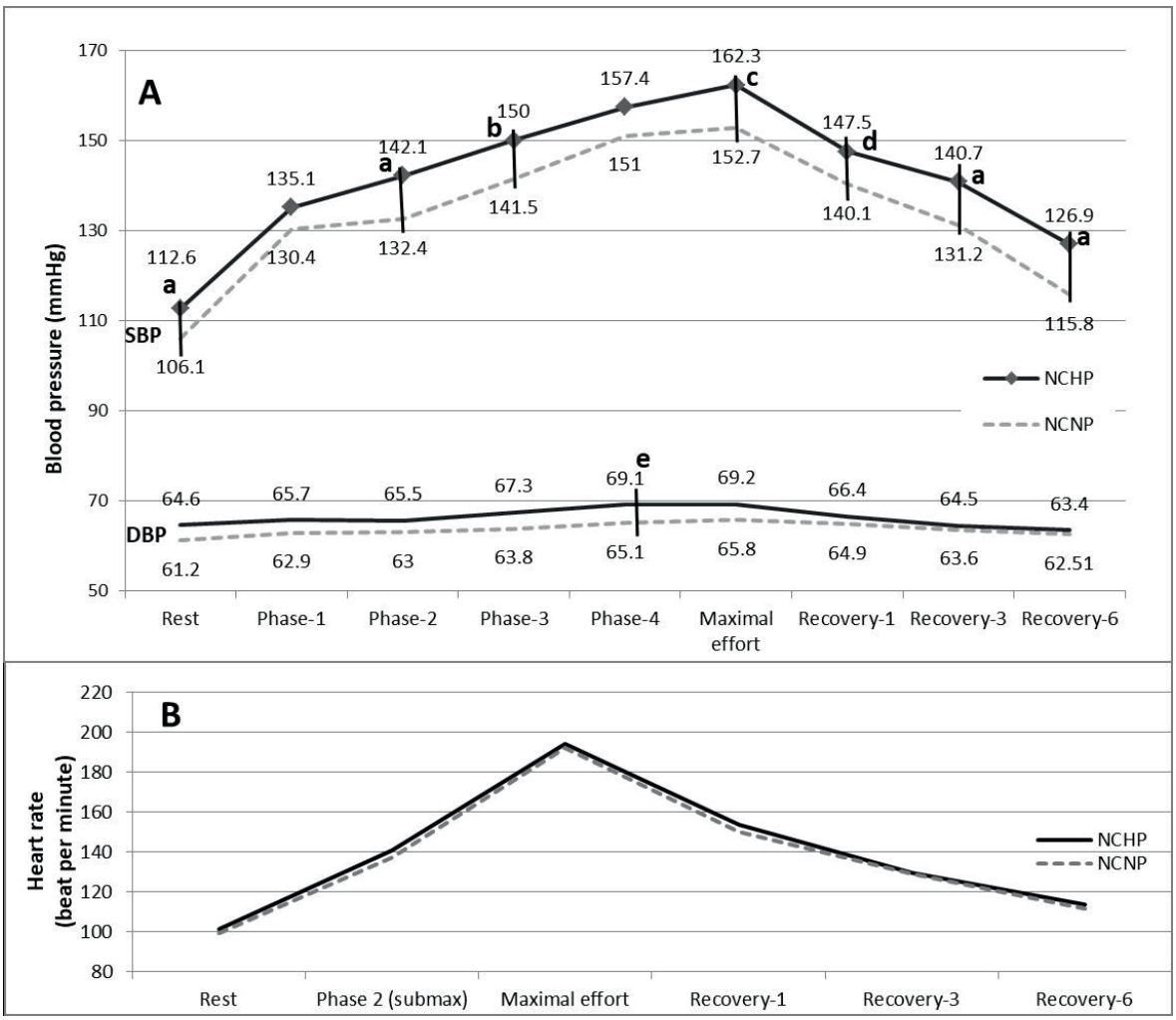

Fig. 1. Graphical presentation of blood pressure (A) and heart rate (B) values obtained during exercise test and recovery period in the study and control groups.

Letters (a, b, c, d, e) indicate specific phase or period at which the difference between groups is statistically significant ($p < 0.05$).

DBP: diastolic blood pressure, NCHP: normotensive children of hypertensive parents, NCNP: normotensive children of normotensive parents; recovery 1-3-6, 1st, 3rd and 6th minutes of recovery period; SBP: systolic blood pressure. $^{a}p = 0.001$, $^{b}p = 0.009$, $^{c}p = 0.007$, $^{d}p = 0.02$, $^{e}p = 0.04$

characterized by abnormal cardiovascular reactions to various stressors.[6] Varying sensitivity levels of adrenergic receptors and sympathetic hyperactivity are suggested for exaggerated cardiovascular response to the stress.[20] Sympathetic hyperactivity is secondary to excessive sympathetic stimuli and/or decreased sympathetic inhibition.[21] This hyperactivity starts in childhood and can be demonstrated in 30% of recently diagnosed hypertensive subjects.[20] Sowmya et al.[22] conducted a study on NCHP and found that their resting SBP was higher than that of control subjects. Similar to our study, the authors didn't observe a difference in DBP or HR responses. Carroll et al.[23] found a correlation between pre-stress resting SBP and SBP measured at year-5 of the follow-up; this was in the Whitehall 2 study, in which the authors also determined that mental stress reactivity was insufficient for identifying future HT.

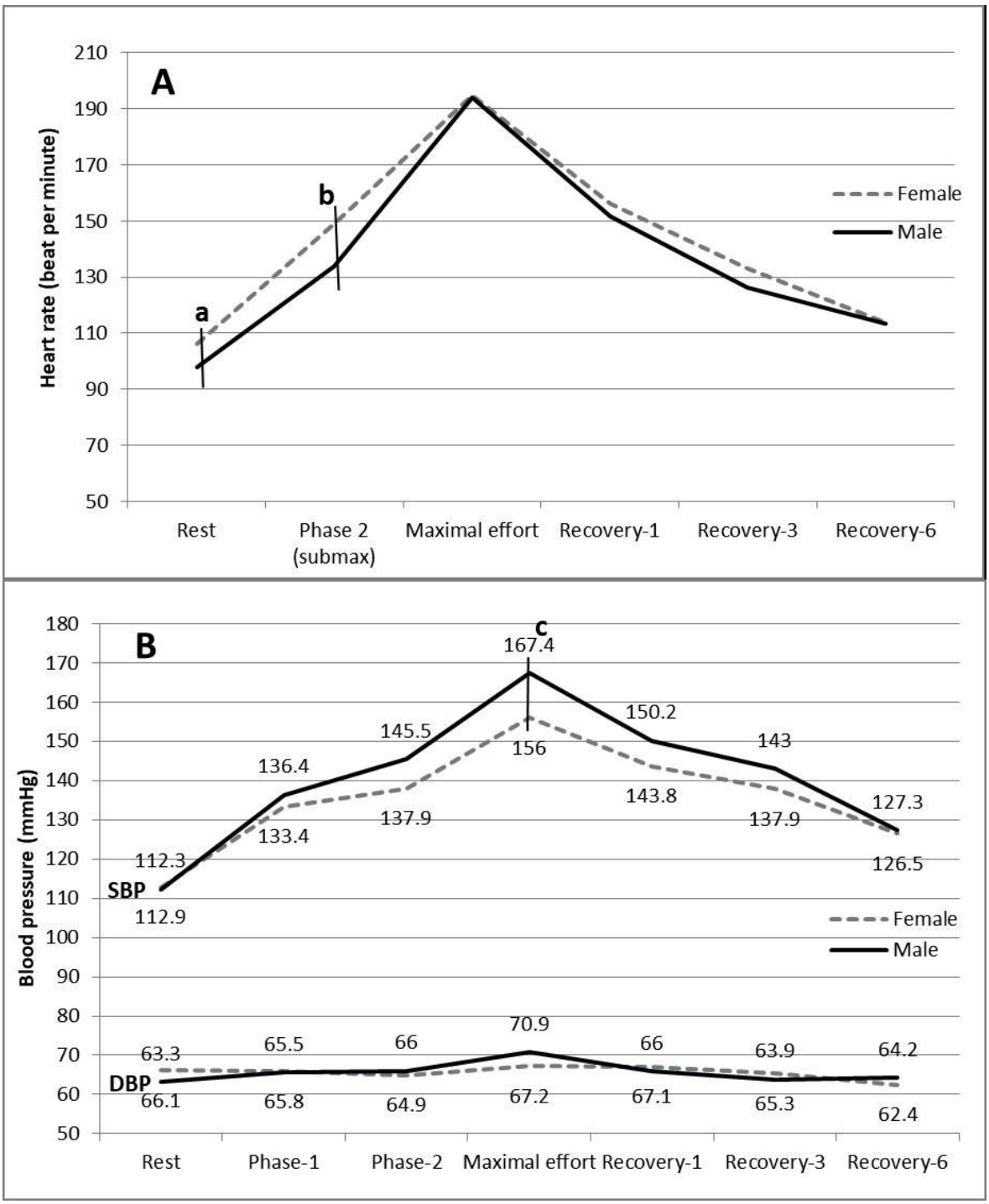

Fig. 2. Graphical presentation of heart rate (A) and blood pressure (B) values obtained during exercise test and recovery period in the study group by gender.

Letters (a, b, c) indicate specific phase or period at which the difference between groups is statistically significant ($p < 0.05$). DBP: diastolic blood pressure; recovery 1-3-6, 1st, 3rd and 6th minutes of recovery period; SBP: systolic blood pressure. [a]$p = 0.04$, [b]$p = 0.01$, [c]$p = 0.03$

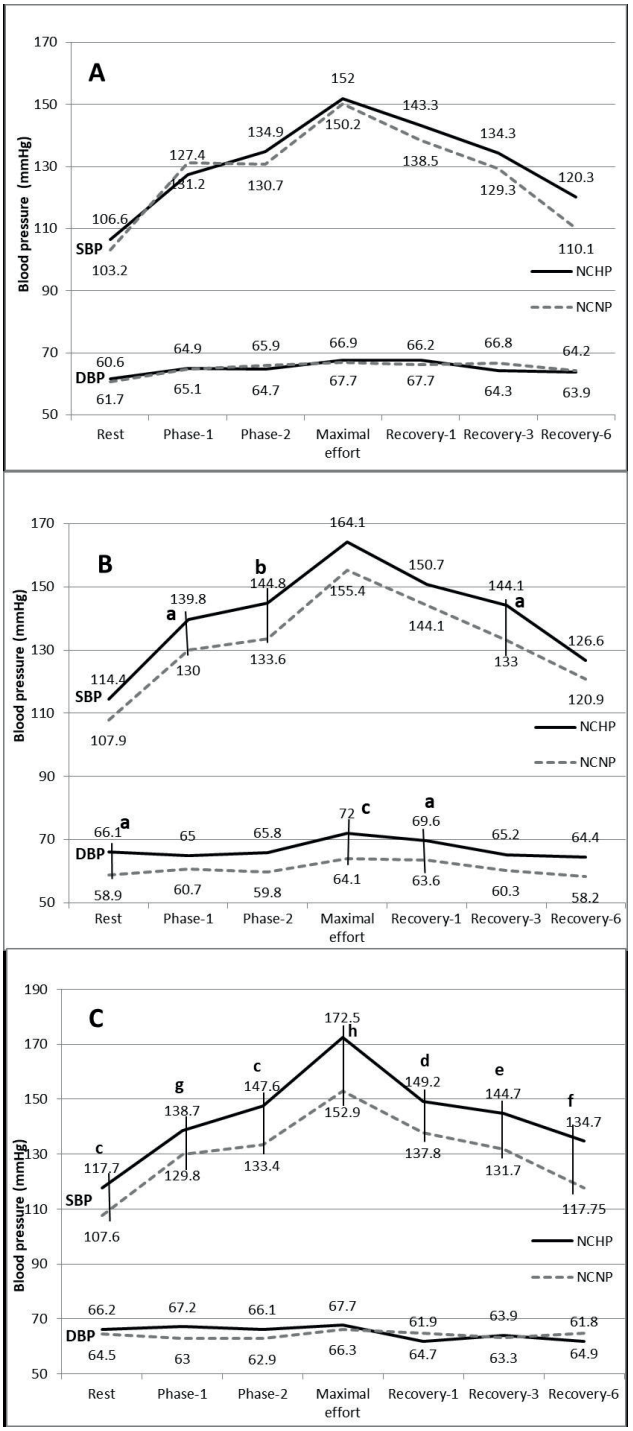

Fig. 3. Graphical presentation of systolic and diastolic blood pressure readings obtained during exercise test and recovery period in six-to-ten years (A), eleven-to-fourteen years (B), fifteen-to-eighteen years (C) of age subgroups.

Letters (a, b, c, d, e, f, g, h) indicate specific phase or period at which the difference between groups is statistically significant ($p < 0.05$).

DBP: diastolic blood pressure, NCHP: normotensive children of hypertensive parents, NCNP: normotensive children of normotensive parents; recovery 1-3-6, 1st, 3rd and 6th minutes of recovery period, SBP: systolic blood pressure. [a]$p = 0.04$, [b]$p = 0.017$, [c]$p = 0.006$, [c]$p = 0.006$, [g]$p = 0.038$. [h]$p = 0.002$, [d]$p = 0.024$, [e]$p = 0.004$, [f]$p = 0.001$

Adult studies like that of Miyai et al.[6] conducted on normotensive men have shown that finding an individual relative risk for developing HT in normotensive adults with slightly elevated resting BP is greatly increased if they exhibit an exaggerated BP response to exercise. These results indicate that the measurement of exercise BP can provide some additional important information concerning the risk for developing HT that cannot be estimated by resting BP alone. The authors also stated that measurements of resting BP often show spurious elevated values because of anxiety, which decreases the reproducibility of results and their usefulness for predicting future HT.

Cardiac stress test data

During the exercise test, phase-2 SBP, phase-3 SBP, phase-4 DBP, and maximal SBP were significantly higher in the NCHP group than in the control group. Wilson et al.[24] determined that although there was no inter-group difference in measurements such as resting BP, vascular resistance, and cardiac output, an exaggerated response (≥230/100 mmHg) to the cardiac stress test was found in 35% of the members of the group with a positive family history and a high normal resting BP. However, there was no standard definition of hypertensive response for a normotensive and asymptomatic subject. Various models were suggested by the authors of different studies. In a study conducted on an adult population, it was determined that for subjects with a BP response of ≥225/90 mmHg in a treadmill exercise test, the risk of HT was 2.3-fold greater at the end of a 32-month period.[25] As suggested by this study and others that are similar to it, the most commonly suggested model is maximal SBP (max-SBP) during maximal exercise.[26] Some authors consider that BP responses recorded during submaximal exercise are of clinical significance.[19] The principle reason is that maximal SBP depends on high-level exercise and the physical condition of the subject.[8] Singh et al.[19] examined adult participants of the Framingham study and demonstrated that exaggerated DBP measured at phase 2 (submaximal phase) of the stress test and exaggerated SBP measured at the third minute of the recovery period were valuable in estimating the development of HT. Schultz et al.[27] conducted a meta-analysis by reviewing adult studies and observed that independent of age, outpatient BP values, and other risks, hypertensive response to submaximal exercise was related to cardiovascular events and mortality. They also stated that the prevalence of masked HT reaches up to 58% in such subjects. We found that both submaximal (phase 2) SBP responses and maximal SBP responses were significantly higher in the NCHP; this finding is supportive of data from those studies.

In some studies, researchers have used extra variables, along with gender and percentile values, when BP responses of subjects were evaluated. For example, Miyai et al.[6] used the heart rate reserve measurement to evaluate the influence of the same metabolic load on BP. Similarly, the change in BP per minute (mmHg/min), the change in SBP relative to resting BP (ΔSBP), and the max DBP have been used in various studies.[26,28-31] Several authors have suggested that BP behavior and BP variability observed during the stress test, rather than maximal BP, are more important for determining the risk of HT. Although we examined changes in SBP and DBP relative to resting BP between two groups, both in phase 2 (submaximal exercise) and maximal exercise, no significant difference was found in terms of those variables ($p > 0.05$). However, Δmax SBP values of the NCHP were higher than those of subjects in the control group, although this finding was not statistically significant ($p = 0.054$).

Recovery period data

During the recovery period, SBP responses at the first, third, and sixth minutes were found to be significantly higher in the NCHP group. Nakashima et al.[32] examined responses of the study population (mean age, 19 years) to the submaximal exercise test and demonstrated that SBP and DBP values recorded for male

subjects immediately after exercise were strong predictors of future HT. Yosefy et al.[13] used the Bruce exercise protocol for study groups and found a relationship between BP ≥160/90 mmHg at the fifth minute of the recovery period and a poor cardiac profile. Similarly, Tsumura et al.[33] conducted a study in which they followed 6557 normotensive adults and found a correlation between each 10 mmHg increase in SBP and DBP measured at the fourth minute of the recovery period and a 1.55-fold relative risk of HT, while Laukkanen et al.[34] linked SBP ≥195 mmHg at the second minute of the recovery period in the study group to an increased risk of myocardial infarction. In this study, we evaluated three stages of the recovery period, including early (first minute) and late (sixth minute) phases of the test, rather than just a single phase. We observed that the SBP response was high in the NCHP group in all three phases of the recovery. But the DBP and HR responses were similar in both groups.

American College of Cardiology and American Heart Association guidelines acknowledges max-SBP ≥214 mmHg and SBP and DBP measured at third minutes of the recovery period – based on the estimated relative risk found in the Framingham Study – as indicators of the possible future HT.[19,35]

Evaluation of data by age groups, gender and hypertension of the parents

Considering our study data, it was observed that children up to 10 years of age had similar cardiovascular reactivity in both groups. But children with a family history of HT showed higher BP responses after 10 years of age. At rest, in the group of 11- to 14-year-olds, a difference was observed in DBP. In older children the difference in SBP responses became remarkable. SBP responses in the first two phases of the exercise test (including the submaximal phase) were significantly higher in children older than 10 years of age. DBP responses were even higher in the group of 11- to 14-year-olds during phases 3, 4, and 5 and during maximal exercise, while elevated SBP was predominant in those 15 years of age and older during those phases and during maximal exercise. Similarly, in the group of 11- to 14-year-olds, a significant difference in DBP responses was observed in the early phase of recovery. SBP responses were higher in the third minute of recovery in the NCHP group. In the group of 15- to 18-year-olds, elevated SBP responses at the first, third, and sixth minutes of recovery were the primary findings in the NCHP group.

We observed various results upon the review of studies which analyzed changes in the BP profiles of children of hypertensive parents over the course of time. In their first study, Li et al.[36] monitored third graders for 5 years and found that the NCHP group showed higher levels of resting BP and increased cardiovascular reactivity than the other children. However, they showed cardiovascular reactivity only in SBP change. van Hooft et al.[37] studied BP and related characteristics in children whose parents both had relatively high BP. The results were compared to those of children whose parents both had a relatively low BP; they were also compared to those of children who had one parent with high BP and one parent with low BP. At the age of 8 years there were no clear differences in BP but at the age of 20 years there was a difference of 7 mmHg for both systolic and diastolic pressure between the high- and low-risk offspring.

In the Bogulasa study, when compared to 5- to 9-year-olds, a stronger relationship was found between BP monitoring of 10- to 14-year-olds and HT in adult years.[38] Also, the effects of parental HT on longitudinal changes in BP have been examined by Mitsumata et al.[39] They stated that the parallel shift of the age–BP relationship by parental HT suggests that a set point of BP is elevated by parental HT before the third decade of life. In our study, we demonstrated increased cardiovascular responses in children older than 10 years of age with family history but who were still normotensive. Moreover, increased cardiovascular reactivity became explicit first in DBP responses after 10 years of age and then in SBP responses after the age of 14 years. An

increased DBP response to an exercise test can be explained by increased peripheral vascular resistance and impaired capacity for exercise-induced vasodilatation. Our results support that increased peripheral vascular resistance may begin at younger ages when children are still normotensive and have normal SBP responses to exercise.

Cardiac output increase during exercise is a function of heart rate x stroke volume. Due to physiological differences between genders, it has been suggested that men have a greater reliance on preload and an enhanced use of the Frank-Starling mechanism whereas females rely on heart rate to increase cardiac output.[40,41] During exercise, an increase in sympathetic activity and a decrease of vagal discharge leads to an increase of heart rate, stroke volume, and myocardial contractility to satisfy energy demands of working skeletal muscles. Therefore, the regulation and homeostatic relationship between BP and cardiac output is achieved through different mechanisms in males and females.[40,41] We found that resting and phase-2 HRs were higher in girls than boys, but maximal SBPs and their changes (Δmax, Δsub) according to resting levels were observed as statistically higher in boys.

Fomin et al.[40] analyzed adolescents' responses to a maximal exercise test and observed that girls had higher levels of resting HR and lower levels of resting SBP while boys displayed higher levels of maximal SBP responses. In the same study, maximal HRs and resting DBP responses of both genders were found to be similar. Dimkpa et al.[41] measured maximal SBP and DBP with SBP responses at the first minute of recovery as being higher in boys; on the other hand, they measured maximal HR and SBP responses at the third minutes of recovery and found the results to be similar in both genders. In the same study, maximal SBP changes (Δmax) were found to be higher in boys compared to resting BP measurements. However, in contradistinction to the findings of the studies mentioned above, in the study of Akdur et al.[42] conducted on healthy Turkish children, this difference wasn't seen between the two genders with regard to maximal HR and SBP. But a linear correlation was observed between max SBP, age, and exercise duration.

By power analysis, for variables other than submax HR, it was noted that studies need to be conducted in larger groups to make a comparison of females and males involving the BP response to the exercise test.

Among the 62 children who constituted the NCHP group, mothers of 37 children and fathers of 25 children had HT. When the exercise test data were compared according to parent HT status, there was no statistical significance between the children whose mother or father had HT. There are different studies in which the leaders have investigated the effect of maternal and paternal BP on childhood BP. For example, it was shown that the hazard ratio of HT development was 1.5 for men with maternal HT only; 1.8 for men with paternal HT only; and 2.4 for men with HT in both parents.[43] On the other hand, DeStefano et al.[44] argued that a mother with HT is a stronger risk factor. But, similar to our study, Mitsumata et al.[39] observed that there was no statistical difference in children's HT development with regard to the mother or father being hypertensive.

The measurement of maximal DBP levels is usually difficult because of technical difficulties and because of noise during the test. Therefore, this is excluded in the majority of studies and SBP responses are the only ones examined. This issue becomes more obvious in clinics where BP is measured manually during the test. However, automated instruments provide more precise DBP and SBP values and more studies on this are underway. Cameron et al.[45] compared data of automated BP assessments using the Tango exercise BP monitor (SunTech Medical Instruments, NC, USA) – the same instrument as the one we used in our study – with data gathered via an invasive method. They found that the results were similar and within a reliable clinical range. Consequently, we think the systolic and diastolic BP values measured in

our study are close to the most accurate values.

It was found that in both the recovery period and during the test, the children with parental HT had more excessive cardiovascular responses to the physical stress than the children without parental HT. These responses were more prominent in children older than 10 years of age. Furthermore, at that age, increased cardiovascular reactivity became explicit first in DBP response and then in SBP response. Because of different periods of physical development, defining a threshold level for hypertensive responses in children is very challenging and a larger pediatric population is needed for study. Therefore, we did not aim to give a threshold level for hypertensive responses.

Our data were obtained cross-sectionally from a relatively small group of children. However, we think that our results can be useful in designing future longitudinal studies in a larger pediatric population. By power analysis, it was considered that the sample sizes of the age groups of NCHP and NCNP were sufficient for comparisons of the BP response to the exercise test among members of the groups. But for variables other than submax (phase 2) HR, it was seen that there is a need for studies to be done in larger groups to make a comparison between females and males of BP response to an exercise test.

Overweight and obese children were not included in the study. We also didn't evaluate sports or leisure time physical activities and lifestyles of the children enrolled in the study.

At the time of this investigation, the BP of some normotensive parents were not measured and the declaration of these families were taken into account.

The exercise test may not be a diagnostic tool for HT, but it can be used to identify patients with abnormal BP responses that may be a precursor to HT. This has the potential to be used for intervention and possibly to prevent or delay the development of HT by the early identification of individuals who are at risk, so that they may introduce modifications to their diet and lifestyle. We believe our study will help expand knowledge on this subject as studies in children are relatively few and many of them have flaws in their methodology.

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Original Article

Is being small for gestational age a risk factor for strabismus and refractive errors at 3 years of age?

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ABSTRACT

Background. Visual problems, cerebral visual impairment, refractive errors and strabismus are commonly found in preterm infants in long-term follow-ups. The aim of this study was to determine the factors that lead to the development of amblyogenic risk factors, such as high refractive errors, anisometropia and strabismus, in the long-term evaluation of preterm infants.

Methods. We retrospectively evaluated children who were screened for retinopathy of prematurity (ROP) and who had a 3rd year ophthalmologic examination. The impacts of sex, gestational age (GA), birth weight (BW), BW for GA, being small for gestational age (SGA), being appropriate for gestational age (AGA), multiple pregnancies and the results of ROP screening on refractive errors and the development of strabismus were evaluated by logistic regression analysis. The SGA and AGA groups were compared in terms of refractive errors and presence of strabismus.

Results. Six hundred and eight children, including 317 (52.1%) males and 291 (47.9%) females, were included in the study. The mean GA was 31 ± 3 weeks (24-36), and the mean BW was 1505 ± 435 g (600-2460). The number of SGA-born children was 101 (16.6%). Manifest deviation was detected in 42 (5.6%) children, and optical correction was required in 101 (16.6%) children. Being an SGA infant and multiple pregnancies were risk factors for refractive errors requiring optical correction, and hyperopia (≥3.00 D) was found to be a risk factor for the development of strabismus in the multivariate regression analysis. Additionally, the SGA group was at high risk for strabismus, hyperopia, high astigmatism and the need for optical correction.

Conclusions. We concluded that SGA seems to be associated with an increased risk of strabismus and a high refractive error. It should be taken into consideration during follow-up examinations of SGA infants.

Key words: premature, retinopathy of prematurity, refractive error, small for gestational age, strabismus.

Visual problems, cerebral visual impairment, refractive errors, strabismus, color vision and visual field defects are more commonly encountered in preterm infants than in term infants in long-term ophthalmologic evaluations because of the unfavorable effects of prematurity on visual and neurologic development.[1] The severity of refractive errors and the incidence of strabismus increase with lower gestational ages and birth weights and with the presence and progression of retinopathy of prematurity (ROP).[2-5] Gulati et al.[6] demonstrated that having low birth weight, independent of gestational age, had a significant role in the development of strabismus. Thus, premature infants and those with low birth weight should be followed regularly after the completion of ROP screening to detect refractive errors and strabismus as well as to prevent the development of amblyopia.[7]

Refractive errors in children are determined by the emmetropization process, which is closely related to the changes in the axial length of the eye and the corneal curvature. Studies on the effects of birth parameters on the emmetropization process have shown that

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children (aged 7-9 years) who are born more mature with higher birth weights and larger head circumferences had longer axial lengths, which did not affect the refractive error because of the flattening of the cornea and a decrease in the corneal refractive power.[8] Another study showed that children born with longer axial lengths had relatively slower increases in the axial length of the eye during the first 3 years of life, and this did not affect the development of refractive errors.[9] Mutti et al.[10] indicated that refractive errors at birth are important in the emmetropization process.

Infants small for gestational age (SGA) in terms of their birth weight are associated with high morbidity and mortality during the prenatal and neonatal periods.[11,12] Both SGA and preterm infants have high risks of developing severe ROP.[13,14] In addition, SGA infants have high risks for neurodevelopmental deficits, cerebral palsy, low visual acuity, blindness, deafness, mental retardation and low academic performance in long-term evaluations.[15-19] Being both SGA and preterm increases these risks even more. Gur et al.[20] showed that the delivery of a term SGA infant was an independent risk factor for long-term ophthalmic morbidity, including ocular inflammation and infections, visual problems and ophthalmic hospitalization. Children born SGA have been shown to have a high risk of developing hyperopia, which may be related to the smaller globe size and the presence of factors causing fetal growth retardation.[21,22]

Although there are many studies on the effect of birth weight and prematurity on long-term ophthalmologic development, studies on the effect of being an SGA infant on long-term ophthalmologic development are limited. Those studies either included a small sample size or included only term or term-preterm infants.[18, 20-25]

In our country, the national vision screening program recommends scanning for amblyopia risk in individuals 3 to 5 years old.[26] American Academy of Ophthalmology, American Academy of Pediatrics and U.S. Preventive Services Task Force recommend screening children for amblyopia and its risk factors at least once when they are between ages 3 and 5 years to detect cases of amblyopia or its risk factors (B category; strong recommendation).[27,28]

In this retrospective study, we evaluated the ophthalmologic examination results of 3-year-old children who were screened for ROP in the neonatal period. We aimed to identify amblyogenic risk factors such as high refractive errors, anisometropia and strabismus and compare SGA and appropriate for gestational age (AGA) premature infants in terms of these risk factors.

Material and Methods

This study was performed in accordance with the principles outlined in the Declaration of Helsinki after it was approved by the Ethics Committee of Etlik Zübeyde Hanım Women's Health Education and Resarch Hospital and registered with the report number 90057706-799 on March 22, 2019. Informed consent was obtained from all individual participants included in the study. A retrospective review was conducted on the medical files of patients undergoing the ROP screening program. Patients who had ophthalmologic examinations at 3 years of age were included in the study. Children who developed cerebral palsy related to periventricular leukomalacia and were treated for ROP were excluded from the study because of the possible effects of these factors on the refractive status of the eye. The patient files were evaluated retrospectively; the sex, gestational age, birth weight, ROP screening results, presence and type of multiple pregnancies, refractive status and presence and type of strabismus were recorded. Infants with birth weights below the 10th percentile according to the Fenton Growth Chart were considered SGA, and those above the 10th percentile were considered AGA.[29]

In our ROP clinic, we screened all infants with birth weights ≤1500 g and gestational ages

of ≤32 weeks and selected infants who were considered to be at risk by the Neonatology Clinic. ROP examinations were performed under topical anesthesia with an indirect binocular ophthalmoscope (Omega 2C, Heine, Germany) and a 20 diopter (D) lens (Volk Double Aspheric, USA). The findings of the ROP screening were recorded according to the guidelines of the International Classification of ROP study.[30]

At the examination performed in children at 3 years of age, fixations, smooth pursuit eye movements, the results of the Hirshberg test for manifest deviations, results of the cover test and prism cover test for latent and manifest deviations, results of the anterior segment evaluations, cycloplegic refractions and results of the retinal examinations were recorded. Cycloplegia was induced by a drop of proparacaine hydrochloride 0.5% (Alcaine, Alcon, USA) followed by two drops of cyclopentolate hydrochloride 1% (Sikloplejin, Abdi İbrahim, Turkey). Retinal examinations were performed by indirect binocular ophthalmoscopy and a 20 D lens.

The spherical equivalent (SE) was used to calculate the myopic and hypermetropic refractive errors and was calculated by adding the spherical power and half of the astigmatic power. The American Academy of Ophthalmology pediatric eye evaluation preferred practice pattern guidelines were used for refractive correction.[28] The significantly high refractive error values, cut off values for anisometropia and optical correction values are shown in Table I. The astigmatic refractive errors were recorded as negative cylindrical values. The axes of astigmatism (≥1.00 D) were divided into three classes: with the rule (WTR) astigmatism 0-15° and 165-180°, against the rule (ATR) astigmatism 75-105° and oblique astigmatism 16-74° and 106-164°.

Statistical analysis

Statistical analysis was performed using SPSS v.21.0 for Windows (IBM Corp. Released 2012, IBM SPSS Statistics for Windows, Version 21.0 Armonk, NY: IBM Corp.). Continuous variables are presented as the mean ± SD; categorical variables are defined as numbers and percentages. Chi-square test was used for categorical variables. Because there was a strong correlation between the refractive errors of the right and left eyes, only data from the right eyes were analyzed (Pearson's r=0.96). Kolmogorov-Smirnov and Shapiro-Wilk tests were used to evaluate the distributions of the data. The differences between the means were evaluated by t-test for normally distributed data and by Mann-Whitney U test for data not normally distributed. Additionally, multivariate logistic regression analysis was used to identify factors significantly associated with strabismus and refractive errors requiring optical correction. Multivariate logistic regression analysis was used for the variables identified as statistically significant ($p < 0.10$) in the univariate analysis. Differences were considered statistically significant when $p < 0.05$.

Results

In the retrospective evaluation of the patient files, 608 children who met the study criteria were identified. Overall, 317 of them were male (52.1%), and 291 of them were female (47.9%). The mean gestational age was 31 ± 3 weeks (24-36 weeks), and the mean birth weight was 1505 ± 435 g (600-2460 g) overall. In terms of the birth weight, 101 children (16.6%) were SGA, and 507 children (83.3%) were AGA infants. The rate of multiple pregnancies was 49.8% (n= 300); 90% (n= 270) of them were twin pregnancies, 8.3% (n= 25) were triplet pregnancies, and 1.8% (n= 5) were quintuplet pregnancies. ROP was detected in 145 (23.8%) children, and all of them spontaneously regressed during the follow-up period.

The mean SE of the whole group was 1.66 ± 1.49 D. The mean SE for the SGA group was 2.12 ± 1.80 D, and that for AGA group was 1.53 ± 1.41 D (p= 0.04, Mann-Whitney U test). Significant refractive error according to the SE was found

in 127 (20.8%) children, including myopia (n= 42) and hyperopia (n= 85). Astigmatism ≥1.00 D was detected in 224 (36.8%) children, 166 (27.3%) children had significant astigmatism (1.00-2.00 D), and 58 (9.5%) children had high astigmatism (≥2.00 D). A total of 84.9% (n= 174) had WTR astigmatism, 6.8% (n= 14) had ATR astigmatism, and 8.3% (n= 17) had oblique astigmatism.

Optical correction was needed in 101 (16.6%) children. Among them, 30 (29.7%) children had both strabismus and refractive error, 23 (22.8%) children had high astigmatism, 17 (16.8) children had anisometropia, 16 (15.8%) children had high hyperopia and 15 (14.9%) children had both high hyperopia and high astigmatism. Anisometropia (≥1.00 D) was detected in 51 (8.3%) children. Significant anisometropia (1.00-2.00 D) was seen in 31 (5%) children, and high anisometropia (≥2.00 D) was seen in 20 (3.3%) children. Strabismus was diagnosed in 34 (5.6%) children, 26 (76.5%) of them had esotropia, 7 (20.6%) of them had exotropia and 1 (2.9%) child had hyperopia.

Risk factors, which may affect refractive errors requiring optical correction and the development of strabismus, were evaluated by univariate and multivariate logistic regression analyses and are given in Table II and Table III, respectively. Multivariate logistic regression analysis showed a strong association between SGA and refractive errors requiring optical correction (OR: 0.37, 95% Cl 0.22-0.62, p <0.01) and between multiple pregnancies and refractive errors requiring optical correction (OR: 0.62, 95% Cl 0.39-0.98, p = 0.04). A statistically significant correlation was detected between the presence of hyperopia (≥3.00 D) and the presence of strabismus in the univariate logistic regression analysis.

A comparison of the demographic and clinical characteristics of patients with SGA (n= 101) and AGA (n= 507) is given in Table IV. Although the mean gestational age of the SGA group was higher than that of the AGA group, the number of children with strabismus, significant hyperopia, high astigmatism or refractive errors requiring optical correction were significantly higher in the SGA group (Table IV).

Discussion

The ophthalmologic examinations performed at 3 years of age in children who were born premature and screened and followed up for ROP revealed that 5.4% had strabismus and 16.6% had refractive errors requiring optical correction in our study. Logistic regression analysis revealed that multiple pregnancies and being an SGA infant were risk factors for refractive errors requiring optical correction and that the presence of significant hyperopia (≥3.00 D) was a risk factor for the development of strabismus. The mean SE was statistically more hypermetropic in the SGA group compared to the AGA group, and the number of children with strabismus, significant hyperopia, high astigmatism and refractive errors requiring optical correction were statistically higher in the SGA group compared to the AGA group.

Studies on preterm infants with ROP that either spontaneously regressed or required treatment showed an increase in the incidence of myopia, anisometropia, astigmatism and strabismus in these infants.[27,31] In our study, the incidence of myopia was 6.9% (n= 42), but optical correction

Table I. Cut-off values for refractive errors used in the study.

Variables	Significant refractive error	High refractive error	Anisometropia	Optical correction
Hyperopia (+, D)	≥ 3.00*	≥ 5.00*	≥ 1.50*	≥4.50 (no deviation) ≥1.50 (with deviation)
Myopia (-, D)	≤ 0.25*	≤ 3.00*	≤ 3.00*	≤ 3.00
Astigmatism (-, D)	≥ 1.00	≥ 2.00	≥ 2.00	≥ 2.00

D: diopter; *: spherical equivalent

Table II. Logistic regression analysis for factors associated with refractive errors requiring optical correction.

Variables	Univariate analysis			Multivariate analysis		
	p	OR	(95 CI)	p	OR	(95 CI)
Gestational age	0.01	0.01	(1.02-1.11)	0.24	1.05	(0.96-1.14)
Birth weight	0.86	1.00	(0.99-1.00)	-	-	-
Small for gestational age	<0.01	0.36	(0.22-0.59)	<0.01	0.37	(0.22-0.62)
Multiple pregnancy	0.02	0.61	(0.40-0.95)	0.04	0.62	(0.39-0.98)
Sex	0.94	1.02	(0.66-1.56)	-	-	-
Retinopathy of prematurity	0.98	1.01	(0.61-1.66)	-	-	-
Gestational age ≤ 27weeks	0.22	1.40	(0.81-2.39)	-	-	-
Birth weight ≤ 1000 g	0.28	0.72	(0.40-1.30)	-	-	-

OR: Odds ratio, CI: confidence interval.

Table III. Logistic regression analysis for factors associated with strabismus.

Variables	Univariate analysis			Multivariate analysis		
	p	OR	(95 CI)	p	OR	(95 CI)
Gestational age	0.02	1.17	(1.02-1.34)	0.14	1.20	(0.96-1.30)
Birth weight	0.76	1.00	(0.99-1.00)	-	-	-
Small for gestational age	<0.01	2.97	(1.42-6.22)	0.07	0.37	(0.22-0.62)
Multiple pregnancy	0.78	1.10	(0.55-2.20)	-	-	-
Sex	0.65	1.17	(0.58-2.35)	-	-	-
Retinopathy of prematurity	0.71	0.86	(0.39-1.89)	-	-	-
Gestational age ≤ 27weeks	0.67	1.20	(0.51-2.81)	-	-	-
Birth weight ≤ 1000 g	0.21	1.60	(1.02-1.34)	-	-	-
Hyperopia (≥3.00D)	<0.001	0.12	(0.05-0.24)	<0.001	0.14	(0.06-0.30)
Myopia(≤0.25D)	0.99	0.00	(0.00-;)	-	-	-
Astigmatism (≥2.00D)	0.10	2.15	(0.85-5.43)	0.82	0.88	(0.31-2.48)
Anisometropia (≥2.00D)	0.02	0.49	(0.18-1.34)	0.17	0.38	(0.09-1.54)

OR: Odds ratio, CI: confidence interval

was not required (myopia ≤ 3.00 D). Children who needed optical correction had one of the following diagnoses: high hyperopia, strabismus with refractive errors, high astigmatism or anisometropia. Holmstrom et al.[7] detected astigmatism at a corrected age of 30 months in 26% of the premature infants included in their study, and they showed that ATR was the most common type. The incidence of astigmatism was 33.7% in our study, and WTR astigmatism was the most common type (84.9%). The incidence of high astigmatism was 7.7% overall, and the incidence of high astigmatism in the SGA group was statistically higher than that in the AGA group. Additionally, the mean SE was statistically more hypermetropic in the SGA group. Rutstein et al.[23] showed that the average spherical refractive error for intrauterine growth-retarded infants was approximately 0.50 D more hypermetropic compared to that in normal birth weight infants. There are studies supporting this finding that being an SGA infant is a risk factor for the development of hyperopia during adolescence.[21,22] In our study, the number of children with hyperopic refractive errors was significantly higher in the SGA group than in the AGA group. The progression of refractive errors in children is determined by the emmetropization process, which is closely related to changes in the axial length of the eye and refractive powers of the cornea and lens. Studies on the emmetropization process showed

Table IV. Comparison of demographic and clinical characteristics of patients with SGA and AGA.

Variables		SGA (n=101)	AGA (n=507)	p value
Gestational age (week)	Mean ± SD	32 ± 3	30 ± 3	<0.01
	(Range)	(25-36)	(24-36)	
Birth weight (g)	Mean ± SD	1260 ± 396	1554 ± 426	<0.01
	(Range)	(600-2190)	(690-2460)	
Sex	Male; n (%)	37 (36.6)	280 (55.2)	<0.01
	Female; n (%)	64 (63.4)	227 (44.8)	
Multiple pregnancy	n (%)	44 (43.6)	256 (50.5)	
Strabismus	n (%)	12 (11.9)	22 (4.3)	0.20
Retinopathy of prematurity	n (%)	27 (26.7)	118 (23.3)	0.03
Spherical equivalent (D)	Mean ± SD	2.12 ± 1.80	1.53 ± 1.41	0.45
	(Range)	(-1.50 to 10.00)	(-2.75 to 8.75)	0.04
Refractive error				
Hyperopia (≥3.00D)*	n (%)	23 (22.8)	62 (12.2)	0.005
Myopia (≤0.25)*	n (%)	5 (5.0)	37 (7.3)	0.39
Astigmatism (≥1.00 D)	n (%)	51 (50.5)	173 (34.1)	<0.01
Astigmatism (1.00-2.00 D)	n (%)	33 (32.7)	133 (26.2)	0.18
Astigmatism (≥2.00 D)	n (%)	18 (17.8)	40 (7.9)	<0.01
Anisometropia (≥1.00D)	n (%)	7 (6.9)	44 (8.7)	0.36
Anisometropia (1.00-2.00 D)	n (%)	3 (2.9)	28 (5.5)	0.13
Anisometropia (≥2.00D)	n (%)	4 (4.0)	16 (3.2)	0.67
Optical correction	n (%)	31 (30.7)	70 (13.8)	<0.001

AGA: appropriate for gestational age, D: Diopter, SD: standard deviation, SGA: small for gestational age, *: spherical equivalent

that children finally became emmetropic with subsidiary changes in these parameters in long-term evaluations.[8,9] Mutti et al.[10] stated that the refractive error at birth is important in the emmetropization process. Özdemir et al.[32] revealed that the axial length shortens as gestational age and birth weight decreased in prematurely born children (5-7 years) who did not develop ROP. Since the refractive state is corrected by the emmetropization process, no significant refractive error develops in these children. We detected statistically significantly more hyperopia in children born SGA than those born AGA. This result may have results from shorter axial lengths in SGA infants. Additionally, factors causing intrauterine growth retardation may adversely affect the emmetropization process in these children. Lim et al.[9] showed that infants with longer axial lengths had smaller increases in the axial length in the first 3 years of life and that this condition did not cause refractive errors. Studies have revealed that SGA infants have a higher risk of low visual acuity, blindness, deafness, neurodevelopmental deficits, cerebral palsy and mental retardation compared to AGA infants.[15-18,33] Although the mean gestational age in the SGA group was higher than that in the AGA group in our study, the incidence of strabismus and refractive errors requiring optical correction were statistically significantly higher in the SGA infants. Studies comparing preterm SGA, term SGA and term AGA infants revealed that the preterm SGA group had worse visual functions and more cases of strabismus than the term AGA group, but there was no statistically significant difference between the term AGA and term SGA groups.[22,24,25] Similarly, Rutstein et al.[23] did not find any significant difference between the term intrauterine growth-retarded

group and term normal birth weight group, but they did not include a preterm SGA group for comparison.

Studies have shown that functional vision, visual motor integration and academic performance are adversely affected in children born SGA, even in those without major neurologic problems.[19,33,34] It has been shown that these functions are much more adversely affected in SGA-born children than in AGA-born children.[33,34] Ley et al.[35] proposed that thinning detected in the neuroretinal rim in young adults born SGA because of intrauterine growth retardation could be due to the loss of axons in the optic nerve caused by fetal circulatory insufficiency. Additionally, Thordstein et al.[36] showed an increase in the latency of visual evoked potentials (VEPs) in intrauterine growth-retarded children, and they proposed that this increased latency may be an indicator of adversely affected intrauterine brain development. Pinello et al.[18] found that SGA infants had lower visual acuity, as measured with Teller Acuity Cards, and lower mental performance, as measured with the Bayley Scale of Infant Development, compared to AGA infants at 1 year of age. This study was performed in a small patient group (n=17), and refractive errors were not included. Additionally, it was not stated whether refractive errors were corrected or not in the evaluation of visual acuity. Although visual acuity was not evaluated in our study, the incidence of refractive errors and optical correction were higher in the SGA group than in the AGA group. Overall, being SGA was a risk factor for the development of refractive errors requiring optical correction.

The incidence of strabismus in childhood varies (2-26%) across studies according to the GA and BW of the child and the presence of ROP and cerebral palsy. Studies have revealed a strong correlation across the birth weight, gestational age and strabismus incidence.[6,31,37-39] In the Millennium Cohort Study[39], which was carried out in the United Kingdom, 14980 children aged 3 years were screened, and the incidence of strabismus was found to be 2.1%. The incidence was 4.6% in the gestational age-matched and birth weight-matched group in our study (GA<37 weeks, BW<2500 g). Gulati et al.[6], in a study in a large population of prematurely born children (n=38055), revealed the incidence of strabismus to be 3% and stated that low birth weight was an independent risk factor for the development of strabismus. Robaei et al.[40] stated that low birth weight infants (1500-2500 g) were at increased risk of developing amblyopia, anisometropia and strabismus compared to normal birth weight infants (≥2500 g) during childhood. Gur et al.[20] showed that being an SGA infant is an independent risk factor for long-term ocular morbidity (up to 18 years after delivery). They found that the SGA group were at a higher risk for strabismus and amblyopia than the AGA group. Fieß et al.[41] detected strabismus in 17.5% of the individuals aged 4-10 years in the preterm group (GA≤37 weeks) and found that GA, hyperopia (≥3.00 D), and astigmatism were risk factors for the development of strabismus. We detected the incidence of strabismus to be 11.9% in the SGA group and 4.3% in the AGA group (p=0.03). Hyperopia (≥3.00 D) was a significant risk factor for the development of strabismus according to the logistic regression analysis. Consistent with our findings, different studies have revealed that hyperopia is a risk factor for strabismus.[42,43] In our study, SGA infants had statistically significantly higher hyperopia, which may be an important risk factor for the development of strabismus in this group.

One of the limitations of our study is that visual acuity was not evaluated because of the retrospective nature of the study. Additionally, ocular biometric measurements could not be performed, and factors causing intrauterine growth retardation could not be evaluated. On the other hand, the large sample size and comparison of SGA and AGA preterm groups are the major strengths of this study.

In conclusion, preterm-born children have a high risk for refractive errors, and being SGA increases this risk even more. It is advised

that preterm infants are closely followed up after the completion of ROP screening for high refractive errors and strabismus to prevent the development of amblyopia.[44] We suggest that pediatricians and ophthalmologists are informed that both children born preterm and those born SGA are at high risk for developing strabismus, high hyperopia and high astigmatism and should be closely and regularly examined for amblyogenic risk factors.

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Case Report

A case of fulminant pneumococcus meningoencephalitis progressing with white matter involvement despite two doses of conjugated pneumococcus vaccine

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ABSTRACT

Background. *Streptococcus pneumonia* is a cause of serious mortality and morbidity, especially among small children. However, currently, it causes lower rates of invasive infections due to successful vaccination programs.

Case. We report an exceptional case of a 6-month-old child with meningoencephalitis caused by *Streptococcus pneumonia* despite the administration of two doses of pneumococcal conjugate vaccine (PCV). Meningitis progressed rapidly and led to widespread damage in parenchymal brain tissue with the emergence of fulminant meningoencephalitis. Computed tomography (CT) and magnetic resonance imaging (MRI) revealed widespread brain lesions, suggesting extensive parenchymal injury.

Conclusion. Such diffuse white matter lesions among pediatric patients with *Streptococcus pneumonia* meningoencephalitis despite two doses of PCV have not been reported previously.

Key words: pneumococcal conjugate vaccine, meningoencephalitis, meningitis, streptococcus pneumoniae, serotype 19F.

Streptococcus pneumoniae is the leading cause of community-acquired invasive bacterial infections in young children and is a cause of serious mortality and morbidity.[1] Pneumococcal conjugate vaccines (PCV) were developed over the last decade to provide effective vaccine protection, particularly in young children. Conjugate vaccines were demonstrated to be effective for reducing transmission and protecting against invasive disease.[2,3]

Complications linked to due *S. pneumoniae* infection occur due to the invasive and immunogenic effects of alpha-hemolytic streptococci. Pneumococcal meningitis causes cerebral vasculitis.[4]

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When both severe meningeal and encephalitic findings are present, the term meningoencephalitis may be used.[5] However, the extension of S. pneumonia infection to the parenchyma of the central nervous system (CNS) in adults and children has only rarely been reported.[5-7]

In this report, we present a 6-month-old infant who developed. *S. pneumoniae* meningitis despite the administration of two doses of PCV and whose meningitis progressed rapidly and led to widespread damage in parenchymal brain tissue with the emergence of fulminant meningoencephalitis.

Case Report

A 6-month-old male patient was referred to the emergency clinic of our hospital with symptoms of high fever, alteration in consciousness, ptosis

of the left eyelid and seizure. It was learned from his history that he had no previous problems. He had projectile vomiting and a high fever for several days. One day before attendance at the hospital, he had changes of consciousness and loss of appetite.

It was also learned that he was the second child of parents who were not relatives and was fed with breastmilk within the first four months and then supplements were added. His neurologic development was appropriate for age. Two doses of pneumococcal conjugate vaccines had been administered.

When he was referred to the pediatric emergency clinic, his general condition was poor and he was unconscious.

His rectally measured body temperature was 39.7°C, heart rate 125 beats/min, blood pressure 80/55 mm Hg and oxygen saturation 96%.

On neurologic examination, anisocoria was present. There was ptosis in the left eye. A light reflex could not be elicited in the left eye. In the right eye, the direct light reflex was positive. The deep tendon reflex could be elicited and foot sole skin reflexes were bilaterally positive. Four extremities were spontaneously mobile, there was no clear lateralizing muscle strength deficit. The Glasgow Coma Score was 7. The child was intubated and accepted to our pediatric intensive care unit (PICU).

Blood count results performed after the patient was admitted were as follows: Hemoglobin: 12 g/dL, white blood cell (WBC): 7800/mm^3, thrombocyte: 347,000/mm^3, C-reactive protein:150 mg/L, PTT/PT:48/24 seconds, and INR: 2.1. Biochemical parameters were found to be normal. Blood and urine cultures were obtained. Viral and bacterial respiratory tract samples were sent for polymerase chain reaction (PCR) analysis. Contrast-enhanced brain computed tomography (CT) was normal.

In a lumbar puncture (LP), Gram staining revealed abundant Gram-positive cocci in pairs. (Fig. 1). Cerebrospinal fluid (CSF) examination revealed a turbid fluid with a WBC count of 250/mm^3 (100% polymorphonuclear cells), protein 420 mg/dl (reference value: 15-45 mg/dl), and glucose 1 mg/dl. Simultaneous blood glucose was 178 mg/dl. Gram-positive diplococcus was seen on a Gram-stained preparation of the CSF.

Acute bacterial meningitis was diagnosed and treatment with intravenous ceftriaxone (100 mg/kg/day), vancomycin (60 mg/kg/day), and dexamethasone (0.15 mg/kg every 6 h) was initiated. In follow-up, there was a clonic seizure in the right arm lasting for 15 seconds; phenytoin was started. Within the first day, both blood culture and cerebrospinal fluid yielded a pure growth of *S. Pneumoniae*, type 19 F. Rifampicin was added to treatment. On a neurologic examination performed one day later, dystonia was detected and clonazepam was initiated. No evidence was found for other (viral) causes of meningitis/encephalitis.

With no improvement to the general status on monitoring, cranial magnetic resonance imaging (MRI) was performed. Ischemic areas were observed in basal ganglions, left dentate nucleus, external capsules, medial lemniscus, corpus callosum splenium, temporal lobes, and the centrum semiovale, showing widespread

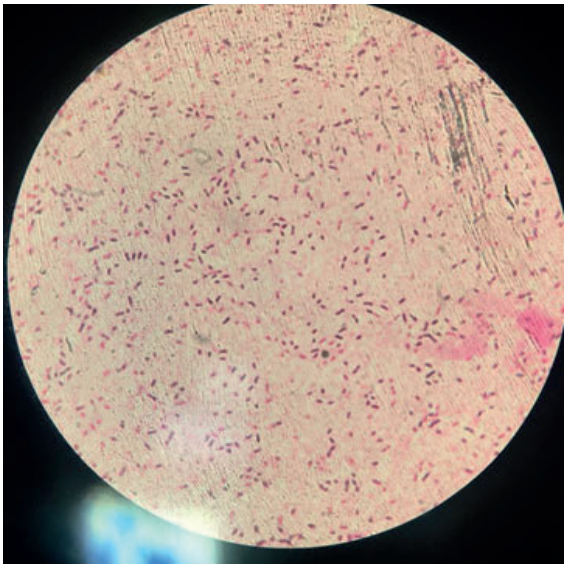

Fig. 1. Diplococci were commonly observed with gram staining of CSF.

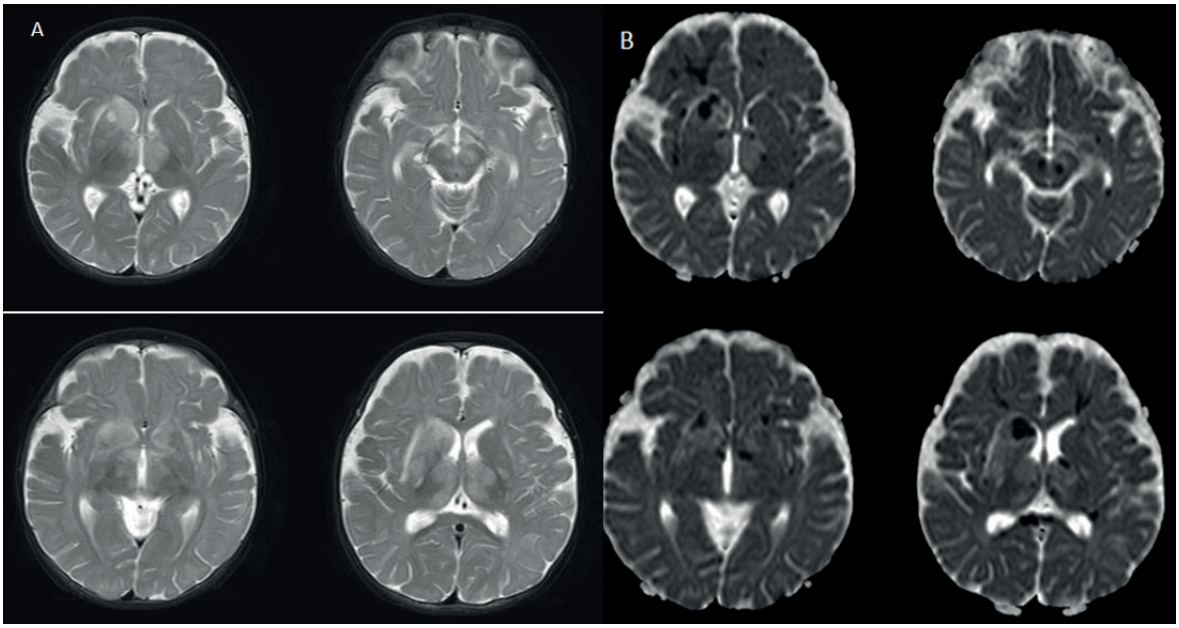

Fig. 2A. T2-weighted cranial magnetic resonance images show hyperintense pathologic signal changes in bilateral lentiform and caudate nucleus as well as in bilateral thalamus, red nucleus, lemniscusmedialis and external capsule. **2B.** Corresponding ADC (Apparent Diffusion Coefficient) maps demonstrate restricted diffusion in hyperintense areas suggesting acute ischemic foci.

diffusion restriction on T2-weighted images (Fig. 2A and B). Diffusion-weighted (DW) MRI was suggestive of meningovasculitis with multiple bilateral small infarcts, possibly secondary to small-vessel vasculitis.

On a follow-up CT 6 days later, hypodense areas were observed in the left dentate nucleus, pons posterior and mesencephalon, thalamus anteromedial and bilateral basal ganglions, external capsule, internal capsule, and the level of the centrum semiovale. Findings were evaluated as secondary to meningoencephalitis. Also, expansion was observed in the ventricles and hydrocephalus had developed. Daily head circumference measurements were planned.

Minimal inhibitory concentration (MIC) levels of ceftriaxone were 0.38 μg/mL. Rifampicin and vancomycin were stopped. Ceftriaxone was continued. The respiratory tract was negative for viral PCR. Levetiracetam was added to the treatment because of his seizures.

On the 12th day of admission to the PICU, the boy's head circumference increased and cranial tomography was performed again. Occasional pathological contrast involvement considered secondary to a linear infarct was observed on the right at the level of the putamen and thalamus. Hypodense areas were observed on the right in both front regions secondary to infarctus in a broad area or linked to cerebritis in the periventricular white matter.

A drain was inserted on the 13th day due to increased hydrocephalus (Fig. 3). Extubation was finally achieved on day 15 after admission, and on day 18 the patient was transferred to the pediatric infectious disease ward.

There was no growth in a follow-up CSF culture. External drainage was removed on the 26th day and a V-P shunt was inserted.

In visual evoked potential tests, the patient had a latency of 195 msec on the right and 122 msec on the left, with clear extension found. Brainstem auditory evoked response identified bilateral sensorineural hearing loss. No immune deficiency was detected in the patient. The patient was discharged to the pediatric infection

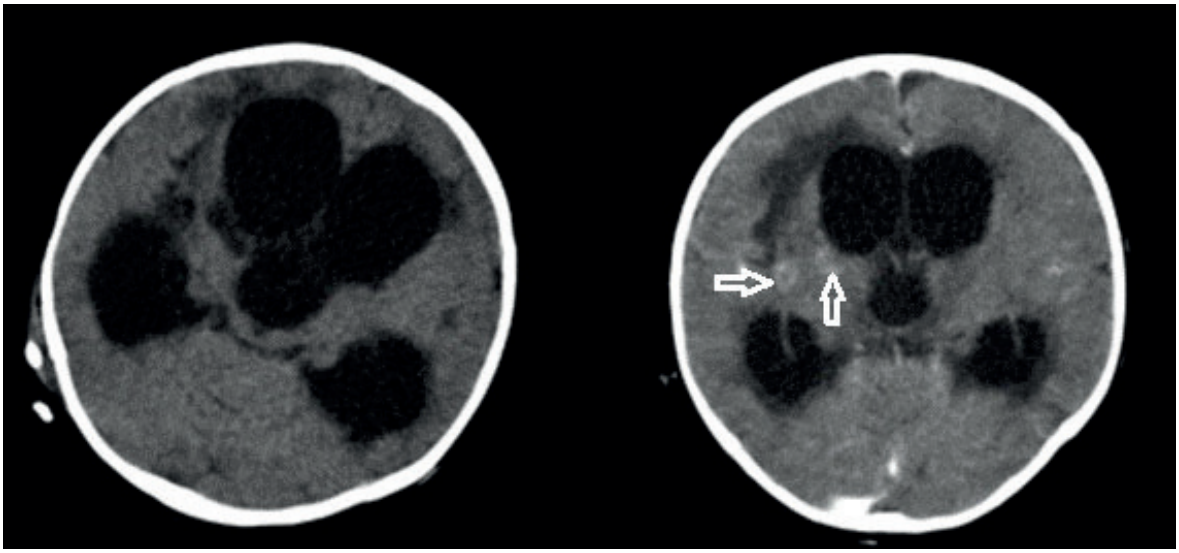

Fig. 3. Control cranial computed tomography.

Dilatation in bilateral lateral ventricle and 3rd ventricle; secondary hypodense areas of chronic infarctus in bilateral frontal periventricular white matter, more pronounced on the right; and hypodense area linked to resorption of transependymal cerebrospinal fluid in the bilateral periventricular region.

ward on the 28th day of hospital admission with levetiracetam, phenytoin, and clonazepam drops.

The patient is currently aged 4 years and continues to attend the rehabilitation center. His mental and motor development is poor, and he has anisocoria and mydriasis in the left eye.

Written consent for publication of this case report and accompanying images was obtained from the parents of the patient.

Discussion

S. Pnemoniae meningitis is an important cause of morbidity and mortality in young children worldwide.[8] Neurologic complications include seizures, diffuse brain edema, hydrocephalus, hearing loss and ischemic or hemorrhagic brain damage.[7] Cerebral vasculopathy is one of the major complications of bacterial meningitis.[9] In a study of pediatric patients by Synder et al.,[10] the rate of cerebrovascular complications associated with bacterial meningitis was reported to be 30%. In a retrospective study of 87 adult cases of pneumococcal meningitis, the incidence of arterial cerebrovascular complications was reported to be as high as 21.8%.[5] The agent that causes these complications is most frequently *S. Pneumoniae*.[9,11]

Thirteen valent pneumococcal conjugate vaccines (PCV13) were integrated into the expanded immunization program in Turkey in 2011.[12] The serotypes in the vaccines were 4,6B,9V,14,18C,19F,23F,1,5,7F,3,6A, and 19A.[11] PCV13, transported under cold chain conditions under supervision within the framework of the Ministry of Health regulations is administered to children at the ages of 2-4-6, and 18 months. The present patient was administered two doses of PCV13 per the routine vaccine protocol. Despite these two doses, the infection had fulminant progression and a clinical tableau of meningoencephalitis was observed with widespread ischemic areas including bilateral basal ganglions, dentate nucleus, external capsules, medial meniscus, corpus callosum splenium and temporal lobes.

Cerebral infarction typically seems to develop within the first few days of the disease with the inflammation of the CNS.[13] The mechanisms leading to cerebrovascular complications in bacterial meningitis are not completely understood and likely are multifactorial.

Invasion of the exudate into the large vessels at the base of the subarachnoid inflammatory brain may play a role. In addition, diverse bacterial components are powerful inducers of proinflammatory cytokines, possibly leading to vasculitis.[11] In cases of meningoencephalitis, local inflammation of the meninges extending to the intracranial blood vessels results in ischemia and subsequent stroke.

Radiologic follow-up and outcomes of meningoencephalitis are poorly documented. In the early course of successfully-treated meningitis, CT scans of the brain are usually normal. Only a few reports about MRI findings in acute *S. Pneumoniae* meningitis or meningoencephalitis have been published.[5,6] Another case reported was a 7-month-old girl. She presented to the hospital with seizures and was unconscious. The first CT scan was normal; however, with no improvement in neurologic status, MRI was taken and pathologic findings were observed. Peculiar, widespread and unique signal abnormalities were found on MRI in this child with meningoencephalitis caused by *S. Pneumoniae* with extensive central nervous white matter injury as well as evidence of thrombosis of the lateral transverse sinus. This was the first pediatric case of diffuse white matter lesions in the early course of disease in *S. Pneumoniae* meningoencephalitis.[5]

Infarctions in basal ganglions develop mostly secondary to chronic infections such as tuberculosis and fungal meningitis.[7] Infarction in basal ganglions has rarely been described in cases of meningoencephalitis associated with S.pneumoniae infection. The only pediatric case reported in the literature was a 4-month old infant.[7] The other three described cases are adults.[14-16] The clinical course of the 4-month-old infant was fulminant and necrosis was seen in bilateral basal ganglions in the autopsy performed after death.[7] There was basal ganglion involvement in one case reported in the literature and white matter involvement in another. However, in the present case, widespread involvement was observed in both regions.

It was reported that vaccine failure is rare. In a study of 161 pediatric cases in the United Kingdom, the vaccine failure rate was found as 0.66/100,000 in those vaccinated with PCV13.[17]

The causes of vaccination failure can be related to the patient, the vaccine or vaccination methods. Causes related to the patient include immune failure, patient age, eating disorder, whether the patient was healthy during vaccination or to the vaccination response in the individual. Causes related to the vaccine include the vaccine not containing some serotypes or genotypes and antigenic interaction and production-stage related reasons. Causes related to vaccination method include mistakes made during vaccine administration, not conforming to cold chain conditions during storage and transportation, and failure to follow the vaccination schedule.[18]

There are cases of infection reported despite vaccination. Basaranoglu et al.[19] reported infection with 19 F strains despite vaccination in two patients. Both patients had underlying neurologic deficits. One of the patients had a pneumonia infection, and the other had meningitis.[19] Park et al.[20] found an infection rate of 21% despite vaccination. The serotypes most commonly causing infection were 6B and 19F.[20] Vaccine breakthrough was reported to comprise 3% of meningitis cases in France.[21] The rate of infection even with vaccination was found as 25% from 2008-2014 in Turkey.[22] Again, in France, meningitis infection with 19F serotype was reported in an immunocompetent fully vaccinated 3-year-old child.[23] Our patient was aged 6 months and had had two vaccination doses administered. The patient had no identified underlying immune deficiency.

To our knowledge, the present case is the first pediatric case report in the literature of involvement of both diffuse white matter and basal ganglions associated with S.pneumoniae meningoencephalitis. Moreover, the disease had fulminant progression despite two doses of PCV13.

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Case Report

Successful intraosseous adenosine administration in a newborn infant with supraventricular tachycardia

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ABSTRACT

Background. Supraventricular tachycardia (SVT) is the most common type of tachycardia in childhood. The incidence is 1-4/1000 in childhood and 0.6/1000 in newborns.

Case. Here we report a 28-day-old male newborn who was diagnosed SVT, admitted to the Pediatric Emergency Department after restlessness that had started three hours before admission and measurement of the heart rate was above 250 beats/min.

Conclusions. This case is presented in order to emphasize that SVT is rare in the neonatal period and SVT is successfully terminated with the administration of intraosseous adenosine.

Key words: adenosine, newborn, intraosseous, adenosine, supraventricular tachycardia.

Supraventricular tachycardia (SVT) is the most common symptomatic tachycardia which requires medical treatment in childhood.[1] SVT attacks occur in 1-4 of every 1000 children. Its incidence in newborn infants is much lower and it has been reported to occur in only 6 out of every 10.000.[2]

Clinical findings in SVT may differ depending on the age of the child and the duration of the SVT. While children can be admitted with the feeling of palpitations, infants can be admitted with pallor, restlessness, lack of nutrition, cyanosis and tachypnea.[3] In SVT of infants, the first 12-24 hours are well tolerated, symptoms may be mild and tachycardia may not be recognized for a long time. Therefore, babies may present with heart failure (tachypnea, decreased weight gain, fatigue while feeding, perfusion disorder).[4]

The goal of acute treatment of SVT is to immediately convert the rhythm to sinus rhythm and prevent the rhythm from recurring. Vagal maneuvers, chemical cardioversion (i.e. adenosine) and synchronized cardioversion can be used in the treatment. The choice of treatment depends on the patient's hemodynamic and clinical status. Vagal maneuvers and adenosine are recommended as the first-line treatment method in infants with stable hemodynamic status.[5] Pediatric Advanced Life Support (PALS) guidelines stated that adenosine can be administered intravenously (IV) or intraosseous (IO) in the treatment of SVT.[6] However, the IO administration of adenosine, which is often administered IV, is controversial.[7] This case is presented to emphasize that SVT is rare in the neonatal period and SVT has been successfully terminated with IO adenosine administration.

Case Report

A 28-day-old male newborn who was born at 38 weeks 2 days via C-section, weighed 3450 grams, and was the first born of a 28-year-old mother was admitted to the Pediatric Emergency Department after restlessness that started three hours before the admission and measurement of the heart rate above 250 beats/min by the family. It was learned that he was

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admitted to the neonatal intensive care unit due to tachypnea at 13 days of age. Tachycardia was detected on the day of hospitalization and he was diagnosed with SVT. Thus; IV adenosine was administered and the SVT attack terminated so he was discharged with oral propranolol treatment after one week of follow-up. Echocardiography performed at his hospitalization was normal. He was using propranolol from 1.5 mg/kg with no family history.

His vital signs were as follows: body temperature: 36.4°C, respiratory rate: 40/min, heart rate: 288 beats/min-rhythmic, systolic blood pressure: 100 mmHg, SpO2:100%. No pathology other than tachycardia was detected on examination. Electrocardiogram findings were narrow QRS waves without P waves (Fig. 1). Therefore, the newborn was diagnosed with SVT. Upon vagal maneuver (ice application to the face) and failure of vascular access (three times), adenosine (0.1 mg/kg) was administered via EZ-IO® pathway from the left tuberosity tibia medial metaphysis and his pulse was reduced to normal limits immediately (Fig. 2). Posterior-anterior lung X-ray imaging was normal. Laboratory tests revealed: Hb: 14.7g / dL, Hct: 46.2%, CK: 463 U / L (0-171U / L), CK-MB (Mass): 12.14 ng/ml (3.6-4.8 ng/ml) Hs - Troponin T: was 297 ng / L (0-14 ng / L). At the 6th hour of the follow-up, the SVT attack repeated, since peripheral vascular access was achieved during this period, adenosine was given IV (0.1mg / kg) and the attack terminated. The infant was discharged from the emergency room at the 48th hour of his follow-up with oral propranolol and called for a control examination one week later. Permission was obtained from the parents for publication of this case and informed consent was obtained from the family.

Discussion

Adenosine, which is frequently preferred after vagal maneuver in hemodynamically stable SVT cases can be administered frequently as IV and rarely as IO.[6]

Adenosine is metabolized by the adenosine deaminase (ADA) enzyme in the erythrocyte membrane in 10 seconds. Therefore, in order to terminate the SVT attack, it must be given in an appropriate dose, with a suitable route and

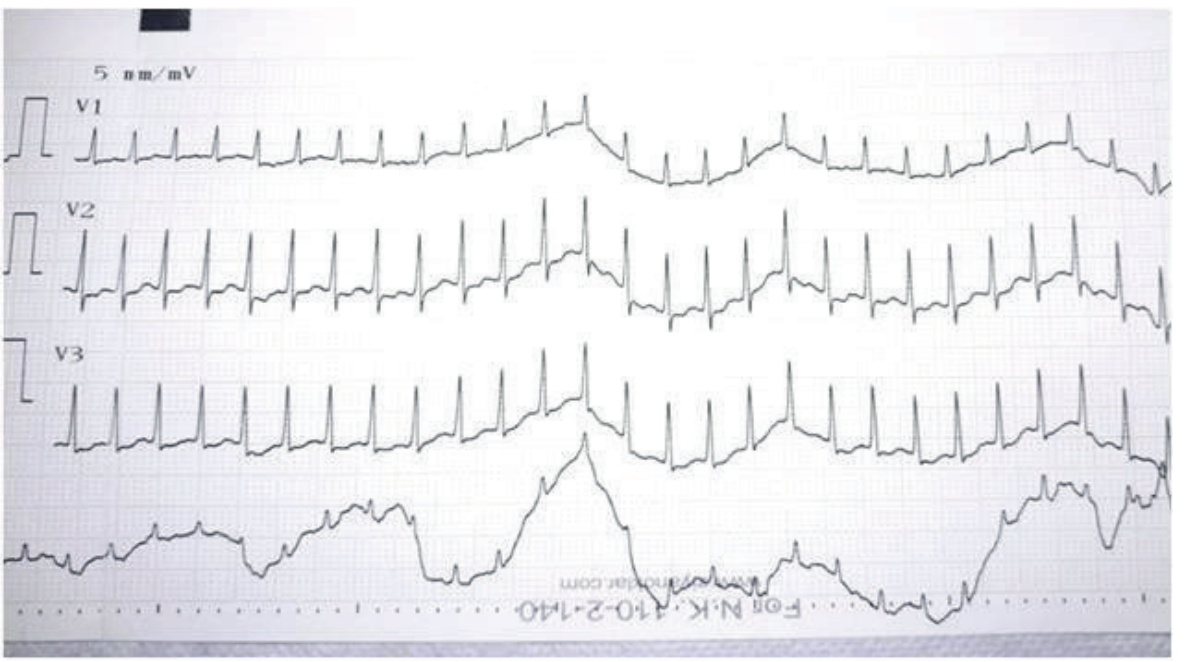

Fig. 1. First ECG of the newborn. Narrow QRS wave tachycardia can be seen.

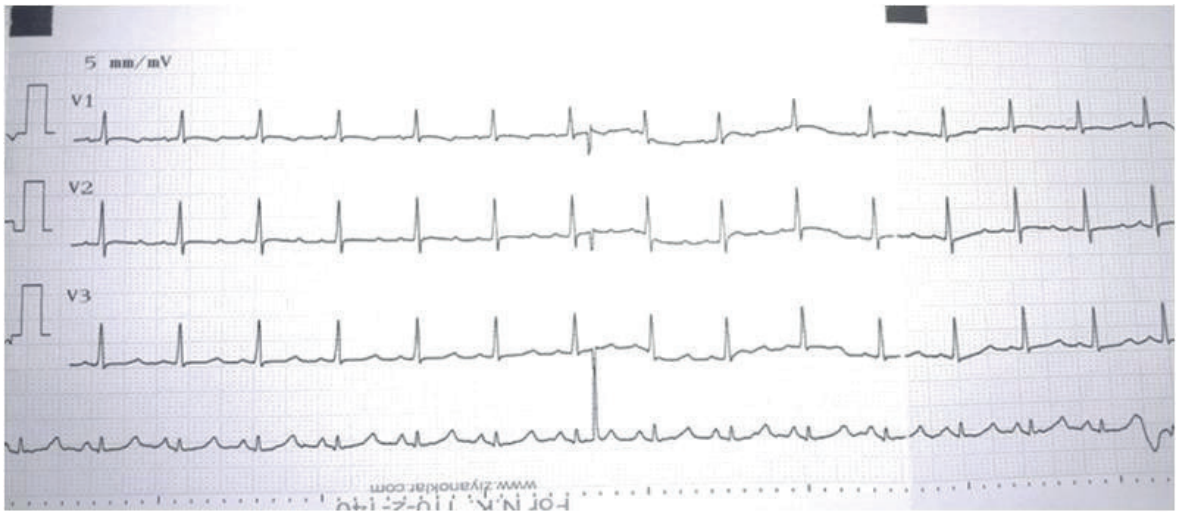

Fig. 2. ECG during IO adenosine administration. Sinus rhythm can be seen.

appropriate method. The recommended dose is 0.1 mg/kg.[8] It is preferred that the vein to be selected is the largest vein closest to the heart and the application of the flush method is very important when administering adenosine.[9,10]

Adenosine is a purine analog used in SVT since 1980. Adenosine stimulates potassium channels by binding to cardiac receptors and inhibiting calcium flow with G-CAMP-dependent mechanism. It acts via hyperpolarization in cardiac myocytes and slows down the transmission in the atrioventricular node[11] and usually terminates SVT within 20 seconds, approximately 72-78% of cases respond to adenosine.[12]

Treatment of SVT is vagal maneuver (ice application to the face, 15-30 second) for hemodynamically stable infants, IV adenosine (0.1 mg/kg) if the vagal maneuver is not effective. If no response is received within two minutes, IV adenosine (0.2mg / kg) is administered for the second time.[13] When the IV route cannot be opened within one minute the IO route can be opened and adenosine can be administered via the IO route. Antiarrhythmic drugs such as amiodarone and procainamide can be used in adenosine resistant SVT cases. In hemodynamically unstable infants, synchronized cardioversion (0.5-1 joule/kg if no response 2 joule/kg) should be applied. (6). The use of IO amiodarone can also be considered when IO adenosine administration fails, but the studies in the literature are mostly on adult patients.[14]

The intraosseous route was first defined in 1922 and has been used more widely in children since 1980s. It is a good alternative for drug and fluid treatment in critical patients who central and peripheral IV route cannot be achieved.[15] IO route should be used in children for three to four hours (maximum 24 hours) and access to the IV route should be obtained as soon as possible to reduce the development of complications related to the IO route.[16] Proximal tibia, distal tibia, sternum, proximal humerus and iliac wing can be used for the IO route. However, sternum should not be preferred in critical patients who may require cardiac resuscitation.[17]

Several different commercially available IO cannulation devices are available. Manual IO needles, battery powered driver (EZ-IO) and impact-driven devices (Bone injection gun [BIG], FAST) are preferred for IO cannulation. Other types of needles may be used if an IO needle or device is not available; these include bone marrow needles, styletted needles, and spinal needles. The device EZ-IO was approved by the Food and Drug Administration in 2004. The device consists of battery powered driver for insertion with different needle

length and gauge for placement in children and adults. Studies in animal and human cadavers demonstrated the superiority of the EZ-IO® over both, the manual needle and the BIG, regarding successful insertion on the first attempt.[18,19]

There is very little literature on both efficacy and administration related to IO adenosine administration in SVT. The first animal study conducted in 30 new weaning piglets in 1994 aimed to determine the effectiveness of IO adenosine and the therapeutic dosage of IO adenosine compared to the peripheral and central venous route. IO adenosine administration was found to be more effective and the therapeutic dosage range was found to be higher than the central venous route and slightly lower than the peripheral venous route.[7]

To the best of our knowledge, there have only been four infants to undergo the IO adenosine treatment because of SVT in the literature. Two of them were newborns, two of them were infants.[20-22] While the newborn cases were successfully treated with 0.1 mg/kg IO adenosine administration; no responses were received from the 2 months old infant with 0.25 mg/kg dose of IO adenosine and 0.2 mg/kg dose from 4 months old infant.[21] Herein we have reported a newborn who experienced the first SVT attack at 13 days of age and the second SVT attack at 28 days of age who successfully responded to 0.1 mg/kg adenosine administered IO during a SVT attack. The fact that successful IO adenosine cases in the literature are also newborns, suggesting that ADA activity may be lower in newborns compared to older ages. A lower level of ADA activity in newborns may be the reason that adenosine administrated by IO route acts without being metabolized. The reason for the absence of IO adenosine administration in the older age group in the literature may be the fact that the IV route is more easily accessed in older patients.

Although SVT is one of the common causes of tachycardia in childhood, it is a very rare condition in newborns. While the effectiveness of IO adenosine in children is controversial, the literature on this subject is very limited. In our case, IO adenosine was successful in terminating the SVT attack. In the treatment of SVT, it is important to choose the appropriate treatment according to the hemodynamic status of the infant and to use appropriate doses of drugs.

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Case Report

Peritoneal dialysis as a life-saving procedure in an extremely low birth weight infant: case report and review of the literature

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ABSTRACT

Background. Acute kidney injury (AKI) is a common condition in the neonatal intensive care unit (NICU), particularly in preterm infants. Management of AKI in neonates is challenging. Peritoneal dialysis (PD) has been preferred as the most applicable modality in neonates when medical therapy fails.

Case. A female infant was born at 24 and 4/7 weeks with a birth weight of 460 grams after an emergency cesarian section from a preeclamptic pregnacy. She developed AKI secondary to sepsis. A neonatal, straight single-cuff Tenckhoff catheter was inserted and PD was started on day 12. PD was discontinued after 6 days, on day 18 with adequate urine output and normalization of kidney function tests. However, the patient died on day 152 secondary to a nosocomial infection.

Conclusion. To the best of our knowlegde, our case is the smallest infant in whom PD was performed succesfully with a PD catheter. PD is a relatively safe, effective and a feasible therapy in the neonatal population even in the smallest infants. PD may be a live-saving procedure in extremely low birth weight infants with severe AKI.

Key words: acute kidney injury, extremely low birth weight, peritoneal dialysis, preterm.

Acute kidney injury (AKI) is defined as a decrease in kidney function associated with an increase in serum creatinine (Scr) levels which may or may not be accompanied by a reduction in urine output.[1,2] AKI has a great impact on morbidity and mortality in critically ill children and those who survive an episode of AKI should have long term follow up with regard to the risk of development of chronic kidney diease.[3,4] Among the neonatal population, AKI although still an underrecognized morbidity, is a common condition in the neonatal intensive care unit (NICU), particularly in preterm infants. It occurs in 40 to 70% of critically ill neonatal intensive care admissions.[5,6] Premature infants, especially those with lower birth weights are susceptible to AKI given to the incomplete nephrogenesis and their lower nephron number.[6,7] AKI has been reported to be associated with morbidity, longer hospital stays and mortality in this vulnerable population.[2,4,6,8]

Management of AKI in neonates is challenging. Prevention of AKI should be the first priority in management. However, data are sparse with regard to interventions to prevent AKI in at risk patients or to improve the outcome once it is established.[4,9] When medical management of AKI fails, the primary therapy is renal replacement therapy (RRT). Although indications for RRT are not very well described among neonates with AKI; refractory acidosis, uremia, electrolye disturbances, inability to provide adequate nutrition and fluid overload are the most common indications. Peritoneal dialysis (PD), intermittent hemodialysis (HD) and continuous renal replacement therapy (CRRT) are three common methods of RRT

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in neonates.[4,7] PD has been preferred as the most applicable modality in neonates so far.[7,10] However, its use has usually been deferred during the course of AKI especially in extremely low birth weight infants (ELBW) due to the fear of technical challenges.[9] In fact, several studies have described successful application of PD in critically ill ELBW infants.[11-21] Herein, we described our experience of PD in an ELBW infant who developed AKI secondary to sepsis.

Case Report

A female infant was born at 24 and 4/7 weeks with a birth weight of 460 grams after an emergency cesarian section. The pregnancy was complicated by preeclampsia. The apgar scores were 3 and 7 at 1 and 5 minutes, respectively. The patient was intubated in the delivery room and was given surfactant in the NICU due to the diagnosis of respiratory distress syndrome and conventional mechanical ventilation was started. The patient developed stage 4 intraventricular hemorrhage on day-3 and she was given an erythrocyte infusion. On day-10, she became hypotensive secondary to sepsis which was refractory to fluid resuscitation and she was given inotrope treatment. On day-11, the infant became anuric with worsening kidney function tests. Anuria was unresponsive to furosemide and Scr and blood urea nitrogen (BUN), were found to be 1.59 mg/dl and 50 mg/dl, respectively. Serum Na, K, Ca, phosphorus and uric acid levels were 184 meq/l, 5.9 meq/l, 10.3 mg/dl, 3.3 mg/dl and 7.8 mg/dl, respectively. On day-12, the patient was still anuric and became edematous with a 15.2 % fluid weight gain from birth. She was transitioned to high frequency oscillatory ventilation from conventional ventilation due to her worsening respiratory status secondary to fluid overload. Given the worsening respiratory and metabolic acidosis (venous pH: 7.20, PCO2:132 mmHg, PO2: 22.4 mmHg, HCO3: 12.4 mmol/l, BE:-11.7 and oxygen saturation % 88), electrolyte imbalance and generalized edema, PD was started on day-12. A neonatal, straight 10Fr single-cuff Tenckhoff catheter (Cook Medical, Bloomington, USA) with a length of 8 cm was inserted with a left paramedian entry site above the umbilicus at the bedside by a pediatric surgeon. Cutaneous and subcutaneous tissues were dissected down to the sheath of the rectus abdominal muscle and the guided PD catheter was inserted and advanced along the peritoneum, and directed to the left lower quadrant of the abdomen with the distal end placed in pelvis. Dialysis was started with a fill-volume of 20 ml/kg for 12 cycles per day. The fill and dwell times were 10 and 60 minutes, respectively. Biocompatible PD solution (glucose 1.36%, Na 132 mmol/L, Cl 95 mmol/L, Ca 1.25 mmol/L, HCO3 25 mmol/L, laktat 15 mmol/L, ph 7.40) was used. On the 3rd day of succesful PD (day-15), she was again placed on conventional ventilation which she tolerated well. Leakage of peritoneal fluid from the exit site was the only complication noted during the dialysis procedure. However, it did not impair PD efficacy and the infant's condition improved with decreasing Scr and BUN levels (0.77 mg/dl and 47.6 mg/dl, respectively) and a urine output of 3.6 ml/kg/day (24 hours of PD). PD was discontinued after 6 days, on day-18. Adequate urine output was maintained without the need for diuretics and renal function tests improved to a BUN level of 20 mg/dl and a Scr level of 0.57 mg/dl and the serum levels of Na, K and HCO3 were 140 meq/l, 4 meq/l and 31mmol/l, respectively with supplementation of 4 meq/kg of Na and 2 meq/kg of K in total parenteral solution without any HCO3 supplementation at this stage. No particular medication was given for renal dysfunction. However, the dosage of antibiotics was re-arranged according to the estimated creatinine clearance. Patient's Scr and BUN levels remained stable during the rest of her hospital stay and the lowest serum creatinine level which was 0.3 mg/dl was detected at day 90 when she was 1715 grams in weight. Renal ultrasonography was performed three times during her hospital stay and all revealed normal ultrasonographic findings without any increase in renal echogenicity and pelvicalyceal dilatation. The patient was never discharged and died on day 152 secondary to a nosocomial

infection which led to worsening symptoms of severe bronchopulmonary dysplasia (BPD) and severe pulmonary hypertension (PHT). No autopsy was performed.

Informed consent was received from the family before the preparation of the manuscript.

Discussion

Preterm infants are susceptible to perinatal and nosocomial infections, hemodynamic alterations, nephrotoxic medications which make them vulnerable to impairement of kidney function besides their physiologic vulnerability given their incomplete nephrogenesis and low nephron number.[6,7,22,23] By using contemporary definitions based on the neonatal modified KDIGO criteria (Table I), the incidence of AKI in low birth weight infants ranges between 19 to 40%.[8,24,25]

Sepsis is also an important risk factor for AKI among neonates. Among preterm infants, incidence of AKI secondary to sepsis has been postulated to be as high as 75.6%.[24] Sepsis has been reported to contribute to AKI secondary to the hypotension associated with systemic inflammation. However, it may directly damage the kidney by effects on microvasculature.[4,27-30]

Our case developed AKI secondary to sepsis. She carried the reported risk factors for AKI such as being an ELBW premature infant and having sepsis which led to hypotension refractory to inotrope support. RRT was considered in our case due to acidosis, uremia and anuria refractory to diuretic therapy which led to significant fluid overload. Providing RRT is the expected standard of care for neonates developing AKI when it is indicated.[10] To our knowledge, our case report represents the smallest infant in whom PD was successful using a standard PD catheter. The smallest infant who was treated with PD reported to date was from Japan who was 24 weeks and 3 days of gestation weighing 264 grams.[16] However, in that male infant a drainage tube was used for PD instead of a standard PD catheter and PD was continued for 32 days. In the study of Stojanovic et al.[19] a large-bore intravenous cannula was used for PD in a 27 week old preterm infant of 470 grams. In the present case, Tenckhoff PD catheter placed in the lower left quadrant was used and dialysis was started with fill volumes of 20 ml/kg. Harshman et al.[11] also used a commercially available PD catheter which was inserted in the left upper quadrant in an ELBW infant (830 grams) for PD with initial fill volumes of 20 ml/kg. In the case series of Macchini et al.[17] Tenchoff catheters were used for two ELBW (630 and 700 grams) infants for PD. In the study of Ustyol et al.[18] Tenckhoff catheters placed in the left lower quadrant were used for PD in 31 neonates, 16 of whom were preterm infants with the lowest gestational age (GA) and birth weight (BW) of 24 weeks and 580 grams, respectively. In other two large case series, PD was performed in a group of preterm infants with a minimum GA and BW of 27 weeks and 1000 gr, respectively using PD catheters in the infra-umbilical position.[12,13] Our case report was unique for a succesfull PD by using a commercially avalaible PD catheter with the placement of the distal end in the pelvis in

Table I. Neonatal KDIGO (Kidney Diseases: Improving Global Outcomes) acute kidney injury definition.

Stage	Serum creatinine (Scr)	Urine output over 24 hours
0	No change in serum creatinine or rise <0.3 mg/dL	>1 mL/kg/h
1	SCr rise ≥0.3 mg/dL within 48 h or SCr rise ≥1.5 to 1.9x reference SCr[a] within 7 days	>0.5 and ≤1 mL/kg/h
2	SCr rise ≥2 to 2.9 x reference SCr[a]	>0.3 and ≤ 0.5 mL/kg/h
3	SCr rise ≥3 reference SCra or SCr ≥2.5 mg/dL[b] or Receipt of dialysis	≤0.3 mL/kg/h

a Reference SCr will be defined as the lowest previous SCr value.
b SCr value of 2.5 mg/dL represents <10 mL/min/1.73m^2.

Table II. Characteristics of extremely low birth weight infants who underwent peritoneal dialysis during their intensive care unit stay.

Authors	Cause of AKI	GA (weeks)	BW (g)	Catheter type/Insertion site	Age at the beginning of PD (days)/PD solution	Duration of PD (days)	Complications	Outcome
Harshman et al.[11]	TTTS	28[3]	830	PD catheter/left upper abdomen	5/1.5% later 2.5%(Dianeal®)	16	None	Recovered
Yu et al.[15a]	Sepsis	26	930	IV catheter/ND	10/Dianeal®	2	Hernia	Recovered
Yu et al.[15a]	PDA, ICH	26	890	IV catheter/ND	25/Dianeal®	2	Peritonitis	Recovered
Yu et al.[15a]	Pneumonia, sepsis	28	900	IV catheter/ND	14/Dianeal®	6	None	Recovered
Yu et al.[15a]	Sepsis, NEC	28	730	IV catheter/ND	26/Dianeal®	3	None	Recovered
Yu et al.[15a]	PDA	26	680	IV catheter/ND	28/Dianeal®	6	None	Recovered
Yu et al.[15a]	PH	27	690	IV catheter/ND	8/Dianeal®	8	None	Recovered
Yu et al.[15a]	ICH	25	700	IV catheter/ND	21/Dianeal®	2	Leakage	Died
Yu et al.[15a]	Sepsis, NEC	28	980	IV catheter/ND	32/Dianeal®	3	Peritonitis	Died
Yu et al.[15a]	NEC, ICH	26	840	IV catheter/ND	18/Dianeal®	2	Leakage, hemoperitoneum	Died
Yu et al.[15a]	PH	26	630	IV catheter/ND	27/Dianeal®	2	None	Died
Yu et al.[15a]	PDA	24	820	IV catheter/ND	26/Dianeal®	3	None	Died
Yokoyoma et al.[16]	Sepsis	24	264	Drainage catheter/ right umbilical region	21/ 1.5% dialysate	32	Peritonitis, leakage	Recovered
Macchini et al.[17]	PDA	ND	700	PD catheter/paramedian entry site	12/ND	9	Leakage	Recovered
Macchini et al.[17]	Sepsis	28	630	PD catheter/paramedian entry site	9/ND	27	Leakage	Recovered
Ustyol et al.[18]	Sepsis	26	600	PD catheter/0.5-1 cm below the umbilicus	14/1.36% or 2.27% (Baxter®)	3	ND	Died
Ustyol et al.[18]	Sepsis	25	750	PD catheter/0.5-1 cm below the umbilicus	11/1.36% or 2.27% (Baxter®)	1	ND	Died

AKI: acute kidney injury, BW: birth weight, GA: gestational age, ICH: intracranial hemorrhage, NEC: necrotizing enterocolitis, PD: peritoneal dialysis, PDA: patent ductus arteriosus, PH: pulmonary hemorrhage, TTTS: twin-twin transfusion syndrome, ND: not defined.

[a] In the study of Yu et al.15, the insertion site was not specified; authors reported that the tip of the catheter was placed in the contralateral iliac fossa, pelvis or subhepatic area. Dianeal® glucose solution with different glucose concentrations (not specified) according to the patient's fluid and metabolic status was used.

* Overall incidents recorded during PD were fluid leakage, blockage of the drain, unstable glycaemia, ventilatory and haemodynamic fluctuations during the filling period requiring increased levels of oxygen. However, these incidents were not specified according to patients.

Table II. Continued.

Authors	Cause of AKI	GA (weeks)	BW (g)	Catheter type/Insertion site	Age at the beginning of PD (days)/PD solution	Duration of PD (days)	Complications	Outcome
Ustyol et al.[18]	Sepsis	24	580	PD catheter/0.5-1 cm below the umbilicus	7/1.36% or 2.27% (Baxter®)	3	ND	Died
Ustyol et al.[18]	Sepsis	30	780	PD catheter/0.5-1 cm below the umbilicus	12/1.36% or 2.27% (Baxter®)	4	Peritonitis	Died
Ustyol et al.[18]	Sepsis	24	700	PD catheter/0.5-1 cm below the umbilicus	8/1.36% or 2.27% (Baxter®)	1	ND	Died
Stojanović et al.[19]	Sepsis	25	690	IV catheter/left site of umbilicus	6/4.25% or 2.5% and 1.5% afterwards (Dianeal®)	3	None	Died
Stojanović et al.[19]	Sepsis	27	470	IV catheter/left site of umbilicus	4/4.25% or 2.5% and 1.5% afterwards (Dianeal®)	2.5	Leakage	Died
Stojanović et al.[19]	Gentamicin	27	890	IV catheter/left site of umbilicus	17/4.25% or 2.5% and 1.5% afterwards (Dianeal®)	28	None	Died
Stojanović et al.[19]	Sepsis	27	880	Umbilical venous catheter/ left site of umbilicus	28/4.25% or 2.5% and 1.5% afterwards (Dianeal®)	48	Peritonitis	Died
Stojanović et al.[19]	Sepsis	27	610	IV catheter/left site of umbilicus	11/4.25% or 2.5% and 1.5% afterwards (Dianeal®)	4	Obstruction	Died
Stojanović et al.[19]	PDA, NEC	25	880	IV catheter/left site of umbilicus	2/4.25% or 2.5% and 1.5% afterwards (Dianeal®)	21	None	Recovered

AKI: acute kidney injury, BW: birth weight, GA: gestational age, ICH: intracranial hemorrhage, NEC: necrotizing enterocolitis, PD: peritoneal dialysis, PDA: patent ductus arteriosus, PH: pulmonary hemorrhage, TTTS: twin-twin transfusion syndrome, ND: not defined.

[a] In the study of Yu et al.15, the insertion site was not specified; authors reported that the tip of the catheter was placed in the contralateral iliac fossa, pelvis or subhepatic area. Dianeal® glucose solution with different glucose concentrations (not specified) according to the patient's fluid and metabolic status was used.

* Overall incidents recorded during PD were fluid leakage, blockage of the drain, unstable glycaemia, ventilatory and haemodynamic fluctuations during the filling period requiring increased levels of oxygen. However, these incidents were not specified according to patients.

Table II. Continued.

Authors	Cause of AKI	GA (weeks)	BW (g)	Catheter type/Insertion site	Age at the beginning of PD (days)/PD solution	Duration of PD (days)	Complications	Outcome
Stojanović et al.[19]	Apnea	25	870	IV catheter/left site of umbilicus	13/4.25% or 2.5% and 1.5% afterwards (Dianeal®)	36	Leakage	Died
Stojanović et al.[19]	Asphyxia	25	700	IV catheter/left site of umbilicus	20/4.25% or 2.5% and 1.5% afterwards (Dianeal®)	22	None	Recovered
Sizun J et al.[20]	Sepsis	28	680	IV catheter/ND	41/1.36% (Dianeal®)	51	ND*	Died
Sizun J et al.[20]	Asphyxia/sepsis	29	640	IV catheter/ND	4 and 67/1.36% (Dianeal®)	49/31	ND*	Died
Sizun J et al.[20]	Asphyxia	25	700	Thoracic drain/ND	5 and 19/1.36% (Dianeal®)	66/70	ND*	Died
Huh J et al.[21]	PDA, PH	25	790	Foley catheter/right lower abdomen	22/1.5% dialysate	12	Obstruction, leakage	Recovered
Presented case	Sepsis	24[4]	460	PD catheter/left paramedian above umbilicus	12/1.36% dialysate	6	Leakage	Died

AKI: acute kidney injury, BW: birth weight, GA: gestational age, ICH: intracranial hemorrhage, NEC: necrotizing enterocolitis, PD: peritoneal dialysis, PDA: patent ductus arteriosus, PH: pulmonary hemorrhage, TTTS: twin-twin transfusion syndrome, ND: not defined.

[a] In the study of Yu et al.15, the insertion site was not specified; authors reported that the tip of the catheter was placed in the contralateral iliac fossa, pelvis or subhepatic area. Dianeal® glucose solution with different glucose concentrations (not specified) according to the patient's fluid and metabolic status was used.

* Overall incidents recorded during PD were fluid leakage, blockage of the drain, unstable glycaemia, ventilatory and haemodynamic fluctuations during the filling period requiring increased levels of oxygen. However, these incidents were not specified according to patients.

an extremely preterm infant with an ELBW. In Table II, a brief review of characteristics of ELBW infants described in the literature who underwent PD during their NICU stay was presented.

Acute PD has been reported to have a high incidence of technical problems in small infants, specifically leakage of peritoneal fluid around the catheter entry site.[9] In a retrospective study of Maizlin et al.[31] where outcome assessment of RRT in neonates were reviewed during an eight year period, the most frequently experienced complications in PD patients were reported to be related to peritonitis (83%), catheter malfunctions (72%) and PD catheter leaks (55%). Hakan et al.[32] reported their 7 year experience of acute PD in 77 neonates and complications of procedure were noted as hyperglycemia ($n = 35$), leaking of dialysate ($n = 13$), peritonitis ($n = 10$), catheter obstruction ($n = 3$), bleeding when inserting the catheter ($n = 3$), exit site infection ($n = 2$), and bowel perforation ($n = 1$). In the above mentioned studies of Ustyol et al.[18], Alparslan et al.[12] and Unal et al.[13] the rate of PD related complications were reported to be 48.4%, 25.9% and 40%, respectively with leakage, occlusion and infection being the most commonly observed complications. In the present case, minimal leakage occurred around catheter entry site which did not impair the efficacy of PD and no revision of the catheter was needed. Leakage from the catheter entry site which is one of the most common complications of PD has been attributed to the inelastic nature of the premature infants' skin which forms a poor seal.[9]

The prognosis of AKI in neonates is mostly dependent on the underlying condition and on gestational age. Among very low birth weight (VLBW) and ELBW neonates, AKI was found to be independently associated with increased mortality.[1,4,25] High mortality rates have also been reported in neonates treated with PD although these mortality rates were usually attributed to the underlying etiology and being premature.[12,13.31,32] The present case died on day 152 of life secondary to a nosocomial infection with worsening symptoms of BPD and PHT. She survived the acute episode of kidney injury with succesfull application of PD.

In a recent survey, it was reported that neonatal AKI was underappreciated, particularly among neonatologists due to a lack of evidence on neonatal AKI.[5] It should be kept in mind that AKI in neonates is common, particularly in neonates with multiple risk factors such as prematurity, sepsis and use of nephrotoxic drugs.[7] Acute PD has several advantages for neonates, particularly for low birth weight neonates due to the relative technical ease of insertion in the setting of NICU and lack of the most challenging technical problems with regard to need for vascular access and an exracorporeal blood circuit or renal support therapy machines as in the case of HD and CRRT. Therefore, PD can be a rescue therapy for ELBW infants with AKI. Our patient represented a good example for a rescue therapy of PD as one of the smallest infants in the literature during the first weeks of life who later maintained normal renal function.

In conclusion PD is a relatively safe, effective and a feasible therapy in the neonatal population even in the smallest infants. To the best of our knowlegde, our case is the smallest infant in whom PD was performed succesfully with a PD catheter. This also suggests that PD may be a live-saving procedure in ELBW infants with severe AKI. In an era in which neonates are routinely supported with many invasive procedures, we should not be reluctant to initiate RRTs with the fear of their small sizes and lower gestational ages which could give them a chance of survival and an improvement in outcome.

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Case Report

Internal carotid artery dissection following blunt head trauma: a pediatric case report and review of the literature

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ABSTRACT

Background. Internal carotid artery dissection (ICAD) is a rare but potentially devastating complication after trauma in the pediatric age group. The diagnosis of traumatic dissection is difficult and is usually recognized only when ischemic symptoms appear. We report a pediatric patient with ICAD due to blunt cerebrovascular injury (BCVI).

Case. A 14-year-old boy suffered major trauma due to a motor vehicle accident. When the first aid team reached the accident site, he was intubated because of his low Glasgow Coma Score (GCS) and then transported to the nearest emergency department. Cranial computed tomography (CT) showed multiple fractures at the skull base and independent bone fragments in both carotid canals. On the 6th day; a brain magnetic resonance imaging (MRI) was performed to detect diffuse axonal injury. There was a loss of signal in the left internal carotid artery (LICA) tract but the limitation of diffusion was not associated with the same side, conversely there was a limitation of diffusion on the other side, affecting a very large area. CT angiography was performed in order to detect a filling defect and showed dissection in the LICA. The patient did not have any specific neurological symptoms associated with ICAD. Low-dose aspirin was utilized as anticoagulant therapy. On the 25th day of admission, the patient's GCS was 14, neurologic examination showed no difference between the right and left sides. He was discharged on the 55th day of the accident and was walking without support.

Conclusion. Our patient was a rare case in pediatrics due to having a clinically silent form of ICAD. It is very difficult to diagnose ICAD dissection during the early phase in cases with BCVI accompanied by multiple trauma. Even in the absence of typical neurological deficit, the possible presence of ICAD should be explored in patients with cranial fractures encompassing the skull base.

Key words: blunt cerebrovascular injury, carotid artery dissection, pediatric intensive care.

Blunt cerebrovascular injury (BCVI) is a rare but potentially devastating complication after trauma, and accounts for approximately 1.5-3.5% of patients admitted to trauma centres.[1] Internal Carotid artery dissections (ICAD) are rare, most of them occur spontaneously but around 4% are secondary to trauma.[2] These statistics are for adult trauma patients and such traumas are rare in the pediatric age group. Dissection can be a diagnostic challenge due to the complexity of the clinical examination in children and delayed onset of symptoms in many cases. Usually, patients cannot be diagnosed until ischemic symptoms appear.[3]

Despite its low incidence, dissecting injury of the supraaortic vessels (carotid artery, vertebral artery etc.) is an important cause of ischemic stroke in children, associated with significant morbidity and mortality rates up to 20%.[4] Arterial dissection may be caused by direct trauma to the artery, hyperextension-rotation of the head with stretching of vessels, basal skull or mandibular fractures, chest-head injuries

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with carotid stretching, and blunt intra-oral trauma.[5-8]

In this case report, we report a rarely seen pediatric case of ICAD development due to blunt head trauma. Although the ICAD developed on the left side, ischemic areas were predominantly located on the right cerebral hemisphere due to diffuse axonal injury (DAI) which was secondary to traumatic brain injury (TBI).

Case Report

A previously healthy 14-year-old male patient suffered major trauma due to a motor vehicle accident. The mechanism of this major trauma was a tractor rollover during harvest. When the first aid team reached the accident site, the boy was lying still on the ground and was immediately intubated because of his low Glasgow Coma Score (GCS) (E1M4V1). He was immobilized and then transported to the nearest emergency site. At his arrival, GCS was 6 (E1M4V1) and all immediately necessary interventions were performed by the emergency team. His cranial, cervical, thoracic and abdominal imaging studies were performed after he was stabilized, and then he was transported to our pediatric intensive care unit (PICU).

At his examination in the PICU, the patient was intubated, bilateral pupils were isochoric with positive light reflex, and all four extremities were equally moving with painful stimuli. Babinski sign was negative. Due to the patient being unconscious and intubated, a cranial nerve exam could not be performed conclusively. He was hemodynamically stable. The hemogram, arterial blood gas and biochemical parameters of the patient were normal. His thorax, abdominal and cervical computed tomography (CT) screenings were normal. In the bone window setting, cranial CT images showed multiple fractures at the base of the skull, and a bilateral styloid process fracture and hemotympanum (Fig. 1).

We noticed clear secretions in the mouth, which seemed similar to cerebrospinal fluid (CSF). These were tested with the beta-2 transferrin test, confirming our suspicions. To detect the basilar skull fracture that was causing CSF leak, a maxillofacial sinus CT was also performed. There were independent bony fragments in both carotid canals, hemorrhagic collections in the sphenoid and ethmoid sinuses, and fractured fragments of the left temporal bone causing independent bone fragments (Fig. 2).

After discontinuing all sedative medications, GCS was reevaluated. Because GCS was under 8 (E1M4V1), intracranial pressure catheterization (ICP) was performed at the bedside. He was followed-up with ICP catheter for five days to minimize TBI. Our goals were to keep ICP <20 mmHg and cerebral perfusion pressure >55 mmHg. On the 6th day of PICU follow-up, his ICP catheter was removed and his neurologic examination was checked after discontinuing sedation. His GCS was 6 (E1M4V1), pupils were isochoric, light reflex was bilateral positive, and all four extremities were moving equally.

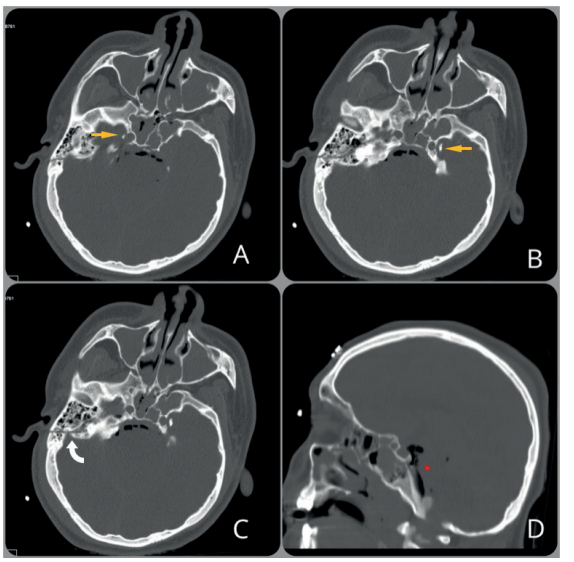

Fig. 1. Initial head CT reveals multiple fractures in skull base including lateral walls of carotid canals on both sides. On image A and B yellow arrows depict the separated osseous fragments. On image C, curved arrow shows longitudinal fracture of right temporal bone. On image D, pneumocephalus (red star) is demonstrated.

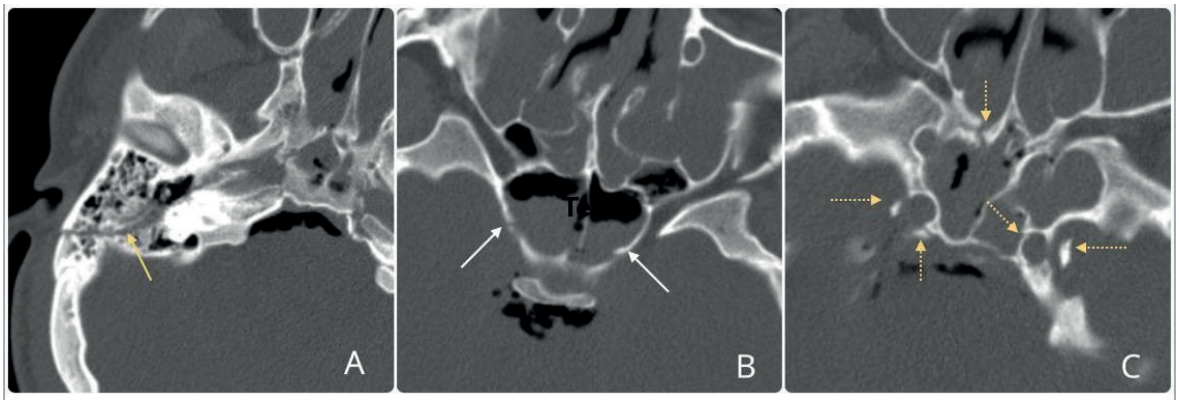

Fig. 2. On image A, fracture of the right temporal bone (yellow arrow). On image B, intense hemorrhagic collections of fractures in the sphenoid sinus and ethmoid cellulites posterior to the nasal septum and filling the secondary sinuses (white arrow) , and on image C, free osseous fragment in both carotid channels (yellow arrow).

On the 6th day after the accident, a brain magnetic resonance imaging (MRI) was performed to detect DAI. When evaluating arteries, we determined a loss of signal in the left internal carotid artery (LICA) tract but diffusion limitation area was not correlated with the region supplied by the LICA. Surprisingly, the diffusion restriction of the right hemisphere was worse than that of the left side (Fig. 3). To verify this loss of signal in the LICA tract, CT angiography was performed and revealed filling defect and presence of intimal flap on the left side of the LICA's cavernous segment and LICA's petrous part, which was verifying results with MRI screening (Fig. 4).

A detailed neurological exam could not be performed due to low GCS and intubation; nevertheless, as far as examination could show, there was no specific neurological deficit (hemiplegia, hemiparesis, facial palsy etc.) that was conclusive for left ICAD. As such, ICAD was only detected during a routine MRI performed on the 6th day of admission. Because it was late for the endovascular intervention and the use of heparin were not suitable due to trauma presence, we only used low-dose aspirin (100 mg/day) as an anticoagulant.

Due to his low GCS (E2M4V1), tracheostomy and percutaneous enteral gastrostomy operations were performed on the 15th day of hospital stay. His neurological state was progressively getting better. On the 25th day of PICU stay, GCS was 14, muscle strength was 2/5 for upper extremities and 3/5 for lower extremities. Surprisingly,

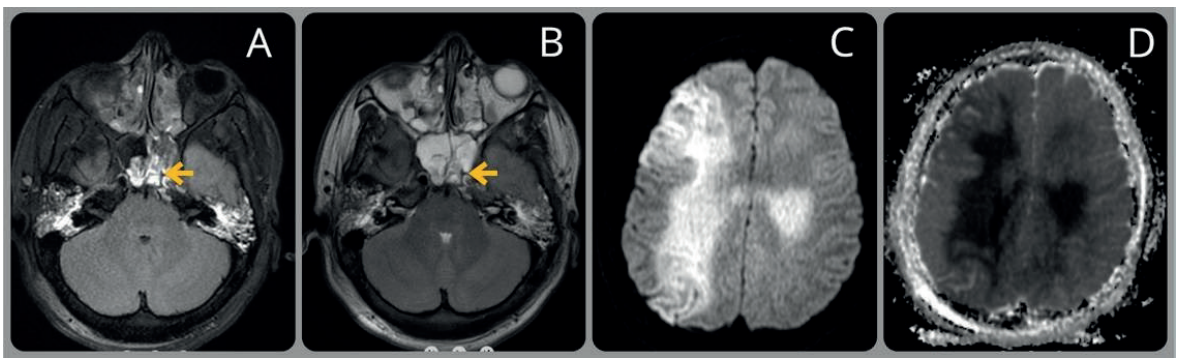

Fig. 3. Diffusion restriction in bilateral watershed areas of brain predominantly on right side is seen on image C and D. Retrospectively we also noticed loss of signal void on left internal carotid artery (yellow arrow) which is in favor of arterial dissection on image A and B.

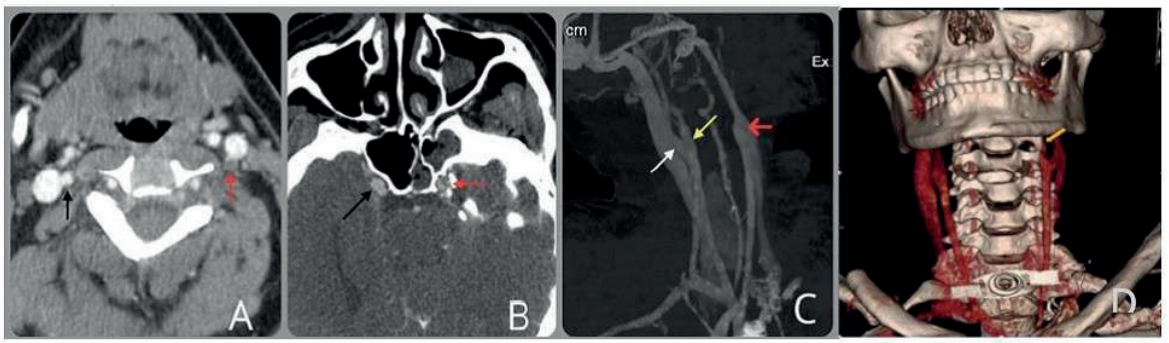

Fig. 4. CT angiography reveals filling defect in cervical portion of the left internal carotid artery (LICA), indicated with red arrow (Image A). At the level of the carotid canal, an intimal flap on the left side is demonstrated (Image B, red arrow). On maximum intensity projection images (Image C and D), it is clearly appreciated that there is no luminal enhancement at neither left common carotid artery from the level of bifurcation nor LICA (red arrows). Only external carotid artery is filled with contrast media which are highly suggestive findings for dissection of LICA. 3D CT angiography reveals filling defect in cervical portion of the LICA, indicated with yellow arrow (Image D).

there was no difference between the right and left sided neurological examinations. There were no findings of cranial nerve paralysis. Daily physiotherapy was performed. During his follow-up, muscle strength reached 4/5 and 5/5 for upper and lower extremities, respectively. When his GCS rose to E4M6V5 on the 51th day of hospitalization, tracheostomy and gastrostomy were closed. As his neurological improvement was very fast he was discharged from the hospital safely on the 55th day of the accident, and he was walking without support.

Informed consent was obtained from the patient's parents for publication.

Discussion

Traumatic carotid artery injuries (CAI) are rare; however, because of the anatomy, there may be important life-threatening complications. It occurs especially in patients with multiple trauma and direct blunt trauma to the neck. Delayed clinical presentation of traumatic ICAD may occur after weeks, months, even years following injury and it has important clinical outcomes.[3] Our case demonstrates that ICAD can be easily missed during the initial trauma survey in patients with multiple trauma, especially in cases of additional TBI. Knowledge of the mechanism and risk factors of the traumatic ICAD is important because it could have consequences for the treatment of these patients. A literature review revealed 21 published cases of ICAD caused by trauma.[6-21] These cases are summarized in Table I.

Pathophysiology

Dissections start with a tear in the intima/media layer of the vessel wall, after which a hematoma develops. Ischemic strokes after ICAD may occur because of thromboembolism, or, less frequently, via artery occlusion due to the hematoma in the vessel wall.[1,22] Dissection can also progress in the subintimal or subadventitial layer, leading to local compression resulting in a loss of function of the adjacent cranial nerves, presenting as Horner syndrome or facial nerve palsy.[1,22]

Dissections may be traumatic or spontaneous. In addition to severe traumas like motor vehicle accidents, direct neck trauma and mild trauma like minor shoulder trauma can also be associated.[12,15,20] Traumatic ICAD may develop in association with the following mechanisms: I- hyperextension and contralateral rotation of the head and neck, II- blunt intraoral trauma that affects the internal carotid artery at the angle of the jaw, III- laceration of the artery due to the skull base and mandible fractures,

Table I. Summary of published case reports of traumatic internal carotid artery dissection.

Author(s) / year of publication	Age (years)	Mechanism of injury	Unilateral/ Bilateral	Symptoms possibly linked with dissection	Neuroimaging	Dissection segment	Specific treatment	Outcomes
1 O'Sullivan[10], 1990	17	Blunt head trauma	Unilateral	Hemiplegia, aphasia	CTA	Intracranial	None	Death
2 Borges[11], 2000	16	Intraoral trauma	Unilateral	Somnolence, seizure, hemiparesis	CTA	Extracranial	None	Hemiparesia
3 Borges[11], 2000	4	Intraoral trauma	Unilateral	Somnolence, motor aphasia, hemiplegia, hemianopia, eyes deviation	CTA, MRA	Intracranial, Extracranial	None	Hemianopia
4 Payton[6], 2004	11	Laser tag accident	Unilateral	Lethargy, dysarthria, eye deviation, tongue deviation, hemiplegia, absence of corneal reflex	MRA	Intracranial	Heparin, aspirin, warfarin	Speech impairment
5 Agner[7], 2006	0.3	Child abuse	Unilateral	Seizure, stiffening	MRA	Intracranial	None	Decreased vision in the left eye
6 de Brost[8], 2006	13	Motor vehicle accident	Bilateral	Loss of consciousness, facial palsy, hemianopia, hemiparesis	MRA	Extracranial	Heparin, aspirin	Complete recovery
7 Pierrot[9], 2006	4.5	Intraoral trauma	Unilateral	Loss of consciousness, hemiplegia, facial palsy	MRA	Extracranial	Heparin, aspirin	Complete recovery
8 Pierrot[9], 2006	3.5	Intraoral trauma	Unilateral	Asymptomatic	MRA	Intracranial, Extracranial	Heparin	Complete recovery
9 Jariwala[12], 2006	17	Motor vehicle accident	Unilateral	Confusion, unipareses	MRA	Intracranial	Aspirin, clopidogrel	Unipareses
10 Lin[13], 2007	7	Water slide injury	Unilateral	Headache, vomiting, facial palsy, hemiplegia, uvula deviation, slurred speech	MRA	Extracranial	Warfarin	Hemiparesis
11 Moriarty[14], 2009	0.8	Spoon trauma	Unilateral	Decreased level of consciousness, hemiplegia	MRA	Intracranial	Heparin	Hemiparesis
12 Tsurukiri[15], 2013	4	Motor vehicle accident	Unilateral	Loss of consciousness, no specific symptom	CTA	Intracranial	None	Complete recovery
13 Orman[16], 2013	3.6	Fall from stroller	Unilateral	Hemiplegia, aphasia	CTA, MRI	Intracranial	Aspirin	Hemiplegia
14 Orman[16], 2013	3.1	Motor vehicle accident	Unilateral	Seizure	CTA, MRI	Intracranial	Aspirin	Complete recovery

CTA: computed tomography angiography, MRA: magnetic resonance angiography, MRI: magnetic resonance imaging.

Table I. Continued.

Author(s) / year of publication	Age (years)	Mechanism of injury	Unilateral/ Bilateral	Symptoms possibly linked with dissection	Neuroimaging	Dissection segment	Specific treatment	Outcomes
15 Orman[16], 2013	1.9	TV fell on the head	Unilateral	Loss of consciousness	magnetic resonance imaging	Intracranial	None	Complete recovery
16 Orman[16], 2013	1	Fall from mother's arm	Unilateral	Hypoesthesia	magnetic resonance imaging	Extracranial	Heparin, Aspirin	Hemiparesis
17 Akbaş[17], 2016	5	Water slide injury	Unilateral	Slurring of speech, right-sided weakness, facial palsy	MRA	Intracranial	Heparin, aspirin	Complete recovery
18 Bent[18], 2016	1.5	Intraoral trauma	Unilateral	Vomiting, lethargia, diminished left extremity movement,	CTA, MRA	Extracranial	None	Hemiparesis, speech impairment
19 Esianor[19], 2017	14	Blunt head trauma	Unilateral	Loss of consciousness, seizure, hemiparesis	CTA	Intracranial	Aspirin	Hemiplegia
20 Zant[20], 2017	0.3	Minor head trauma	Unilateral	Eye deviation, encephalopathy	MRA	Intracranial	Heparin	Unipareses
21 Cebeci[21], 2018	10	Minor shoulder trauma	Unilateral	Headache, nausea, vomiting, dysphasia, facial palsy	MRA	Extracranial	Heparin	Complete recovery
22 Present case	14	motor vehicle accident	Unilateral	Loss of consciousness, no specific symptom	CTA, MRA	Intracranial	Aspirin	Complete recovery

CTA: computed tomography angiography, MRA: magnetic resonance angiography, MRI: magnetic resonance imaging.

IV- a combination of head-thorax trauma with overstretching of the internal carotid artery, V- direct application of force to the neck.[1] The frequency of ICAD is especially high in cases with accompanying carotid or petrous bone fractures in association with skull base fractures due to blunt trauma.[23] We also identified a skull base fracture extending to the lateral wall of the carotid canal in our patient.

Spontaneous ICADs are more common in the intracranial region, and traumatic dissections of the ICA in the head and neck region are most frequently located in the extracranial segments of the vessel. Concerning the ICA, most of the traumatic dissections occur below the skull base.[24-26] In our case, blunt trauma-related ICAD was observed in the intracranial segment of the ICA.

Clinical Symptoms

The most common signs and symptoms are hemipareses, headache, aphasia, dysphasia, cranial nerve palsy, anopsia and an altered level of consciousness. CAI may present with an ischemic event such as transient ischemic attack (TIA) or stroke before reaching the hospital. Other manifestations may include ipsilateral headache, Horner syndrome, neck pain, bruit, and tinnitus.[27] In cases with traumatic mechanism, bleeding through the oral cavity, nostrils or ears can be detected as well. The diagnosis is relatively late due to the presence of other lesions related to trauma and this causes important sequalae.[28] In our case, no specific neurological findings could be detected, and a detailed neurological evaluation could not be performed because of TBI and unconsciousness. In the 21-case literature review we have reported, it is evident that cranial nerve paralysis and neurological findings such as hemiplegia, hemiparesis are at the forefront. However, due to the lack of clinical findings suggestive of ICAD, the diagnosis was delayed in our case.

There is usually a significant time interval between trauma and neurological symptoms in such patients, even though some cases have been shown to have immediate findings. The interval between blunt trauma and neurological deficits can be hours, days, or even months.[22,29] Especially in children, the dissection may remain in the subadventitial layer rather than the subintimal layer, which may account for a delay in presentation.[29] This delay between the moment of dissection and the occurrence of neurological symptoms is the critical factor that makes diagnosis difficult. Further, it is not at all clear that early detection would have found a treatable lesion after a stroke that is clinically evident hours or days after the injury. Reports of strokes developing after initial negative screening have been made.[30] On the other hand, the time interval between injury and onset of symptoms offers the possibility of screening for CAD and initiating therapy before the neurological symptoms become clear.

Diagnosis

Whilst the demonstration of an initial flap, double lumen sign or string sign (areas of adjacent stenosis and dilatation) on conventional catheter angiography remains the gold standard for diagnosis of CAD; non-invasive diagnosis with duplex ultrasound (USG), CT angiography (CTA) or MR angiography (MRA) is being increasingly used. Duplex USG has poor vision of the intracranial aspects of a dissection and it also provides limited information about small intimal tears and it is difficult to interpret when there is a hematoma in the neck.[1]

CTA is prominently used as diagnostic modalities for the detection of BCVI, especially considering the acute situation in the emergency room of severely injured patients. Further development of CT scanners (>64 slices) shows comparable results in sensitivity to MRA scans.[2] However, to get additional information about a possible CVI, it can be necessary to include CTA into the protocol of the whole-body CT. To rule out patients that need an additional CTA, the modified "Denver Screening Criteria" (Table II) can be helpful.[32]

Table II. Modified Denver screening criteria for BCVI.

Sign of BCVI	Risk factors for BCVI
Arterial bleeding	High-energy trauma mechanism combined with:
Cervical hematoma	Le Fort II/III fractures
Focal neurological deficiency	Cervical spine fractures
Neurological findings not matching with CT findings	Basilar skull fracture with carotid canal involvement
Ischemic insult seen on a secondary CT scan	Diffuse axonal injury with GCS ≤ 6
Cervical heart murmur	Near hanging with anoxic brain injury
	Combination of TBI and thorax trauma

BCVI: blunt cerebrovascular injury, CT: computed tomography, GCS: Glasgow coma scale, TBI: traumatic brain injury.

Imaging with an MRI scan combined with the MRA is considered to be the gold standard for the detection of carotid artery dissections.[32] It determines dissections in up to 99% of cases and provides additional information about concomitant injuries (i.e. diffuse axonal injuries, acute infarction, fractures, etc.).[2] But it also has certain limits, especially during the diagnosis of critically injured patients with trauma. Besides the long duration of the scan, on the one hand, there exist restrictions in the use of potentially life supporting devices (i.e. pacemakers/iron-based metal implants, etc.), while on the other hand, there is a possibility that MRI availability is limited, especially in smaller trauma centers.[31] The choice of the screening method may change with regard to the clinical setting and patient condition. In our 16-case literature review, it was determined that diagnosis was most commonly performed via MRA. In our case however, the diagnosis was confirmed via CTA after suspicious signal-loss findings were identified in MRI imaging.

Therapeutic options

In general, asymptomatic patients with low-grade dissections are treated conservatively with medical management and close imaging. There are several therapeutic options to treat cerebrovascular dissections, including open surgery, endovascular management (stenting, endovascular thrombolysis, thrombectomy), thrombolysis, anticoagulant and antithrombotic therapy.[31]

Surgical options are difficult and risky in the acute phase of the dissection.[33] This is why they usually do not belong in the first line of therapy in the acute phase. However, there are certain cases where operative treatment is necessary (i.e. to restore the blood flow in a case of distinct tear of the vessels or complete occlusions without ischemic intracranial lesions).[31]

The literature on the endovascular treatment (stenting) of traumatic ICAD is still limited to small series based on adult patients with relatively short follow-up. A proportion of the dissections occur at the skull base or in the intracranial region, and are therefore inaccessible to surgical or endovascular therapy. However, recent studies of stenting for CAD show excellent early and one-year patency rates and a low major adverse event rate.[34] Endovascular local thrombolysis is thought to be useful especially to prevent thromboembolic cerebral insult, but they still present high risks in the setting of a severely injured patient with multiple fractures or TBI, as presented in our case.[2,31]

Antithrombotic or antiplatelet treatments are recommended in patients with neurological symptoms; whereas endovascular intervention is suggested only when the neurological status of a patient deteriorates under conservative medical treatment.[35] Antithrombotic treatment consists of either anticoagulation, typically with intravenous heparin followed by warfarin, or antiplatelet therapy with aspirin. Anticoagulation is typically preferred over

antiplatelet therapy in severe stenosis or pseudoaneurysm –assuming that it prevents thromboembolic complications more effectively. Patients who are unable to receive anticoagulants were treated with antiplatelet therapy.[36] In adults, anticoagulation therapy is suggested for 3 to 6 months to prevent injuries progressing to a higher injury grade, and to reduce the number of strokes.[36] Thrombolysis regimens, including recombinant tissue plasminogen activator or urokinase, are used to restore blood flow in some cases. But these approaches require an early diagnosis. The rationale of antithrombotic therapy is that the mechanism of the majority of strokes in CAD is due to thromboembolism.[36]

In the pediatric population, the treatment of CAD is still controversial and more studies are needed. The use of antiplatelet therapy is even more controversial for patients who suffer a stroke following an intracranial dissection because of a very real risk of intracranial haemorrhage.[21] Unfortunately, patients who suffered from blunt carotid injuries typically have closed head injuries, solid organ injuries, and/or pelvic fractures that prevent the use of early anticoagulation. When other concomitant injuries are present, then the optimal type and time of treatment should be considered with an interdisciplinary approach.[37] Pandey at al.[38] recommended 3 months of anticoagulation therapy and then antiplatelet therapy. In our case, as there were no specific symptoms and the diagnosis was made in the later period, we only used low-dose aspirin as an antiaggregant therapy. Anticoagulant therapy was not suitable for our patient due to multiple trauma.

Prognosis

Blunt trauma-related ICAD is known to carry a high rate of devastating neurologic morbidity (60%) and mortality (19–43%). Interestingly, a significant number of patients (66–73%) may be asymptomatic upon initial presentation, developing delayed neurologic symptoms anywhere from 1 hour to 7 days after injury.[8,9,22,29] CAD patients (33.7%) may present with an ischemic event at the time of presentation. As the severity of vessel injury worsens, stroke and mortality rates consequently increase.[31] In our review of the 21 pediatric patients with ICAD, 47.6% (n=11) of cases did not have neurological symptoms at admission. The death rate was 4.8% (n=1) and 40% (n=8) of survivors had a complete recovery. However, it must be noted that ICAD was accompanied by TBI –which may have influenced neurological outcomes.

It is difficult to diagnose ICAD in the early phase in patients with TBI accompanied by multiple trauma. Even in the absence of typical neurological deficit (as was the case in our patient), the possible presence of ICAD should be explored in those with cranial fractures encompassing the skull base. Regarding therapeutic options, bleeding risk is one of the most challenging aspects of treatment considerations, especially in the presence of multiple trauma (i.e. pelvic fractures, or haemorrhagic traumatic contusion).

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Case Report

Clitoromegaly caused by ovarian stimulation in a preterm newborn: ovarian hyperstimulation syndrome of preterm babies

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ABSTRACT

Background. Preterm ovarian hyperstimulation syndrome (POHS) is an uncommon disorder characterized by prematurity, hypogastric and upper leg swelling, high serum estradiol and gonadotropin levels, and ovarian cysts. Immaturity of the gonadal axis is accepted as the cause. But still, other etiological factors are suspected.

Case. A preterm baby who was born at 24 gestational weeks was referred to our clinic for ambiguous genitalia on day 118 of life. Labia majora and clitoris was edematous. Clitoris length was 1.5 cm. On laboratory evaluation: 17OH-Progesterone: 1.84 ng/ml, dehydroepiandrosterone sulphate (DHEA-S): 139 μg/dl, total testosterone (T.T): 88 ng/dl, luteinizing hormone (LH): 22.5 mIU/l, Follicle stimulating hormone (FSH): 15.7 mIU/l, estradiol (E_2): 447 pg/ml. Karyotype analysis was 46, XX. There was a 25x14x12 mm ovarian cyst detected on ultrasound. On follow-up, E_2 levels and cyst size increased, and there was 4 mm pericardial effusion on echocardiography at the time.

Conclusion. In this paper, we present a case with POHS and to discuss possible pathophysiological mechanisms and treatment. This is the first case of POHS developing pericardial effusion.

Key words: preterm ovarian hyperstimulation syndrome, clitoromegaly, ovarian cyst, pericardial effusion.

Ovarian hyperstimulation syndrome of preterm babies (POHS) is a rare syndrome of preterm girls characterized by tissue edema especially in hypogastric and vulvar areas and upper leg, high levels of gonadotropic hormones and presence of ovarian cysts. Preterm birth causes insufficient negative feedback mechanism due to the immaturity of hypothalamic-pituitary-gonadal (HPG) axis and early disappearance of placental sex steroids. Therefore, this situation has been held responsible for the pathogenesis of syndrome.[1] Still, other etiological factors are suspected because not all preterm babies suffer from the syndrome. It must be kept in mind in the differential diagnosis of ambiguous genitalia.

Here we present the case and clinical presentation of a preterm infant who was referred for ambiguous genitalia and diagnosed with POHS in order compare with the data in literature and discuss the pathogenetic mechanisms.

Case Report

A preterm baby who was born at twenty fourth gestational week with 770 grams birth weight, was referred to our outpatient clinic to be evaluated for ambiguous genitalia on day 118 of life (40^{+5} GW). History revealed that it was a preterm birth because of fetal distress, the

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mother had betamethasone treatment in the prenatal period; the baby had been admitted to the neonatal intensive care unit (NICU) for prematurity, respiratory distress syndrome and apnea for 117 days and was on mechanical ventilator for 40 days. On 35th day of NICU stay (29 GW), detecting body edema localized in hypogastric area, upper legs, labia majora and clitoris, laboratory tests were performed for total protein, albumin, urea, creatinine and electrolytes which were normal and there was no cardiac pathology on echocardiography. In spite of decreased edema in hypogastric area and upper legs, she was referred for persistent clitoromegaly. On presentation, labia majora and clitoris were edematous. Clitoris length was 1.5 cm (upper limit of clitoral length for 40 GW is 6 mm) (Fig. 1A).[2] There were two urogenital orifices and there were no gonads palpation. Thelarche was tanner stage 2, pubarche was 1. On laboratory evaluation, ACTH: 24 pg/ml (1-46 pg/ml), 17OH-Progesterone: 1.84 ng/ml (0.53-1.86 ng/ml), DHEA-S: 1393 μg/dl (1-45 μg/dl), Androstenedione (AS): 1.8 ng/ml (0.18-0.80 ng/ml), total testosterone (T.T): 88 ng/dl (0-40 ng/dl) , LH: 22.5 mIU/l (0.02-7.0 mIU/l) , FSH: 15.7 mIU/l (0.24-14.2 mIU/l), E_2: 447 pg/ml (0-36 pg/ml). Karyotype was 45, XX. There was a 25x14x12 mm multilocular cyst in right ovary detected on ultrasound (Fig. 1B). The patient was reevaluated frequently at the clinic with laboratory tests and ultrasound, and wasn't started on any medication since the diagnosis was PHOS was suspected. On postnatal day 128, E_2 levels were increased as well as the size of the cyst in the ovary, endometrium was measured 3 mm. There was 4 mm pericardial effusion on echocardiography at the time. The patient was seen more frequently then, due to risk of ovarian torsion and rupture of the cyst. On day 165 of life, E_2 levels and the size of the ovarian cyst decreased significantly. At

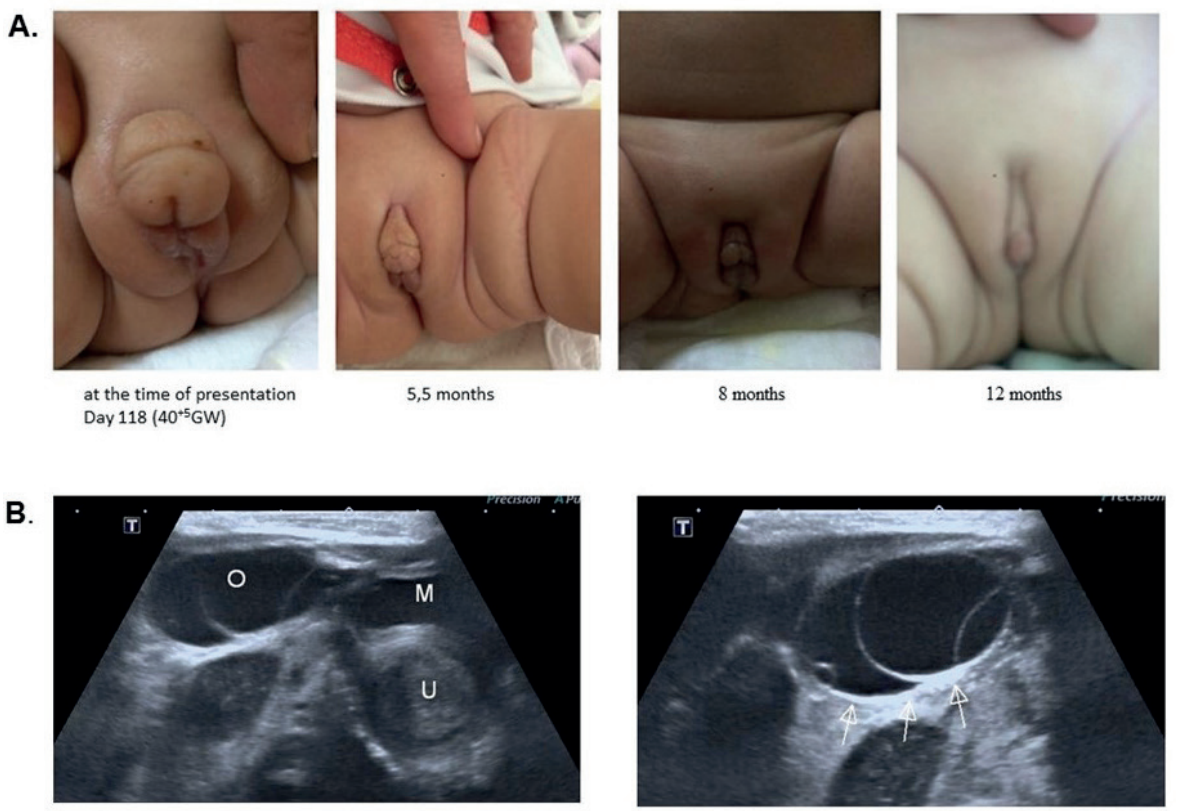

Fig. 1A. Physical examination- external genitalya, **B.** Giant ovarian cyst in pelvic USG seen at 5 months (the arrows point to the cysts).

8 months of age, physical examination was normal, gonadotropin levels were decreased and the ovarian cyst disappeared (Fig. 1A, 1B). On her last visit at the age of 1, bone age was 15 months. Echocardiography was normal with no pericardial effusion. Laboratory and ultrasound findings of the patient are given in Table I. Informed consent was obtained from the parents.

Discussion

The activation period of the HPG axis in the first months of life is thought to have an important role on development of gonads and reproductive function. This axis can be suppressed by the low levels of sex steroids in term babies and moderate increases in E_2 levels can be observed.[3,4] On the other hand, in preterm babies, immaturity of HPG axis and sudden decrease in levels of placental sex steroid results in disrupted negative feedback mechanism, increased gonadotropin levels, ovarian hyperstimulation causing cysts and very high levels of E_2 which altogether result in POHS.[5] Since it is not seen in all preterm babies, it is postulated that other mechanisms play a role in POHS pathogenesis. In ovarian hyperstimulation syndrome (OHSS) seen in adult females and characterized by ovarian follicular cysts, generalized edema and increased levels of gonadotropins and E_2; three mechanisms are held responsible: gestational spontaneous OHSS which is the result of increased placental production of endogenous hCG, iatrogenic OHSS caused as a complication of drugs used for in vitro fertilization and OHSS caused by increased hCG/LH sensitivity because of FSH receptor mutation.[6] All of the three situations are the result of very high levels of hCG/LH or increased sensitivity of hCG/LH with stimulation of FSH receptors. Hence it is thought that variable levels of LH can be an important factor for development of edema in POHS.[1,6] Since the development and resolving of edema and ovarian cysts occur at the same time in POHS, vascular endothelial growth factor secreted from theca and granulosa cells, is thought to have a role in edema.[7] But ovarian cysts are not specific for POHS. In 30-34% of healthy newborn babies / fetuses, single or multiple ovarian cysts can be found.[1] There is also a report of a POHS case without a functional ovarian cyst.[6] Starzky et al.[1] in an evaluation of 9 cases of POHS, showed there is no correlation of disease severity and levels of E_2 as in OHSS. In our patient, decreased levels of E_2 was accompanied by regression of clinical symptoms. This lack of uniform correlation between disease severity and E_2 levels can result from the difference of sensitivity of peripheral E_2 receptors among patients.

Severe complications such as ascites, acute renal failure, hypovolemic shock, pleural and pericardial effusion caused by capillary leak syndrome in OHSS are not defined in POHS cases and this can be the result of decreased peripheral E_2 receptor sensitivity. To the best of our knowledge, this is the first case of pericardial effusion in POHS. Minimal pericardial effusion detected in the period when E_2 levels were highest, was absent in the control echocardiography when E_2 levels were normal. Clinical presentation of severe OHSS in adults has been reported as the development of pleural effusion and, much less frequently, pericardial effusion.[8,9] In a Belgian multicenter study, Delvigne indicated that in 128 patients, there was 3% incidence of pericardial effusion in OHSS. Development of pericardial effusion with cardiac tamponade is a very rare but life-threatening complication in OHSS.[9] The pathogenetic chain of OHSS has not been clarified completely. OHSS is associated with an activation of renal and ovarian angiotensin systems and a release of vasoactive substances, such as vascular endothelial growth factor (VEGF) and interleukins 1, 2, and 6, which modify the permeability of the vascular beds.[7,10-12] An important role is probably played by tumor necrosis factor or estrogenes.[13,14] The minimal pericardial effusion detected when E_2 level was highest in our patient, disappeared when the E_2 level returned to normal. This supports the possible role of E_2 in the pathophysiology. No symptoms of estrogen

Table I. Clinical and laboratory parameters at presentation and on follow up.

	Day 35 (29GW)	Day 118 (40^{+5}GW)	Day 128	5 months	5,5 months	8 months	12 months
Thelarche (Tanner stage)		2	2	2	2	2	2
ACTH (1-46 pg/ml)	36	24					
17OHP (0.53-1.86 ng/ml)	2.5	1.84					
DHEA-S (1-45 μg/dl))		1393	1008	218			
1-4ΔAS (0.18-0.80 ng/ml)		1.8					
T.T (0-40 ng/dl)	66	89	22				
LH (0.02-7.0 mIU/l)	15	22.5	20.6	2.82	4.2	<0.7	<0.7
FSH (0.24-14.2 mIU/l)	20	15.7	8.9	5.8	7.2	5.6	4.8
E_2 (0-36 pg/ml)	497	447	>1000	>1000	160	34	<12
Pelvis USG							
Uterine size Endometrial thickness (mm)		35x12x14	36x12x15	37x17x15 E: 3	37x15x17 E. 3	33x18x13 E: 3	20x13x10
Right ovary size Cyst size (mm)		26x14x14 25x14x12	29x18x22 27x15x20	42x38x25 40x33x24	38x23x32 35x23x30	23x9x15 multiple cysts (Largest: 9 mm)	12x11x8 follicular cyst (2-3 mm)
Left ovary size Cyst size (mm)		10x8x6 -	17x11x10 follicular cyst (2 mm)	19x9x11 follicular cyst (2 mm)	20x8x11 -	18x15x13 -	17x11x9 -
Echocardiography				4mm pericardial effusion			Normal
Bone age							1 year 3 months

ACTH: adrenocorticotrophic hormone, 17OHP: 17OH-Progesterone,
DHEA-S: dehydroepiandrosterone sulphate, AS: androstenedione , T.T: total testosterone,
LH: luteinizing hormone, FSH: follicle stimulating hormone, E_2: Estradiol, E: Endometrial thickness

were reported in 21 POHS in spite of very high E_2, except 5 cases of stage 2 thelarche and one case of vaginal bleeding.[15,16] This is explained by decreased sensitivity of peripheral E_2 receptors as a result of immature gonadal axis.[5,15,16] In our case, stage 2 thelarche, increased size of uterus and increased endometrium thickness were detected. These different clinical presentations support the idea that sensitivity of peripheral E_2 receptors can vary among people.

Clitoris edema in POHS, as in our case can give an image of ambiguous genitalia. Patients with clitoromegaly who are 46, XX must be evaluated for congenital adrenal hyperplasia. Ovarian cysts are a presentation common to both congenital adrenal hyperplasia and POHS.[17] Normal levels of 17OHP, preterm birth and long term follow up in NICU were factors for ruling out congenital adrenal hyperplasia and a faster conclusion to the diagnosis of POHS.

The treatment of POHS is conservative with close follow up if there is no rupture of ovarian cyst or risk of torsion.[1] In our search of the literature, we found the majority (21) of cases to have resolved spontaneously, other than 4 complicated cases (2 treated with medroxyprogesterone acetate, 1 surgery, 1 surgery + medroxyprogesterone acetate). Our patient was seen in frequent outpatient visits for rupture of ovarian cyst or torsion. Laboratory results and clinical signs were completely normal on 8 months of postnatal age.

In conclusion; POHS should be considered in the differential diagnosis in preterm babies referred for clitoromegaly after congenital adrenal hyperplasia is ruled out. In spite of severe clinical signs, these symptoms resolve spontaneously without treatment as seen in our patient. Although pericardial effusion is seen in adult OHSS, it is the first case defined in POHS. Therefore, the patients should be seen frequently for rupture of ovarian cyst or torsion or other complications such as pericardial/ pleural effusions. Advanced research can enlighten the exact pathogenesis of the disease.

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Case Report

A rare pediatric case of neurobrucellosis with bilateral optic neuritis

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ABSTRACT

Background. The estimated incidence of central nervous system involvement in brucellosis ranges between 0 and 17.8%. Optic neuritis is infrequently seen in the clinical presentation of neurobrucellosis. Only six cases of neurobrucellosis manifesting with optic neuritis have been previously reported in the literature during childhood. Moreover, four of these were isolated optic neuritis.

Case. An 11-year-old boy presented with the complaint of bilateral visual loss which was more prominent in the left eye than the right. He was diagnosed with brucellosis two months prior. His fundus examination revealed mild papilledema of the right eye and remarkable papilledema of the left eye. Brucella agglutination titer of serum was 1/640. Cerebrospinal fluid (CSF) cultures were negative, but polymerase chain reaction (PCR) examination in CSF was positive for Brucella melitensis. Antibiotic and pulse methylprednisolone treatments were administered. The visual acuity returned incompletely within the 12-month follow-up period.

Conclusion. Isolated optic neuritis is a rare manifestation of neurobrucellosis in children.

Key words: optic neuritis, neurobrucellosis, children.

Brucellosis is a common zoonotic disease that is seen worldwide and mainly raises a public health problem in Mediterranean countries, including Turkey.[1,2] It has been considered a notable illness, particularly in endemic areas of Turkey. The number of cases decreased from 14 644 (morbidity rate, 20.32/100 000) in 2005 to 4173 (morbidity rate, 5.30/100 000) in 2015 in Turkey. However, after 2015 the morbidity rate has revived and reached 7.99 in 2017.[3] All age groups and both genders are affected. In endemic areas, children represent 20 – 25% of cases.[2] It is a multisystem disease that mostly affects the hematopoietic, musculoskeletal, genitourinary, cardiovascular, respiratory, and central nervous systems. The incidence of central nervous system involvement in brucellosis ranges between 0 and 17.8% in various reports. Neurologic involvement of Brucella are infrequently encountered in childhood; the proportion of neurologic system involvement is 0.8% of children with systemic brucellosis.[4] Neurologic system involvement presents as either a component of the current systemic disease or can be isolated. Clinical presentation of neurobrucellosis consists of meningitis, meningoencephalitis, meningovascular involvement, peripheral neuropathy, radiculopathy, cranial nerve involvement, and behavioural abnormalities. Meningitis and meningoencephalitis have been the most frequent presentation in clinical series.[5]

The rate of ocular involvement was found to be 3.35% in patients with brucellosis. Uveitis was the most frequent ocular presentation. The less common manifestations of ocular involvement were keratoconjunctivitis, corneal ulcers, iridocyclitis, choroiditis, optic neuritis, papilledema, and endophthalmitis.[6]

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Optic neuritis presents considerably less commonly in children than adults, and most cases are due to an immune-mediated process following an antecedent viral illness. Post-infectious, post-vaccination inflammation, Leber's hereditary optic neuropathy (LHON), and infectious causes (Bartonella, syphilis, Lyme, Toxocara, and toxoplasmosis can damage the optic nerve.). Optic neuritis has also been due to acute infection with Epstein Barr Virus (EBV), Borrelia, measles, mumps and varicella. In one series including patients with optic neuritis of all ages, children comprised 5% of cases. Optic neuritis may be associated with infections of sinuses or orbital components and infiltrative or infectious diseases of the brain and meninges that involve the optic nerves.[7] Optic neuritis may occasionally be the first manifestation of a demyelinating disease such as multiple sclerosis.[8] Optic neuritis related to Brucella infection is scarce and rarely reported in the literature.

One patient who suffered from optic neuritis in the course of systemic brucellosis is presented.

Case Report

An 11-year-old boy presented with the complaint of bilateral visual loss which was more prominent in the left eye than the right. The child was the sixth child of the family, with no remarkable prenatal or neonatal event and with healthy psychomotor development. He had been diagnosed with brucellosis with fever, arthralgia, and weakness two months prior. The diagnosis had been confirmed by positive serologic tests. The patient's parents had also suffered the same findings in the last year and had been diagnosed with brucellosis.

Moreover, the family lives in a rural area, in which brucellosis is endemic and usually consumes unpasteurized dairy products, especially soft cheese. Oral antibiotic treatment had been prescribed, consisting of co-trimoxazole and rifampicin for six weeks. Although his constitutional symptoms had regressed, he had gradually decreasing visual acuity for the last ten days. He had no vaccination nor infection history in the previous month.

A detailed ophthalmic examination of the patient was performed. Best-corrected visual acuity (BCVA) was counting from one-meter on the right eye, and hand motion on the left eye. Direct light reflexes were weak in both eyes. No relative afferent pupillary defect was detected with biomicroscopic slit-lamp examination. Intraocular pressure was measured normally by Goldmann applanation tonometer. Fundus examination revealed mild optic disc swelling on the right eye, and remarkable optic disc swelling on the left eye. Visual field test could not be performed because the patient did not cooperate with the test. Other systemic and neurologic examinations were all normal.

Blood cell counts, liver function tests, serum electrolytes, and erythrocyte sedimentation rate were within normal limits. Antinuclear antibodies, serum antibodies for Ebstein Bar Virus (EBV), cytomegalovirus and toxoplasma gondii were unremarkable. Brucella agglutination titer of serum was 1/640. Lumbar puncture revealed clear cerebrospinal fluid (CSF) with normal opening pressure which was 80 mm/H2O (normal range, 60-200 mm/H2O) and white blood cell count of three cells/mL, glucose 45 mg/dl (normal range, 40-70 mg/dl), and protein 65 mg/dl (normal range, 15-45 mg/dL). Unfortunately, we did not find simultaneous blood glucose levels because the physicians who performed the lumbar puncture, failed to evaluate the concurrent blood glucose level. CSF cultures were negative for four weeks, but polymerase chain reaction (PCR) examination in CSF was positive for Brucella melitensis.

His contrast-enhanced brain magnetic resonance imaging (MRI) had no pathologic findings. Visual evoked potential testing (VEPs) showed a late response with low amplitude in both eyes. The right and left P100 latencies were 130 ms (reference range 80-120 ms) and 145 ms, respectively. The auditory brain stem response study revealed normal responses.

Antibiotic therapy with doxycycline (6 mg/kg/day) and rifampicin (20 mg/kg/day) was administered for six months and ceftriaxone 100 mg/kg/d for the first three weeks. Pulse methylprednisolone treatment (30 mg/kg/day), was initiated for three days and continued (1 mg/kg/day) throughout eleven days. Partial reversal of visual acuity was observed within the 12-month follow-up period. BCVA was counting from three meters on the right eye and, 0.15 with the Snellen chart on the left eye at the last ophthalmologic examination. Papilledema improved; however, both discs were pale, which is a sign of optic atrophy. Brucella agglutination titer of serum was 1/320 for immunoglobulin G type antibodies and negative for immunoglobulin M type antibodies at the 12-month follow-up period.

Written informed consent was received from his parents. Parents were fully informed.

Discussion

Neurobrucellosis usually emerges with nonspecific manifestations and may imitate various pathologies. Symptoms and signs can arise at the acute or chronic period, but neurologic symptoms are rarely the initial complaint. The history of ingesting milk or dairy products, lack of typical signs of other neurological diseases, and amelioration of symptoms with appropriate treatment in a clinical history are clues for physicians.[2,5]

Optic neuritis and other cranial nerve involvement may be part of the neurologic participation of brucellosis, such as meningitis or meningoencephalitis. Documented cranial nerve involvement of brucellosis includes vestibulocochlear, trigeminal, facial, abducens, oculomotor, and optic nerves. Any cranial nerve may involve isolated, or two and more nerves may participate in neurobrucellosis.[9,10]

Optic neuritis is very rare in children with neurobrucellosis. To date, six case reports have been reported. Four patients had isolated optic neuritis.[11,12,14,15] Two patients also had other cranial nerve involvement along with the optic nerve.[10,13] It has been denoted that antibiotic and prednisolone therapy was given to the patients in these reports. While optic neuritis had regressed in some of the patients, the rest of the patients had recovered with a sequel of vision impairment.

Our patient had been diagnosed with brucellosis in the last few months. Fever and arthralgia had recovered with antibiotic therapy for six weeks. However, vision loss developed after a fortnight of the end of the treatment. Acute visual impairment along with the history of diagnosis with brucellosis, ingesting unpasteurized milk products, living in the village and endemic area for brucellosis, lack of typical signs of a known other neurological disease, and a serum agglutination titer higher than 1:640 were essential data for suspicion of brucellosis. Moreover, the diagnosis was confirmed with PCR examination of CSF. Probable other causes of optic neuritis were distinguished with studies for autoimmune diseases, viral and parasite agents. The development of optic neuritis despite the treatment of brucellosis for six weeks was associated with the failure of the therapy.

A diagnosis of neurobrucellosis can be established by the isolation of Brucella species from blood, bone marrow or CSF. Serum and CSF titer higher than 1:160 and 1:80, respectively, abnormal CSF findings with increased protein and lymphocytic pleocytosis reinforce the diagnosis in the laboratory.[5] Recently, it has been issued that PCR assay could be useful as a sensitive and accurate diagnostic tool as well as blood culture.[1] In our patient, Brucella was verified with PCR assay.

The treatment of central nervous system complications of brucellosis poses a particular problem because of the need to achieve high concentrations of drugs in the CSF. Recently, it has been reported that ceftriaxone-based regimens provided significantly more therapeutic success than the oral regimen and argued that the achievement of ceftriaxone

is due to its high rate of free diffusion to body fluids.[16] Ciprofloxacin, combined with doxycycline and rifampicin, were found to be useful in the treatment of neurobrucellosis.[17] Doxycycline, rifampicin and ceftriaxone were given to our patient. Ciprofloxacin was not chosen due to its severe side effects in children.

In the differential diagnosis of optic neuritis; probable infectious causes should be investigated. A CSF glucose concentration less than 40 mg/dL or a ratio of less than two-thirds of the plasma glucose level is considered abnormal. Very low CSF glucose values mostly occur in acute bacterial meningitis, but mildly to moderately low values are commonly seen in fungal, parasitic, protozoal, spirochetal, and tuberculous meningitis. A low CSF glucose level is less common in viral meningitis but can also appear with noninfectious conditions, including plasma hypoglycemia, meningeal carcinomatosis, sarcoidosis, chemical meningitis, and subarachnoid haemorrhage.[18] We had no simultaneous CSF glucose but increased CSF protein value. Since, we have already no doubt about the diagnosis of neurobrucellosis in that period with the patient's history, clinical findings, and laboratory results, we thought that the lack of concurrent blood glucose level was acceptable. Anti-Aquaporin-4 and anti myelin oligodendrocyte glycoprotein antibodies can be studied for Neuromyelitis Optica in the presence of clinical suspicion and the relevant imaging findings. Otherwise, increased intracranial pressure due to neurobrucellosis must be kept in mind. Such patients also may come to remedy with similar symptoms and findings of optic neuritis.[19,20] Therefore, to determine CSF, pressure by lumbar puncture is the rule for definitive diagnosis. Also, LHON should be kept in mind in a patient with vision loss. However, LHON usually presents with subacute visual failure, which develops in several months in young adults. Besides, other neurologic abnormalities such as postural tremor, peripheral neuropathy, myopathy, or movement disorders can be associated with LHON.[21]

Isolated optic neuritis as a manifestation of neurobrucellosis is very rare in children. To date, four case reports have been issued. In this respect, when a patient presents with optic neuritis for a differential diagnosis a thorough evaluation is critical to differentiate viral pathogens from bacterial pathogens since the therapy needs necessary antibiotics.

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