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CHILDREN VICTIMS OF DISASTER – THEIR NEED FOR SPECIAL PROTECTION*

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Children are inevitably faced with stress-for the child, birth is stressful, the slightest runny nose or elevation in temperature is stressful, not being given a particular toy at any given time is stressful. Stress in normal life is ordinary for the child an is mitigated ordinarily by loving parents, relatives, caregivers, doctors. The topic of this session is stress that is not at all ordinary. It is the stress caused by "difficult circumstances", by war, by natural disasters, by pestilence, by famine, by abuse, by sexual abuse, by exploitation, economic and otherwise. Children attempting to survive under "difficult circumstances" need special protection commensurate with the particular conditions that cause the stress. In this presentation I shall dwell upon the child victims of disasters and the stress they undergo as a result.

As many of us are aware, the concept of special Protective Measures was developed by a Committee on the Rights of the Child, in order to provide guidance for those states party to the Convention on the Rights of the Child. This was in response to the plight of children in circumstances of war and other forms of large scale violence, of exploitation and sexual and other abuse, of detention and imprisonment, as well as to harmful and disabling exploitative child labor and for children separated from parents and family by circumstance.

The identification and assessment of potentially harmful situations form the basis of the design for appropriate basic services and protective measures for children at risk.

For those children already exposed to conditions potentially harmful to their development and well-being, special measures that can alleviate, if not compensate for, the harm already done to them need to be taken, together with the provision of access to basic services and overall protection and security.

Victims of Violence

Violence has always been and always will remain an important factor among the causes of stress in children. It is a matter of fact that violence seems to become more pervasive as the level of economic development decreases. This

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** Honorary President of the Union of National Pediatric Societies of Turkish Republics.

ratio seems to be global. The violence referred to here is not that which the child is prey to outside the home. Most often, an infinitely sad causal chain of victimization can be perceived among the perpetrators and victims of domestic violence. Domestic violence is a much greater source of stress for the child than the violence it perceives outside the home, stressful as that may be. The aggressor within the home is usually either a parent or a close caregiver, known intimately by the child and upon whom the child is dependent for security and "protection" as well as for love. The immediate effect for the child is chaos, a loss of its sheet anchor. Thus begins the perilous drifting, without trust, without security, with at best a "dangerous" love. The child swiftly learns to repress its natural curiosity, its affection, its natural reactions. And the symptoms of post, traumatic stress disorder appear.

For the parents, themselves more often than not victims of childhood abuse, the reactions of their children are not seen for the depression and/or stress-induced neurosis they usually are, but as signs of sullenness or worse still, of "being spoilt". It is essential for the therapist to explain and ensure the parents', caretaker's or teacher's cooperation, as the case may be. The therapist and/or clinician must take into account the special features of each case accordingly. A complex interactive model of disaster-related child psychopathology needs to be constructed if one hopes to achieve the emergence of a stable personality after the disaster.

Victims of Economic Exploitation

The child victims of economic exploitation need special protection. As with domestic violence, there seems to be a positive correlation between lack of economic development and the pervasiveness of child labor. It is important to emphasize however, that one is not referring here to the ordinary after-school jobs children do in order to augment their pocket money, but to the relentless drudgery children are subjected to in menial, exhausting tasks that are more reminiscent of slavery than anything a civilized society should allow.

This form of in human labor at young ages has dire consequences for the child, both physically and mentally. Their young bodies, usually already malnourished, exhausted by long hours of work, are even less resistant to disease. Carrying heavy loads leads to deformed bones, and the general lack of hope for change leads to a deformed view of existence, of life.

UNICEF and the ILO are seeking to eliminate child labor in the garment industry in India, and in order to provide those children with educational opportunities currently denied them, have jointly launched a series of programs. These include educational grants and family allowances to compensate for the income lost to the family by the removal of the child from the work force.

These efforts by the international community are welcome and deeply appreciated. However, the problem posed by child labor and even more deplorably, by child homelessness, is vast and in dire need of increased world awareness.

Victims of Sexual Abuse

The sexual abuse and exploitation of children is a worldwide phenomenon that unfortunately knows no economic or cultural boundaries. The fact that it is more widespread and blatantly commercial in economically less privileged countries should not blind us to the pervasiveness of the evil.

The World Congress Against the Sexual Exploitation of Children, which gathered together representatives of more than 122 states as well as the representatives of more than 400 NGOs and a large number of intergovernmental organizations, was the culmination of a global mobilizatilon against the commercial sexual exploitation of children initiated by the End Child Prostitution in Asian Tourism (ECPAT) campaign.

The World Congress is but a beginning, albeit an important and essential one, yet the road ahead is long and, due to the extreme nature of the problem, very arduos. No one can allow himself to flag in the effort to eradicate this most evil phenomenon.

Victims of Natural Disasters

Earthquakes, fires, floods and other natural disasters are among the factors that traumatize children as well. The symptoms of this form of trauma are not in essence different. All the elements of post traumatic stress disorder manifest themselves. A growing body of literature addresses this form of psychopathology resulting from natural disasters; these studies note that children afflicted by natural disasters exhibit such typical symptoms of post-traumatic stress disorder as anxiety, aggression and regressive behavior.

Victims of Armed Conflict

Of all the horrors that humankind is heir to, war is arguably the worst. It is invariably man-made, and therefore should be avoidable. A multitude of wars of every description are being waged all over the globe at present. Children are the innocent victims of bilateral, multilateral, civil, guerrilla and ethnic warfare: children come directly under fire; must bear arms willy-nilly; and are the victims of torture, maiming and brainwashing. Children are the helpless spectators of the death, injury or defeat of their parents, the hapless part and parcel of endless migrations caused by the necessity of fleeing death and destruction. It is self-evident that the physical survival of children must have absolute priority. Yet, a great deal of attention needs to be given to the emotional well-being of these children in order to avoid the many appalling psychological problems they face, as well as to break the spiral of violence that festering emotional wounds are known to cause from one generation to the next.

In the climate of violence and fear that wars bring about, some families manage to protect their children from the worst emotional damage that war causes. Many, if not most, however, are physically incapable of doing so or they are so overwhelmed by events that they are themselves in dire need of care and protection. The same applies to the community. Some communities manage to harbor their children against the rigors of war. Others, themselves exhausted, can do little. It is then up to the national and local governments, civil sectors and the international community to provide succor.

In the very short term it is of course a human and moral imperative to help child victims of war in every possible way. For those of us who wish to see war obliterated from the face of the earth, however, it may well be the height of rational self-interest, in the long-term, to invest and invest heavily in the moral and emotional well-being of the children of war, in order to eradicate as much as possible the impulses to violence and aggression implanted in them by their experiences.

The United Nations Convention on the Rights of the Child, which came into force on September 2 1990, gives both ethical and political legitimacy to direct involvement by the international community in the protection of the rights of children in zones of conflict.

How this is to be done is a question that requires careful consideration both of war-induced traumas and of their avoidance where possible.

Recent research concerning very diverse theatres of war, from the former Yugoslavia, particularly Bosnia-Herzegovina, to Lebanon, Central America, Mozambique and South Africa, indicates that the war-related experiences of children are multifarious and that their effects can continue over considerable periods of time.

Research conducted into the experiences of children during the war in Lebanon (1988) showed that, on average, a Lebanese child was subject to five or six different types of traumatic experience during its lifetime. These can be summarized according to a scale of frequency as: exposure to shelling and combat, 90%; displacement, 54%; seeing the injury, torture, death or intimidation of a person or persons close to it, 50%. The children of Iraq and Kuwait during the Gulf War were exposed to similar horrors, at similar frequency. In Mozambique, however, children were even more directly involved in the war as victims of abuse, torture, kidnapping and subsequent brainwashing, and by being forced to become soldiers trained to kill.

In the name of ethnic cleansing in Bosnia children have been forced to assimilate or have simply been murdered. No one yet knows the full toll that the wars in the former Yugoslavia have tken. One relatively small yet potent tragedy concerns the children born of rape. Unwanted by their mothers or their mothers' families,

unknown and unsought by their fathers, these totally innocent children were victims of war even before being born and many are condemned to an institutionalized childhood.

Similarly, children growing up in the Israeli-occupied West Bank, forced to grow up amid constant political, ethnic and religious tension, to say nothing of economic, social and educational discrimination, who have often witnessed their homes being bulldozed, cannot be expected to become future model citizens. Innocent Azeri child victims of the 1992 Armenian invasion in Hodjali (Xocalı) in Karabagh who survived the massacre are subject to all kinds of stress secondary to their difficult circumstances.

Whatever may cause the trauma, the effect on children is remarkably similar when they are studied by age group. On the level of immediate reaction there may quite often be signs of regression, taking the form of habitual bed-wetting, a refusal to become toilet trained, regression of speech patterns. Disturbed sleep and nightmares become the norm among many; other widespread symptoms include short attention spans, inability to concentrate on anything for any period of time, learning disabilities where there had been none before, re-enactment games constantly played and replayed, brief states of hyperactivity followed by periods of lethargy, detachment and at times avoidance of adults, even those nearest to the child before the trauma.

In developmental terms the child feels itself doubly, sometimes trebly, betrayed by the adults closest and dearest to it. In the first instance, the closest adults have not "protected" it from the trauma; in the second, the adult has "betrayed" the child by causing the trauma, by being himself a victim, or worse, by dying and leaving the child quite bereft; and third, by behaving in ways totally incommensurate to the moral dicta previously inculcated into the child. Thus, the whole system of role models falls into disarray and with it the moral development of the child may sometimes be forever interrupted.

The total chaos war creates and the disruption of normal patterns of cause and effect and of the laws of probability reduce the adults' belief in reason. The child sometimes ends up having chaos in all its dimensions as the only recognizable reality it possesses. Under these circumstances of utter randomness a child's reactions, ranging from total nihilism to total altruism are equally logical, as would be its belief in a number of supernatural entities and irrational sequences. Given these factors it is not easy to predict whether a child will turn into a psychopath or a saint. Thus the mitigating and the remedial factors in the child's immediate and wider environment, as well as its own development, need to be taken into account in order to render the child more resilient.

In general it seems that certain forms of parenting and rearing, involvement of the community, the degree to which personal identity has developed in the child, how well the notion of self has developed, and a strong bonding with the parent,

most significantly the mother, all seem to be important factors in the degree to which children can tolerate the trauma they face daily during war time.

In conclusion, providing protection for child victims of disaster, shielding children adequately and appropriately from the multitude of disasters that they may face, is not an easy task. But what renders us human is our constant attempt to achieve the impossible. Therefore we must continue to struggle to render the world a better place... possible only through the health and happiness of all our children.

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GENDER DISCRIMINATION AND DEPRIVATION: CURRENT SITUATION AND PROSPECTS FOR ALLEVIATION*

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Worldwide, there is a tremendous concern towards violence against the girl-child. The title of this paper is broader and may connote a discrimination against either sex. However, it is recognized that gender discrimination usually means violence against women and girls. I will start with specific issues which are good indicators of the plight of many girl-children in the world.

Gender Violence

- Researchs shows that the main locus of violence is within the household. Socialization into accepting or committing violence starts at home where children witness their father beat or abuse their mother or when they themselves are abused.
- Reports of incestuous rapes against female children are increasing, not only in developing countries, but in the developed as well.
- Pedophilia, which involves the trafficking of minors by international syndicates, has reached alarming proportions.
- The commercial sex industry caters to the preference of customers for female virgins who usually are very young women between the ages of 12 to 15; male customers' preference for young virgins is also fueled by their belief that they can avoid HIV infection if they "use" virgins.
- At least two million girls per year suffer female circumcision. Eighty-five to 114 million girls are estimated to have been genitally mutilated in Egypt and Sudan. Researchers report that girls as young as five to nine years old are subjected to genital circumcision despite legal restrictions. Genital mutilation may lead to social and mental problems and even death. Aside from the health problems that this practice causes, cultural taboos deprive the child of a healthy social development. After circumcision, her status becomes that of a woman. She is not allowed to socialize with boys her age and is subjected to strict codes of modesty.

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- The trend is increasing where women minors are sent, through illegal ways, to work as overseas migrant workers for some countries.
- The earliest forms of gender violence occur as feticide, prenatal sex selection and infanticide as a consequence of son-preference in most cultures.

Discrimination

- In the allocation of resources (i.e., food and money for education), in the context of competing gender and generation demands in poor households, the girl-child is usually given lower priority than that accorded to boys.
- Cultural beliefs and social hierarchies place more household responsibilities on adolescent girls than on boys their age. In settings where mothers earn money outside the home, they take over much of the mother's tasks and responsibilities. When accidents occur to their infant siblings, there have been reports that they are violently punished for negligence.
- The health services specific to needs of adolescent girls are either inadequate or nonexistent. Health professionals are usually untrained or insensitive to sexuality and reproductive health problems of young women and adolescents.
- Early marriage, which may also be prearranged, exposes the girl-child to obstetrical risks and can shorten life span. This also hinders further educational or employment opportunities.

Deprivation

- Cultural beliefs in some communities such as food taboos during menstruation, deprive the girls of critically needed nutrition.
- Most cultures deprive girls of an education for a number of reasons.
- Social norms and power structures deprive young women of opportunities to participate meaningfully in community affairs and political events.
- Young women, some as young as 12 to 15 years old, are recruited to work in sweat shops like garment and electronics factories and are deprived of protection of labor laws. The focus on child survival has inadvertently diverted attention away from the situation of millions of violated, discriminated and deprived girl-children. This picture does not even include the situation of girl-children in very difficult circumstances like the street children and children who are living in war-torn areas.
- According to a 1994 WHO statement, the vast majority of female adolescents in developing countries suffer from iron deficiency. At least 25 percent of adolescent girls in developing countries are affected by iodine deficiency, a common cause of mental retardation.

In an October 1994 press release, the World Health Organization called attention to the plight of adolescent girls. "Their health is jeopardized because often they have a low status in their families and in their workplaces, and crucially fewer opportunities for education, training and employment. In such an atmosphere, they face hazards such as child marriage, child prostitution, genital mutilation, assault during pregnancy, courtship or dating violence and sexual harassment and abuse".

In many countries, young women suffer from double neglect because they are neither regarded as children or adults. Dr. Hiroshi Nakajima, Director-General of WHO, states: "More and more, changing global conditions are placing greater strains on young people, modifying their behavior and relationship which are increasingly exacerbating health problems. These problems often fall most heavily on young women. It is often action by others that is a prime root cause of many of these problems, detrimental not only to themselves, but to their future families and society as a whole".

Dr. Nakajima's remarks remind us of the many adverse impacts of aggressive capitalist marketing on the values and desires of the young, who are among the primary targets of advertisements. The tobacco industry, for example, has spent billions of dollars on advertising which is designed to create a bigger market among the young generation which can raise a number of ethical issues. In North America, the population which registered the highest increase in cigarette consumption is that of teenage girls. A larger percentage of the world's population is acquiring the tobacco habit. The trend reflects the greater availability of cigarettes to teenagers, worldwide.

A Framework for Understanding The Situation of the Girl - Child

There are two factors which stand out when we examine the issues besetting the girl-children of the world: GENDER AND GENERATION. They are suffering from double neglect because they are women but they are neither children (who have been the subject of many child survival programs) or adults (who at least have certain prerogatives in society). Women, in general, are discriminated and deprived the world over. Adolescent women are in a worse situation because they are women and they are adolescents.

Cultural, sociological, political and economic structures and dynamics work in an interrelated fashion to sustain the double neglect and obstruct efforts at improvement. A very good illustration is gender, both as an analytic and operational concept.

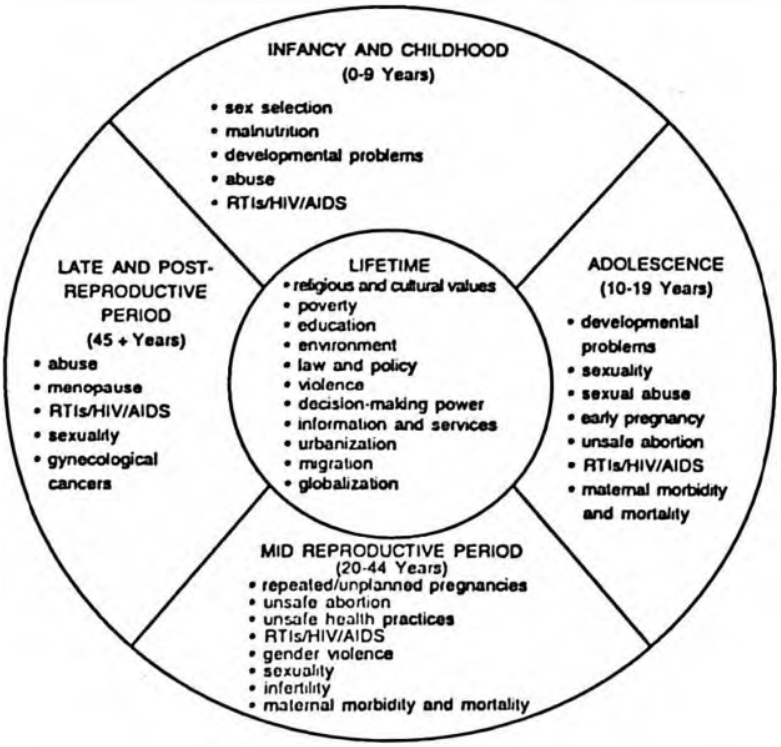
The Special Programme of Research in Human Reproduction (HRP), which is cosponsored by the UNDP, the UNPF, the WHO and the World Bank, explains gender as follows: "Gender" is used to describe those characteristics of men and women which are socially constructed in contrast to those which are

biologically determined. This social construction makes gender a dynamic concept which looks at the system formed by the interrelations between men and women in the context of society. These interrelations vary widely within and between cultures and are affected by the values of society made explicit through law, and religious and cultural practices. Gender roles change over time and over an individual's life stages. In practically all cultures, women have a lower status than men. Even in countries where discrimination against women and girls may not be evident, a deeper study will reveal a subtle existence of discrimination.

A gender analysis reveals the power relations between men and women in which women are usually subordinate. In reproductive health, a gender approach examines how gender differences determine differential exposure to risk; access to benefits of technology, information, resources and health care; and the realization of reproductive and sexual rights and responsibilities.

The Life Cycle Approach

It has been convincingly shown in various fora and reports that the holistic or integrated approach is the appropriate way of addressing health concerns. The life cycle approach is the holistic way of addressing the situation of the girl-child. It affirms that the health of the girl is dynamically located in a continuum such that, for example, to have healthy women, we should promote the health of the fetus, the infant, the child, the adolescent, the adult and the elderly. This diagram has been developed by researchers and advocates of reproductive health rights of women (Fig. 1). It can be very well used to illustrate the life cycle



Fiig. 1: Life cycle approach to sexual and reproductive health.

approach to addressing the situation of the girl-child. We are not advocating that reproduction is the only or even the primary role of women. On the contrary, we take reproductive health as the totality of the health of women.

In the diagram we see the different stages in the life of the woman and the various health problems that are usually associated with each stage. Let me focus on the stages of infancy and childhood and adolescence. The health problems that usually plague children in the stages have been mentioned earlier in my paper: sex selection (which can lead to abortion or female infanticide), malnutrition, developmental problems, abuse and reproductive tract infections (RTI). In adolescence, the problems are usually those which have something to do with their biological and social development: their sexuality, sexual abuse, early pregnancy, unsafe abortion (as well as social ostracism), RTIs, maternal morbidity and mortality.

The innermost circle shows the factors which influence and contextualize these various health concerns. These are: religious and cultural values, poverty, education, environment, law and policy, violence, decision-making power, information and services, urbanization, migration and globalization.

Prospects for Improvement

The WHO Global Commission on Women's Health recognizes that young people are themselves a great resource for promoting health and human development. "Young people are very sensitive to injustice, and it is for this reason that there is hope in enhancing gender equity between the sexes".

Information and education work at the community level can target the young generations as they are the most open to new ideas and have the flexibility to adopt new ways of establishing and of forging relationships.

Education

The most promising strategy is education of young women. Let me present excerpts from "Girl's Education: A Lifeline to Development, The State of the World's Children 1996 UNICEF":

"For several decades now, female literacy has been recognized as a critical factor for both health and national development. Recent international conferences in Cairo (population) and Beijing (women) have affirmed the necessity of education for the empowerment of women.

It is a sad fact that if global figures are perused, there are twice as many girls out of school compared to boys and twice as many women who are illiterate adults as men. Earlier, in both the Convention on the Rights of the Child, and the Convention on the Elimination of All Forms of Discrimination Against Women, it has been emphasized that it is a basic human right for girls to have a basic educatilon.

Examples of the effects of education are as follows: An educated woman is likely to marry at a later age. She has fewer children. An extra year of schooling for girls has been shown by crosscountry studies to reduce fertility rates by 5 to 10 percent. It has also been demonstrated that children of an educated mother are more likely to survive. In India, the infant mortality rate of babies whose mothers have received primary education is half that of children whose mothers are illiterate.

An educated woman will be more productive at work with higher pay. Studies from a number of countries suggest that an extra year of schooling will increase a woman's future earnings by about 15 percent, compared with 11 percent for a man, clearly demonstrating that the dividend for educational investment is often higher for women than men.

The good news is that in the last two decades, significant progress in girls' education has been made with combined primary and secondary enrolment for girls in developing countries rising from 38 percent to 68 percent, with high rates in East Asia (83 percent) and Latin America (87 percent). On the other hand, the bad news is that in the least developed countries, enrolment rates are only 47 percent at the primary level and 12 percent at the secondary level.

To improve girls' access to education, experience has shown in several countries that the following contribute positively: Parental and community involvement with a partnership between families and community is important in developing curriculum and managing children's education. Low-cost basic education should not only be free or cost very little but should provide stipends and scholarships wherever possible to compensate families for the loss of the girl's household labor. A flexible timetable would enable girls to help at home and still attend classes. Schools close to home would lessen parental worry about girls travelling long distances and in some countries, many parents prefer their daughters to be taught by women.

Early childhood care enhances girls' self-esteem and prepares them for school. Learning materials must be relevant to the girl's background, presented in the local language, and must avoid reproducing gender stereotypes. In brief, education is best started in early childhood and girls should be given equal educational opportunities as boys. "Remember, educate a girl and you educate a woman; educate a mother and you educate a family".

Advocacy

Advocacy, particularly legislative advocacy, has been found to provide a conducive environment for social transformation and the promotion of human rights. Advocacy should involve the citizenry, especially the family, the media, the Academe, the church, non-governmental organizations and the legal system.

Advocacy should be directed towards achieving the following:

- *Change of attitudes-in the girl herself, her parents and the public*: Through the media, schools, family, community.
- *Data collection*: By medical societies, obstetric and pediatric societies, governmental and non-governmental organizations.
- *Provision of equal services in*: Health/nutrition, education, reproductive education, social services.
- *Social mobilization by*: Community organizations, religious groups, cultural groups, professional organizations, media.
- *Legislation and implementation of legal provisions on*: Prohibition of prenatal gender selection, banning of female genital multilation, enforcement of laws against infanticide, protection of children vs. exploitation, compulsory primary education.
- *Acceptance and adherence to international instruments protecting the girl child*:

  The Geneva Declaration on The Rights of the Child, 1954
  Universal Declaration on The Rights of the Child, 1959
  International Covenant on Civil and Political Rights, 1966
  The UN Convention on the Elimination of All Forms of Discrimination Against Women, 1979
  The UN Convention on The Rights of the Child, 1989
  The World Conference on Education for All, 1990
  The International Conference on Nutrition, 1992
  The International Conference on Population and Development, 1994
  The Fourth World Conference on Women, 1995

- *International aid restrictions to countries that do not comply.*

Research and Data Collection

Necessarily, statistical data on gender discrimination must be available for planning, strategies and interventions. Research will provide data essential for legislative advocacy. Research data is crucial in lending credence to legislative advocacy to facilitate deliberations on a proposal. Research data would be the basis of information, education and communication materials.

Public Education and Information

Research data should be shared with the public, with community organizations, religious and cultural groups, professional organizations and media. This can bring about a mobilizatilon which can target as one of its primary objectives an attitudinal change in the girl herself, her parents and the public.

Reforms in the Health Care Delivery Systems

It is encouraging to note that progressive initiatives are now being taken by medical schools in reforming their curricula towards the production of more gender-sensitive and gender-responsive health care professionals. Health care institutions should continue to establish units and services which are specifically aimed at responding to gender-related health needs. It is obvious that increasing attention is being given to ethical issues in health care and health research. But we need to do more. Let us establish more networks and partnerships regionally and globally so that we can maximize our efforts and our impact on international trends.

Pediatricians should become involved as individual citizens with pediatric societies, putting up a collective voice that can be heard loud and clear by policy makers, legislators and the whole community.

Let me end by quoting a poem written by Dr. Sultan Arif Zuberi:

I Am the Poor Rural Woman

I am the poor rural woman
Surrounded by ignorance and superstition
Despite this age of modern civilization
Without health care and without education
I am the poor rural woman of this nation

The day of my birth is a day of grief
I toil till my death without relief

In darkness and dirt my newborns arrive
Death haunts me whilst I am giving life

My father, my husband, even my son
No one thinks of me as a person
I am no better than the cattle I feed
Is life only to graze and breed?

I am the subject of learned discourse
Reformers write papers full of remorse
Politicians raise slogans to further my cause
But my status however remains as it was

False promises do not endure
"True Will" only effects a cure
If you wish to build a nation new
Give me the rights which are my due

If justice is denied to me
From bondage no one will be free
My strength will make the nation strong
Just like the land to which I belong

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ANTIBIOTIC USE IN NEONATAL SEPSIS*

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Neonatal sepsis is a life-threatening emergency and any delay in treatment may cause death. Initial signs of neonatal sepsis are slight and nonspecific. Therefore, in suspected sepsis, two or three days empirical antibiotic therapy should begin immediately after cultures have been obtained without awaiting the results. Antibiotics should be reevaluated when the results of the cultures and susceptibility tests are available. If the cultures are negative and the clinical findings are well, antibiotics should be stopped. Because of the nonspecific nature of neonatal sepsis, especially in small preterm infants, physicians continue antibiotics once started. If a baby has pneumonia or what appears to be sepsis, antibiotics should not be stopped, although cultures are negative. The duration of therapy depends on the initial response to the appropriate antibiotics but should be 10 to 14 days in most infants with sepsis and minimal or absent focal infection.

In infants who developed sepsis during the first week of life, empirical therapy must cover group B streptococci, Enterobacteriaceae (especially E. coli) and Listeria monocytogenes. Penicillin or ampicillin plus an aminoglycoside is usually effective against all these organisms. Initial empirical antibiotic therapy for infants who developed sepsis beyond the first days of life must cover the organisms associated with early-onset sepsis as well as hospital-acquired pathogens such as staphylococci, enterococci and Pseudomonas aeruginosa. Penicillin or ampicillin and an aminoglycoside combination may also be used in the initial therapy of late-onset sepsis as in cases with early-onset sepsis. In nosocomial infections, netilmicin or amikacin should be preferred. In cases showing increased risk of staphylococcal infection (e.g. presence of vascular catheter) or Pseudomonas infection (e.g. presence of typical skin lesions), antistaphylococcal or anti-Pseudomonas agents may be preferred in the initial empirical therapy.

In some centers, third-generation cephalosporins in combination with penicillin or ampicillin have been used in the initial therapy of early-onset and late-onset neonatal sepsis. Third-generation cephalosporin may also be combined with an aminoglycoside in places where aminoglycoside-resistance to this antibiotic is high. However, third-generation cephalosporins should not be used in the initial therapy of suspected sepsis, because 1) extensive use of cephalosporins for initial therapy of neonatal sepsis may lead to the emergence of drug-resistant microorganisms (this has occurred more rapidly as compared with the aminoglycosides), 2) Antagonistic interactions have been demonstrated when the other beta-lactam antibiotics (e.g. penicillins) were combined with cephalosporins.

Infections due to gram-negative bacilli can be treated with the combination of a penicillin-derivative (ampicillin or extended-spectrum penicillins) and an aminoglycoside. Third-generation cephalosporins in combination with an aminoglycoside or an extended-spectrum penicillin have been used in the treatment

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of sepsis due to these organisms. Piperacillin and azlocillin are the most active of extended-spectrum penicillins against Pseudomonas aeruginosa. Among the third-generation cephalosporins, cefoperazone and ceftazidime possess anti-Pseudomonas activity. Ceftazidime was found to be more active in vitro against Pseudomonas than cefoperazone or piperacillin. New antibiotics for gram-negative bacteria resistant to other agents are carbapenems, aztreonam, quinolones and isepamicin. Enterococci can be treated with a cell wall-active agent (e.g. penicillin, ampicillin, or vancomycin) and an aminoglycoside. Staphylococci are susceptible to penicillinase-resistant penicillins (e.g. oxacillin, nafcillin and methicillin). Resistant strains are uniformly sensitive to vancomycin. A penicillin or vancomycin and an aminoglycoside combination result in a more rapid bacteriocidal effect than is produced by either drug alone. *Key words: newborn infant, sepsis, antibiotic therapy.*

Despite the much more sophisticated diagnosis and management of neonatal sepsis in recent years, it is still a major cause of neonatal morbidity and mortality. It is estimated that the incidence of neonatal sepsis varies from less than one to eight cases per 1000 live births. The incidence of sepsis will be influenced markedly by the quality of intrauterine life, host factors, and environmental factors. Therefore, the incidence of neonatal sepsis in preterm infants is one in 40 (or higher) newborns.

In the preantibiotic era mortality from neonatal sepsis exceeded 90 percent, but with the availability of antibiotics it has fallen to a range of 10 to 50 percent. The incidence of neonatal sepsis and rate of mortality have not decreased during the past decade and may even have increased because of the development of life support techniques that have permitted the survival of the extremely premature or otherwise high-risk neonate[1-9].

Two patterns of disease, early-onset and late-onset, have been associated with systemic bacterial infections during the first month of life.

Early-Onset Disease

Early-onset disease presents as a fulminant, multisystemic illness during the first few days of life. The mortality is high, varying in some series between 15 and 50 percent. These infants have a history of one or more significant obstetric complications. Among these risk factors are premature delivery or low birth weight, premature rupture of membranes, chorioamnionitis, maternal peripartum infection, abnormal vaginal flora (e.g., group B streptococci carrier, sexually transmitted disease, bacterial vaginosis), obstetric manipulations (e.g., vaginal exams, internal fetal monitoring) in the presence of ruptured membranes, septic or traumatic delivery and fetal hypoxia. It is unusual for a full-term infant to develop early-onset sepsis after an uneventful pregnancy and delivery[10].

Most of the cases are due to group B streptococci (GBS), gram-negative enteric bacteria and Listeria monocytogenes. These pathogens are usually acquired from the birth canal during delivery. The source of bacteriemia is frequently unapparent, but careful inspection may reveal a focus, such as infection of the

umbilical stump. Bacteria can be inoculated through the skin by use of obstetric forceps, and organisms may infect the skin and soft tissues if abrasions or congenital defects are present. Transient bacteriemia may accompany procedures, such as endotracheal suctioning, that traumatize mucosal membranes.

In cases with prolonged rupture of membranes, initial colonization of the neonate usually takes place after rupture of the maternal membranes. If delivery is delayed, however, vaginal bacteria may ascend and in some cases produce inflammation of the fetal membranes, umbilical cord and placenta. Fetal infection may then result from aspiration of infected amniotic fluid. Infection of the mother at the time of birth, particularly genital infections, may play a significant role in the development of infection in the neonate. Transplacental hematogenous infection during or shortly before delivery is also possible.

Late-Onset Disease

Late-onset disease may occur as early as five days of age, but is more commonly recognized after the first week of life. The mortality rate is lower than in early-onset sepsis-approximately 10 to 20 percent. Infants may have a history of obstetric complications, but these are less characteristic than in early-onset disease. Bacteria responsible for late-onset sepsis include those acquired from the maternal genital canal and organisms acquired after birth from human contacts or from contaminated equipment or materials. Some organisms, such as E. coli, GBS and L. monocytogenes, may be responsible for both early-onset and late-onset diseases, whereas others, such as S. aureus and Pseudomonas aeruginosa, are usually associated with late-onset disease.

Initial Empiric Therapy

The signs of neonatal sepsis are very subtle, particularly in the early stages, and may not be clinically distinguishable from those caused by other common neonatal problems. Frequently it is the mother or nurse who first notices that the baby is not quite as well as he has been, he is quieter and stiller than usual, perhaps a little pale, and either feeds poorly or vomits. Some time later "harder" signs develop.

Neonatal sepsis is still a life-threatening emergency. Any delay of diagnosis and treatment may have devastating consequences. Isolation of a pathogenic microorganism from the blood is the most specific method of diagnosing neonatal sepsis. Bacterial growth is evident in the majority of cultures of blood within 48-72 hours. However, antimicrobial treatment of neonates with suspected sepsis should begin immediately after appropriate cultures have been obtained. Waiting for the results of the cultures may cause delay in the beginning of therapy which may adversely affect the prognosis of sepsis. Even a four-hour delay may increase mortality rate.

The empirical therapy for presumed sepsis is benign as compared to the consequences of not treating the truly infected infant. The adage that "three days of ampicillin and gentamicin never killed anybody" has some merit in this context.

After the two or three-day empirical therapy with antibiotics, the choice of antibiotics should be reevaluated when results of cultures and susceptibility tests become available. If the cultures are negative and the clinical findings of the patient are well, antimicrobial therapy should be stopped. Otherwise resistant gram-negative colonization is quite high. Possible reasons why antibiotics are not stopped include the nonspecific nuture of signs of sepsis in neonates, physicians' reluctance to discontinue antibiotics once started, and the logistical difficulty of obtaining routine culture results at weekends. However, if the baby has pneumonia, or what looks like sepsis, antibiotic therapy should not be stopped, even if blood culture is negative.

Decreasing gestational age is associated with increased rates of infection. The ruling out of sepsis in the immature neonate is very difficult. Therefore, antibiotic therapy for suspected sepsis is frequently initiated at birth in small preterm infants and continued for five or more days, despite a negative blood culture[11].

Infants born to women who have received intrapartum antibiotics represent a difficult treatment dilemma for the clinician because culture growth may be inhibited by exposure to intrapartum treatment. Therefore, all symptomatic infants should be treated for at least 10 days, even if cultures show no growth. For asymptomatic newborns, decisions can be made according to cultures and laboratory data (white blood cell count < 5000/mm^3 or > 30.000/mm^3, immature/total leukocytes > 0.2, C-reactive protein > 0.8 mg/dl, microerythrocyte sedimentation rate > 15 mm/hr). When the sepsis screening tests are negative in an asymptomatic infant, the likelihood of infection is very low, and the treatment can safely be discontinued. In general, full course antibiotic treatment should be given in an asymptomatic preterm infant who has a positive screen. In asymptomatic full-term infants, closer follow up is needed before the beginning of antibiotic therapy[1, 12, 13].

Selection of an empirical antibiotic regimen should be based on:

– Postnatal age at the onset of disease: Because different microorganisms are responsible for early- or late-onset disease, the choice of antimicrobial agents also differs.

– Patient-specific factors: the patient's clinical conditions (including invasive procedures) and previous antibiotic therapy.

– Bacterial prevalence: the bacterial species most likely to cause infection.

– Bacterial susceptibility: antibiotic resistance pattern in one's own hospital. Antimicrobial agents play a major role in the ecology of the microbial flora in the nursery. Extensive use of these drugs helps to eliminate sensitive strains

and allows proliferation of resistant strains. Thus, there is a selective pressure toward colonization by microorganisms that are resistant not only to the antimicrobial agents used in the hospital but also to other similar drugs, because of cross-resistance patterns.

– Pharmacokinetical properties of the antibiotic.

A combination of two antibiotics should be initiated in suspected neonatal sepsis.

– Empirical therapy must cover most of the pathogens which cause sepsis.

– Synergistic effects of antibiotics (e.g. penicillin + aminoglycoside for GBS).

– Some infecting organisms are likely to develop resistant mutants during therapy (e.g. Pseudomonas species).

– Higher bactericidal serum activity is required than can usually be achieved with a single agent (e.g. enterococci, Listeria).

Early-Onset Sepsis

In infants who developed sepsis during the first week of life, empiric therapy must cover GBS, Enterobacteriaceae (especially E. coli) and Listeria monocytogenes. The bacteriology of neonatal sepsis in Europe is, in general, similar to that in the United States. In tropical areas, a different pattern is seen: E. coli, Klebsiella and Serratia species are the dominant causes of neonatal sepsis; GBS are infrequent causes. In this part of the world, the majority of early-neonatal infections are probably caused by gram-negative bacteria, rather than by GBS as in the United States. The difference in the incidence of GBS may reflect a genetic factor or differences in sexual practices. In developing countries, multiple-resistant hospital acquired bacteria, which are transmitted by lack of hygiene, may cause early-onset infections.

Penicillin or ampicillin plus an aminoglycoside combination is generally effective against all these organisms. Ampicillin and an aminoglycoside combination provides broader antimicrobial activity. Compared with penicillin, ampicillin has increased efficiency against L. monocytogenes, as well as against some gram-negative pathogens, E. coli and Proteus mirabilis.

Most GBS are highly sensitive to penicillin and can be treated with penicillin or ampicillin alone. But infections due to GBS can be treated with a combination of penicillin or ampicillin and an aminoglycoside. Although aminoglycosides are relatively ineffective against GBS in vitro, when added to penicillin or ampicillin, they enhance the antibacterial activity[1].

Listeria monocytogenes are also susceptible to penicillin or ampicillin and can be treated with either of these drugs. But based on in vitro synergy studies, combination therapy with either penicillin or ampicillin and an aminoglycoside has been recommended[1].

Late-Onset Sepsis

Initial empirical antimicrobial treatment for infants who developed sepsis beyond the first few days of life must cover the organisms associated with early-onset sepsis as well as hospital-acquired pathogens such as Staphylococci, Enterococci and Pseudomonas aeruginosa.

Penicillin or ampicillin and an aminoglycoside combination may also be used in the initial therapy of late-onset suspected sepsis as in cases with early-onset sepsis. In nosocomial infections, netilmicin or amikacin should be preferred. In some hospitals, strains which cause nosocomial infections have undergone considerable alterations during the past 20 years, with a gradual increase in resistance to kanamycin, gentamicin and tobramycin. Fortunately, amikacin, and in some instances netilmicin, have retained their activity in this setting. Amikacin is resistant to degradation by most of the plasmid-mediated bacterial enzymes that inactivate other aminoglycosides. Therefore, it is held in reserve for treatment of hospital-acquired gram-negative infections that are suspected or proven to be multiple-resistant.

If there is an increased risk of staphylococcal infection (e.g. presence of vascular catheter), antistaphylococcal penicillin or vancomycin plus an aminoglycoside may be used in the initial antibiotic therapy. A ceftriaxone and vancomycin combination has also been used in the empirical therapy of late-onset sepsis[14]. In cases where there is increased risk of Pseudomonas infection (e.g. presence of typical mucocutaneous skin lesions), anti-Pseudomonas agents may be preferred in the initial empirical therapy. But we recommend using these antibiotics according to the results of the culture rather than routinely.

In some centers third-generation cephalosporins in combination with penicillin or ampicillin have been used in the initial therapy of early-onset and late-onset neonatal sepsis. Third-generation cephalosporin may also be combined with an aminoglycoside in some centers in places where aminoglycoside-resistance to this antibiotic is high[14-17]. The main advantages in using third-generation agents are excellent activity against the major pathogens of newborns, including aminoglycoside-resistant gram-negative bacilli, and excellent CSF penetration, as well as their safety and tolerability.

However, third-generation cephalosporins should not be used in the initial therapy of suspected sepsis because these antibiotics are not active against L. monocytogenes[1, 3]. Extensive use of cephalosporins for initial therapy of neonatal sepsis may lead to the more rapid emergence of drug-resistant microorganisms among gram-negative bacilli than has occurred with the aminoglycosides[18, 19].

Gram-negative Enteric Bacilli

Infections due to E. coli and K. pneumonia can be treated with the combination of a penicillin-derivative (ampicillin or extended-spectrum penicillins depending

on the isolate) and an aminoglycoside. Third-generation cephalosporins alone or together with an aminoglycoside may also be used in the treatment of such infections, although occasionally these organisms are resistant to cephalosporins[20]. In a study, ceftriaxone/gentamicin and azlocillin/gentamicin combinations have been found to have equal efficiency and reliability in the treatment of neonatal sepsis[21].

The treatment of Enterobacter species, Serratia species, Citrobacter species, indol-positive Proteus species and P. aeruginosa is more controversial. All these organisms carry a chromosomally encoded inducible beta-lactamase. Normally, this enzyme is under repressor control, and many isolates appear sensitive to penicillins, cephalosporins and monobactams. However, exposure to a beta-lactam antibiotic results in induction of expression of the enzyme which persists as long as the inducer is present. When mutation occurs in the beta-lactamase repressor gene, production of beta-lactamase is permanently induced and the organism becomes resistant to beta-lactam antibiotics. Even organisms initially susceptible to a beta-lactam antibiotic may become highly resistant during therapy.

Third-generation cephalosporins are poor inducers of beta-lactamase expresion, but are sensitive to these enzymes and are significantly associated with the development of repressor mutations. Like the third-generation cephalosporins, the extended-spectrum penicillins are poor inducers of beta-lactamase expression. On the other hand, these antibiotics are seldomly associated with repressor mutation and therefore may have therapeutic advantages[1,21,22]. Therefore, infections due to these gram-negative bacilli should be treated with a combination of an extended-spectrum penicillin and an aminoglycoside.

Nevertheless, third-generation cephalosporins in combination with an aminoglycoside have been used in the treatment of sepsis due to these organisms. Among the third-generation cephalosporins, cefoperazone and ceftazidime (and cefsulodin) possess anti-Pseudomonas activity. Ceftazidime was found to be more active in vitro against Pseudomonas than cefoperazone or piperacillin.

Both synergistic and antagonistic interactions have been demonstrated when the other beta-lactam antibiotics (e.g. penicillins) were combined with cephalosporins. Antagonism may be related to the ability of cephalosporins to induce beta-lactamase production which inactivates penicillins. Therefore, the use of third-generation cephalosporins in combination with penicillins should be avoided. However, it has been reported that early diagnosis and treatment with piperacillin plus cefotaxime reduced the mortality rate of sepsis[23].

Extended-spectrum penicillins are carboxypenicillins and acylampicillins. Most pathogens incriminated in neonatal sepsis are susceptible to these antibiotics, but their most important feature is activity against P. aeruginosa and certain

Proteus species that are resistant to ampicillin. Extended-spectrum penicillins are susceptible to staphylococcal beta-lactamases and are not reliable for treating staphylococcal disease.

Carboxypenicillins are carbenicillin and ticarcillin. Antimicrobial activity of ticarcillin is similar to that of carbenicillin with the exception that ticarcillin is more active against P. aeruginosa. The co-administration of clavulanic acid (a potent beta-lactamase inhibitor) with ticarcillin significantly enhances the antibacterial activity of the drug against several organisms, including many ticarcillin-resistant strains.

Acylampicillins include the ureidopenicillins (mezlocillin and azlocillin) and piperacillin. Piperacillin and azlocillin are the most active of extended-spectrum penicillins against P. aeruginosa. Mezlocillin, the least active of the three, is at least as effective as ticarcillin against this organism[24].

Although aminoglycosides exhibit somewhat similar activity against most gram-negative bacilli, tobramicin has the greatest anti-Pseudomonas activity. Amikacin is the only drug of this class that provides activity against Serratia species.

Alternative for Resistant Strains

Carbapenems: Imipenem is the first of new beta-lactam antibiotics, the carbapenems. It is combined with cilastin. Cilastin has no antibacterial activity, but is a potent inhibitor of dehydropeptidase-1, the renal tubular brush border enzyme that metabolizes imipenem. Its spectrum of activity includes most aerobic and anaerobic gram-positive and gram-negative bacteria[25]. There are synergistic interactions between imipenem and aminoglycosides[26]. Antagonistic interactions are usually observed when imipenem is combined with other beta-lactams, probably as a result of chromosomal beta-lactamase induction by imipenem. Both imipenem and cilastin penetrate well into the CSF in the presence of meningeal inflammation. However, neurotoxicity associated with imipenem has limited its usefulness in cases with meningitis. Emergence of imipenem-resistant strains during therapy with this drug is rare except for P. aeruginosa. In a high percentage of cases of P. aeruginosa infection treated with imipenem, resistance has emerged during the course of therapy[27]. Meropenem is another carbapenem which under investigations seems to have somewhat broader gram-negative activity than imipenem[28].

Aztreonam: Aztreonam is a synthetic monocyclic beta-lactam (monobactam) antibiotic[25]. But this drug is stable to hydrolysis by beta-lactamases and does not induce chromosomal beta-lactamase production. The antimicrobial activity of aztreonam differs from those of other beta-lactam antibiotics and more closely resembles that of an aminoglycoside. Its aminoglycoside-like activity, good CSF penetration and absence of nephrotoxic or ototoxic side effects make aztreonam

potentially useful when combined with ampicillin for the treatment of neonatal sepsis. When combined with aminoglycosides, aztreonam interacts synergically against P. aeruginosa and many gram-negative enteric bacilli[29, 30].

Isepamicin: Isepamicin is a new aminoglycoside that has activity against many bacteria that are resistant to other aminoglycosides[31, 32].

Quinolones: The quinolones, or floroquinolones, are bactericidal by inhibiting bacterial DNA replication[25]. Ciprofloxacin alone, or in combination with other antibiotics, has been used in some newborn centers in the treatment of gram-negative infections due to organisms (including P. aeruginosa) resistant to all other agents. However, the quinolones have not yet been approved for use in children, because of a concern for a possible effect of the quinolones on cartilage development in young children. To date, studies in older children seem to show no cartilage damage after treatment with quinolones. Magnetic resonance imaging and histopathological monitoring of ciprofloxacin use suggest that the quinolones do not cause arthropathy in humans as in experimental animals. Ultimately the quinolones will likely be approved for use in children[33-35]. However, the quinolones do not penetrate the blood-brain barrier well and are not, therefore, used to treat meningitis.

Enterococci

In general, enterococci are resistant to many antibiotics including cephalosporins, penicillinase-resistant penicillins and aminoglycosides. Furthermore, vancomycin inhibits but fails to kill these organisms. However, the cell wall-active antibiotics facilitate bacterial uptake of the aminoglycosides. Therefore, enterococci can be treated with a cell wall-active agent (such as penicillin, ampicillin, or vancomycin) and an aminoglycoside. In recent years high-level resistance to aminoglycosides and penicillin and vancomycin has prevalence among enterococci. Therefore management of infection caused by multiple resistant enterococci is a therapeutic dilemma[36-38].

Staphylococci

Because S. epidermidis is present on the skin, isolation of the organism from cultures of blood may represent skin contamination but may also be an important episode of bloodstream invasion. A repeat culture of blood may assist in differentiating contamination from bloodstream invasion.

The apparent increased incidence of S. epidermidis sepsis has been associated with increased survival of very small premature infants with immature immune systems and with the introduction of invasive procedures for maintenance and monitoring of the infants, including long-term vascular access devices.

Coagulase-negative staphylococci are the predominant cause of vascular-catheter-related infections. Staphylococcus aureus is more aggressive and associated with more complications than coagulase-negative staphylococci[39].

Most hospital-acquired strains of staphylococci are usually resistant to penicillin, ampicillin and cephalosporins. Staphylococci susceptible to penicillinase-resistant penicillins such as oxacillin, nafcillin and methicillin. Oxacillin may be preferred to nafcillin and methicillin because of their side effects. Some strains of staphylococci have become resistant to penicillinase-resistant penicillins. However, such strains are uniformly sensitive to vancomycin[40].

Although the activity of aminoglycosides against gram-positive bacteria is limited and resistant strains of staphylococci emerge rapidly during exposure to aminoglycosides, a penicillin or vancomycin and aminoglycoside combination results in a more rapid bacteriocidal effect than is produced by either drug alone[41].

Various studies suggest that teicoplanin is highly effective and safe in neonatal staphylococcal infections[42]. However emergence of teicoplanin-resistant coagulase-negative staphylococci is not rare[43, 44].

Duration of Therapy

The duration of therapy depends on the initial response to the appropriate antibiotics but should be 10 to 14 days in most infants with sepsis and minimal or absent focal infection. The minimal duration of therapy is 21 days for infants with meningitis due to gram-negative bacteria. Meningitis caused by GBS and L. monocytogenes should be treated for a minimum of 14 days[1-4, 45].

Side Effects of Anitibiotics

There are some side effects of antibiotics used in the treatment of neonatal sepsis[46].

1. Nephro- and ototoxicity due to aminoglycosides: Aminoglycoside clearance is dependent on renal glomerular filtration which is markedly decreased in neonates, especially those preterm. These drugs appear to be less nephrotoxic and ototoxic in neonates than in older patients, and the role of serum concentration monitoring should be limited to specific neonatal patients.

Numerous factors intervene in bringing about aminoglycoside-induced kidney damage, such as factors related to the antibiotic itself (intrinsic toxicity, administration route, type of monitoring of blood concentrations), those related to the subject treated (neonatal age, constitutional sensitivity), and other related to associated pathology (neonatal anoxia, renal hypoperfusion, respiratory distress-mechanical ventilation, hyperbilirubinemia, electrolyte disorders, and even the acute sepsis calling for antibiotic therapy), as well as pharmacological factors (concomitant therapies such as diuretics, indomethacin and other antibiotics, particularly glycopeptides and cephalosporins)[47].

2. Bleeding disorders due to third-generation cephalosporins: Bleeding disorders associated with the use of third-generation cephalosporins have been documented. Hemostatic abnormalities can be mediated by several mechanisms. The most important mechanism is interference with the production of vitamin K-dependent clotting factors. This is most commonly observed with moxalactam and cefamandole therapy, and is rare with cefotaxime and ceftriaxone. This side effect is usually avoidable or reversible by the administration of supplemental vitamin K[48].

3. Kernicterus risk and antibiotics: Hyperbilirubinemia is frequently observed in neonates, and serious neurological complications such as kernicterus can be precipitated when the concentration of unconjugated bilirubin is abnormally increased. The administration of drugs which bind to albumin and compete with bilirubin can increase the possibility of such a complication. Antibiotics could be classified into four groups: high-level displacers (sulfisoxazole, sulfamethoxazole, dicloxacillin, cefoperazone, ceftriaxone), intermediate-level displacers (moxalactam, nafcillin), low-level displacers (aztreonam, carbenicillin) and nondisplacers (mezlocillin, cefuroxime, kanamycin). Antibiotics with a tendency to displace bilirubin should be avoided in jaundiced newborns whenever appropriate alternatives are available[49].

4. High sodium contents of extended-spectrum penicllins: Sodium contents of extended-spectrum penicillins are important in the treatment of neonatal infections (5 mEq/g in carbenicillin and ticarcillin; 2 mEq/g in azlocillin, mezlocillin and piperacillin)[24].

Prophylaxis

1. Group B Streptococcal infection: In places where GBS carrier rate is high, the ideal approach toward preventing GBS neonatal disease involves intrapartum administration of antibiotics to colonized women because 30 to 70 percent of infants born to women colonized with GBS become colonized themselves during the delivery. Among colonized newborns, disease occurs in one to two percent[50].

The American Academy of Pediatrics (AAP) recommended universal screening of pregnant women at 26 to 28 weeks of gestation for vaginal or anorectal colonization with GBS[51]. This strategy prevents more cases but at greater cost. Screening all women with risk factors (e.g. preterm labor, premature rupture of members, fever during pregnancy, chorioamnionitis, multiple gestation) is simple, effective, inexpensive and avoids unnecessary antibiotic use[52-58].

If the cultures are positive, antibiotic therapy should be given to the mother. Treatment should include intravenous ampicillin or penicillin until delivery. When maternal cultures are negative for GB, the occurrence of neonatal GBS infection is very low. However negative cultures do not exclude the possibility of neonatal infection caused by other bacteria.

Vaginal disinfection with a chlorhexidine gel during labor modestly reduces group B streptococcal vertical transmission. Because the method is cheap, simple and safe, it should be considered for routine use[59].

2. Premature rupture of membranes: PROM and chorioamnionitis occur in approximately 10 and one percent of all pregnancies, respectively. Neonatal infections can be documented in one percent of infants delivered to women with PROM alone, and in 10 percent of infants born to women with PROM and clinical amnionitis. The risk for neonatal sepsis is much higher in preterm infants. An intrauterine infection was found in two thirds of women presenting with preterm PROM[60, 61].

Therefore intrapartum broad-spectrum antibiotics that provide anaerobic coverage (e.g. ampicillin with or without sulbactam) should be administered to any woman with premature rupture of membranes or clinical chorioamnionitis[62-64]. However, antibiotics should not be routinely administered to women in preterm labor with intact membranes[65].

In infants born to mothers with PROM, neonatal signs of infection including leukopenia, leukocytosis, thromboytopenia, and positive gastric aspirate cultures are not good predictors of sepsis. Thus the administration of prophylactic antibiotic therapy (same as early-onset sepsis) in these cases may be warranted in preterm infants[60]. However, it may be unnecessary to administer prophylactic antibiotics to term, appropriate-for-gestational-age infants born after PROM, except in cases with a low Apgar score and maternal chorioamnionitis[66].

3. Meconium aspiration: Antibiotic prophylaxis is usually done for newborn babies intubated at birth for aspirating meconium from the trachea to prevent pneumonia and sepsis. However, a recent study indicates that well-term babies who are intubated for aspirating meconium need not be put on routine antibiotic cover. But this prophylaxis may be needed in preterm infants[67].

4. Staphylococcal infection: Hexachlorophene bathing after birth decreases staphylococcal colonization, but this chemical is ineffective against gram-negative enteric bacilli.

5. Antibiotic use during invasive procedures: (e.g. endotracheal intubation, vascular catheterization) has no effect on the prevention of nosocomial infections. Attempts to prevent nosocomial bacteriemias by routinely administering prophylactic antibiotics should be avoided because of the possibility of development of resistant organisms[68].

Although staphylococcal infections are high in patients who have vascular catheterization, duration of catheterization is not found to be a significant predictor of risk for catheter-related sepsis[69], and prophylactics with an antibiotic are not recommended[70].

Topical mupirocin is routinely applied to insersion sites of vascular catheters of neonates. However, mupirocin resistance in coagulase-negative staphylococci, has been reported after topical prophylaxis for the reduction of colonization of central venous catheters[71].

Nosocomial Infection Control Measures

Several measures have been instituted to control epidemics of antibiotic-resistant gram-negative bacilli[72]. The most common measures include:

1. Closing the unit to new admissions until control of the outbreak is underway.

2. Cultures from the health personnel: The nose, throat, anus and hands of health personnel potentially harbor gram-negative pathogens. However, these cultures usually never yield significant levels of carriage even in the midst of an outbreak.

3. Reinforcing hand-washing practices. Gram-negative contaminants can be resistant to simple washing with nonmedicated soap and water. Repeated hand-washing in the hospital reduces the colonized bacteria, but they are able to replicate during nonworking hours.

4. Establishing a barrier between infected or colonized patients and those who do not harbor the resistant organism. However, most resistant organisms arise from the patient's endogenous flora rather than outside sources. Sophisticated genotyping of multiple hospital isolates confirms that a marked majority of gram-negative organisms colonizing or infecting hospitalized patients are distinct from one another, even among patients occupying the same unit at the same time. Only 10 to 20 percent of gram-neative bacillary infections seem to be caused by cross-contamination from one patient to another, and in those instances it is unusual for more than two patients to be affected by a single isolate.

5. Restriction of the use of the antibiotic to which the offending strain is resistant.

6. Modifying routine regimens to include newer antibiotics. This strategy only delays the problem because of developing resistance to new antibiotics.

7. Limiting the use of third-generation cephalosporins since these agents seen particularly prone to rapidly induce resistance to themselves and other beta-lactam agents.

8. Rotation of antibiotics to decrease emergence of resistance.

9. Use of multiple antibiotic regimens rather than monotherapy.

Colonization rates with resistant gram-negative bacteria have been known to fluctuate widely without any change in antibiotic practice. Even with strict antibiotic control, colonization and infection with resistant organisms rarely disappeared entirely. Consequently antibiotic-resistant gram-negative pathogens will remain in the hospital environment for years.

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CHRONIC LUNG DISEASE OF THE VERY LOW BIRTH WEIGHT INFANT – IS IT PREVENTABLE?*

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SUMMARY: Ogawa Y. (Professor of Pediatrics, Saitama Medical Center, Saitama Medical School, Saitama, Japan). Chronic lung disease in the very low birth weight infant - is it preventable? Turk J Pediatr 1998; 40: 35-44.

In Japan, chronic lung disease (CLD) is defined as an oxygen requirement greater than that obtainable in room air at 28 days of age, with symptoms of persistent respiratory distress and a hazy or emphysematous and fibrous appearance upon chest x-ray. A total of 4964 infants weighing less than 1500 g at birth and born in 1990 were admitted to and cared for at level II and III neonatal care centers in Japan. A total of 4293 infants (86.3%) survived at 28 days after birth.

Analyses of infants who developed CLD through their preceding illnesses and chest x-ray findings resulted in the classification of CLD into six types. Types I and II are defined as CLD following the acute stage respiratory distress syndrome (RDS). Type I is the typical case of bronchopulmonary dysplasia (BPD) as described previously, whereas Type II shows atypical radiological findings, namely only diffuse haziness without typical emphysema and fibrosis. Type III has a history of intrauterine inflammation. Chest x-ray shows the typical bubbling and cystic appearance described in the original report of Wilson-Mikity syndrome or neonatal pulmonary emphysema in the very low birth weight infant. Type III also has atypical radiological findings in cases with intrauterine infection. Type IV does not have a history of either intrauterine inflammation or RDS but shows typical emphysematous and fibrous appearance upon chest x-ray. Type V includes those with atypical chest x-ray appearance similar to Type II but without history of RDS and intrauterine inflammation.

CLD is a heterogeneous condition which shows different spectra. However, the cardinal event is common to all types - the excessive inflammatory response caused by various insults to the immature airways and alveoli, such as oxygen, barotrauma, infection and so on. The excessive inflammatory response leads to lung tissue damage and the abnormal healing process due to immaturity, (such as vitamin A deficiency and insufficient oxygen radical scavenging system) and results in dysplasia and metaplasia of the respiratory system. The treatment of respiratory distress due to CLD also acts as an insult to the lungs and thus forms a vicious cycle. The different spectra of the disease are most possibly attributed to the difference in the timing and the kind of insults to the lungs. In Type I and II CLD, the insults are given in the first hours of life when the infants with surfactant deficiency receive high concentrations of oxygen for stabilization before the surfactant replacement. In Type III and III' CLD the insults are most likely given before birth.

Excessive and sustained inflammatory response in the lungs with different onset times may result in the development of Types IV and V CLD. The strategy for the prevention of CLD should be different according to the origins and causes. The prevention of Types I and II CLD, or CLD following RDS, should be accomplished by successful prophylactic surfactant replacement therapy. Another procedure may be the application

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of high frequency oscillatory ventilation (HFOV) in the acute stage of RDS or at the time of stabilization right after birth. Types III and III' CLD present the most difficult challenge for prevention strategy because the disease process already started before birth. At the moment there are no effective measures for prevention. The strategy for the prevention of Types IV and V CLD may reside in the early detection and treatment of patent ductus arteriosus, sepsis and airway infection including pneumonia. *Key words: chronic lung disease, very low birth weight infant, classification, pathogenesis, prevention.*

Neonatal Mortality in Japan

The Committee on the Newborn of the Japan Pediatric Society has been conducting every five years the nationwide survey on the mortality of the very low birth weight infants who are cared for at the neonatal centers in Japan. According to the recent report[1], 50 infants born in 1990 and 132 infants in 1995 were below 500 g at birth and their neonatal mortality rates were 82.0 and 70.5 percent, respectively. The mortality of infants weighing from 500 to 999 g at birth improved from 26.9 percent in 1990 to 21.8 percent in 1995. When the infants weigh more than 700 g, there is more than an 85 percent chance of survival in our country at present (Fig. 1).

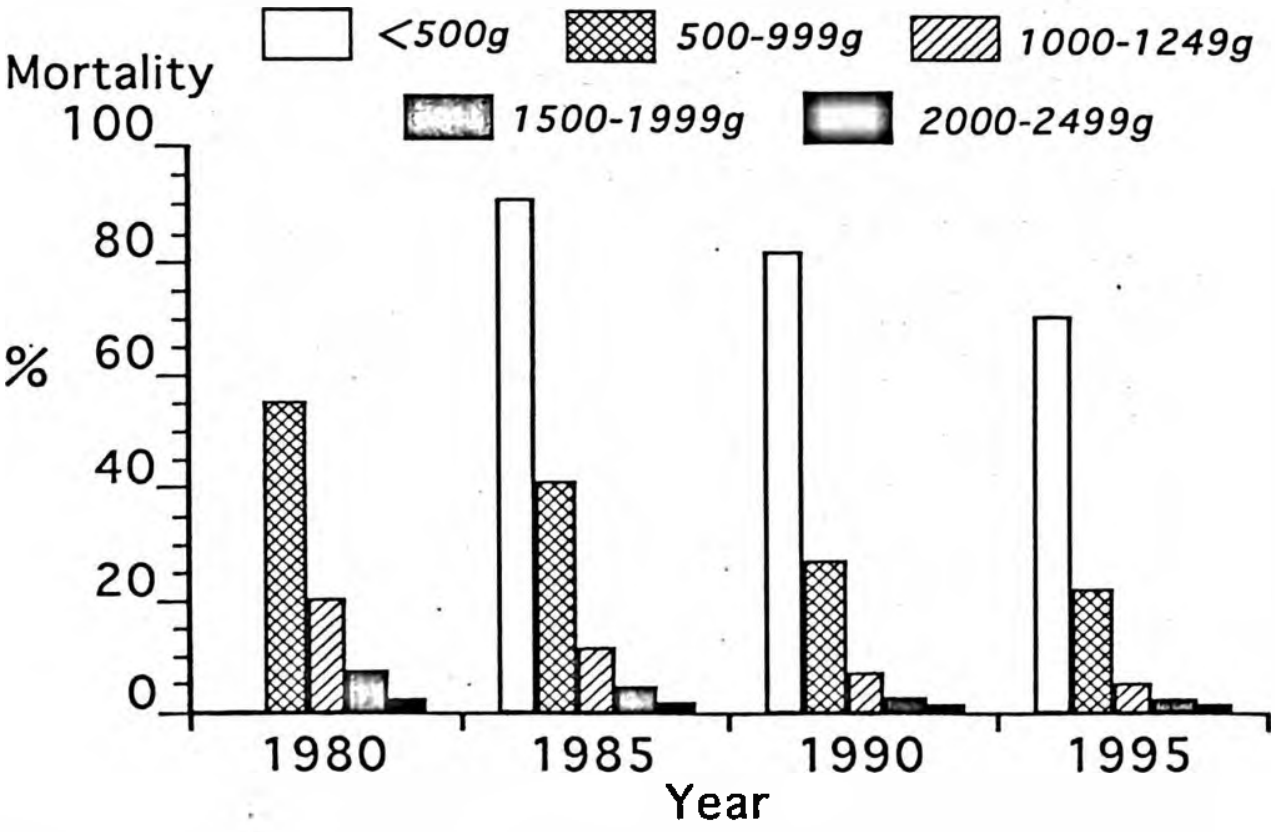

Fig. 1: Neonatal mortality rates by birth weight groups in Japan. No data for < 500 g infants born in 1980 were available. Statistically significant reduction in mortality was observed again in 1995 with the weight groups of 500 to 999 g and 1,000 to 1,499 g when compared with the data for 1990 (The Committee on the Newborn, Japan Pediatric Society, 1996).

However, follow-up study at the age of three years on the surviving extremely low birth weight infants (below 1,000 g) revealed that approximately 25 percent of them are suffering from a variety of sequelae, and pulmonary sequelae mostly due to chronic lung disease (CLD) accounted for approximately 5 percent[2]. Thus, the establishment of a strategy for the effective treatment and prevention of CLD should be most urgent and important at the present time.

Incidence of CLD

According to a previous report[3], nearly 50 percent of neonatal survivors weighing less than 1,000 g at birth are thought to be affected with CLD. In past reports, CLD was simply defined as a condition that requires an extra oxygen inhalation beyond 28 days after birth. However, this definition may result in the overdiagnosis of CLD. Many premature infants with apnea are given low concentrations of oxygen beyond 28 days after birth without any signs of chronic respiratory distress.

A nationwide survey for the incidence of CLD in infants born in 1990 was conducted with a newly established definition[4]. CLD was defined as an oxygen requirement greater than that obtainable in room air at 28 days of age, with symptoms of persistent respiratory distress and a hazy or emphysematous and fibrous appearance upon chest x-ray. Respiratory distress caused by congenital anomalies of the respiratory system was excluded.

A total of 4,964 infants weighing less than 1,500 g at birth and born in 1990 were admitted to and cared for at 301 level II and III neonatal care centers in Japan. Those infants comprised approximately 90 percent of total very low birth weight infants born in Japan. There were 1,817 infants with a birth weight below 1,000 g. A total of 4,293 infants (86.3%) survived at 28 days after birth and neonatal mortality rates decreased consistently with each 100 g weight group (Fig. 2). The survival rates in infants weighing below 1,000 g and between 1,000 and 1,499 g at birth were 73.7 and 93.9 percent, respectively.

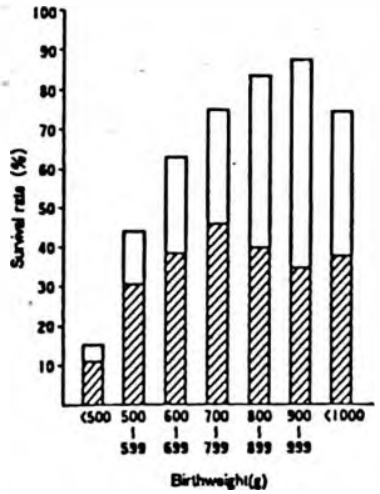

Fig. 2: The survival rates (total column length) and the rates of survivals without CLD (shaded column) by birth weight groups in the extremely low birth weight infants born in 1990 in Japan.

A total of 981 (22.9%) neonatal survivors were registered as having CLD. The decreasing incidence was consistently observed with increased birth weight. There was a 48.2 percent incidence of CLD among neonatal survivors with a birth weight below 1,000 g and an 11.3 percent incidence among infants weighing between 1,000 g and 1,499 g (Fig. 2, Table I).

Table I: Survival and Incidence of CLD by Birth Weight

		Survival at 28 Days		CLD	
Birth Weight (g)	No. of Infants Admitted	No.	%	No.	%
< 500	60	9	15.0	7	77.8
500 - 599	150	66	44.0	44	66.7
600 - 699	316	199	63.0	113	56.8
700 - 799	389	291	74.8	168	57.7
800 - 899	394	329	83.5	153	46.5
900 - 999	508	445	87.6	161	36.2
1000 - 1249	1376	1284	93.3	239	18.6
1250 - 1499	1771	1670	94.3	96	5.7
Total	4964	4293	86.5	981	22.9

Classification of CLD

Analyses of 981 infants who developed CLD through their preceding illnesses and chest x-ray findings resulted in the classification of CLD into six types (Fig. 3). Types I and II are defined as CLD following the acute stage of respiratory distress syndrome (RDS). Type I is the typical case of bronchopulmonary dysplasia (BPD) as initially reported by Northway et al.[5]. The difference in Types I and II resides in the chest x-ray findings. Type I shows the typical findings compatible to the original description by Northway et al.[5]. On the other hand, Type II shows atypical findings, namely only diffuse haziness without typical emphysema and fibrosis.

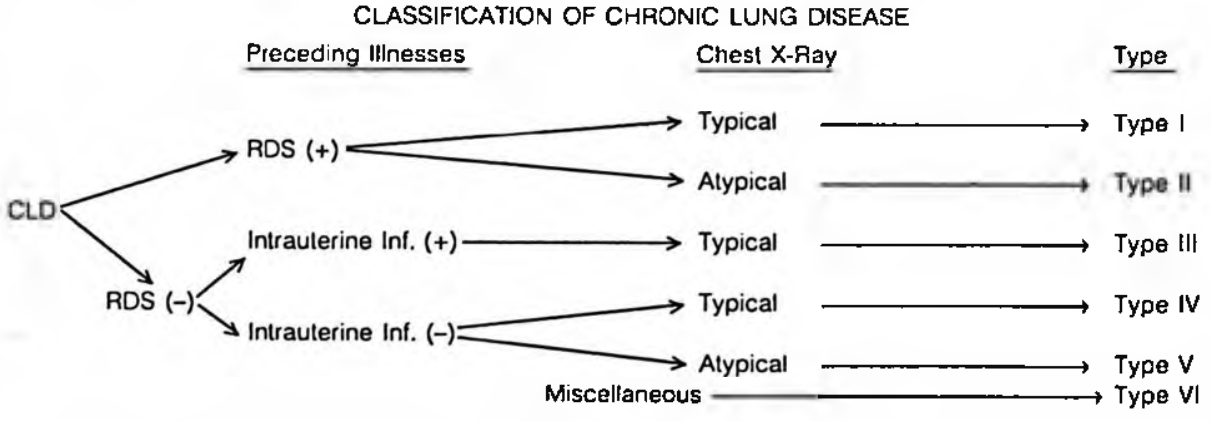

Fig. 3: Classification of chronic lung disease by preceding illnesses and chest x-ray findings (Ogawa Y, et al., 1992).

Type III has a history of intrauterine inflammation evidenced by high IgM levels at or shortly after birth, or histological proof of chorioamnionitis of the placenta or funisitis. Chest x-ray shows the typical bubbling and cystic appearance described in the original report of Wilson-Mikity syndrome[6] or in neonatal pulmonary emphysema of the very low birth weight infant reported by Fujimura et al.[7].

Type IV does not have the history of either intrauterine inflammation or RDS but shows typical emphysematous and fibrous appearance upon chest x-ray.

Type V includes those with atypical chest x-ray appearance similar to Type II but without a history of RDS and intrauterine inflammation.

Approximately 61 percent of infants developed CLD namely Types I and II following the acute stage of RDS in spite of surfactant replacement therapy with surfactant-TA shortly after birth. However, nearly half of them showed a hazy appearance and not a typical emphysematous and fibrous shadow on chest x-ray and were classified into Type II (Table II).

Table II: Distribution of CLD and Mortality by Type

Type	No. of Infants	%	Mortality	%
I	288	29.4	27	9.4
II	312	31.8	14	4.5
III	142	14.5	15	10.6
IV	118	12.0	3	2.5
V	121	12.3	6	5.0
Total	981	100.0	65	6.6

A total of 142 very low birth weight infants (14.5%) developed the type of CLD reported as neonatal pulmonary emphysema of Wilson-Mikity syndrome, or Type III. All of them had a history of intrauterine inflammation evidenced by the elevated serum IgM at birth or by histologically proven chorioamnionitis of the placenta.

The remaining 239 infants did not have RDS nor the apparent evidence of intrauterine inflammation. Approximately half of them, 118 infants, showed a typical x-ray appearance and were classified as Type IV. However, chest x-ray findings were hazy in 121 infants, and they were classified into Type V.

The overall mortality was 6.6 percent. Infants classified into Type III showed the worst rate (10.6%) and Type I had 9.4 percent (Table II). The poor prognosis of Type III prompted us to survey further. In 1992, a total of 178 infants from eight major neonatal centers weighing below 1,500 g at birth who had serum IgM levels over 30 mg/dl within 24 hours after birth were studied. One hundred and fifty infants or 84.3 percent survived their first month. Among these neonatal

survivors, 35 infants had RD and 28 of them (80%) developed CLD. The CLD infants were equally divided in Type I and II. On the other hand, among 115 infants without RDS, 52 infants (or 45.2%) developed CLD. Thirty-seven infants (or 71.2%) showed a typical bubbly appearance on chest x-ray and were classified as Type III. However, 15 out of 52 infants (or 28.8%) showed only diffuse haziness similar to Type II (Fig. 4). Therefore, a new group, Type III; was added to the classification and this revised classification has been adopted for the recent nationwide survey conducted on the infants born in the year of 1995 (Fig. 5).

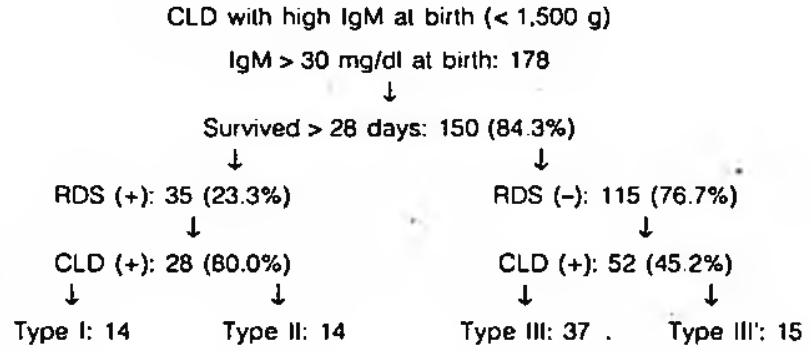

Fig. 4: Surveys on the very low birth weight infants with high serum IgM levels at birth and chronic lung disease.

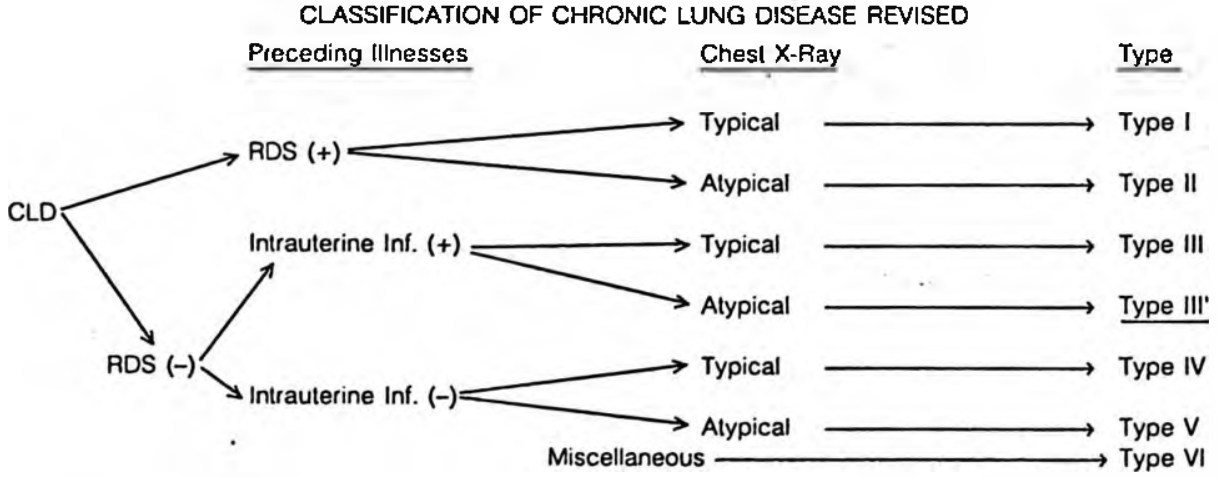

Fig. 5: Revised classification of chronic lung disease. Type III CLD following intrauterine inflammation but with atypical x-ray appearance was added to the previous classifications.

Pathophysiology of CLD

CLD is a heterogeneous condition which shows different spectra. However, the cardinal event is common to all types-the excessive inflammatory response caused by various insults to the immature airways and alveoli, such as oxygen, barotrauma, infection and so on. The excessive inflammatory response leads to the lung tissue damage and the abnormal healing process due to immaturity,

such as vitamin A deficiency and an insufficient oxygen radical scavenging system, and results in dysplasia and metaplasia of the respiratory system. The treatment of respiratory distress due to CLD also acts as an insult to the lungs and creates a vicious cycle. The different spectra of the disease are most possibly attributed to the difference in the timing and the kinds of insults to the lungs.

Our studies have shown the important roles of several cytokines and chemical mediators in the development of CLD[8-10]. Recent studies demonstrated the increased concentration of granulocyte elastase α 1-proteinase inhibitor complex in the tracheobronchial aspirates of Type III infants in the first 48 hours of life[7, 11]. Interleukin-8 (IL-8), which is known as a potent chemoattractant of the granulocyte, is also significantly higher in the tracheal aspirates within 48 hours of life from infants with Type III CLD[11]. These data suggest that the insult causing the lung damage occurred shortly before birth.

On the other hand, in infants with Types I and II CLD or CLD following RDS, granulocyte elastase α 1-proteinase inhibitor complex levels in the tracheobronchial aspirates remain low in the first hours of life but start to rise after 48 hours[12]. Similarly, the levels of IL-8 in the tracheobronchial aspirates of infants with Types I and II CLD remain low in the first 48 hours but start to rise thereafter[12]. Interestingly, there is a good correlation between FiO2 within 48 hours of life and IL-8 concentrations in the tracheobronchial aspirates taken between 48 hours after birth and day five, which suggests that one of the most potent insults to the lungs for CLD might be the high concentration of oxygen given for stabilization in the first hours of life[12].

Granulocyte elastase α 1-proteinase complex levels in the tracheobronchial aspirates from infants with Types IV and V CLD show various rising patterns after 48 hours of life[13]. IL-8 also shows a similar pattern as seen in granulocyte elastase α 1-proteinase complex[13]. The area under the curve from day 0 to 28 depicting the concentrations of these two agents is significantly higher in infants with Types IV and V CLD than in infants who did not develop CLD.

The achievements in our laboratory and from others may lead us to conclude that different causative insults to the lungs with different timings will produce different spectra of the disease, though the inflammatory response of the lungs is a common pathophysiology. In Types I and II CLD, the insults are given in the first hours of life when the infants with surfactant deficiency receive high concentrations of oxygen for stabilization before the surfactant replacement. In Types III and III' CLD our data clearly support the idea that the insults are most possibly given before birth. At the moment it is not possible to identify the specific insult(s) clearly, but certain kinds of infection are highly suspected.

In our survey, approximately 53 percent of infants with high IgM levels at birth developed CLD. Excessive inflammatory response in the lungs in the perinatal period may be the cardinal event in this type of CLD. On the other hand,

excessive and sustained inflammatory response in the lungs with different onset times may result in the development of Types IV and V CLD. Our previous studies revealed that, in addition to IL-8 and granulocyte elastase, other cytokines and chemical mediators such as platelet-activating factor (PAF)[10], leukotrienes[14], and tumor necrosis factor (TNF)-α[15] are present in increased amounts in the tracheobronchial aspirates from infants with symptomatic patent ductus arteriosus, sepsis and pneumonia.

Strategy for Prevention of CLD

The strategy for the prevention of CLD should be different according to the origins and causes because, as mentioned above, the different times of onset and causes result in the different spectra of the disease.

The prevention of Types I and II CLD, or CLD following RDS, should be achievable with successful prophylactic surfactant replacement therapy. Meta-analysis of prophylactic administration studies showed the event rate ratio as 0.75, namely, approximately 25 percent reduction of CLD by the treatment. A recent trial in Japan also showed significant reduction of severe CLD by the prophylactic administration of surfactant-TA as soon as the surfactant deficiency was proven by a stable microbubble rating on the gastric aspirates at birth[16]. In our nationwide survey almost half of the infants with a history of RDS who later developed CLD showed atypical x-ray findings and were classified as Type II;[3] classifications into this group further increased in infants born in 1995. It could be speculated that most of the infants classified into Type II might have developed Type I CLD or typical BPD, if they had not been given exogenous surfactant in the acute stage of RDS. Thus, the strategy for the prevention of CLD following RDS (Types I and II) resides in the application of a simple and quick method for detecting surfactant deficiency at birth and administration of prophylactic surfactant replacement therapy.

Another procedure may be the application of high frequency oscillatory ventilation (HFOV) in the acute stage of RDS or at the time of stabilization right after birth. HFOV can reduce the inspired oxygen concentration quickly and prevent barotrauma caused by the conventional ventilation in which a large volume and high pressure are applied.In addition, our recent study has demonstrated the reduction of the surfactant consumption by HFOV.

Types III and III' CLD are the most difficult to prevent, because the disease process starts before birth. At the moment there are no effective measures for prevention. Further research into the pathogenic process of these types of CLD by an interdisciplinary team of obstetricians and neonatologists is necessary.

Strategy for the prevention of Types IV and V CLD may reside in the early detection and treatment of patent ductus arteriosus, sepsis and airway infection, including pneumonia. The excessive hydration often causes symptomatic patent ductus arteriosus. Therefore, all very low birth weight infants should be nursed and cared for in the closed incubator with the minimum necessary amount of hydration. Care in the radiant warmer bed with a large amount of hydration should be avoided.

The early detection of infection may be accomplished by the application of acute phase reactants score (APR score). It is a scoring system for the elevation of three acute phase proteins, CRP, α-1-acid glycoprotein and haptoglobin, in case of acute infection[17]. The elevation of all three proteins above normal limits is scored as three and interpreted as the presence of acute bacterial infection. The levels of those three proteins can be measured in a few minutes with a minimum amount of blood samples.

Screening for infection and early treatment in the very low birth weight infant should contribute to the reduction of Types IV and V CLD.

A recent study reported that the congenital alveolar proteinosis has a surfactant protein B (SP-B) deficiency due to a genetic anomaly and that patients with some types of SP-B deficiency may possibly be diagnosed as having CLD of unknown causes, or Type VI CLD[18]. The ultimate strategy for this type of CLD may be gene transfer therapy.

Our final goal is the prevention of the preterm births. Meanwhile, the correct diagnosis and classification of CLD should be adopted in all studies and surveys in order to establish the strategy for the prevention and effective treatment of all types of CLD.

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IN UTERO DEFECATION: A NEW CONCEPT*

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SUMMARY: Çiftçi AÖ, Tanyel FC. (Department of Pediatric Surgery, Hacettepe University Faculty of Medicine, Ankara, Turkey). In utero defecation: a new concept. Turk J Pediatr 1998; 40: 45-53.

According to the current concepts, the human fetus does not defecate, and passage of meconium into the amniotic fluid is an indicator of fetal distress. However, the literature consists of reports in which fetal defecation is postulated to be a physiologic event. In light of these reports and our observations, we have developed the hypothesis that fetal defecation is a physiologic event independent from fetal distress and associated with a clearance mechanism of the amniotic fluid. This hypothesis has been proved by a series of experimental studies. We have shown that goat fetuses defecate the contrast medium into the amniotic cavity in the absence of fetal distress. We have clearly demonstrated for the first time the transport of radioactive meconium through the gastrointestinal tract into the amniotic fluid by using a radiopharmaceutical agent. It is known that the clearance mechanism of the amniotic fluid is supressed under fetal distress conditions. We suggest that meconium stained amniotic fluid is not related to meconium passage due to fetal distress; rather, it reflects impaired clearance of amniotic fluid containing meconium because of physiologic in utero defecation. This is discussed in detail with a review of the literature. *Key words: fetal physiology, in utero defecation.*

The human gastrointestinal tract has secretory, digestive, absorptive, and barrier functions. In addition, it also serves as an endocrine organ and as a part of the immunologic system. Its development is mainly completed during the fetal period, and an alimentary system is ready to meet the demands of nutrition after birth. This development is under the influence of endogenous and exogenous factors. The genetic endowment of the organism, regulated by an intrinsic "biologic clock", controls this sequential development, which is modulated by exogenous factors in the form of luminal influences such as amniotic fluid and various systemic influences (maternal, fetal, and neonatal neuroendocrine milieu)[1].

The gastrointestinal tract appears morphologically prepared for oral feeding by the end of the second trimester. Bowel peristalsis is reported as early as the 8th week of gestation, while swallowing is observed at the 16th week[2]. Intestinal motor activity of the gut moves the intraluminal contents from one specialized region of the gut to the next. Infants of less than 30 weeks' gestation exhibit disorganized random peristaltic contractions, and those of 30-33 weeks have short bursts of motor activity called "fetal complexes". Thereafter, co-ordinated migrating motor complexes are present[3]. This peristaltic development is also responsible for the

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intestinal passage of the fetus[4]. Today, there is no doubt that the intraluminal content is transported by gastrointestinal peristalsis during intrauterine life[2, 4-6]. This peristalsis increases with gestational age. In general, the older the fetus, the more intraluminal content descends through the gastrointestinal tract.

The intraluminal content (meconium) originates from secretions and desquameted cells of the fetal digestive tract as well as, to a lesser degree, from swallowed amniotic fluid. Meconium was named by Aristotle, who thought that it kept the fetus asleep in the uterus. Hippocrates stated that the presence of meconium in the fetal intestine was proof of the fact that the "fetus sucks inside the womb"[2]. From studying the meconium patterns of fetuses, it was found that major changes occur in the distribution of meconium within the intestine between 13 and 21 weeks of gestation. Meconium first becomes detectable to the eye from the 13th week and, until the 18th week, it is predominantly in the small intestine, with some accumulation in the colon. After the 21st week, all fetuses showed a build up of meconium in the rectum[7-9]. The chemical composition of meconium also changes substantially throughout gestation due to numerous transformations of the gastrointestinal system with regard to motility and absorption functions[10, 11]. Its water content varies from 70 to 80 percent and 80 percent of its dry weight is made up of mucopolysaccharides. It contains small quantities of serum proteins and many enzymes. Among them, those originating from the digestive tract, such as disaccharidases, dipeptidases, lysosomal enzymes and trypsin, constitute the majority[12, 13].

The development of the gastrointestinal tract for digestive, absorptive, secretory and endocrine functions occurs simultaneously with that for motility function. Digestion and absorption of carbohydrates, proteins and lipids through different parts of the gastrointestinal tract are shown in the human fetus[14-16]. The fetus gut secretes several hormones which have trophic, secretory and motor effects[17]. Analysis of enterochromaffin cells in the bovine fetus gut revealed that serotonin may be the chemical inducer of muscular motility[18]. Epithelial absorptive and secretory cells are found in the human fetus intestine starting from the 8th week of gestation[19].

As outlined above, the human gastrointestinal tract undergoes numerous transformations, and the fetus can perform a wide spectrum of physiologic functions including sucking, swallowing, intestinal transport, and absorption as well secretory and endocrine functions. However, the last step of nutrition, in other words in utero defecation (the passage of meconium into the amniotic fluid), is not accepted as a physiologic function of the fetus. According to the current concepts, in utero defecation results in meconium-stained amniotic fluid and is believed to be associated with fetal distress as first described in 1858[20]. However, some authors suggest that meconium passage into the amniotic fluid alone is not necessarily a sign of fetal distress, as no definitive cause of fetal distress was found in 12 to 25 percent of deliveries complicated with meconium-stained amniotic fluid[5-7, 20, 21].

Additionally, meconium-stained amniotic fluid was described as a common obstetric finding with an incidence ranging between seven and 30 percent of all deliveries[6]. But, of the infants born with meconium-stained amniotic fluid, only 2.1 percent have developed meconium aspiration syndrome[23]. The high incidence of meconium-stained amniotic fluid versus the low incidence of complications and the absence of maternal and fetal distress conditions in a quarter of the cases render the current belief about in utero defecation questionable.

In light of these findings, we have developed the hypothesis that fetal defecation is a physiologic event independent from fetal distress and associated with a clearance mechanism of the amniotic fluid. A series of experimental studies was performed on this hypothesis. These studies are outlined below.

Study I

An experimental study was performed to investigate gastrointestinal motility and meconium passage, with simultaneous blood gas measurements, in the fetuses of eight pregnant goats at 110 to 114 days' gestation (full term = 147 to 155 days). With the goats under halothane anesthesia, a nasogastric tube and a heparinized central venous catheter were inserted into the fetuses. Twenty-four hours after surgery, 10 ml of gastric juice from the fetus was replaced with a nonhydrosoluble contrast medium, and serial roentgenograms and blood samples (for PO_2, and PCO_2 measurement) were taken every four hours. All fetuses began to pass the contrast medium into the amniotic cavity within 16 to 22 hours, and central venous blood gas values were normal[5].

Study II

An experimental study was performed to investigate the excretion function of the liver, gastrointestinal motility, and in utero defecation by radionuclide techniques in 24 New Zealand white rabbit fetuses at 25 days' gestation (full term = 31 to 32 days). Technetium-99 m (^{99m}Tc)-HIDA (a derivative of iminodiacetic acid) (0.1 ml) containing 1 millicurie (mCi) of radioactivity was injected into the gluteus muscle of each fetus which had been exposed through the uterus. After replacing the fetus and uterus into the abdomen, and beginning one hour after injection, a live fetus was killed each hour for 24 hours. Tissue samples from the lung, heart, stomach, kidney, bladder and liver; meconium in the proximal, mid and distal bowel, and amniotic fluid were taken. The radioactivity of each sample was determined by a gamma counter and the percentage uptake per gram of tissue was calculated. The very low radioactivity levels detected in the stomach, kidney and bladder indicated the in vivo stability of ^{99m}Tc-HIDA. ^{99m}Tc-HIDA was predominantly trapped by the liver via systemic circulation and is excreted into the gastrointestinal tract, through which it passes into the amniotic fluid[24].

Study III

An experimental study was performed for further confirmation of the meconium passage into the amniotic fluid by means of radionuclide techniques. Forty-eight New Zealand white rabbit fetuses at 25 days' gestation (fullterm = 31 to 32 days) were divided into two groups as A (n: 24) and B (n: 24). Technetium-99m (^{99m}Tc)-HIDA (0.1 ml) containing 1 mCi of radioactivity was injected into the gluteus muscle of each fetus which had been exposed through the uterus. Surgical closure of anus by a purse-string suture was performed in Group B.

After replacing the fetus and uterus into the abdomen, and beginning one hour after injection, a live fetus was sacrificed each hour for 24 hours in both groups. Tissue samples from the lung, heart, stomach, kidney, bladder and liver; meconium in the proximal, mid and distal bowel; and amniotic fluid were taken. The radioactivity of each sample was determined by a gamma counter and the percentage injected dose (uptake) per gram of tissue (%ID/g) was calculated. ^{99m}Tc-HIDA was predominantly trapped by the liver via systemic circulation and excreted into the gastrointestinal tract in both groups, through which it passed into the amniotic fluid only in Group A. The very low radioactivity levels detected in the amniotic fluid of Group B came from the urinary tract and indicated the in vivo stability of ^{99m}Tc-HIDA[25].

The result of the first study revealed that goat fetuses pass the contrast medium into the amniotic cavity in the absence of fetal distress with normal central venous blood gas values. This finding suggests that in utero defecation is independent from fetal distress. In the second study, we have clearly demonstrated for the first time the transport of radioactive meconium through the gastrointestinal tract into the amniotic fluid. Demonstrated passage of an excreted radiopharmaceutical agent through the fetal liver into the gastrointestinal tract and amniotic fluid, respectively, suggests that fetal defecation is a physiologic event. The result of the third study strongly supports the physiologic intestinal passage of meconium into the amniotic fluid, in other words in utero defecation.

Apart from our studies, the literature consists of evidence related to physiologic in utero defecation. The presence of anal meconium has been interpreted as positive proof of intrauterine defecation. Fetal defecation was considered to be a routine physiologic event through the second trimester until anal sphincter innervation is completed[7]. The concept of fetal defecation in early and mid-pregnancy was strengthened by the findings of high levels of both disaccharidases and intestinal alkaline phosphates (both specific to the fetal gut) in amniotic fluid during pregnancy[26,27]. Fetal defecation in early and mid-pregnancy can explain high amniotic fluid bilirubin levels, which peak at 17 weeks, plateau, and then gently fall as gestation proceeds. Presence of fetal defecation can be postulated in many cases of Rh-negative (and thus unaffected)

infants who have shown low but definite levels of bilirubin in amniotic fluid following amniocentesis in an Rh-negative woman with antibodies[7]. As much as 10 to 20 percent of total amniotic fluid protein comes from the fetal gut, suggesting that the mode of entry into the amniotic sac may be by fetal defecation[15]. The observation of numerous meconium pigment laden macrophages in the membranes of a placenta without gross staining suggested the possibility of silent intrauterine defecation with subsequent clearance of meconium from the amniotic fluid by fetal swallowing and/or macrophage uptake[28]. Defecation into the amniotic sac and subsequent meconiophagy were observed as normal occurrences in guinea pigs in experimental studies[29].

Prenatal detection of anorectal atresia is also considered evidence of fetal defecation[30]. Dilated bowel seen on prenatal sonography may be due to retention of meconium which normally passes into the amniotic cavity. Lastly, various conditions that specifically induce exaggerated fetal intestinal peristalsis, such as abortion by means of prostaglandins or fetal drug withdrawal, are associated with meconium passage even in the very premature human fetus without distress. This finding indicates that intestinal peristalsis plays the major role in the passage of meconium[6].

The second part of our hypothesis is mainly based on the clearance mechanism of the amniotic fluid. Continuity of the fetal gut lumen with the amniotic cavity is achieved when the buccopharyngeal membrane ruptures during the third week and the cloacal membrane during the seventh, establishing free circulation of amniotic fluid through the gastrointestinal tract[1].

Amniotic fluid plays an important role in gastrointestinal tract development[31] and nutrition of the fetus[32]. Amniotic fluid contains a range of physiologically active macromolecules. Receptors for epidermal growth factor, present in amniotic fluid, have been identified on fetal enterocytes at as early as 12 weeks' gestation[1]. This growth factor is believed to play a major role in intrauterine gastrointestinal development. The presence of fetal enzymatic activities in the amniotic fluid reveals the passage of meconium into the amniotic fluid.

Amniotic fluid provides 10 to 14 percent of the nutritional requirements of the fetus[32]. Long-term total parenteral nutrition results in degenerative changes of intestinal mucosa in adults. Enteral nutrition should be commenced to prevent these atrophic changes. The fetus lives in a total parenteral nutrition environment. Enteral nutrition provided by fetal swallowing is just as important in ensuring normal gastrointestinal homeostasis and growth in the fetus as it is in the adult receiving long-term total parenteral nutrition.

Recent studies have revealed that ingested amniotic fluid protein undergoes proteolysis in the fetal alimentary tract and the amino acids thus made available are utilized in protein synthesis by the fetus[34]. Additionally, intraamniotic galactose

infusion causes not only up-regulation of its own mucosal transport but also that of glucose along the entire fetal small intestine[35]. These findings reveal that the use of intraamniotic nutrition as a mode of fetal therapy, while speculative at present, offers possibilities for the future.

Apart from nutritive characteristics, amniotic fluid was found to contain fibronectin[36], and surfactant proteins A and D[37]. The presence of these proteins raises the possibility that amniotic fluid also has a role in the antibody-independent recognition and clearance of pathogens.

Amniotic fluid represents a dynamic fetal compartment and its turnover rate is very high. The volume increases from 20 to 30 ml at ten weeks to 800 ml at 30 weeks. The human fetus exchanges the amniotic volume totally by urinating, swallowing and respiratory tract secretions every 24-48 hours in the last trimester[24]. Fetal urine becomes the chief source of amniotic fluid and its ingestion the most important route for its elimination. This exchange caused by fluid dynamics, fetus and amniotic cells form the effective clearance mechanism of the amniotic fluid.

Fetal swallowing is the principal route of the clearance mechanism and the volume of swallowed amniotic fluid varies directly with the amniotic fluid volume. What biochemical or physical stimulus exhorts the fetus to vary its swallowing activity is not known, but this mechanism serves to stabilize the amniotic fluid volume and plays a major role in the clearance mechanism[1, 19]. It is shown that fetal swallowing, in other words the clearance mechanism of the amniotic fluid, is supressed in fetal distress conditions[5, 24]. Fetuses suffering from maternal distress are not able to normally release the intestinal content into the amniotic cavity[38]. Thus, we suggest that meconium-stained amniotic fluid is not related to meconium passage after fetal distress; rather, it reflects impaired clearance of amniotic fluid containing meconium caused by in utero defecation.

Meconium staining of the placental membranes and umbilical cord is a surface phenomenon and is proportional to both meconium concentration and the period of exposure. There is a critical difference between the presence of meconium in the amniotic fluid and meconium staining[22]. Evidence available from in vivo and in vitro observations suggests that a minimum of four to six hours is required between passage of meconium into the amniotic fluid and staining[28]. During this time, meconium is picked up by macrophages and simultaneously transported into the placental plate with fetal swallowing of the amniotic fluid[39]. Both of these mechanisms work to clear amniotic fluid from meconium under normal circumstances. However, under fetal distress, the clearance mechanism is impaired and thus meconium is stained.

Meconium-stained amniotic fluid causes amniotic epithelial destruction and vascular damage[39]. It also produces umbilical vein contraction[40] resulting in fetal hypoperfusion and distress. Both of these factors aggravate the impaired clearance of amniotic fluid and result in a vicious cycle in intrauterine life (Fig. 1).

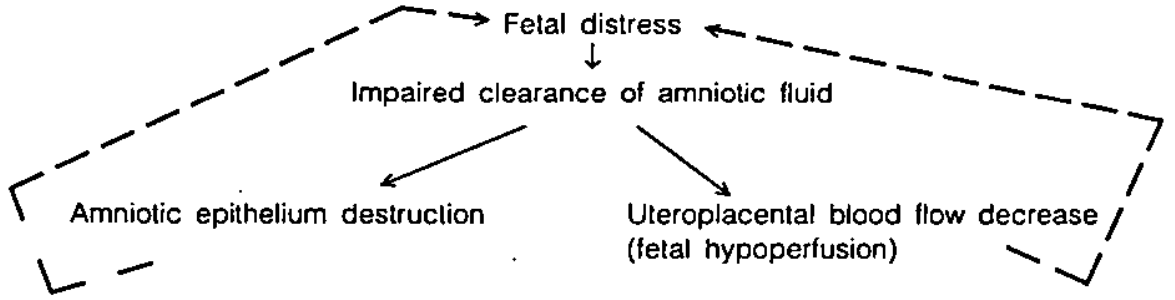

Fig. 1: Vicious cycle revealing the relation between fetal distress and amniotic fluid dynamics.

Our hypothesis also has many implications in various pediatric surgical fields which have until now been obscure[41, 42]. Chemical damage to the bowel in gastrochisis and to the spinal cord in myelomeningocele was accepted to be caused by fetal urine. Urinary ascites is a common symptom in newborns with obstructive uropathy. However, these patients do not present the signs or symptoms of chemical bowel damage such as intestinal dysfunction, peritonitis or morphological abnormalities. On the other hand, patients with meconium peritonitis show a diffuse chemical peritonitis induced by the various contents of meconium. On the basis of these findings, it appears more likely that the chemical damage of a primarily normal bowel or spinal cord is not related to urine content, but rather to the passage of meconium or, in other words, in utero defecation.

In light of our studies and the evidence in the literature, we suggest that in utero defecation is a physiological entity independent from fetal distress. Experimental studies on the clearance mechanism of the amniotic fluid is currently under evaluation in our research unit.

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THE RESULTS OF LONG-TERM GROWTH HORMONE REPLACEMENT THERAPY IN TURKISH CHILDREN WITH GROWTH HORMONE DEFICIENCY*

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SUMMARY: Yordam N, Kandemir N, Alikaşifoğlu A (Endocrinology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). The results of long-term growth hormone replacement therapy in Turkish children with growth hormone deficiency. Turk J Pediatr 1998; 40: 55-60.

From a total of 118 patients treated for growth hormone deficiency, 37 (23 boys, 14 girls) have reached their final height. Twenty-five patients had isolated growth hormone deficiency (IGHD) and 12 had multiple pituitary hormone deficiency (MPHD). Growth hormone deficiency was diagnosed and treated late in both boys and girls. The mean height standard deviation score (SDS) for chronological age (CA) increased significantly from -4.43 to -1.94 during the therapy. The target height was not achieved in boys or girls nor in MPHD and IGHD groups, although they have reached the third percentile of the normal Turkish population. The height and chronological age of the patients at the start of the treatment correlated significantly with final height in all patients. Therefore, early diagnosis and treatment is important to complete catch-up growth in growth hormone deficient patients. The height prognosis is improved with administration of a recombinant form of human growth hormone (GH) as daily subcutaneous injections with a dose of 0.1 IU/kg, when compared to the earlier studies with pituitary GH. *Key words: growth hormone deficiency, final height, growth hormone treatment.*

A recombinant form of human growth hormone (GH) has been available for replacement therapy in children with growth hormone deficiency for about ten years. Long-term results of the studies have shown the beneficial effect of GH treatment in improving severe growth deficits existing at the onset of therapy. However, previous results were obtained mostly from patients receiving intramuscular injections of pituitary-derived GH three times/week[1-5]. With the introduction of daily subcutaneous injections of recombinant human growth hormone, growth velocity increased significantly with the expectations of a better final outcome[6].

This report is a retrospective analysis of growth data of 37 patients who have reached their final height from a total of 118 patients treated for growth hormone deficiency (GHD).

Material and Methods

A total of 118 patients were diagnosed with growth hormone deficiency and managed in the Pediatric Endocrinology Unit of Hacettepe University between

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the years of 1986 and 1995. Thirty-seven of them who reached their final height were included in this study.

The following criteria were used for the diagnosis of GHD:

1. A growth velocity below the third percentile according to Tanner growth charts[7].
2. A peak serum GH concentration of less than 10 ng/ml during two pharmacological stimulation tests (L-DOPA and insulin stimulation tests). In prepubertal and early pubertal children with a bone age over eight years, one of the growth hormone stimulation tests was repeated after priming with sex steroids. In boys, a depot preparation of testosterone (100 mg/m^2) was used six to eight days prior to the stimulation test and in girls, ethynyl estradiol (50 mg/m^2) was given over a period of three days prior to the stimulation test[8].

Replacement therapy for other trophic hormone deficiencies was started at least three months prior to growth hormone therapy. Height was measured by Harpenden stadiometer and converted to SDSs to allow comparison of data in children, using reference values at different ages[9]:

$$SDS = \frac{X - \bar{X}}{SD}$$

where X = measurement, $\bar{X}$ and SD = the mean and standard deviation, appropriate for age and sex. Bone age was determined according to the method of Greulich and Pyle[10]. Target heights, corrected for sex, were determined with the use of standard equations[11];

boys, 1/2 (maternal + paternal height + 13),
girls, 1/2 (maternal + paternal height - 13).

Patients were treated with recombinant human growth hormone at a dose of 0.1 IU/kg administered as daily subcutaneous injections, seven times/week.

Each patient was followed up every three months, with the usual clinical and laboratory such as height, weight, pubertal stage and total blood count, routine biochemistry and thyroid hormones. Bone age was determined every six months.

Treatment ended when a bone age of at least 14 years (girls) or 16 years (boys) was reached.

Data were analyzed using Statistical Package for Social Sciences for Windows v. 5.01 (SPSS, Inc., USA). Descriptive data are expressed as mean (SD). Means of paired data were compared by Wilcoxon signed rank test. Means of non-paired data were compared by Mann-Whitney U test. Correlations were made with the Spearman rank test. Differences were considered significant at $p < 0.05$.

Results

Table I shows the auxological data of patients before and at the end of the GH therapy. Twenty-five patients had isolated growth hormone deficiency (IGHD) and 12 had multiple pituitary hormone deficiency (MPHD). None of them had an organic cause for GHD. The mean peak GH response during the L-DOPA stimulation test was 4.1 (2.0) ng/ml in the IGHD group and 1.2 (0.8) ng/ml in MPHD group. During the insulin stimulation test it was 2.5 (2.4) ng/ml and 1.5 (1.6) ng/ml, respectively.

Table I: Auxological Data of All Patients and Patients with Isolated Growth Hormone Deficiency (IGHD) and Multiple Pituitary Hormone Deficiency (MPHD) Before and at the End of Therapy

	IGHD (n = 25)	MPHD (n = 12)	All Patients (n = 37)
Chronological age (CA, years)			
Mean (SD)	12.0 (2.3)	11.5 (3.0)[a]	11.85 (2.59)
Bone age (BA, years)			
Mean (SD)	8.5 (2.9)	6.1 (2.3)[b]	7.75 (2.93)
Height SDS for CA			
Mean (SD)	-4.3 (1.2)	-4.6 (1.3)[a]	-4.43 (1.29)
Height SDS for BA			
Mean (SD)	-1.1 (1.4)	0.1 (2.0)[a]	-0.74 (1.75)
Pretreatment height velocity			
cm/year, Mean (SD)	3.3 (1.0)	3.0 (0.6)[a]	3.26 (0.97)
Final height SDS			
Mean (SD)	-2.06 (0.8)	-1.7 (0.4)[a]	-1.94 (0.74)
Target height SDS			
(Mean (SD)	-1.1 (0.7)	-1.01 (0.6)[a]	-1.07 (0.72)
Duration of therapy, months			
Mean (SD)	45.6 (17.1)	56.2 (18.8)[a]	49.6 (18.1)

a: $p > 0.05$.
b: $p < 0.05$.

Growth hormone therapy started late in both boys and girls but significantly later in boys than in girls ($p < 0.05$, Table II). The administration of growth hormone increased growth velocity effectively and the increment was sustained during the therapy (Fig. 1). As a result, the mean height SDS showed a significant increase during the therapy from -4.43 to -1.94. In the MPHD group, the mean bone age was significantly retarded compared to that in the IGHD group, whereas all other auxological parameters were not significantly different at the start of

the treatment. The target height was not achieved in either MPHD or IGHD groups, but the mean difference between final height and target height was similar in both groups.

Table II: Auxological Data of Boys and Girls Who Have Reached Their Final Height

	Boys (n = 23)	Girls (n = 14)
Chronological age (CA, years) Mean (SD)	12.67 (2.38)	10.49 (2.42)[a]
Bone age (BA, years) Mean (SD)	8.24 (2.89)	6.94 (2.88)[b]
Height SDS for CA Mean (SD)	-4.46 (1.30)	-4.38 (1.31)[b]
Height SDS for BA Mean (SD)	-0.43 (1.54)	-1.26 (1.9)[a]
Pretreatment height velocity (cm/year) Mean (SD)	3.36 (1.06)	3.07 (0.80)[b]
Final height, cm Mean (SD)	161.8 (4.5)	149.0 (4.8)
Target height, cm Mean (SD)	168.8 (2.7)	154.3 (7.1)
Final height SDS Mean (SD)	-1.79 (0.6)	-2.10 (0.7)[b]
Target height SDS Mean (SD)	-0.84 (0.4)	1.49 (0.9)[a]
Duration of therapy, months Mean (SD)	48.8 (17.8)	54.3 (19.6)[b]

a: $p < 0.05$. b: $p > 0.05$.

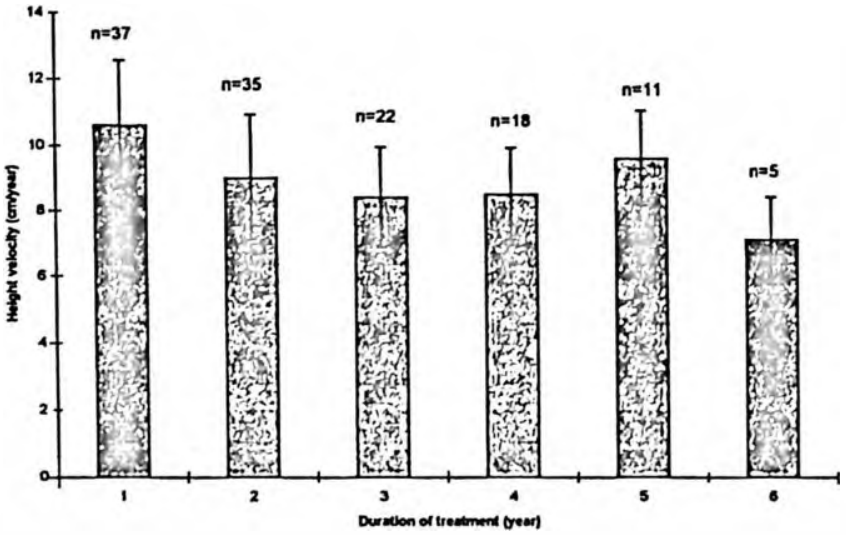

Fig. 1: The mean growth velocity of 37 patients during growth hormone therapy.

No significant difference was found in bone age, height SDS for CA, pretreatment height velocity and duration of therapy between girl and boys (Table II). Target height was not achieved in either sex, although they reached the third percentile of normal Turkish men (162 cm) and women (148.5 cm)[12]. The duration of therapy was not significantly different in either group ($p > 0.05$). The height and chronological age of the patients at the start of the treatment correlated significantly with final height in all patients ($r = 0.44$; $p < 0.05$, $r = 0.47$; $p < 0.05$).

During the therapy, serum T_4 levels decreased in eight patients with isolated growth hormone deficiency; Na-L thyroxin was added to their therapy. In two patients, myalgia and elevated creatine phosphokinase (CPK) levels were observed. The clinical and laboratory investigations suggested myositis in these patients as reported previously[13].

Discussion

Until 1985, human pituitary GH was given three times a week at low doses because only small amounts were available. The results of the studies with pituitary GH showed the failure of this therapy to normalize the final height in growth hormone deficient children[1,2,4,5]. To optimize the replacement therapy, the dose regimen for GH treatment has changed after the production of rhGH in terms of frequency and route of administration. Recently, better final outcomes have reported daily subcutaneous injection of rhGH[14-17].

In this study, a final height SDS of -1.94 was achieved which is similar to the results obtained in other studies. The correlation of final height with height and chronological age at the start of the treatment underlines the importance of early diagnosis and treatment in growth hormone deficiency.

Price and Ranke[18] reported final height in 95 children with idiopathic GH deficiency. Their median final height SDS was -1.03 which is higher than our findings. This is possibly due to earlier diagnosis and treatment and also to the less severe growth retardation of their patients at the start of the treatment (-4.43 vs -2.80).

In our study, the mean final height SDS was slightly higher in the patients with MPHD than in the patients with IGHD, although the difference was not significant. Similar results were obtained by Severi[19], whereas in other studies a better final outcome was reported in the patients with MPHD[1,4]. These controversial results emphasize that there are many different factors affecting final height in growth hormone deficient children.

In conclusion, the overall height gain and final height observed in this study appear promising although target height was not achieved. Analysis of the factors associated with final height may improve the management protocols and consequently a better final outcome could become possible.

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LATEX SENSITIVITY AMONG HOSPITAL EMPLOYEES AND ATOPIC CHILDREN*

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SUMMARY: Saraçlar Y, Çetinkaya F, Tuncer A, Şekerel B, Hovanec-Burns D, Ünver E. (Allergy and Asthma Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Latex sensitivity among hospital employees and atopic children Turk J Pediatr 1998; 40: 61-68.

Allergic reactions to latex products are an important health problem for health care workers and children. To investigate the prevalence of latex and latex-associated food sensitivities among hospital employees and atopic children, 61 hospital employees (44 nurses, 13 cleaning staff, 4 technicians) and 40 atopic children were evaluated by in vivo and in vitro testing methods. All subjects were also skin prick tested with common inhalant allergens and some cross-reactive food allergens to latex. In addition, all subjects were evaluated using an enzyme-linked immunometric assay for detection of specific IgE to inhalant allergens and to the known food latex cross-reactant food allergens (banana, chestnut, peanut and kiwi fruit). Latex challenges were performed in 12 history-negative and anti-latex IgE positive atopic children. Seven of the 61 hospital staff (11.4%) and four of the 40 atopic children (10%) showed skin reactivity to latex. By serologic testing, hypersensitivity to latex was found in 30 subjects, to banana in 23, to chestnut in 37, to peanut in 32, and to kiwi fruit in 22 subjects. Latex challenges were negative in all of the children who were tested. Total IgE was higher than expected in 32 subjects and 50 individuals tested positive for specific IgE to common inhalant allergens (AlaTOP). These results indicate that latex allergy may be a health problem for our hospital staff and atopic children. In vitro testing may detect latex-specific IgE in atopic children even when no history of an adverse reaction to latex is present. *Key words: latex sensitivity, hospital employees, atopic children.*

Latex is derived from the milky sap of the rubber tree Hevea brasiliensis and has been used widely in medical supplies for decades. However, over recent years, many cases of latex IgE-mediated allergy have been described with clinical manifestations ranging from contact urticaria and bronchial asthma to anaphylactic shock[1-3]. Reactions to latex are more commonly encountered in those working in the latex industry, hospital operating room staff, and surgical

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patients[4,5]. This study was undertaken at a university hospital and a children's hospital to assess the prevalence of latex and latex-associated food sensitivities among hospital employees and atopic children in the care of the Pediatric Allergy Department.

Material and Methods

Seventy employees of the university hospital and 40 atopic children were evaluated with regard to latex allergy. The employees took part voluntarily in the study following the declaration of the study in the hospital. The children were selected randomly among those with positive skin prick tests to common allergens. The study was described in detail to all participants (and their parents where appropriate) and informed consent obtained. Those subjects in whom skin tests were contra-indicated were excluded from the study. Skin prick tests were performed on the volar aspect of the forearm using Stallerpoint needles (Stallerpoint, Laboratorie des Stallergenes, Fresnes Cedex, France). Skin prick tests were made with serial 10-fold dilutions of latex extract in phosphate-buffered saline (weight/volume concentrations ranged from 1:10000 to 1:10) (Stallergenes)[6]. Histamine phosphate (1 mg/ml) was used as the positive control and phosphate-buffered saline as the negative control. The cutaneous reactions were read after 15 minutes and were evaluated according to the size of wheal and erythema. Skin prick tests were defined as positive if the mean wheal diameter was > 3 mm and mean erythema > 5 mm larger than the negative control[7]. Skin tests were also performed with extracts of certain grasses (Poa mix, C. dactylon, P. pratensis, D. glomerata, A. sativa, Festuca), trees (Ulmus, Quercus, Populus, Platanus, Salix), weeds (Chenopodium, Artemisia, Plantago, Salsola kali), cat and dog danders, some fruits (peanut, kiwi fruit, chestnut and banana), Dermatophagoides pteronyssinus (DP) and Dermatophagoides farinae (DF).

In addition, total IgE concentration; specific IgE to latex, banana, kiwi fruit, chestnut, and peanut; and specific IgE to inhalant allergens (AlaTOP) were measured using the AlaSTAT assay (Diagnostic Products Corporation, Los Angeles, USA). The results of these tests were divided into six classes as reported by the manufacturer. Samples recorded as class 0 to 0-1 were considered negative, samples reported as class I or above were considered positive. Latex challenges were done in 12 history-negative and anti-latex IgE positive atopic children as described by Kelly et al.[2]: After explaining the risk of the test to the patients, a finger tip was cut from a surgical glove, dampened with water, and placed on one finger for 15 minutes. If no reaction was seen an entire glove was placed on the hand for the same length of time.

Results

The study was completed with a total of 101 subjects: 44 nurses (40 of whom were working in the operating room), 13 cleaning staff, 4 technicians and 40 atopic children. Nine of the hospital employees were excluded from the study because they failed to react to a histamine control skin prick test, probably due to an inhibiting agent received. The demographic and clinical data of hospital employees and atopic children are shown in Table I. Varying allergic diseases were diagnosed in 33 (54%) hospital employees (20 nurses, 9 cleaning staff, 4 technicians) by means of clinical history and physical examination. Positive skin test reactions to latex were found in seven of the hospital staff compared to four of the atopic children (Table II). All of the subjects with a positive skin test to latex had concurrent allergic diseases. Skin tests with common allergens were positive in four of seven hospital employees and in all of the children (in both groups reactions to pollens were predominantly positive). The subjects with positive latex tests did not have a higher prevalence of other specific allergies. The results of the skin prick tests with latex and other allergens can be seen in Table III. The results of the in vitro tests were as follows: total IgE values were higher than expected in 32 individuals; AlaTOP tests were positive in 50 individuals. Specific IgE to latex was present in 300 individuals, to kiwi fruit in 22 individuals, to banana in 19 individuals, to chestnut in 37 individuals and to peanut in 32 individuals (Table IV). Only five of the 11 subjects showing positive skin tests for latex had latex-specific IgE. One of the five also demonstrated specific IgE to banana, chestnut and kiwi fruit. Latex challenges were negative in all of the children who were tested.

Tablel I: Characteristics and Clinical Diagnoses of the Study Population

Characteristics	Hospital Employees	Atopic Children	Total
Number of participants	61	40	101
Gender (M/F)	10/51	28/12	38/63
Age (years)	32 ± 8	11.8 ± 2.3	
Diagnoses			
Asthma	6	29	35
Rhinitis	7	–	7
Asthma + rhinitis	2	10	12
Urticaria	5	–	5
Contact dermatitis	3	–	3
Eczema	3	–	3
Drug allergy	4	–	4
Asthma + latex allergy	2	–	2
Asthma + contact dermatitis	1	1	2

Table II: Results of in Vivo and in Vitro Tests with Latex

	Latex-Specific IgE (+)				Latex-specific IgE (–)			
Skin Test	N	CS	T	AC	N	CS	T	AC
Positive skin test with latex	1	3	–	1	1	2	–	3
Negative skin test with latex	3	2	–	20	39	6	4	16
Total	4	5	–	21	40	8	4	19

N: nurse. CS: cleaning staff.
T: technician. AC: atopic children.

Table III: Results of Skin Prick Tests with Common Allergens, Latex, and Latex Food Cross-Reactant Allergens

Antigen	Hospital Staff Positive (%)	Atopic Children Positive (%)
LATEX	7 (11.5)	4 (10.0)
MGP	9 (14.7)	35 (87.5)
MWP	8 (13)	36 (90)
MTP	4 (6.5)	29 (72.5)
Dog dander	4 (6.5)	5 (12.5)
Cat dander	5 (8.2)	10 (25)
DP + DF	4 (6.5)	33 (82.5)
Banana	1 (1.6)	13 (32.5)
Chestnut	1 (1.6)	–
Kiwi fruit	–	–
Peanut	3 (5)	3 (7.5)

MGP : mixed grass pollens. MWP: mixed weed pollens.
MTP : mixed tree pollens. DP : Dermatophagoides pteronyssinus.
DF : Dermatophagoides farinae.

Table IV: Results of the Positive in Vitro Tests in the Study Groups

Test	Hospital Staff (n: 61) Number (%)	Atopic Children (n: 40) Number (%)	Total (n: 101) Number (%)
AlaTOP	23 (37.7)	27 (67.5)	50 (49.5)
Elevated IgE	8 (13.1)	24 (60)	32 (31.7)
Chestnut-specific IgE	20 (13.1)	17 (42.5)	37 (36.6)
Peanut-specific IgE	7 (11.5)	25 (62.5)	32 (31.7)
Latex-specific IgE	9 (19.7)	21 (52.5)	30 (29.7)
Banana-specific IgE	8 (14.75)	15 (37.5)	23 (22.8)
Kiwi-specific IgE	6 (9.8)	16 (40)	22 (21.8)

Discussion

Latex allergy results from an IgE-mediated hypersensitivity reaction to constituent proteins retained in finished latex products such as surgical gloves, condoms, balloons, catheters, elastic thread, rubber bands and elastic adhesives. It has been increasingly associated with intraoperative anaphylaxis and occupation-related allergy[4, 6]. Latex contains at least 16 proteins of different molecular weights (the actual figure could well be nearer to 240 different proteins). These may be altered or partially degradded by the use of ammonia in preservation shortly after collection[6]. The increasing prevalence of human immunodeficiency virus has led to a heightened awareness concerning the importance of latex in medical practice[1]. The greater frequency with which gloves are being used may be resulting in increased contact with, or inhalant sensitization to, latex products, leading to an increasing prevalence of occupational latex allergy. Another reason for increasing latex sensitization could be inhalation of urban air which may contain abundant latex particles[8]. Latex products had been widely used for a number of years before the first report of latex-induced urticaria by Nutter[9] in 1979. Since then there have been numerous reports of IgE-mediated reactions to latex, suggesting a dramatic increase in its incidence[10-12]. A wide range of clinical manifestations have been associated with latex hypersensitivity from contact urticaria, rhinoconjunctivits and asthma to severe anaphylaxis[9, 12, 13]. Children with spina bifida, patients with genitourinary tract anomalies requiring daily bladder catheterization, health care workers, atopic patients and individuals with tropical fruit allergy have all been reported as having an increased risk of latex sensitivity[14-17]. In this study the latex skin test positivity rate was 11.4 percent among hospital employees (Table II). This figure has been reported as 4.7 percent by Vandenplas et al.[18] as 17 percent by Yassin et al.[11] and as 14.1 percent by Iacobelli et al.[19]. Among hospital personnel, operating room nurses are known to be at an increased risk of developing latex sensitization and allergy[10, 11]. Sensitivity to latex was identified in two of the 40 nurses by skin testing whereas four (9.1%) were identified by in vitro testing to possess specific IgE to latex (Table IV). This data is in agreement with latex positive rates of five to 10.7 percent previously reported by Vandenplas et al.[18] and Lagier et al.[10] for operating room nurses. Of the additional hospital personnel studied, nine of 13 cleaning staff were identified as allergic, with two subjects reporting contact dermatitis when wearing latex gloves. Latex sensitivity in these two subjects was confirmed by skin test. Using in vitro testing, five of the cleaning staff demonstrated latex-specific IgE. The technicians constituted the smallest group of hospital employees tested in this study, but none had a positive latex test either in vitro or in vivo. The high prevalence of allergies among hospital employees may represent selection bias, with those having a history of allergy being more willing to enter the study.

Within the pediatric populatilon, four showed a positive skin test to latex while 21 children had latex-specific IgE by in vitro testing. None of these children had a history of adverse reactions to latex products or foods known to cross-react with latex, including banana, chestnut, peanut or kiwi fruit. These children may have been sensitized to latex in their infancy by sucking latex pacifiers or playing with rubber toys or balloons[20]. but the negative results of the latex challenges suggest that this sensitization is not clinically important now. Similar observations were reported by Shield and Blaiss[21] who found that three of 44 atopic children had positive skin tests to latex without any history of latex-associated reactions. These results support the idea that these tests may detect latex-specific IgE in atopic individuals with no past history of known latex exposure[21, 22]. Reinheimer et al.[22] found that among those subjects undergoing evaluation with regard to allergy, 12 percent were positive for latex-specific IgE without having a history of latex exposure and that most of these subjects were less than 18 years of age. In another study, Ownby et al.[23] reported detectable anti-latex IgE antibodies in 1000 blood donors, most of whom (61%) were also positive in the CAP assay.

The association of latex hypersensitivity with banana, chestnut, avocado and kiwi fruit allergy has been described recenty, and the presence of cross-reactivity between them has been shown through radioallergosorbent test (RAST) inhibition[24-27]. Blanco et al.[28] described 17 patients with immediate allergic reactions to avocado: 10 were allergic to latex, eight to chestnut, eight to banana, four to kiwi fruit and four to walnut. In our study, specific IgE to certain foods were determined with the AlaSTAT assay and were found to be positive predominantly in atopic children (Table IV). The cross-reactivity between latex and the above-mentioned fruits will be tested by elimination-provocation tests, and the follow-up results will be documented. Latex may cross-react not only with foods, but also with pollens: Appleyard et al.[26] reported cross-reactivity between latex, ragweed and blue grass allergens. In this study, the atopic children were positive to grass, weed and tree antigens. Some researchers have suggested that profilin, an actin binding protein, may be responsible for these cross-reactions between latex and certain fruits[29, 30]. Our results also support the findings of Moneret-Vautrin et al.[31] that atopy may be a risk factor for latex sensitivity even without known exposure.

The specificity of in vitro assays for latex sensitivity is low, as documented in a study by Ownby et al[23]. In our study, AlaSTAT assay gave positive results in 20 (55%) of 36 children and in five (9.2%) of 54 adults with negative latex skin test. A possible explanation for this discrepancy may be as follows: AlaSTAT assay gives cross-reactivity between latex and other allergens such as pollens: Since all of our atopic children were sensitive to common allergens, this may have led to this high positivity. Unfortunately, we could not perform inhibition

assays because of technical difficulties, but this has already been reported several times[24-27]. Our results may not be confirmative, but may be suggestive for cross-reactivity between latex and some foods. On the other hand, there is no available standardized latex extract for skin tests and we have not performed intradermal tests with latex because of the risks. If we had performed intradermal tests. We believe the positive results with skin testing would have increased.

We think those children with either in vivo or in vitro positive latex tests should be followed up until adulthood with tests and that some precautions should be instituted for their job selections. These follow-up tests will shed light on whether these observations are an epiphenomenon in time.

In conclusion, latex allergy is a rapidly emerging health problem of particular concern among atopic children and hospital staff. Early diagnosis by reliable methods and avoidance represent the best approaches to this growing problem.

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SALMONELLA GASTROENTERITIS IN CHILDREN*

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SUMMARY: Yurdakök K, Abo Asaker EAE, Berkman E. (Department of Social Pediatrics, Hacettepe University Institute of Child Health, Ankara, Turkey). Salmonella gastroenteritis in children. Turk J Pediatr 1998; 40: 69-78.

Among 20,100 children with gastroenteritis admitted to Hacettepe University İhsan Doğramacı Children's Hospital Diarrhea Training and Treatment Unit between April 1987 and December 1994, 508 Salmonella strains were isolated. Epidemiology, clinical pictures, laboratory findings, and outcome of these patients are discussed. Salmonella gastroenteritis represented 2.5 percent of all diarrheal cases during the study period. The highest number of isolations of Salmonella strains were reported between June and October. Salmonella serogroup B was the most common isolated strain (77%) followed by serogroup D (21%) and serogroup C (2%). Progressive decrease among group B isolations were noted between 1991-1994 with a concomitant increase in group D isolations. S. typhimurium was the most common serotype and overall represented 52 percent of the strains. Bloody diarrhea was found to be present in 27 percent of all cases. It is noted that the patients infected with group B strains had a higher rate of bloody diarrhea than the patients infected with group D strains (30% versus 15%, $p < 0.05$). Dehydration was present in 14 percent of the cases. We noted that severe dehydration (0.2%) and electrolyte disturbances (1.5%) were rare among our patients. none of the cases had a complication or an extraintestinal manifestation of Salmonella gastroenteritis. No deaths were reported. *Key words: Salmonella, gastroenteritis, children.*

Acute infectious diarrhea is still an important health problem among children in developing countries. Every year about 3.2 million children in these countries under five years of age die due to acute gastroenteritis[1]. Salmonella gastroenteritis continues to be one of the main causes of acute infectious diarrhea worldwide[2]. Although Salmonella gastroenteritis is a mild self-limiting infection in most individuals, infants are at the greatest risk for both dehydration and complications[3]. In this paper we reviewed the relative importance of Salmonella in the etiology of childhood diarrheal diseases as well as the clinical characteristics of children with Salmonella gastroenteritis admitted to the Diarrhea Training and Treatment Unit (DTTU) of Hacettepe University İhsan Doğramacı Children's Hospital.

Material and Methods

During the period from 1 May 1987 to 31 December 1994, 20,100 children with diarrhea under 16 years of age were admitted to our DTTU. This unit obtains routine fresh stool specimens from all patients for isolating and identifying

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Salmonella and Shigella. Stool cultures were positive for Salmonella in 508 cases. Among these, only the files of 415 patients were available for further analysis. Data obtained from the case files included history, age, sex, duration of Salmonella stool excretion, clinical and laboratory characteristics on admission, and the outcome.

Diarrhea is defined as a change in the child's normal stool pattern, characterized by an increase in the frequency (at least three discharges per day) and increase in the liquidity of fecal discharges. Diarrhea is accepted as acute when the duration is less than 14 days, persistent when it is more than 14 but less than 30 days, and chronic if it is more than 30 days. Dehydration is diagnosed and patients are managed according to WHO criteria[4]. Malnutrition is defined according to Gomez classification[5].

The specimens were inoculated onto plates of Shigella-Salmonella (SS) agar, Selenite F broth and eosin-methylene blue (EMB) agar. All media were incubated at 37 °C for 24 hours. Selenite F enrichment broth was incubated overnight and sub-cultured at 18 hours on to the Salmonella-Shigella (SS) agar. Salmonella strains are identified by standard biochemical tests, including inoculation of suspicious colonies into tubes of screening media [triple sugar iron agar (TSI), urease broth and indole broth]. Salmonella isolates suspected by above mentioned biochemical tests are further tested by the slide agglutination technique employing polyvalent and monospecific antisera for somatic (O) and flagellar (H) antigens to detect serogroups and serotypes (by using antisera from Difco Laboratories, Defroit, USA). The Kauffman-White serotyping scheme is used for classification[6]; however, Salmonella serotypes are not routinely identified in all cases due to the unavailability of antisera for flagellar antigens.

Stool is considered to be bacteriologically clear from Salmonella when two or three consecutive culture-negative stool samples are taken at one to three days' interval.

Data were analyzed using SPSS and Epi-info program. Analyses were also performed according to isolated Salmonella serogroups. The significance of differences for categoric data was tested by chi-square or Fisher's exact test. Student's t test and analysis of variance were used for parametric data. Non-parametric data were analyzed by Wilcoxon-Mann-Whitney U test.

Results

During the study period, 508 (2.5%) Salmonella strains were isolated among 20,100 diarrheal admissions. There were variations in the number of Salmonella isolates reported from year to year, with the lowest number being in 1988 and the highest reported in 1989 (1.2% and 3.3% of all diarrheal cases, respectively, $p < 0.05$) (Fig. 1). Although Salmonella gastroenteritis seemed to be occurring through all the months, most cases were seen between June and October. The highest number of isolations was reported in October and the lowest in December (12.4% and 4.5% of all diarrheal admissions, respectively) (Fig. 2).

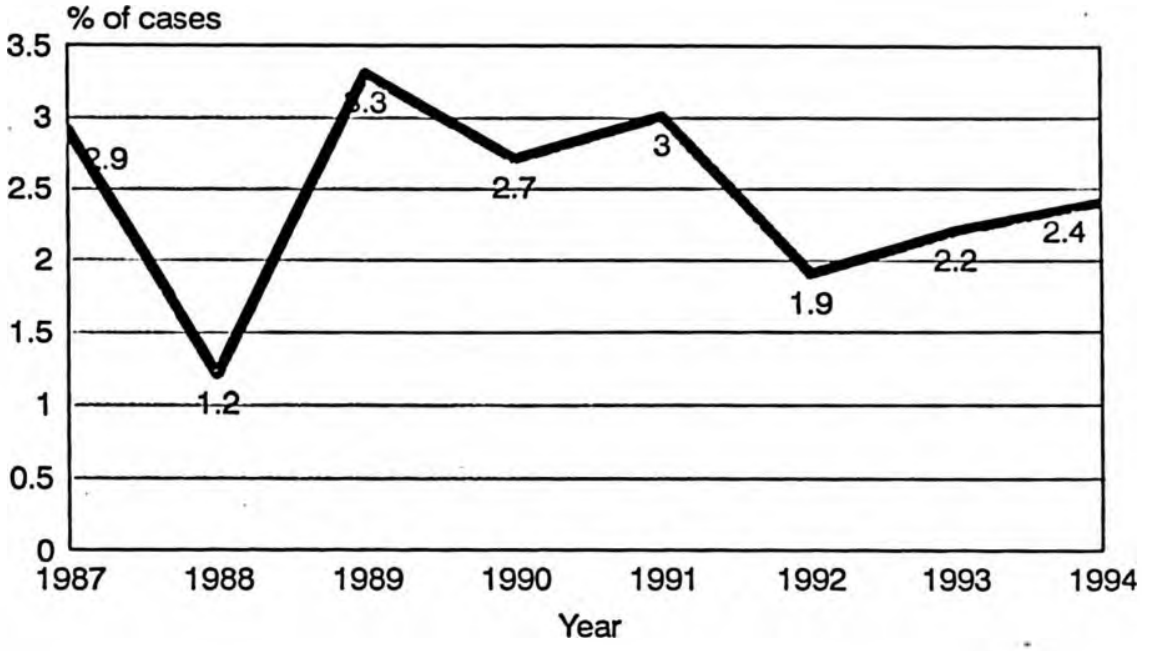

Fig. 1: Distribution of Salmonella gastroenteritis as percentage of all diarrheal admissions.

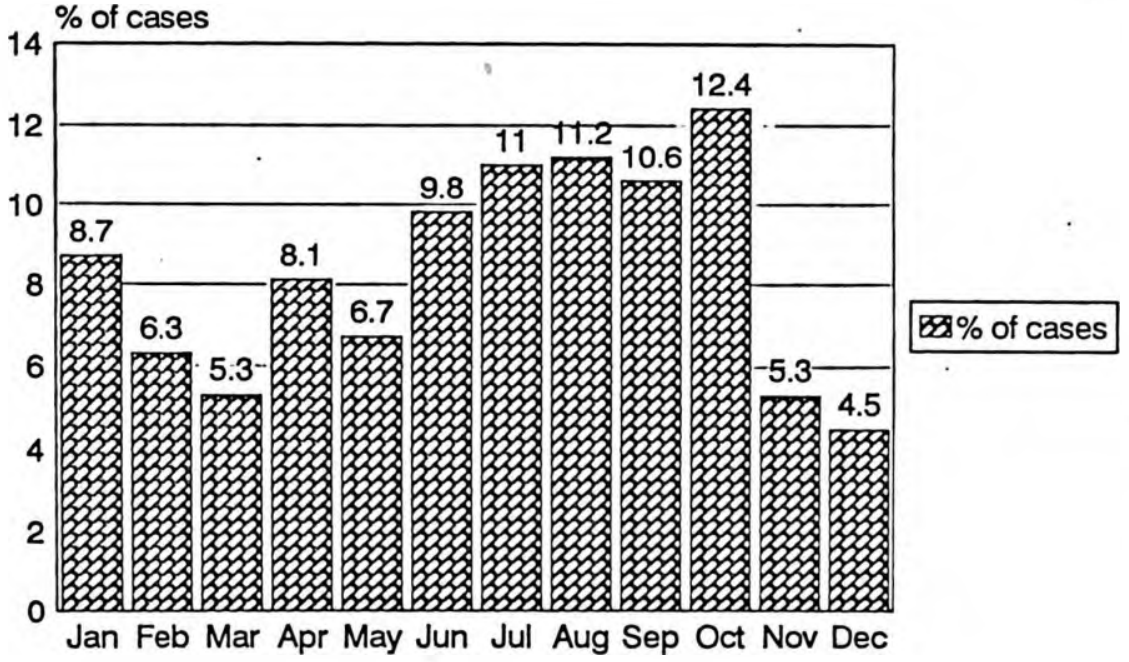

Fig. 2: Distribution of patients with Salmonella gastroenteritis by months during the study period.

Files of 415 patients with Salmonella gastroenteritis were available for further analysis. Male-female ratio was 1.47 (247/168). Salmonella serogroup B was the most common isolated strain (77%) followed by Salmonella serogroup D (21%) and Salmonella serogroup C (2%) (Table I).

Salmonella serotypes were determined in 247 of the 320 Salmonella serogroup B isolates. Among these, 88% (217/247) were Salmonella typhimurium and 12% (30/247) were Salmonella paratyphi B.

Table I: Clinical Characteristics, Laboratory Findings and Outcome of 415 Children with Salmonella Gastroenteritis

Features	No.	%
Age groups (months)		
0-3	30	7
3-12	121	29
12-60	170	41
> 60	94	23
Duration (days)*	5.1 ± 0.3	
No. of stool (per day)*	6.5 ± 0.2	
< 5	109	27
5-10	256	65
> 10	33	8
Blood in stool #	105/393	27
Mucus in stool #	214/390	55
Fever	222	54
Vomiting	213	51
Abdominal pain	96	23
Convulsions	7	2
Dehydration		
Mild	36	9
Moderate	21	5
Severe	1	0.2
Total	58	14
Electrolytes		
Hyponatremia #	4/74	5
Hypernatremia #	2/74	3
Hypokalemia #	5/74	7
Hyperkalemia #	4/74	5
Malnutrition		
First degree	131	32
Second degree	23	6
Third degree	1	0.2
Total	155	38
Duration of excretion (day)†*	11.7 ± 1.0	
Isolated Salmonella groups		
serogroup B	320	77
serogroup C	9	2
serogroup D	86	21
No. of associated infections♦	62	15
No. of hospitalized cases	14	3
No. of patients received antibiotics	114	27

* Values are mean ± SE.
# No./Screened cases.
† Data available in 197 cases.
♦ Respiratory and urinary tract infections.

Figure 3 and Table II show distribution of Salmonella serogroups by years. A progressive decrease among serogroup B isolations was noted between 1991-1994 with a concomitant increase in serogroup D isolations. However, serogroup B was still the most prevalent strain during the study period (Table II).

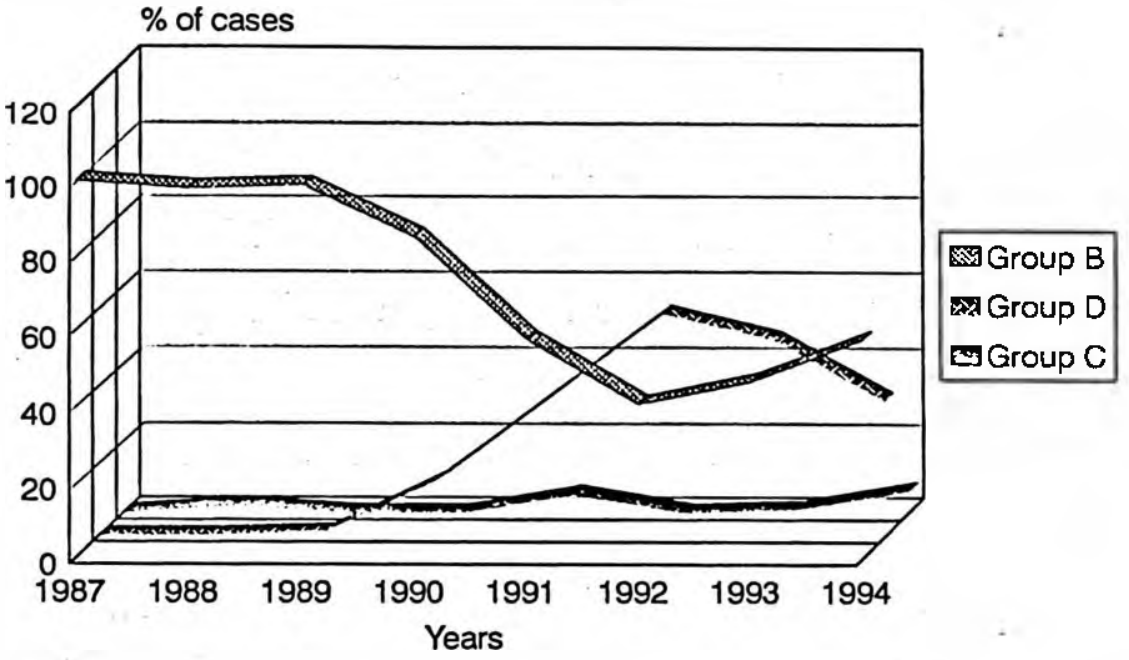

Fig. 3: Distribution of isolated Salmonella serogroups by years.

Table II: Distribution of Salmonella Groups by Years

	No. of Patients (%)							
	1987	1988	1989	1990	1991	1992	1993	1994
Group B	69 (100)	42 (98)	107 (99)*	55 (85)*,**	39 (58)**	16 (41)	24 (47)	38 (58)
Group D	0	0	1 (1)†	10 (15)†‡	25 (37)‡	23 (59)	26 (52)	24 (36)
Group C	0	1 (2)	0	0	3 (5)	0	1 (1)	4 (6)
Total	69	43	108	65	67	39	51	66

Statistical comparisons: *, ‡: $p < 0.05$, **: $p = 0.001$, †: $p < 0.001$.

Major presenting symptoms and signs are shown in Table I. Thirty-six percent of the patients were under one year of age, seven percent being younger than three months. Age distribution of patients according to isolated Salmonella serogroups is shown in Table III and Figure 4. Salmonella serogroup B was isolated significantly less in patients over five years of age than in infants aged between three and 12 months (69% and 84% respectively, $p < 0.05$) (Table III). In contrast, Salmonella serogroup D was identified significantly more in patients over five years of age than in patients between three and 12 months of age (31% and 13% respectively, $p < 0.05$) (Table III).

Table III: Age Distribution of Patients According to Salmonella Serogroups

Age Groups (Months)	Group B	Group D	Group C	Total
0-3	24 (80)	5 (17)	1 (3)	30
3-12	102 (84)*	16 (13)**	3 (3)	121
12-60	129 (76)	36 (21)	5 (3)	170
> 60	65 (69)*	29 (31)**	0 (0)	94
Total	320 (77)	86 (21)	9 (2)	415

Figures in parentheses show the percentage of patients in each age group.
Statistical comparison: *, **: $p < 0.05$.

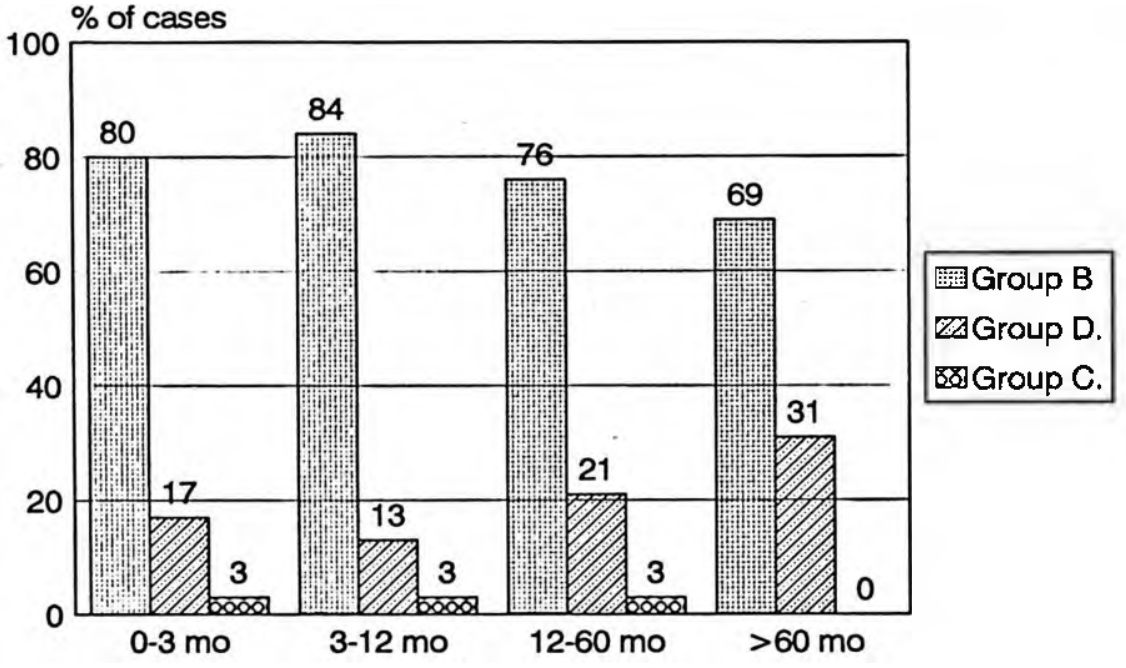

Fig. 4: Age distribution of patients with Salmonella gastroenteritis.

Duration of diarrhea on admission varied from one to thirty days with a mean of 5.1 ± 0.3 days. Nine patients (2%) had persistent diarrhea on admission.

Stool output varied from three to 20 times per day, with a mean of 6.5 ± 0.2. Eight percent of the patients had daily stool output of more than 10. Diarrhea was watery in 73 percent and bloody in 27 percent of the cases (Table I). Patients infected with group B strains had more bloody diarrhea on admission than those infected with group D strains (30% versus 15%, $p < 0.05$) (Table IV).

Fever was present in 54% and vomiting in 51% of the cases (Table I). The presence of fever and vomiting did not differ significantly among the serogroups (Table IV).

Abdominal pain was present in 96 cases (23%). Fifteen of them (3.6%) had a severe clinical picture resembling acute abdomen and required pediatric surgery consultation but none were diagnosed as having acute abdomen or required surgery.

Table IV: Clinical Characteristics and Outcomes of Patients According to Salmonella Serogroups

	Group B (n: 320)	Group D (n: 86)	Group C (n: 9)
Male/Female	189/131	52/34	6/3
Age (months)*	38.4 ± 2.6†	56.0 ± 5.4†	26.3 ± 8.2
Duration of diarrhea (days)*	5.8 ± 0.6†	3.0 ± 0.2†	3.6 ± 0.9
No. of stools (per day)*	6.6 ± 0.2	6.2 ± 0.4	7.4 ± 1.8
Blood in stool #	90/304 (30)†	12/80 (15)†	3/9 (33)
Mucus in stool #	170/301 (56)	39/80 (49)	5/9 (56)
Fever #	178/320 (56)	37/86 (43)	7/9 (78)
Vomiting #	161/320 (50)	50/86 (58)	2/9 (22)
Abdominal pain #	65/320 (20)†	29/86 (34)	2/9 (22)
Convulsion #	7/320 (2)	0/86 (0)	0/9 (0)
Dehydration #			
Mild	28/320 (9)	5/86 (6)	3/9 (33)
Moderate	15/320 (5)	6/86 (7)	0/9 (0)
Severe	1/320 (0.3)	0/86 (0)	0/9 (0)
Total	44/320 (14)	11/86 (13)	3/9 (33)
Malnutrition (degree) #			
First	104/320 (33)	25/86 (29)	2/9 (22)
Second	16/320 (5)	7/86 (8)	0/9 (0)
Third	0/320 (0)	1/86 (1)	0/9 (0)
Total	120/320 (38)	33/86 (38)	2/9 (22)
Duration of excretion days	11.7 ± 1.2	10.9 ± 1.4	20.7 ± 13.7
No. of hospitalized #	13/320 (4)	1/86 (1)	0/9 (0)

* Values are mean ± SD.
# No./screened cases.
† Statistical comparisons: $p < 0.05$.

Seizure was rare among our patients. Seven patients (2%) developed convulsions. One of them was hospitalized due to suspected meningitis, but cerebrospinal fluid examination was normal. Another patient had a history of epilepsy. Of the remaining five, three had febrile convulsions and the other two had hypernatremia.

Dehydration was present in 14 percent (58/415) of the cases. Severe dehydration and electrolyte disturbances were uncommon features (Table I).

Overall, fourteen patients (3%) were hospitalized. Septicemia had been suspected with initial clinical findings in three patients, but blood cultures were found to be positive in only one. Other hospitalizations were due to clinical deterioration such as weakness, high fever, severe vomiting, dehydration with

electrolyte disturbances, severe dehydration, encephalopathy, and clinical toxic appearance. All hospitalized patients responded to appropriate treatment and were discharged from the hospital. No deaths were recorded.

Antibiotics were given to 28 percent (114/415) of the patients.

One hundred ninety-seven patients were further followed up for Salmonella excretion in stool. Among them, 34.5 percent continued to have positive stool culture for more than two weeks. Duration of Salmonella excretion varied from five to 48 days with a mean of 11.7 ± 1.0 days. The mean duration of Salmonella excretion in patients under three months of age (n: 18) was 12.9 ± 2.7 days, while it was 13.9 ± 3.4 days in patients between three and 12 months of age (n: 47), 11.3 ± 1.0 days in those between 12-60 months of age (n: 89) and finally 9.8 ± 1.1 days in children over five years of age (n: 43). Differences in the mean duration of Salmonella excretion among the age groups were not significant (for all comparisons $p > 0.05$).

Patients who received antibiotics (n: 60) had a longer duration of Salmonella excretion than those without antibiotic treatment (n: 137) (15.4 ± 2.8 versus 10.1 ± 0.7 days, $p = 0.016$).

Regarding complications, only one among the clinically suspected patients proved to have bacteremia. None of our patients had extra-intestinal manifestations or any other complications.

Discussion

Salmonella represents 0-15 percent of all diarrheal cases in developing countries[2]. Despite yearly variations, the overall isolation rate of Salmonella in our series was 2.5 percent. Salmonella gastroenteritis has a peak incidence in the late summer and early fall, with the highest number of isolations being reported from July through October[7]. Similarly, most of our cases were reported between June and October, the highest being in October.

Previous reports indicate that the majority of Salmonella gastroenteritis cases occur among children less than one year old, which is explained to be due to dietary habits and reduced resistance to infection[8-10]. In our study, only 36 percent of the cases were under one year of age, seven percent being younger than three months. As breast-feeding provides protection from Salmonella infections, this may be explained by the high rate of breast-fed infants Turkey: 95 percent of children are breastfed and the median duration of breast-feeding is 12 months[11].

Similar to reports from the United States[7], Hong Kong[10], and Iraq[8], Salmonella group B, especially S. typhimurium, was the most frequently isolated serotype in our DTTU. However, since 1990, Salmonella group D has emerged as one of the major causes of Salmonella gastroenteritis, and this was the case in our

series, especially in the older children. An increasing isolation rate of serogroup D is also reported from the United States[12]. According to a study from Saudi Arabia, the majority of Salmonella gastroenteritis cases seen between July 1990 and June 1991 were due to serogroup D, and the mean age of the patients was 3.6 years[13].

Dehydration and electrolyte disturbances were not striking features in our series. One of the reasons for this may be the relatively lower frequency of stool output. Only eight percent of our patients had stool output more than 10 times per day while it was reported to be 26 percent by Lui et al.[10]. Moderate to severe dehydration was found to be present in 19 percent of their cases[10] and in the some percentage as reported by Yamamoto and Ashton[9], while it was present in only 5 percent of our cases. In both previously-mentioned studies, almost all patients were under 12 months of age, which may also contribute to the relatively higher dehydration rates.

Bloody diarrhea is known to be more frequent in younger children than in adults[14]. As their mean age was younger, Salmonella group B infected patients in our study had more bloody diarrhea on admission. Overall, bloody diarrhea was present in 27 percent of our patients. This was similar to the finding reported by Lui et al.[10] and Yamamoto and Ashton[9] where 19.5 and 34 percent of their cases, respectively, had bloody diarrhea.

Two percent of the patients with Salmonella gastroenteritis may have pseudoappendicitis[14]. In our study, almost four percent of our patients had severe abdominal pain requiring pediatric surgery consultation, but none of them were diagnosed to have acute abdomen or required surgery.

Regarding other complications, only one patient (0.2 percent of all cases) developed bacteremia in this study, which was improved with antibiotics (ceftriaxone). Yamamoto and Ashton[9] noted that complications (such as osteomyelitis and bacteremia with septic shock) occurred in three percent of their patients. The rare incidence of complications in our study may be explained by the increasing isolation rate of Salmonella group D since 1990 and its tendency to occur relatively in older age groups.

Death occurs rarely in Salmonella gastroenteritis. With the recent outbreak of S. enteritidis in the United States, less than 0.5 percent of cases resulted in death[12]. On the other hand, Lui et al.[10], reported that four percent of infants with Salmonella gastroenteritis died. In our study no death was recorded. This may be due to the relatively higher ages at the time the disease occurred, and the rare evidence of complications or dehydration.

The median duration of Salmonella excretion was approximately five weeks following Salmonella gastroenteritis[15]. Our data indicate that 34.5 percent of the patients continued to have a positive stool culture for two weeks following the

infection, and the mean duration of excretion was 11.7 ± 1.0 days. The cause of this short duration is most likely due to collection of specimens in most patients via rectal swabs instead of directly from the stool as they did not have diarrhea any longer. It is known that culture obtained from the stool is more likely to be positive than the specimens collected via rectal swabs[16]. Therefore, the length of Salmonella excretion in this study has limited reliability. Despite its limitation, our data showed that use of antibiotics prolonged Salmonella excretion, which is in agreement with the classical knowledge[17].

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THE EFFECTS OF L – CARNITINE ON RESPIRATORY FUNCTION TESTS IN CHILDREN UNDERGOING CHRONIC HEMODIALYSIS*

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SUMMARY: Kavukçu S, Türkmen M, Salman Ş, Önvural B, Oktay G, Karaman Ö, Çevik NT. (Hemodialysis and Transplantation Institute, and Departments of Pediatrics and Biochemistry, Dokuz Eylül University Faculty of Medicine, İzmir, Turkey). The effects of L-carnitine on respiratory function tests in children undergoing chronic hemodialysis. Turk J Pediatr 1998; 40: 79-84.

Respiratory functions are affected during hemodialysis. Ultrafiltration rate, acid-base balance and the strength of respiratory muscles have been suggested as important factors in adults undergoing chronic hemodialysis. L-carnitine is crucial for energy producing utilization fatty acid and, possible amino acids. Carnitine treatment has been associated with hypertrophy of type I muscle fibers. Carnitine supplementation in non-dialysis patients increases exercise tolerance. Eventually, administration of L-carnitine to adult hemodialysis patients improves exercise capacity, energy metabolism and muscle mass. This study was performed to investigate the chronic effects of L-carnitine treatment on respiratory functions in children receiving chronic hemodialysis therapy. Predialytic and postdialytic respiratory function tests were performed in ten children with end-stage renal disease before and after a three-month L-carnitine treatment period. The mean age was 12 ± 4 years. L-carnitine was administered at a dose of 20 mg/kg intravenously at the end of each hemodialysis session. Mean predialytic serum carnitine values before and after the carnitine treatment period were 21.8 ± 3 and 132.0 ± 48.5 mmol/L, respectively, and the increase was significant ($p < 0.05$). Respiratory function tests performed just before the carnitine treatment period implied bronchospasm that was clinically vague and could only be detected by a significant decrease in FEV1/FVC, PEF and FEF25-75 values ($p < 0.05$). Nevertheless, at the end of the three-month carnitine therapy period these respiratory function parameters did not show any significant variation. Hence, it is implied that carnitine therapy might have prevented the subclinic bronchospasm that developed in children during hemodialysis. *Key words: L-carnitine, respiratory functions, hemodialysis.*

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In the maintenance hemodialysis patients, loss of renal mass, limited dietary intake of meat and dairy products, and dialytic loss of L-carnitine during hemodialysis are the factors believed to increase the propensity towards deficiency or depletion of carnitine in the body[1]. The alterations in respiratory functions during hemodialysis in adults have been shown previously[2-5]. Exercise capacity, muscle mass and energy metabolism may affect respiratory function tests[2,3,5]. L-carnitine is crucial for energy producing utilization fatty acid and, possibly, amino acids. Carnitine treatment has been associated with hypertrophy of type I muscle fibers. Carnitine supplementation in non-dialysis patients increases exercise tolerance. Eventually, administration of L-carnitine to adult hemodialysis patients improves exercise capacity, energy metabolism and muscle mass[6,7]. Casciani et al.[8] have reported that astenia, cramp and dyspnea after exertion showed a ratio inversely proportional to the blood concentrations of carnitine. Because no detailed study has been done on children documenting any relation between serum L-carnitine and respiratory function tests, this study investigates the effects of carnitine treatment on respiratory functions of chronic hemodialysis patients in the pediatric age group.

Material and Methods

Ten pediatric age group chronic hemodialysis patients (9 male, 1 female) were enrolled in this prospective study. Clinical characteristies of the patients are shown in Table I. All the patients received orally essential amino acids, calcitriol, calcium carbonate, B complex vitamins, folic acid and iron supplementation, while two also received nifedipine, captopril, and prazosin as antihypertensives. Five of the patients were on a thrice weekly program and the remainder a twice weekly program, each session lasting four hours. All the children were moderately malnourished as detected by body mass indices (BMI) and triceps skin fold thickness measurements; these parameters did not change throughout the study period. All the patients had normal cardiac functions echocardiographically. Toray-321 hemodialysis machines were employed. Hollow fiber cuprophane membranes with surface areas that approximate 75 percent of the calculated body surface were used. Acetate dialysates were utilized throughout the study. Routine heparin protocols were applied. Hemodialysis was effective for all patients, with urea reduction rates of 60 percent or higher. Before the initiation of the study all the patients underwent clinical and radiological evaluation for their respiratory functions and no evident pathology was detected. An automatic spirometer (Vitalograph PFT2 Spirometer, Vitalograph Ltd., Buckingham, England) was employed for all the patients. Tests were performed in a 45 ° semi-sitting position pre- and postdialytically. All pulmonary tests were repeated three times at room temperature, with the best performed test curve taken into consideration.

The parameters investigated were Vital Capacity (VC), Forced Vital Capacity (FVC), Forced Expiratory Volume in one second (FEV1), FEV1/VC, FEV1/FVC, Peak Expiratory Flow (PEF) and Forced Expiratory Flow between 25 and 75 percent of expired vital capacity (FEF25-75). All participants were older than six years of age and cooperative. Results were reliable and no patient needed to be excluded from the study.

Table I: Clinical Characteristics of the Participants

Case No.	Sex	Age	Primary Renal Disease	Treatments Per Week	Time on Dialysis (Months)
1	M	16	Chronic pyelonephritis	3	5
2	M	14	Chronic pyelonephritis	2	3
3	M	16	Unknown	3	14
4	M	7	Obstructive nephropathy	2	3
5	M	10	Chronic glomerulonephritis	3	5
6	F	15	Amyloidosis	3	21
7	M	11	Unknown	3	14
8	M	10	Amyloidosis	2	3
9	M	12	MPGN	2	3
10	M	7	Chronic pyelonephritis	2	8

MPGN: Membranoproliferative glomerulonephritis, M: male, F: female.

Acceptable values for FVC, FEV1 and PEF lie within 100 ± 20 percent of the predicted values. For FEF, the range is 100 ± 35 percent of the predicted value. Among the pediatric age group, FEV1/FVC should be greater than 75 percent of the predicted value. VC, FVC, FEV1 and PEF values decrease in obstructive disorders[9]. Obstructive disorders are also associated with FEV1/FVC below 75 percent of the predicted value[9]. Body weights, the arterial line blood gases, hematocrit, blood urea nitrogen (BUN), plasma creatinine and electrolytes were also measured. Wieland et al.'s[10] enzymatic colorimetric method was used for the measurement of total serum carnitine level. During the treatment period L-carnitine was administered at the dose of 20 mg/kg intravenously at the end of each dialysis session for three months. Same pulmonary function tests and other measurements were repeated after this treatment period.

VC, FVC, FEV1, FEF25-75 and PEF data are expressed as a percentage of predicted values for age, sex, weight and height for each case (Table II). FEV1/VC and FEV1/FVC data are shown as percentage of deviation from predicted values. A negative sign indicates a decrease from predicted value. Data are shown as mean ± standard deviations. Information obtained by described pulmonary functions tests before and after the L-carnitine treatment period was compared. Each child served as his or her own control. In the statistical evaluation of the obtained data, nonparametric Wilcoxon test and correlation analysis were used.

Table II: The Predialytic and Postdialytic Findings Before and After L-Carnitine Treatment Period

	Before L-Carnitine Treatment			After L-Carnitine Treatment		
	Predialytic	Postdialytic	P	Predialytic	Postdialytic	P
Serum carnitine (mmol/L)	21.8 ± 4.4	8.7 ± 1.9	< 0.01	132.9 ± 48.5	39.1 ± 18.1	< 0.01
VC	131.6 ± 43.8	87.4 ± 24.0	NS	75.1 ± 5.0	68.9 ± 5.4	< 0.05
FVC	68.4 ± 4.7	67.4 ± 6.9	NS	74.4 ± 6.1	74.0 ± 4.9	NS
FEV1	66.0 ± 4.0	61.3 ± 6.6	NS	71.4 ± 6.6	73.0 ± 4.7	NS
FEV1/VC	-26.2 ± 11.2	-14.1 ± 9.5	NS	-8.0 ± 4.9	-0.6 ± 2.2	NS
FEV1-FVC	-2.2 ± 2.5	-8.1 ± 3.2	< 0.05	-3.3 ± 3.2	-1.0 ± 2.0	NS
FEF 25-75	61.1 ± 6.4	51.1 ± 8.1	< 0.05	67.7 ± 7.8	68.9 ± 6.6	NS
PEF	55.0 ± 5.1	46.0 ± 6.9	< 0.05	62.1 ± 6.4	65.5 ± 5.3	NS

VC: Vital capacity, FVC: Forced vital capacity, FEV1: Forced expiratory volume in 1 second, FEF25-75: Forced expiratory flow between 25 and 75 percent of expired vital capacity, PEF: Peak expiratory flow. VC, FVC, FEV1, FEF25-75 and PEF data are shown as a percentage of the predicted values. Data shown as mean ± standard deviation. FEV1/VC and FEV1/FVC data are shown as a percentage of deviation from predicted values. Negative sign indicates a decrease from predicted value.

Results

The data obtained before and after the L-carnitine treatment period are shown in Table II. There was a significant decrease in serum carnitine levels during dialysis both before and after the L-carnitine treatment period ($p < 0.05$). Predialysis serum carnitine levels after the L-carnitine treatment period were significantly higher than those obtained before the L-carnitine treatment period ($p < 0.05$). End-dialytic serum carnitine levels, and other parameters observed before and after the L-carnitine treatment period, did not show significant difference. Body weights, potassium and other biochemical and hematologic variables were not significantly different before and after the L-carnitine treatment period. Postdialytic body mass indices (BMI), expressed as a percentage of the expected values, prior to and after the L-carnitine treatment period were 81.1 ± 3.7 and 82.1 ± 3.8, respectively. While a statistically significant difference between predialytic serum carnitine values before and after the treatment period was found ($p < 0.05$), the increase of body mass indices during the same time period was not significant. Before the L-carnitine treatment period, significant decreases in FEV1/FVC, FEF25-75 and PEF values were noted between the pre- and post-dialytic measurements ($p < 0.05$). After the L-carnitine treatment period, only the vital capacity (VC) measurements showed a significant decrease ($p < 0.05$). The decrease in the vital capacity in the period prior to L-carnitine treatment was not significant. When the relation between the rate of changes in the parameters and the rate of changes in the carnitine levels before and after the L-carnitine treatment period were analyzed, a significant positive correlation was found between the rate of changes in the carnitine levels and those in FEV1/VC at the beginning of hemodialysis ($r: 0.84$, $p < 0.05$).

Discussion

During the periods both before and after commencing L-carnitine treatment significant decreases in carnitine levels were detected by the end of dialysis ($p < 0.05$), demonstrating that carnitine was lost during hemodialysis, as is consistent with the literature[6, 11, 12]. Subsequent to L-carnitine administration significant increases in predialytic serum carnitine levels were observed.

Volume overload, metabolic acidosis and uremic toxins are known as the main factors affecting the respiratory function tests in end-stage renal disease patients[13]. While alleviating these factors, hemodialysis may also cause undesirable changes in respiratory functions[2]. Some studies suggested no change in respiratory functions[3], while others detected restrictive changes due to volume overload[2] in the adult hemodialysis population. There is no detailed study reported for the pediatric age group on this issue. In this study, prior to carnitine treatment, postdialytic FEV1/FVC, PEF, FEF25-75 values declined significantly which most likely indicates bronchospasm. The cause of this bronchospasm was beyond the scope of this study. After commencing carnitine treatment, predialytic serum carnitine levels increased significantly, hence it may be suggested that the carnitine therapy is responsible for the prevention of this subclinic broncospasm that developed during hemodialysis. Some studies implied that during hemodialysis, carnitine may cause blockage of the lipooxygenase route so that arachidonic acid can be metabolized via the cyclooxygenase route; therefore, formation of mediators that are responsible for bronchospasm may have been prevented by carnitine administration[14].

Before and after the carnitine therapy, when the relation between the rate of changes in hemodialysis parameters and the rate of changes in serum carnitine levels were investigated, a significant positive correlation was observed between the changes of carnitine levels and the FEV1/VC at the beginning of hemodialysis ($r: 0.864$, $p < 0.05$). This may also support the theory that carnitine has an effect in preventing bronchospasm during hemodialysis. All cases were reevaluated after the L-carnitine treatment and the postdialytic workup revealed a decrease in vital capacity while the rest of the tested respiratory function parameters did not show any significant change. Carnitine has a positive effect on striated muscle strength and exercise capacity. In this study, in the period following carnitine treatment, only postdialytic vital capacity showed a significant decrease, which depicts that carnitine does not affect the respiratory function tests by the proposed mechanism. A decline in the vital capacity both prior to and following the carnitine treatment could be explained as loss of strength during hemodialysis, which cannot be prevented by the carnitine treatment. The possible effect of respiratory muscles on respiratory function tests has been ruled out due to the negligible increase of body mass index in our cases. On the other

hand, results of respiratory function tests after carnitine treatment have not implied an improvement of respiratory muscle insufficiency by carnitine replacement.

In conclusion, it was felt that hemodialysis displayed subclinic bronchospasm in children who did not receive carnitine treatment whereas this subclinic bronchospasm did not appear following carnitine treatment. Here we consider carnitine as a factor that could prevent the bronchospasm which may occur during hemodialysis.

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PLASMA THROMBOMODULIN LEVELS IN EARLY RESPIRATORY DISTRESS SYNDROME*

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SUMMARY: Yurdakök M, Yiğit Ş, Aliefendioğlu D, Dündar S, Kirazlı Ş. (Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Plasma thrombomodulin levels in early respiratory distress syndrome. Turk J Pediatr 1998; 40: 85-88.

Infants with respiratory distress syndrome (RDS) undergo hemodynamic alterations in both the pulmonary and systemic vascular beds that predispose these infants to microvascular damage. In addition, disseminated intravascular coagulation (DIC) is frequently encountered in preterm infants with advanced RDS. In preterm infants with RDS, the plasma status is not known. Therefore, we studied plasma thrombomodulin levels in 25 preterm infants who did or did not develop RDS within the first few hours of life. The mean plasma thrombomodulin levels were found to be similar in the two groups (8.12 ± 10.20 ng/ml vs. 18.30 ± 22.77 ng/ml, respectively, $p > 0.05$ by Mann-Whitney U test). It seems that plasma thrombomodulin levels are normal in the earlier stages of RDS before the occurrence of severe vascular damage and DIC due to hypoxemia. *Key words: newborn infant, thrombomodulin, respiratory distress syndrome.*

The vascular endothelium is metabolically active in the regulation of coagulation. The vascular endothelial cells produce various important antithrombotic substances, such as plasmin activators, heparin-like enzymes and others. Thrombomodulin (TM) is one of these endothelial products. It neutralizes thrombin-clotting activity and accelerates the thrombin-catalyzed activation of protein C, thereby limiting clotting activity. Although TM is mainly found on endothelial cell surfaces, it is also present in the circulating blood. This soluble form of TM appears to be active in its endothelial form[1].

Respiratory distress syndrome (RDS) is an important cause of hypoxemia in preterm infants. Infants with RDS undergo hemodynamic alterations in both the pulmonary and systemic vascular beds that predispose these infants to microvascular damage, increased capillary permeability and pulmonary interstitial

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edema. In addition, DIC is frequently encountered in preterm infants with advanced RDS[2]. An increase in TM levels, in both hypoxemia and DIC, point to endothelial cell damage[3]. In the setting of adult RDS, proteases released from leukocytes may be responsible for the release of TM into the circulation[4]. Disseminated intravascular coagulation (DIC) also significantly increases the soluble TM level. In DIC syndrome, activated proteolytic enzymes in the coagulation-fibrinolysis system may induce the release of TM[5].

In preterm infants with RDS, the TM status is not known. We previously reported (in preterm infants who developed RDS) normal plasma fibrinogen, antithrombin III, protein C, tissue plasminogen activator[6], thrombin-antithrombin III complex and prothrombin fragment 1.2[7], but lower D-dimer and higher plasminogen activator inhibitor (PAI)[6] and von Willebrand antigen (vWF-Ag) levels[8] within the first few hours of life, as compared to the control group. According to these findings, DIC is not a prominent event in early (or developing) RDS. higher D-dimer, PAI and vWF-Ag levels are probably related to abnormalities in the fibrinolytic system due to lung damage and local platelet activation in RDS.

Therefore, we studied plasma TM levels in 25 preterm infants who did or did not develop RDS within the first few hours of life.

Material and Methods

Blood samples for fibronectin testing were obtained by umbilical artery catheterization within six hours after birth and were immediately mixed with 3.8 percent trisodium citrate according to the hematocrit level. The tubes were centrifuged at approximately 3,000 rpm for 10 minutes within 30 minutes of collection. The plasma was stored at -20 °C for less than one month before the procedure. The plasma TM levels were measured by a one-step sandwich enzyme-linked immunosorbent assay (ELISA) using polyclonal antibody (Diagnostica Stago, Asnieres, Cedex, France) raised against human TM[9].

Results

Among the 25 infants, 10 who were in stable clinical condition served as the control group. Fifteen developed RDS, which was considered to be present if all of the following diagnostic criteria were fulfilled: symptoms of respiratory distress within one hour after birth and present for at least 24 hours, respiratory support including mechanical ventilation, and typical findings on lung x-ray and arterial blood gas analysis. None of the infants with RDS had any other disease.

The mean plasma TM levels were found to be similar in the two groups ($P > 0.05$ by Mann-Whitney U test; Table I).

Table I: Plasma Thrombomodulin Levels in Preterm Infants with or without RDS (mean ± SD)

	Controls (n = 10)	Infants with RDS (n = 15)
Gestational age (weeks)	32.4 ± 2.1 (30-36)	29.9 ± 2.7 (26-34)
Birth weight (g)	1704 ± 558 (1120-3050)	1397 ± 652 (520-2650)
Plasma thrombomodulin (ng/ml)	18.30 ± 22.77 (0.00-66.10)	8.12 ± 10.20 (0.00-35.17)

Discussion

Normal plasma TM levels are not clearly defined even in healthy adults. Results appear to be highly dependent on the ELISA method used for measuring the TM concentration. With the method used in the present study, the normal values of TM were found to be 30-40 µg/L[3]. Although Aurrousseau et al.[10] reported that the TM plasma levels were markedly increased at birth in healthy children (up to 110 ng/ml), normal values of endothelium-derived coagulation variables in infants and children are less obvious. In this study, we found normal plasma TM levels in preterm infants who did and did not develop RDS in the first six hours of life. It seems that plasma TM levels are normal in the earlier stages of RDS before the occurrence of severe vascular damage and DIC due to hypoxemia. However, further studies are required to determine the plasma TM status in the later (or developed) stages of the disease.

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A COMPARISON OF DIFFERENT FILTERS FOR WHITE CELL REDUCTION*

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SUMMARY: Yaprak I, Yercen N, Akşit S, Akdeniz F, Türker M, Çağlayan S. (Department of Pediatrics, Social Security Tepecik Teaching Hospital, İzmir, Turkey). A comparison of different filters for white cell reduction. Turk J Pediatr 1998; 40: 89-95.

Removal of white blood cells (WBCs) from blood components before transfusion by filters with at least 3 log_{10} depletion may prevent or delay leukocyte-associated transfusion reactions such as HLA alloimmunization, non-hemolytic febrile reactions, transmitted infections (e.g., CMV, HTLV-1), and immunomodulation. The aim of this study was to compare the leukocyte removal efficiency (LRE) of six commercial bedside filters that are said to achieve 3 log_{10} (Bio R-01, Leucostop 4LT-1, Pall RC 50) and 4 log_{10} (Bio R-01 Plus, Pall RC 400, Pall RC XL-1) WBC depletion. A total of 430 units of whole blood ranging from 32 to 92 for each filter type were analyzed by an automated counter before and after filtration. Postfiltration blood samples were also evaluated for WBCs by Nageotte chamber. All the filters demonstrated leukocyte removal about 1 log_{10} less than the manufacturer's claim. The fourth generation filters showed a better performance than the third generation filters. Of them, Pall RC XL-1 showed the best efficacy with 99.93 percent leukocyte removal and a median residual WBCs of 1.6×10^6 per unit. These results indicate that the fourth generation filters, which are designed for the filtration of packed red cells, in particular Pall RC XL-1, are also able to reduce WBCs from whole blood below the critical antigenic leukocyte load (5×10^6), and can be efficiently used for polytransfused patients to prevent alloimmunization. *Key words: leukocyte removal efficiency, bedside filters, thalassemia, allimmunization, blood transfusion.*

The use of WBC-reduced red blood cells (RBCs) has been shown to prevent or delay a wide range of adverse transfusion effects, including recurrent non-hemolytic febrile reactions, refractoriness to platelet transfusion, alloimmunization to leukocyte antigens, transmission of cell-associated viruses (e.g. cytomegalovirus, human T-lymphotropic virus-1), and possibly immunosuppression[1-6].

In the 1980's, different filtration techniques were used in order to reduce WBCs from the blood components, such as the spin-cool-filter technique and microaggregate filtration[7-9]. Recently, different polyester filters suitable for use both in the laboratory and at the bedside became available[1, 10]. These filters

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do not require prefiltration procedures and are claimed to be more efficient[1,2]. Third generation filters are said to deplete WBCs by 3 $\log_{10}$ with a removal efficiency of 99.9 percent and fourth generation filters by 4 $\log_{10}$ with a removal efficiency of 99.99 percent per blood unit[2].

American Association Blood Banks (AABB) proposed that WBC-reduced RBCs must contain fewer than 5×10^6 WBCs per unit to prevent alloimmunization[11]. This degree of WBC reduction can be achieved by filtration of RBCs and platelet concentrates through the third and fourth generation bedside or laboratory-type WBC filters[1,2].

In our Thalassemia Center, bedside filtration has been the standard method of transfusion since 1991. However, we doubted the efficacy of bedside filters in decreasing WBCs when whole blood was used because we could not find any study on this subject in the literature. The aim of this study, therefore, was to compare six different commercially available bedside white cell-reduction filters for leukocyte removal efficiency from the whole blood.

Material and Methods

This study was carried out with six different white cell reduction polyester fiber filters of third and fourth generation at the patients' bedsides in the Thalassemia Center of Social Security Tepecik Teaching Hospital. A total of 430 whole blood units filtered through six different white cell filters were analyzed before and after filtration by an automated counter; postfiltration leukocyte count was obtained by Negeottę chamber. The filters were compared in terms of leukocyte removal efficiency, log reduction and residual leukocyte count per unit of blood.

Filters

The third and fourth generation filters used and the number of the filters from each filter type are given below:

Third generation filters (n = 196).

1. Bio R-01 (Biofil, Medolla, Italy), n = 92
2. Leucostop 4LT-1 (Miramed, Italy), n = 72
3. Pall RC 50 (Pall Corp. Glen Cove, NY), n = 32

Fourth generation filters (n = 234)

1. Bio R-01 Plus (Biofil, Medolla, Italy), n = 90
2. Pall RC 400 (Pall Corp., Glen Cove, NY), n = 54
3. Pall RC XL-1 (Pall Corp., Glen Cove NY), n = 90

Blood Units

Whole blood units that were provided from our hospital's blood bank and drawn from healthy donors were used for filtration. Each unit of blood was 400 ± 25 ml in 63 ml CPDA. The age of blood units were one to 28 days and the storing temperature was 4 °C.

Filtration Procedure

Bedside filtration was carried out by two experienced nurses of the Thalassemia Center in the transfusion room. The blood units were kept at room temperature until the transfusion was started (30 to 45 minutes after the unit's removal from the refrigerator).

The filtration procedure followed the manufacturer's instructions. After the filters were connected to the plastic blood bags, all, except Bio R-01 Plus, were primed with blood by a soft manual squeezing of the bag, whereas Bio R-01 Plus was primed spontaneously by its own "auto-venting system". The filtration procedure was then left to spontaneous gravity and the transfusion was started. The transfusion of each unit was accomplished in an interval ranging from 50 to 90 minutes. A new filter was used for each unit of blood.

Evaluation

Both prefiltration and postfiltration blood samples were analyzed for complete blood count by an automated counter (T 660, Coulter Electronics Inc., Hialeah, Florida, USA). The postfiltration specimens taken from the distal end of the connecting tube of the filter, with very low concentrations of WBCs, were also counted manually using a hemocytometer (Negeotte chamber) with a light microscope, according to the method described by Masse et al.[12] One hundred µl of the sample was mixed with 900 µl of Turk's solution (1 ml 1% Gention Violet plus 3 ml glacial acetic acid) in a test tube to prepare 1:10 dilution. The diluted sample was thoroughly mixed and left to rest for 10 minutes at room temperature, to allow the WBCs to stain. We then placed 100 µl of this sample on the Nageotte chamber (Saaringia, West Germany) and allowed it to rest again for 10 minutes before counting by a light microscope (40 x objective). A 50 µl grid (an area of 40 rectangles) was than counted. Each sample was counted by two different pediatricians and the average of the two was taken into consideration. The filters were tested at random and the doctors were not informed about the filter used.

For every filter used in the study, the number of leukocytes per µl, lukocyte removal efficiency (LRE), residual lukocyte count per unit (RLc) and log reduction capability were calculated as follows:

$$\text{Leukocyte/µl (Negeotte)} = \frac{\text{number of counted cells}}{\text{volume counted (µl)}}$$

$$\text{LRE (\%)} = \left(1 - \frac{\text{Postfiltration (effluent) leukocytes/µl}}{\text{Prefiltration (influent) leukocytes/µl}}\right) \times 100$$

$$RLc = Leukocyte/\mu l \times 1000 \times unit\ volume\ (ml)$$

$$Log\ reduction = \log_{10} \frac{Prefiltration\ (influent)\ leukocytes/\mu l}{Postfiltration\ (effluent)\ leukocytes/\mu l}$$

Statistical Analysis

To compare the six different filters, one-factor analysis of variance (ANOVA) was used for measured continuous values and chi-square test for nominal data. When the F statistics were found significant ($p < 0.05$), repeated t tests were used. Correlation analysis was performed to investigate any relationship between the parameters.

Results

Prefiltration and postfiltration WBC counts, hemoglobin levels, filtration time and age of blood in the filter groups are shown in Table I. There were no significant differences among the six groups in terms of filtration time, age of blood and prefiltration and postfiltration hemoglobin values by ANOVA. A comparison of the leukocyte depletion performances of the filters is shown Table II. Median leukocyte removal efficiency is highest in the filter group of Pall RC XL-1 (99.3%) and lowest in the group of Bio R-01 (97.45%).

Table I: Prefiltration and Postfiltration Data on the Six Different Filters*

	Bio R-01 (n = 92)	Leucostop 4LT-1 (n = 72)	Pall RC 50 (n = 32)	Bio R-01 Plus (n = 90)	Pall RC 400 (n = 54)	Pall RC XL-1 (n = 90)
Hemoglobin (g/dl), mean ± SD						
Prefiltration	12.3 ± 1.4	12.5 ± 1.5	12.5 ± 1.5	13.0 ± 2.0	13.1 ± 2.2	11.8 ± 1.6
Postfiltration	12.1 ± 1.4	12.3 ± 1.4	12.5 ± 1.2	12.9 ± 2.1	13.0 ± 2.1	12.0 ± 1.9
WBc (coulter), x $10^3/\mu l$						
Prefiltration	5.8 (3.2 - 11.0)	6.6 (2.1-9.9)	5.5 (3.1 - 11.0)	6.5 (2.6 - 12.2)	7.3 (3.6 - 19)	6.0 (2.7-9.9)
WBCs/µl (Negeotte)						
Postfiltration	148 (2 - 980)	46 (1 - 580)	41 (8 - 492)	10 (1 - 280)	10 (1 - 50)	4 (1 - 30)
Filtration time (mins), mean ± SD	72 ± 10	71 ± 9	70 ± 8	72 ± 10	70 ± 9	68 ± 10
Age of blood (days), mean ± SD	10.7 ± 7.4	9.7 ± 7.9	10.8 ± 7.8	10.1 ± 7.7	10.0 ± 8.0	9.6 ± 8.1

* Values are presented as median (range) unless otherwise noted.

Table II: A Comparison of the Leukocyte Depletion Performances of the Filters

Performance	Bio R-01 (n = 92)	Leucostop 4LT-1 (n = 72)	Pall RC 50 (n = 32)	Bio R-01 Plus (n = 90)	Pall RC 400 (n = 54)	Pall RC XL-1 (n = 90)
Leukocyte removal efficiency (%)*	97.45 (89.30 - 99.97)	99.30 (90.80 - 99.97)	99.25 (90.90 - 99.97)	99.85 (97.40 - 99.99)	99.86 (99.40 - 99.99)	99.93 (99.40 - 99.99)
WBC reduction (log_{10})	1.59	2.16	2.13	2.82	2.86	3.18
Residual leukocyte count/unit*	5.9×10^7	1.8×10^7	1.6×10^7	4×10^6	4×10^6	1.6×10^6
Residual WBC count $< 5 \times 10^6$ per unit, n (%)**	8 (9)	20 (28)	2 (6)	52 (58)	28 (52)	82 (91)

* Median (range).
** $P < .0001$.

There were considerably great statistical differences ($P < .0001$) among the six filter groups in decreasing WBC count below the critical antigenic load (5×10^6), If Pall RC XL-1 were excluded from the analysis, the other two fourth generation filters were comparable in this regard (58% and 52% for Bio R-01 Plus and Pall RC 400, respectively).

Third generation filters generally showed a median of approximately 2 log_{10} WBC removal and the fourth generation filters about 3 log_{10} WBC depletion. The most efficient was Pall RC XL-1 with a 3.18 log_{10} WBC removal. There was no statistically significant correlation between the filtration time and postfiltration WBC number ($P > .05$).

Discussion

Leukocytes are largely responsible for adverse transfusion reactions, such as HLA alloimmunization and, in turn, development of nonhemolytic febrile reactions and refractoriness to platelet transfusions. Reduction of WBCs in blood components by filters before transfusion with about 3 log_{10} depletion can prevent these adverse reactions. For a higher degree of purity, new generation filters with a 4 log_{10} WBC depletion are now available[1, 2, 13, 14].

In several comparative studies, different results have been reported on the efficacy of various filters for WBC removal[1, 2, 15-17]. In the study of Sirchia et al[10], they tested only one filter (Pall RC 100) and found a median of 20×10^6 residual WBC count per 2 units of RBC and better results per one unit of RBC. Bontadini et al.[2] compared six different white cell reduction filters and found that two of the third generation filters demonstrated an efficacy of about 3 log_{10} WBC reduction. But they performed only five experiments for each filter type. Koerner

et al.[15] also compared five different filters for leukocyte removal from red cell concentrates and they determined median WBC removal efficiencies between 98.1 and 99.9 percent similar to our results.

The Thalassemia Center in our hospital is very busy, with about 50 patients attending each week for blood transfusion. For this reason, our blood bank sometimes cannot meet the requirements of WBC-filtered packed RBCs for thalassemic children. Since 1991, therefore, we have also been using bedside WBC-reduction filters in the filtration of whole blood as well as in that of packed RBCs. However, we could not find any study in the literature that investigated the effectiveness of white cell filters for whole blood.

Our results showed that all the filters generally reduced WBCs about 1 $\log_{10}$ less than the manufacturer's claim. It may have occurred because samples postfiltration for WBC counts were taken at the end of the filtration process. However, as can be expected, the fourth generation filters were capable of greater leukocyte removal from whole blood and, subsequently had lower residual leukocyte counts than the third generation filters ($P < .001$). But, there was no uniformity for WBC reduction even among the same generation filters. For example, of the third generation filters, Leucostop 4LT-1 and Pall RC 50 demonstrated median WBC reductions slightly higher than 2 $\log_{10}$ (2.16 $\log_{10}$ and 2.13 $\log_{10}$, respectively), while Bio R-01 decreased WBCs less than 2 $\log_{10}$ (1.59 $\log_{10}$). Likewise, among the fourth generation filters, only Pall RC XL-1 removed WBCs from whole blood more than 3 $\log_{10}$ (a median of 3.18 $\log_{10}$). This filter was also succesful in 91 percent of the filtrations in decreasing residual WBCs less than 5×10^6, the limit for residual leukocytes per unit, proposed by the American Association of Blood Banks to prevent alloimmunization[11]. Wenz[18] has termed the concentration of leukocytes necessary to cause clinical symptoms of transfusion reactions as critical antigenic leukocyte load (CALL), and the concentration of WBCs necessary to cause sensitization as critical immunogenic leukocyte load (CILL). This requires the administration of approximately 10^6 to 10^7 WBCs. Thus, even with 10^7 WBCs, polytransfused patients are largely saved from adverse transfusion reactions. In our study, a total of six febrile transfusion reactions were observed only in the filter groups of Bio R-01 (4 cases) and Leucostop 4LT-1 (a cases). These filter groups also had the highest residual WBC counts. However, there was no statistically significant difference ($p > .05$) among the groups regarding the number of febrile reactions.

From the data presented here, we conclude that fourth generation filters, preferably Pall RC XL-1, can be used to reduce the level of residual WBCs in whole blood (when packed RBC is not available) below the threshold that is thought to result in alloimmunization.

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EVALUATION OF RENAL FUNCTIONS IN CHILDREN WITH CONGENITAL HEART DISEASE BEFORE AND AFTER CARDIAC ANGIOGRAPHY*

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SUMMARY: Noyan A, Küçükosmanoğlu O, Yıldızbaş D, Özbarlas N, Anarat A, Anarat R. (Departments of Pediatric Nephrology and Cardiology, Çukurova University Faculty of Medicine, Adana, Turkey). Evaluation of renal functions in children with congenital heart disease before and after cardiac angiography. Turk J Pediatr 1998; 40: 97-101.

Radiocontrast nephrotoxicity, which has increased in incidence with widespread use of radiological methods in medicine, is a serious complication of radiocontrast materials. In this study, we have prospectively investigated whether children with cyanotic congenital heart disease are at risk for radiocontrast nephrotoxicity with the use of a nonionic low osmolar contrast agent. Thirty-five children (17 cyanotic and 18 acyanotic patients) who underwent diagnostic cardiac catheterization were subjects of the study. The age range was from five days to 13 years. The volume of contrast material was 3.11 ± 1.37 ml/kg in cyanotic patients and 2.67 ± 0.86 ml/kg in acyanotic patients. Blood samples and timed urine samples were taken from all patients 24 hours before and 48 hours after cardiac catheterization. Blood urea nitrogen, creatinine, sodium, and phosphorus in serum, and creatinine and N-acetyl-β-D-glucosamine in urine were analyzed. There was not a statistically significant difference between the values before and after angiography. As a result, we could find no evidence of radiocontrast nephrotoxicity with the use of a nonionic contrast agent in cyanotic and acyanotic patients who underwent cardiac angiography. *Key words: cardiac angiography, radiocontrast nephrotoxicity.*

Radiocontrast nephrotoxicity (RCN), a serious complication of radiocontrast materials, has increased in incidence with widespread use of radiological methods in medicine. While the incidence of radiocontrast nephrotoxicity in adults with no risk factors is given as 47 percent, in cases with diabetes or preexistent kidney disease, this incidence rises to 90 percent[1]. Although radiocontrast investigations are employed frequently as diagnostic tools in pediatrics, we do

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not have adequate knowledge about the incidence of RCN in children. In this study, we have prospectively investigated whether children with cyanotic congenital heart disease (CHD) are at risk for RCN by comparing the glomerular and tubular functions in children with cyanotic and acyanotic CHD before and after cardiac angiography.

Material and Methods

The subjects of this study were 35 children who underwent cardiac catheterization in the Pediatric Cardiology Department of Çukurova University Faculty of Medicine between March and June 1996 as a result of various congenital heart diseases. Seventeen children (8 girls, 9 boys) had cyanotic and 18 (9 girls, 9 boys) had acyanotic congenital heart disease. The age range of the cyanotic patients was 5 days to 14 years (mean 4.23 ± 4.61 years) and of acyanotic patients was 1.5 to 13 years (mean 5.44 ± 3.04 years) (Table I). Cardiac catheterization and angiography were performed using standard techniques. Lopamidol was used for angiography. The volume of contrast material was 3.11 ± 1.37 ml/kg in cyanotic patients and 2.67 ± 0.86 ml/kg in acyanotic patients. Procedure duration was less than 30 minutes for all patients.

Table I: Comparison of Clinical Variables of the Cyanotic and Acyanotic Patients

	Cyanotic (n = 17)	Acyanotic (n = 18)
Age (year, mean ± SD)	4.23 ± 4.61	5.44 ± 3.04
Male (%)	53	50
Contrast material volume (ml/kg)	3.11 ± 1.37	2.67 ± 0.86
Mean Htc (%)	50.3 ± 5.7	36.3 ± 3.2
Diagnosis	10 Tetralogy of Fallot	7 Ventricular septal defects
	3 Double outlet right ventricle	5 Atrial septal defects
	4 Transposition of great arteries	3 Pulmonary stenoses
		1 Patent ductus arteriosus
		1 Atrioventricular septal defect
		1 Rheumatic heart disease

Laboratory methods: Blood samples and timed urine samples were taken from all patients 24 hours before and 48 hours after cardiac catheterization. Urea nitrogen, creatinine, sodium, phosphorus and calcium in serum and creatinine in urine were analyzed with Cobas Mira autoanalyzer. N-acetyl-β-D-glucosamine (NAG) in urine was measured by spectrophotometric absorption of 3-cresolsulfophthalein sodium at 580 nm. The Wilcoxon test was used to test the significance between values before and after angiography within the same group and correlation was calculated according to the Pearson equation. Values are expressed as mean ± SD and p value ≤ 0.05 was considered significant.

Results

Comparison of laboratory parameters before and after cardiac angiography in the cyanotic and acyanotic groups is shown in Table II. The NAG values of the cyanotic group before and after cardiac angiography were 3.29 ± 1.95 U/day and 3.37 ± 1.56 U/day, respectively ($p > 0.05$). The NAG values of the acyanotic group before and after the procedure were 2.88 ± 1.17 U/day and 3.09 ± 1.68 U/day, respectively ($p > 0.05$). The fractional excretion of sodium (FeNa) values of the cyanotic group before and after angiography were 0.91 ± 0.67 and 0.87 ± 0.84, respectively ($p > 0.05$) and of the acyanotic group were 1.01 ± 0.76 and 1.02 ± 0.65, respectively ($p > 0.05$). Creatinine clearance (CrCle) values before angiography were 89.1 ± 3.11 ml/min/1.73 m^2 in the cyanotic group and 74.22 ± 5.86 ml/min/1.73 m^2 in the acyanotic group. The values after angiography were found to be 90.69 ± 3.24 ml/min/1.73 m^2 and 78.12 ± 5.07 ml/min/1.73 m^2, respectively. There was not a statistically significant difference between the values of the two groups.

Table II: Comparison of Laboratory Parameters Before and After Cardiac Angiography in Cyanotic and Acyanotic Groups

	Cyanotic Group (n = 17)			Acyanotic Group (n = 18)		
	Before	After	P	Before	After	P
NAG	3.29 ± 1.95	3.37 ± 1.56	p > 0.05	2.88 ± 1.17	3.09 ± 1.68	p > 0.05
FeNa	0.91 ± 0.67	0.87 ± 0.84	p > 0.05	1.01 ± 0.76	1.02 ± 0.65	p > 0.05
CrCle	89.1 ± 3.11	90.69 ± 3.24	p > 0.05	74.22 ± 5.86	78.12 ± 5.07	p > 0.05
SCr	0.51 ± 0.14	0.53 ± 0.16	p > 0.05	049 ± 0.14	0.53 ± 0.14	p > 0.05
BUN	15.31 ± 7.18	12.41 ± 3.11	p > 0.05	13.98 ± 4.77	14.61 ± 5.17	p > 0.05
TRP	0.90 ± 0.04	0.93 ± 0.05	p > 0.05	0.90 ± 0.04	0.91 ± 0.04	p > 0.05
SCa	9.7 ± 61	10.01 ± 0.98	p > 0.05	9.5 ± 0.97	10.04 ± 0.96	p > 0.05

NAG (U/day) : N acetylglucosaminidase.
FeNa : Fraetional excretion of sodium.
CrCle (ml/min/1.73 m^2) : Creatinine clearance.
SCr (mg/dl) : Serum creatinine.
BUN (mg/dl) : Blood urea nitrogen.
TRP : Tubular reabsorption of phosphorus.
SCa (mg/dl) : Serum calcium.

Tubular reabsorption of phosphorus (TRP) values of the cyanotic group before and after angiography were 0.90 ± 0.04 and 0.93 ± 0.05, respectively. The same values for the acyanotic group were 0.90 ± 0.04 and 0.91 ± 0.04, respectively. There was also no statistically significant difference between the TRP values before and after the angiography ($p > 0.05$). The serum Ca^{++} (SCa) values of both groups before and after angiography showed no statistically significant difference ($p > 0.05$). The Ca^{++} values of the cyanotic group were 9.70 ± 0.61 mg/dl and 10.01 ± 0.98 mg/dl and of the acyanotic group were 9.50 ± 0.97 mg/dl

10.04 ± 0.96 mg/dl, respectively. There was no correlation observed between the dosage of the radiocontrast material and NAG and serum creatinine differences of the groups before and after angiography.

Discussion

Cardiac catheterization and angiography carry certain risks of morbidity and mortality[2]. One of the risks associated with this procedure is nephrotoxicity. Since an adequate definition of RCN does not exist, reports of its incidence in adults vary from study to study[3-7]. The incidence of RCN in children is even less well documented. However, one fact known for certain is that in the presence of risk factors (such as renal insufficiency, diabetes mellitus, hypertension, congestive heart failure etc.) the incidence of RCN increases significantly. The relationship of glomerular abnormalities to cyanotic CHD has long been recognized[8, 9]. Studies of autopsy material have revealed various glomerular changes in cyanotic CHD[8, 10]. A number of speculative mechanisms have been proposed, including hypoxia, polycythemia, chronic hypercapnia, increased pressure in the right side of the cardiac circuit and increased postglomerular resistance[8]. The true mechanism of these abnormalities is not known. In this study we have investigated whether children with cyanotic or acyanotic CHD constitute a risk group for RCN. NAG is a lysosomal enzyme which is found in renal tubular cells and its activity in urine increases markedly in case of renal damage[11]. Even though glomerular and tubular parameters are useful in diagnosing RCN, NAG may be an important criterion for early diagnosis as in renal transplant patients and certain drug nephrotoxicities[11, 12]. However, as was the case in other studies, we also could not determine significant differences betweenn NAG values before and after cardiac catheterization in conjunction with use of low osmolality agents[13, 14]. In some studies done on RCN, one indicator has been an increase in serum creatinine of greater than 50 percent from baseline values[7]. In this study, no increase to this extent was observed in either group. In addition, no significant difference in creatinine clearance was observed in either group. Controversy exists regarding whether the dose of contrast media administration is related to the development of RCN[10]. In our study, we could not find a correlation between the dosage of the contrast material and NAG and serum creatinine differences of the groups before and after angiography.

As a result, we could not find any evidence of RCN with the use of iopamidol in pediatric cyanotic and acyanotic patients who underwent cardiac angiography. However, in evaluating this result, it should be kept in mind that the volume of contrast material given to the patients in our study was not the maximum dose. We can say that cardiac angiography using not-too-high volumes of nonionized low osmolar contrast material is rather safe, in terms of nephrotoxicity, for children with acyanotic and cyanotic CHD.

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FREQUENCY OF CARDIOVASCULAR AND GASTROINTESTINAL MALFORMATIONS, LEUKEMIA AND HYPOTHYROIDISM IN CHILDREN WITH DOWN SYNDROME IN TRABZON, TURKEY*

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SUMMARY: Aynacı FM, Orhan F, Celep F, Karagüzel A. (Deparments of Pediatrics and Medical Biology, Karadeniz Technical University Faculty of Medicine, Trabzon, Turkey). Frequency of cardiovascular and gastrointestinal malformations, leukemia and hypothyroidism in children with Down syndrome in Trabzon, Turkey. Turk J Pediatr 1998; 40: 103-109.

This study was carried out to determine the frequency of congenital heart defects, cholelithiasis, hypothyroidism and leukemia in 31 children with Down syndrome. Twenty children (71.4%) had congenital heart defects. Ultrasonography was performed on 29 and two of these (6.9%) had cholelithiasis. Tests for hypothyroidism in 24 children identified hypothyroidism in three (12.5%). Leukemia was diagnosed in three children (10%) (one with congenital, two acquired). One patient with congenital hypothyroidism underwent surgery on the third day of life because of annular pancreas and duodenal atresia. *Key words: Down syndrome, congenital heart defect, hypothyroidism, cholelithiasis, annular pancreas, leukemia.*

The presence of an extra chromosome 21 results in the best recognized and most frequent human chromosomal syndrome, Down syndrome[1]. Worldwide, the prevalence of Down syndrome is 1 in 700 births and boys outnumber girls 1.3 to 1.0[1-4].

Ophthalmic problems (refractive error, strabismus, nystagmus, cataracts, blepharitis and keratoconus), hearing loss (60 to 90% of the children), dental or oropharyngeal problems, skin problems (thin hair and sensitive skin), congenital heart diseases, and endocrine and musculoskeletal abnormalities (hypotonia, joint laxity, joint dislocations) have all been described in Down syndrome[1-18].

In this report, hypothyroidism, cholelithiasis, and cardiac and hematologic abnormalities were investigated in 31 children with Down syndrome.

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Material and Methods

This study was carried out in 31 children (16 boys, 15 girls) with Down syndrome admitted to the Pediatrics Department of Karadeniz Technical University Faculty of Medicine, Trabzon. The patients were aged between four hours and 15 years (mean 44.2 ± 21.2 months).

Chromosomal studies were carried out on cultures of peripheral blood lymphocytes and metaphase smears were prepared by standard procedures.

According to the results of the chromosomal analysis, echocardiographic investigation for heart defects was necessary in 28 cases (93.3%). Thyroid hormones (T_3, T_4, TSH, free T_3, free T_4) were tested in 24 children (80%) for hypothyroidism. Ultrasonographic examination was made in 29 patients (96.6%) for cholelithiasis. All of the patients were evaluated for leukemia.

Standard radioimmunoassay procedures were utilized for the determination of T_4 and TSH levels in serum. In the newborn period, hypothyroxinemia was defined as a T_4 level < 2 SD of the mean at the time of the testing period. Hyperthyrotropinemia was defined as a TSH level > 20 μU/ml. Persistent primary hypothyroidism was defined as hypothyroxinemia with concomitant hyperthyrotropinemia on the confirmation testings, with or without clinical symptoms.

Results

Twenty patients (96.7%) had classic trisomy 21. Translocation was detected in one case.

Twenty children (71.4%) had congenital heart defects including ventricular septal defect (VSD), atrial septal defect (ASD), mitral insufficiency (MY), Fallot tetralogy (FT), endocardial cushion defect and patent ductus arteriosus (PDA) (Table I). In the neonatal period and during childhood, ASD was found to be the most common heart defect (75% and 40%, respectively).

Table I: Congenital Heart Defects in 20/28 Children with Down Syndrome

	Patient		Sex	
Heart Defect	No.	%	Female	Male
ASD	8	40	3	5
VSD	6	30	3	3
MY	2	10	–	2
ASD ± VSD	1	5	–	1
Tetralogy of Fallot	1	5	1	–
Endocardial cushion defect	2	10	1	1
Total	20	71.4	8	12

ASD: Atrial septal defect. VSD: Ventricular septal defect. MY: Mitral insufficiency.

Of the 24 cases tested for hypothyroidism two had congenital hypothyroidism and one had acquired hypothyroidism. Annular pancreas and duodenal atresia were identified in the first patient with hypothyroidism, and surgery was performed on the third day of life. The second patient had congenital leukemia associated with hypothyroidism. The third patient was an eight-month-old male. Therapy of thyroxin was started in all three patients.

Cholelithiasis was found in two of the 29 children (15 boys, 14 girls) examined by abdominal ultrasonography. These cases were 25-day-old and 11-month-old male patients. No symptoms were present in either of the patients which suggested cholelithiasis.

Leukemia was identified in three patients. The first patient was a four-hour-old male, admitted to our clinic with symptoms and signs of bleeding, hepatomegaly (4 cm) and splenomegaly (7 cm). Peripheral blood smear revealed 45 percent blastic cells; bone marrow and flowcytometric examination were consistent with M_2 leukemia. He died eight days after admission. The second patient was a one-and-a-half-year-old male. He was followed as M_5 leukemia and died one and a half years after chemotherapy. The third patient had L_1 type of acute lymphoblastic leukemia (ALL) diagnosed at 14 years of life and has been followed up with chemotherapy. Physical and laboratory examination of these patients revealed hepatosplenomegaly and anemia.

Discussion

In previously unsuspected cases, the diagnosis of Down syndrome usually can be made at birth on the basis of the physical examination. The infant has microcephaly, with flattening both of the occiput and face; the nose is low and there is an upward slant of the eyes with epicanthal folds. Eyes often have speckled irides (Brushfield spots). The ears and mouth are small, but tongue is large. The joints are hyperextensible. The hands and fingers are short and broad. The fifth finger shows clinodactyly[1,2,5]. A single palmar crease often appears on the palms. Most children with Down syndrome have dermatologic problems such as thin hair, sensitive skin and alopecia[2,9]. In addition, there is a high prevalence of ophthalmic findings such as strabismus (50%), nystagmus (35%), cataracts (3%), blepharitis and keratoconus[2]. Suyugül et al.[11] evaluated eye findings of 44 cases with Down syndrome. They observed slanting palpebral fissures (88.6%), epicanthus (47.7%), blepharitis (9.0%), Brushfield spots (38.6%), peripheric iris hypoplasia (40.9%), strabismus (3.8%) and myopia (35.8%).

Ninety-four percent of cases with Down syndrome are due to non-disjunction, three percent to parental translocation (usually 14/21) and three percent to mosaicism[12,14]. In Turkey, Balcı[5] found that 93.6 percent of 1000 cases with

Down syndrome were due to regular type, 6.2 percent to translocation and 0.5 percent to mosaicism. In our study, the rate of 96.6 percent regular type was compatible with literature.

The most common medical problems in the newborn period result from congenital heart disease (CHD) and intestinal blockage. Approximately 40 to 50 percent of children with Down syndrome are born with CHD[16]. Most commonly an endocardial cushion defect, other cardiac defects include tetralogy of Fallot, atrial septal defects, PDA and VSD[16]. In a prospective study to determine the incidence of cardiovascular malformations in neonates with Down syndrome, 50 percent of babies had CHD. The most common cardiac anomaly was VSD (41.1%) and with decreasing frequency, others were PDA (17.6%), ASD (11.8%), ASD and PDA (11.8%), hypertrophic cardiomyopathy (5.9%), hypertrophic obstructive cardiomyopathy (5.9%), and complex cyanotic heart disease (5.9%)[8]. In our study, eight cases were newborn and four out of five of babies (80%) had CHD (75% ASD, 25% VSD).

Cardiac malformations are found in at least 40 percent of patients with Down syndrome[2,3,17]. There is a distinctive spectrum of cardiac defects with an overpresentation of endocardial cushion defects compared with the general population. The most common lesions (in decreasing order of frequency) include common atrioventricular canal, VSD, ASD, tetralogy of Fallot and PDA. Left-sided obstructive lesions such as coarctation and valvar aortic stenosis are rare. Transposition of the great arteries has not been reported[10]. In Turkey, Atalay et al.[15] first described 100 cases with Down syndrome examined by echocardiography. In their report, CHD was detected in 36 percent of these cases (41.7% of these were diagnosed with an endocardial cushion defect and 30.5% with VSD). Tetralogy of Fallot was shown as the most common cyanotic heart disease in the same report. In 1997, the incidence of CHD with Down syndrome was determined as 52.3 percent by Günbey et al.[18]. The most common CHD was endocardial cushion defect (50%). Others were ASD (22.7%), VSD (23.6%), tetralogy of Fallot (5%), bicuspid aortic valve (5%) and tricuspid insufficiency (5%). The incidence of CHD in our study, 71.4 percent, was higher than in others and the most common type of CHD was ASD. Our results in the neonatal period and during childhood were different from those reported by Hoe et al.[8], Atalay et al.[15], Günbey et al.[18] and Normand et al.[19]. This may be due to our small number of cases.

Thyroid dysfunction and infertility are the most significant endocrinologic disorders in patients with Down syndrome[2]. Hypothyroidism occurs in approximately 15 percent of children with Down syndrome prior to adolescence[20]. Studies of thyroid function in children with Down syndrome have shown a prevalence of acquired hypothyroidism that varies widely, from two to 27 percent[21]. In school-aged

children with Down syndrome, hypothyroidism was found in three percent[6]. Fort et al.[22] found an incidence of persistent primary congenital hypothyroidism in infants with Down syndrome about 28 times more than in the general populatilon. In our study, we determined two cases with congenital hypothyroidism (8.3%). The cause of congenital hypothyroidism in infants with Down syndrome remains unknown. It has been assumed that impaired immune surveillance in Down syndrome is a primary mechanism[22].

Five percent of the children with Down syndrome have gastrointestinal abnormalities such as duodenal atresia, Hirschsprung's disease, annular pancreas and anal atresia[23]. The incidence of congenital duodenal obstruction in Down syndrome is 300 times higher than in the general population[3]. Despite the fact that several malformations associated with Down syndrome were seen, we noted only eight reports in the literature, including our own, cholelithiasis in patients with Down syndrome[24-26]. We therefore examined 28 of the cases for cholelithiasis by ultrasonography and found only two infants with cholelithiasis who had a history of polycythemia and hyperbilirubinemia in the neonatal period. In our cases, only three patients (10%) had a history of polycythemia in the neonatal period and two of these (66.6%) had gallstones. History of hyperbilirubinemia in the neonatal period was detected in eight patients. In four of these, jaundice disappeared on phototherapy. One normalized following exchange transfusion, and one case recovered spontaneously. According to studies by Balcı et al.[27] and Bostanoğlu[28] the prevalence of cholelithiasis in 286 Down syndrome patients was 5.2 percent (15 patients).

Annular pancreas is frequently associated with other malformations. Among 52 cases reported by Salzer et al.[29], there were nine children with Down syndrome. This rate is higher than in our study (3.3%). Incidence of gastrointestinal anomaly in our study was 10 percent.

Children with Down syndrome carry an elevated risk of developing clonal hematologic disorders and a 10-fold increased risk of leukemia during the first decade of life[10]. Down syndrome patients have about a one percent risk of developing acute non-lymphoblastic and lymphoblastic leukemia during their lifetimes[30].

Transient myeloproliferative disorder and subsequent acute myeloid leukemia (AML) occur with increased frequency in infants and children with Down syndrome[31]. Transient acute leukemia noted during the first few days of life mimics acute lymphoblastic leukemia (ALL); the hematologic status of these neonates returns to normal in one to four months with only supportive therapy[31-33].

In our study congenital leukemia was determined in one patient and acute lymphoblastic leukemia in another patient. Incidence of leukemia in our study was found as 10 percent.

In view of our findings, it is suggested that children with Down syndrome must be evaluated for cholelithiasis, especially if a history of polycythemia in the neonatal period is present. But the number of our cases was small. We feel that further studies, involving large series, must be evaluated for incidence of cholelithiasis.

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ISOVALERIC ACIDEMIA*

Clinical Presentation of 6 Cases

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SUMMARY: Tokatlı A, Coşkun T, Özalp İ. (Metabolism and Nutrition Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Isovaleric acidemia: clinical presentation of 6 cases. Turk J Pediatr 1998; 40: 111-119.

A retrospective study is reported on the clinical outcome of six patients with isovaleric acidemia (IVA) diagnosed during the last 20 years at the Metabolic Unit of Hacettepe University Children's Hospital. IVA is only one of many inborn errors of metabolism that may have an acute or a late, intermittent presentation. Generally, the diagnosis cannot be made by clinical or routine clinical chemical investigations, although the odor of "sweaty feet" is a presenting symptom. An unusual urinary odor, which was present in all of our patients, should lead to a thorough screening for organic acidemia at any age. Here, we have reported six patients with IVA. Two pairs were siblings. All, except one patient, had positive family history of sibling deaths and all parents were related. In our series, only two patients presented during the neonatal period and both died during the acute crisis. The other four patients presented after the neonatal period and were categorized as having a chronic intermittent form of IVA. Two cases showed normal development despite repeated metabolic decompensations; one patient was diagnosed during the first attack, but he was mentally and motor retarded. The other one died during the metabolic crisis. The presented cases clearly illustrate that IVA can be managed successfully once the diagnosis is made. But lack of early recognition may lead to severe psychomotor retardation or death. *Key words: isovaleric acidemia, sweaty feet odor.*

Isovaleric acidemia (IVA) is a disorder of leucine catabolism caused by deficient activity of isovaleryl-CoA dehydrogenase with autosomal recessive inheritance[1]. Two clinical forms are distinguished: 1. acute neonatal form, and 2. chronic form with recurrent attacks of severe ketoacidosis.

If untreated, patients may suffer from permanent brain damage or die, but if the condition is managed with a low-leucine diet, L-carnitine and glycine, they may remain clinically well unless challenged by an infection[2].

Here, a retrospective study is reported on the clinical outcome of six patients diagnosed with IVA during the last 20 years in our clinic.

Case Reports

Six patients who have been diagnosed at the Metabolic Unit of Hacettepe University Children's Hospital as having IVA are included in this study. Clinical and laboratory data of the patients were obtained from hospital records. Some clinical details of the cases are given in Table I.

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Table I: Some Clinical Characteristics of Cases with Isovaleric Acidemia

Patient	Age Sex	Consan-guinity	Family History	Presenting Symptoms	Clinical, Laboratory Findings	Treatment	Outcome
1-(MŞ)*	2½ years male	+	–	vomiting, lethargy, irritability	lethargy, "cheesy" odor, metabolic acidosis	IV fluid, $NaHCO_3$	died
2-(NŞ)*	13 months female	+	+	vomiting, lethargy, fever	lethargy, "sweaty feet" odor, ketonuria, metabolic acidosis	IV fluid, $NaHCO_3$, carnitine, low protein diet	alive
3-(ZŞ)**	7 days female	+	+	poor sucking, lethargy	tachypnea, coma, "rancid" odor, metabolic acidosis, anemia, thrombo-cytopenia	IV fluid, $NaHCO_3$, antibiotic	died
4-(HŞ)**	4 years male	+	+	lethargy, develop-mental delay	lethargy, "sweaty feet" odor, metabolic acidosis	IV fluid, $NaHCO_3$, carnitine	alive, mental-motor retarded
5-Baby Ç	5 days male	+	+	poor feeding	hypotonia, dehydration, lethargy, irregular respiration, "sweaty feet" odor, metabolic acidosis, neutropenia	IV fluid, $NaHCO_3$, antibiotic	died
6-(TK)	5½ years male	+	–	pallor, dark urine, chickenpox, altered mental status	deep breathing, pale and subicteric skin, lethargy, chickenpox, hemolytic anemia, metabolic acidosis	IV fluid, $NaHCO_3$, blood transfusion, carnitine, glycine	alive

* siblings.
** siblings.

Case 1 (MŞ): The two-and-one-half-year-old boy was admitted to the hospital with a short history of vomiting, and became rapidly unwell with lethargy and irritability. He was the product of an uncomplicated term delivery born to third degree relative parents. Two older female siblings were well. His developmental milestones were reported to be normal by the parents.

On admission, he was lethargic and acidotic, and a "cheesy" smell was noticed on his breath. He rapidly lapsed into coma. He was found to have a metabolic acidosis (pH: 6.99, HCO_3: 4.66 mmol/L). His plasma electrolytes and blood glucose were normal as were his hemoglobin and white cell count. He was treated with intravenous fluids and sodium bicarbonate, but his condition did not improve over the next hours and he died. Organic acid analysis of his urine by gas chromatography-mass spectrometry (GC-MS) led to the diagnosis of IVA.

Case 2 (NŞ): A thirteen-month-old girl was well until she presented to a local hospital with a 48-hour history of vomiting, lethargy and fever. The child was treated with intravenous fluid and bicarbonate. She was transferred to our hospital. She was the sibling of Case 1. Our findings on physical examination were limited to a slight lethargy. An odor of "sweaty feet" was noticed on her urine. The patient required 1 mg/kg/day of sodium bicarbonate to maintain a serum bicarbonate of 22 mEq/L for 48 hours. She was then discharged on a low protein diet and carnitine.

Fifteen days following discharge, she was rehospitalized because of urinary infection, vomiting, dehydration and slight metabolic acidosis. Serum concentration of sodium was 142 mEq/L, potassium 5.8 mEq/L, chloride 108 mEq/L. Urine ketone was 4+. She was treated with intravenous bicarbonate and antibiotics. The urinary organic acid pattern showed the typical pattern for IVA with increased excretion of isovalerylglycine, isovaleric acid, β-OH butyrate, acetoacetate and lactate.

Two more admissions for acute infectious laryngitis and viral hepatitis were necessary at the ages of two and four years. The patient is now 10 years old: her growth and neurological evaluatilon are normal, and her school performance is good. She is still on a low-protein diet and is taking 100 mg/kg/day carnitine orally.

Case 3 (ZŞ): The patient, a girl, was the seventh child of parents who were second cousins; four of her siblings had died between one and nine months of age. The infant was well at birth, but began to refuse feeding and started vomiting on the seventh day of life. When she was hospitalized at a local hospital, a presumptive diagnosis of sepsis neonatorum was made and laboratory investigations revealed acidosis. Parenteral broad spectrum antibiotics and sodium bicarbonate solutions were given. Her condition improved and she was discharged on a high protein-high caloric diet on the 17th day of admission. She

was brought to our hospital the next day with lethargy and poor sucking. She was noted to be tachypneic and to have gastrointestinal bleeding. A rancid odor was noticed on her body but this clue could not be identified. Her hemoglobin was 9.4 g/dl, and white-cell count 16.000/mm^3. Thrombocytopenia was also noticed on her blood smear. The serum electrolytes were normal, but carbondioxide content was low (6.4 mEq/L). The initial clinical impression was sepsis. Antibiotic therapy was started, and intravenous bicarbonate was given. However, the patient continued to deteriorate, and profound coma developed within 12 hours. She died soon thereafter.

The specific diagnosis of IVA was suggested after her sibling (Case 4) was diagnosed as having IVA.

Case 4 (HŞ): A four-year-old boy was brought to hospital with a complaint of lethargy. He was the 10^{th} child of consanguineous healthy parents. The pregnancy was uneventful and the infant was normal at birth. Developmental delay was noticed by his parents. His family history was suggestive for a metabolic disease: Five of his siblings had all died in the first year of life with vomiting, poor sucking and altered consciousness. On admission, physical examination revealed a well-grown (weight 18.5 kg, 50^{th}-75^{th} percentile; height 109 cm, 90^{th}-97^{th} percentile) and slightly encephalopathic child. He was responsive to verbal stimuli. The blood pH was 7.2, HCO_3: 12.1 mmol/L. IVA was provisionally diagnosed because of the characteristic odor, and intravenous infusion of sodium bicarbonate and carnitine was started. Organic acid analysis showed increased isovaleric acid, isovalerylglycine and other conjugates, confirming the diagnosis.

The child was discharged on reduced protein intake supplemented with glycine and carnitine.

When he presented with generalized seizures at six-and-one-half years of age, EEG showed diffuse abnormalities, and antiepileptic therapy was started. He is now seven years old-his developmental assessment showed delays in most areas but his physical examination gave normal results otherwise.

Case 5 (Baby Ç): A five-day-old male infant was the third child of consanguineous healthy parents and the product of a twin pregnancy. The first child of the couple had been normal at birth, but had become lethargic on the sixth day of life and died. The second pregnancy was uneventful and the babies were born by cesarean section delivery. They were breastfed and seemed well until the third postnatal day when they presented with seizures and were noted to feed poorly and to be tachypneic. One twin died on the fifth day. Baby Ç was transferred to the neonatal intensive care unit. On admission, he was hypotonic, hypothermic (rectal temperature 35.5 °C), dehydrated and lethargic with signs of respiratory distress. Newborn reflexes were absent. The blood

glucose concentration was 47 mg/dl, venous blood pH: 7.1, and HCO_3: 12.8 mmol/L. Hemoglobin was 20.4 g/dl and the white cell count was low (1,600 mm^3). Urinalysis revealed a 2+ test for protein and a negative test for ketones. The first clinical impression was sepsis neonatorum. Intravenous glucose, sodium bicarbonate and antibiotic therapy were started. The patient's condition worsened within 12 hours and "sweaty feet" odor was noticed on the urine. The respiratory arrest necessitated artifical ventilation; however, his condition deteriorated rapidly and the baby died on the sixth day of life.

The specific diagnosis was confirmed by urinary organic acid analysis by GC-MS. It showed a typical pattern for IVA.

Case 6 (TK): A five-and-one-half-year-old boy was hospitalized with chickenpox, hemolytic anemia, encephalopathy and metabolic acidosis of unknown origin. He was the full-term product of an uneventful pregnancy and delivery. He had normal developmental milestones. His parents were first degree relatives and his two siblings were healthy. At five months and two, four and five years of age, he had been brought to other hospitals with altered mental status, dark urine and vomiting. On each admission, metabolic acidosis and deep anemia were shown, but their etiology could not be determined and the disease remained undiagnosed. All these conditions had been combined with several infectious diseases. On this admission, the body temperature was high (39.1 °C), and physical examination revealed deep breathing, increased pulse rate, pale and subicteric skin with papules, and early and late vesicles with crusts spread to his face, scalp and trunk. There were vesicles on the oral mucous membrane. He was lethargic and ill-looking but arousable. A "sweaty feet" odor was noticed on his body and urine. The clinical picture during this period was dominated by the following hematological abnormalities: The laboratory findings revealed a severe metabolic acidosis with a base deficit of -15.8 mmol/L (pH: 7.2, HCO_3: 9.6 mmol/L). Urinalysis showed 3+ ketones. The hemoglobin was 6.6 g/dl and the reticulocyte count was 3.2 percent with normal white cell count (6,000/mm^3). The peripheral blood smear revealed macrocytosis and polychromatophilia and few spherocytes and fragmented erythrocytes. His blood samples were taken and thereafter transfusions of packed red cells were given. The first impression was an underlying metabolic disease and his blood ammonia, lactate and pyruvate levels were determined. They were within normal limits; however, his plasma amino acid analysis revealed high leucine and glycine levels. The lethargy and acidosis resolved with continuous administration of intravenous fluids of dextrose and bicarbonate. He was noted to be aroused more easily by the second day of therapy and was alert by the third day.

The blood smear findings, the elevated reticulocyte count and elevation of the unconjugated bilirubin level were the overt features of a hemolytic anemia. The plasma hemoglobin concentration was increased; serum haptoglobin was absent.

The osmotic fragility studies and autohemolysis were normal. The hemoglobin electrophoresis did not demonstrate any pathologic pattern. Direct and indirect Coombs' tests were negative. The bone marrow was markedly hyperplastic and showed erythroid predominance. The acid serum (Ham) and sucrose lysis tests were repeated twice but gave negative results.

The diagnosis of IVA was confirmed by demonstrating markedly increased concentrations of isovalerylglycine, 3-OH isovaleric acid and free isovaleric acid in the urine by GC-MS. The patient was discharged on a low-protein diet, and carnitine was prescribed (100 mg/kg/day) orally.

At the age of six-and-one-half years, he was hospitalized again with fever, cough, back pain, vomiting and lethargy. He was diagnosed as having empyema, and hematological and metabolic crises. Closed drainage was instituted and he was treated with intravenous antibiotics, bicarbonate and carnitine infusions. Glycine was added to the therapy and repeated blood transfusions were required. The clinical response was good. The patient was discharged on the 15th day of admission with a low-protein diet, supplemental glycine and carnitine.

He is now 12 years old, and his physical growth and school performance are good. He has not experienced any metabolic decompensation or hemolytic crisis for the last five and one half years.

Discussion

Isovaleryl-CoA dehydrogenase catalyzes the conversion of isovaleryl-CoA to 3-methylcrotonyl-CoA and enzyme deficiency results in toxic accumulation of isovaleric acid and other related organic acids. The disease is characterized by the excretion of isovalerylglycine and 3-hydroxyisovaleric acid (which give the name of disease) and the typical urine odor. Two forms of clinical presentation are common: 1. Acute neonatal form or neonatal onset form occurs within two weeks of birth. Initial symptoms include vomiting, dehydration, listlessness and acidosis[3]. 2. Chronic and intermittent form or late onset form is characterized by exacerbations in the first year of life. Attacks occur during periods of stress, such as viral or bacterial infections, or the ingestion of high-protein foods. Patients may present with vomiting, lethargy progressing to coma, metabolic acidosis characterized by an elevated anionic gap and ketonuria with a distinctive "sweaty feet" odor[4].

Here, we have reported six patients with IVA. Two pairs were siblings (Cases 1-2 and Cases 3-4). All, except for Cases 1 and 6, had positive family history of sibling deaths and all parents were related.

In our series, only two patients, Cases 3 and 5, presented during the neonatal period. In the neonatal form of IVA, affected patients are usually seen during the first two weeks of life with a syndrome of poor sucking, vomiting, lethargy

progressing to coma and ketoacidosis. However, it is known that the neonate has a limited repertoire of responses to severe overwhelming illness and thus the major clinical signs and symptoms are non-specific. As a result, many neonates with metabolic disease succumb without having received a specific diagnosis and with their clinical picture having been attributed to other common conditions such as sepsis[5]. In this group, two neonates were considered as having sepsis despite positive sibling histories and the strange odor detected on their bodies. Even the specific diagnosis of Case 3 was suggested only after her sibling (Case 4) was diagnosed as having IVA many years later. Case 5 was one of a set of twins; the other child having died with the same clinical picture. It could be considered that he, too may have had IVA. The morbidity and mortality of IVA in the neonatal period is high[3]. In our series, these two patients died during the acute crisis.

Four other patients presented after the neonatal period, and were categorized as having the chronic intermittent form of IVA. The age range of presentation was broad: 13 months to four years. Case 6 was diagnosed as having IVA at five-and-one-half years of age, but he had first presented at five months of age. It is interesting that the disease presented in different phenotypes in the same family: Cases 3 and 4 were siblings. One of them presented during the neonatal period, but in the other, developmental delay was the unique feature of IVA until four years of age, when he developed an acute attack.

Recurrent attacks of coma and lethargy are the main presentations of the chronic intermittent form of organic acidemias. The most frequent variety of coma is that presenting with ketoacidosis, although in rare cases, ketosis may be absent. In our series, lethargy and vomiting were the major symptoms in all cases; only Case 1 sank into coma despite supportive measures. The others were responsive to supportive therapy.

Hypoglycemia is rare in patients with IVA. All patients in this group were normoglycemic during acute metabolic crises.

The typical odor of IVA, which is the excellent key to the diagnosis, was noticed in all cases, although it was identified only in four cases. In Cases 1 and 3, a "cheesy" or "rancid" odor was noticed, but this important clue could not be appraised.

The clinical syndrome of IVA is dominated by the neurological findings, but the severe hematological abnormalities are also frequently described in the disease. Inhibition of hematopoietic cellular metabolism by toxic derivative compounds interferes with maturation of bone marrow and is responsible for the hematological findings of IVA[6]. These hematological findings are concomitant with ketoacidosis, but sometimes they are the presenting symptoms. Pancytopenia is a characteristic feature of this syndrome. Neutropenia is regularly observed in both neonate and late onset forms of organic acidurias. Thrombocytopenia occurs only in infancy and anemia only in the neonatal period[7].

In this series, the hematological findings were observed in only three patients. In Case 3 the hemoglobin was low and thrombocytopenia was noticed on the blood smear, but the white cell count was high. In Case 5, neutropenia (1,600/mm^3) was noted, but the hemoglobin and thrombocyte counts were normal. All these findings were attributed to sepsis neonatorum but in retrospect they were compatible with the diagnosis of IVA. It could be said that they were the contributory factors to the cause of death in these neonates.

The hematological abnormalities as described above are reported in the literature, but there has been no report about hemolytic anemia in IVA. In Case 6, at least six hematological and metabolic crises triggered by infectious diseases were noted. Despite many efforts, no explanation could be found for the cause of hemolysis. However, it could be said that the hemolytic crises were precipitated by infection which triggered metabolic crises or acidosis. With appropriate management, the hemolytic crisis has not recurred in this patient.

Cases 2 and 6 showed normal development despite repeated metabolic decompensations. Case 4 was diagnosed during the first attack, but the was mentally and motor retarded. Generally, a normal mental development or a mild mental retardation have been described in this disease. The pyschomotor development of children with IVA may be completely normal[8]. This point draws more attention to the potentially lethal hematological abnormalities. Patients with this controllable disease can be lost because of hemolytic disease, hemorrhage or neutropenic sepsis.

The presented cases clearly illustrate that IVA can be managed successfully once the correct diagnosis is made. Its diagnosis requires a high index of suspicion in neonates presenting with a clinical picture resembling that of sepsis and in older children presenting with repeated acidotic attacks, lethargy and certain hemotological abnormalities in the presence of parental consanguinity and/or positive history for sibling deaths. The unusual urinary odor which was present in all of our patients should have led to a through screening for organic acidemias and thus to the diagnosis of IVA.

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RECURRENT MENINGITIS ASSOCIATED WITH CONGENITAL PARAVERTEBRAL DERMAL SINUS TRACT*

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SUMMARY: Andıran N, Coşkun T, Özaydın E, Seçmeer G. (Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Recurrent meningitis associated with congenital paravertebral dermal sinus tract. Turk J Pediatr 1998; 40: 121-125.

Recurrent meningitis is a rare but important event that needs to be searched for a predisposing factor. Congenital dermal sinuses occurring in the midline are among the etiological factors. Here, an 18-month-old boy with three attacks of recurrent meningitis due to a paramedian dermal sinus tract is presented. Klebsiella was the cultured causative agent. The lesion was suspected on physical examination and demonstrated by lumbosacral magnetic resonance imaging. To the best of our knowledge, this is the first case in English-language literature of the paravertebrally located dermal sinus tract resulting in recurrent meningitis. Therefore, a careful physical examination, especially including the paravertebral region beside the midline, is essential. Magnetic resonance imaging is a non-invasive descriptive method in the evaluation of congenital dermal sinus tracts. *Key words: dermal sinus tract, magnetic resonance imaging, recurrent meningitis.*

Recurrent meningitis (RM) is a rare event defined as any reappearance of clinical and laboratory signs and symptoms of bacterial meningitis after adequate and successful treatment of a preceding meningitis, regardless of the time of reappearance.

RM is generally associated with a predisposing factor. The presence of an acquired or congenital anatomical communication between cerebrospinal fluid (CSF) and a mucocutaneous site, or defects in host immunity, especially in humoral and complement systems, predisposes to recurrent meningitis[1]. It constitutes an important problem in both the determination of cause and the treatment.

Congenital dermal sinuses, mostly occurring at lumbosacral and occipital regions in the midline, are among the important etiological factors of RM. Today, magnetic resonance imaging (MRI) makes it possible to provide detailed anatomical configurations of the sinus tracts and the associated cyst preoperatively[2, 3].

Here, a case with a right paramedian sacral dermal sinus tract and an associated dermoid cyst is reported with MRI findings.

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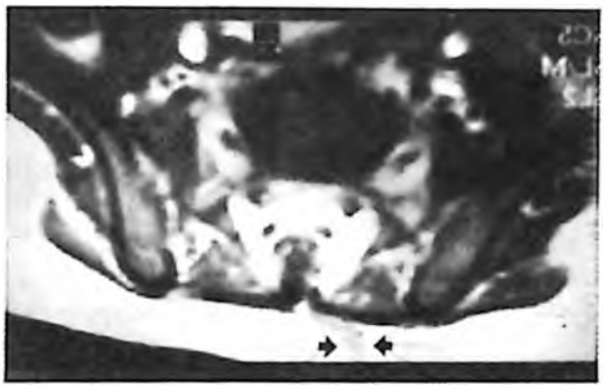
Case Reports

An 18-month-old male patient was referred to our hospital because of RM. He had been admitted and treated at his local hospital for two attacks of purulent meningitis three and five months previously. Physical examination revealed a well developed and well nourished child in nonapparent distress, with minimal nuchal rigidity, a temperature of 38 °C, pulse rate of 130/min, and respiratory rate of 26/min. There was no obvious dimple, or hyperpigmented or hairy lesion along the spine or in the occipital region. An approximately 0.5 cm in diameter hard subcutaneous lesion, 2 cm away from the midline to the right at about L5-S1 paravertebral localizatilon, was palpable. Leukocyte count was 8900/mm^3 and the peripheral smear revealed 60 percent polymorphonuclear leukocytes, 7 percent bands, 27 percent lymphocytes and 6 percent monocytes. Lumbar puncture disclosed a cloudy CSF with a leukocyte count of 2,000/mm^3, with almost all cells in the sediment being polymorphonuclear. The CSF contained a protein of 142 mg/dl, a glucose of 38 mg/dl simultaneous with a blood glucose level of 106 mg/dl.

Blood, urine and CSF cultures were obtained and a combined therapy with intravenous cefotaxime and vancomycin was instituted. Forty-eight hours after admission, klebsiella sensitive to cefotaxime was identified in the CSF culture. Immunological studies showed normal serum immunoglobulin levels and CH50. Plain radiographs of the skull and the spine were normal, but in order to exclude a spinal anomaly, a lumbosacral MRI was done. A right paramedian dermal sinus tract at S2 level and a lumbosacral dermoid cyst at L5-S2 level were detected (Figs. 1 and 2). Having controlled the infection with 10 days' antibiotic treatment, the patient underwent an exploratory surgery. The dermal sinus tract and intradural dermoid cyst containing hair were completely excised. Histopathological examination confirmed the diagnosis. After surgical intervention, the patient had an uneventful recovery with no neurological sequelae.

Fig. 1: The sagittal T1-weighted section of the lumbosacral magnetic resonance image showing the dermoid cyst at L5 to S2 level.



Fg. 2: The right paramedian dermal sinus tract demonstrated in the transverse section of the lumbosacral magnetic resonance image (between the two arrows).

Discussion

An incomplete separation of neuroectoderm and epithelial ectoderm between the third and fifth weeks of intrauterine gestational development results in the formation of a dermal sinus tract. The common form of this congenital anomaly is a tract that extends from the skin to the conus medullaris ending in a cyst: epidermoid, if lined by stratified squamous epithelium or; more commonly, dermoid, if the lining also comprises skin appendages like hair follicles and sebaceous glands[4]. An infected dermal sinus tract that extended into the dura was first reported by Moise[5] in 1926. They can present as a dimple in the skin or as associated cutaneous manifestations such as a hyperpigmented patch, a hairy nevus or hemangioma[4,6]. However, these defects may be unremarkable without any cutaneous stigmata and can be easily overlooked by clinicians. Although these sinus tracts are mostly located on the midline, in our patient, it was located at paravertebral position without any remarkable sign. To the best of our knowledge, this is the first paravertebrally located dermal sinus tract case reported in the English language literature.

Dermal sinus tracts have been found in patients ranging in age from early childhood to 25 years, and 60 percent were discovered due to the presenting meningitis[7]. In most cases of lumbosacral defects, the delayed diagnosis of the fistula to the spinal canal leads to RM. Lieb et al.[8] found developmental anatomical abnormalities as the underlying cause in 23 of 25 patients with RM; the remaining two patients had traumatic CSF leaks and no immunodeficiency was found. All 25 of their cases had anatomical lesions. This was perhaps noticed because the authors are neurosurgeons. Kline[9] studied 47 cases gleaned from the literature, including children and adults, with predisposing factors including congenital CSF fistula (in 55% of cases), traumatic or surgical CSF fistula (in 17%), immunodeficiency (in 21%) and unknown causes (in 6%). The rate of 21 percent immunodeficiency cited by Kline seems an overestimate, since

it is deducted from the literature review, because immnodeficiencies are more enthusiastically reported than cases of developmental or traumatic anatomical lesions without special features. Therefore, in the case of RM, a developmental or traumatic anatomical defect must be primarily suspected and investigated.

The most common etiological agents for meningitis in these patients include S. aureus, S. epidermidis, S. pneumonia, H. influenzae, E. coli, proteus species, Salmonella, anaerobic microorganisms and polymicrobes[2, 3, 8, 10-16]. Another distinct feature of the present case was the detection of klebsiella as the cultured microorganism of the meningitis; to our knowledge, the first reported case of such in English language literature.

The lumbosacral MRI of the patient enabled us to discover the dermal sinus tract and the associated dermoid cyst preoperatively. This was a noninvasive investigation, obviously superior to the previous methods such as sinography or myelography in the evaluatilon of dermal sinus tracts.

Clinicians should be suspicious and make a careful physical examination of patients who present with RM in order to not overlook an underlying insidious lesion located at paraspinal regions beside the midline. Enthusiasm in the identification of the microorganism is vital for the treatment of choice.

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CONGENITAL EPULIS OF THE NEWBORN*
A Case Report

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SUMMARY: Talim B, Yiğit S, Oran O, Akçören Z. (Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Congenital epulis of the newborn: a case report. Turk J Pediatr 1998; 40: 127-129.

Congenital epulis of the newborn is a rare benign tumor, also known as a congenital gingival granular cell tumor. Although it is a benign lesion, the tumor may cause feeding and respiratory problems when too large or when multiple tumors exist. In this article, a case of congenital epulis is presented and its treatment is discussed.
Key words: epulis, newborn.

Congenital epulis of the newborn is a rare benign tumor, also known as a congenital gingival granular cell tumor. It was first described in 1871, and fewer than two hundred cases have been reported since then[1].

This benign pedunculated mass arising from the alveolar ridges of the maxilla or mandible, which is covered with oral mucosa, is excised surgically, since it can cause respiratory and feeding problems[1,2].

In this article, a case of congenital epulis is presented and the treatment is discussed.

Case Report

A thirty-minute-old female infant was admitted to the Neonatal Intensive Care Unit of Hacettepe University Children's Hospital for the evaluation and management of the mass originating from the lower jaw. She was born at 40 weeks of gestation by spontaneous vaginal delivery following an uncomplicated pregnancy and labor.

Physical examination was unremarkable, except for the 3 x 2 x 2 cm had mass protruding from the mouth and originating from the incisor area of the mandibular gum pad on a 5-6 mm pedicle. The entire mass was covered with oral mucosa (Fig. 1). Though respiration was unaffected, the mass interfered with lip closure and feeding.

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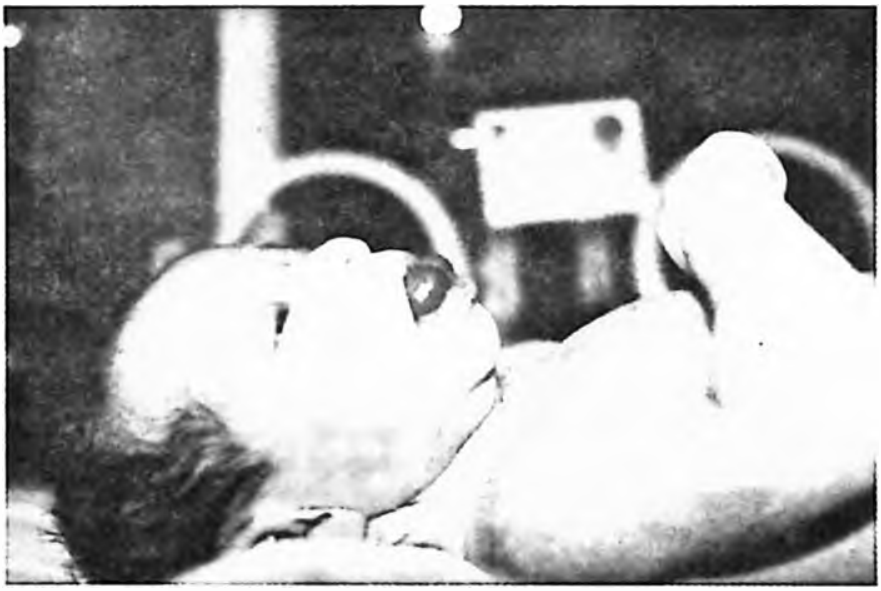

Fig. 1: General appearance of the mass.

The mass was fully excised surgically under local anesthesia the following day and the wound closed with firm sutures. Postoperative wound healing was uncomplicated.

Histopathological examination of the mass revealed clusters of large round or oval pale-staining granular cells containing centrally placed prominent nuclei (Fig. 2). The cells were separated by thin connective tissue in some areas. The whole mass was covered by stratified squamous epithelium. All those features were consistent with congenital epulis of the newborn.

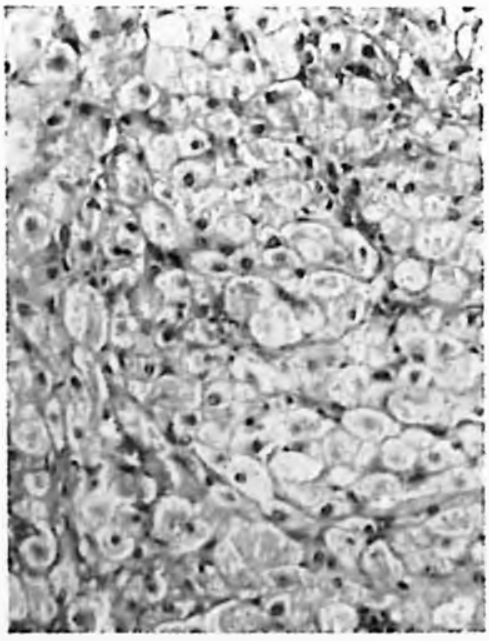

Fig. 2: Large round-oval cells with pale-staining fine granular cytoplasm and prominent nuclei. (Hematoxylin and eosin stain, x 20).

Discussion

Congenital epulis is a rare benign lesion occurring in the newborn, of unknown etiology. It is a pedunculated tumor originating from the gingiva, firm in consistency, with a size ranging from several millimeters to 9 centimeters[1].

Females are affected 10 times more than males[1]; however, cytogenetic and hormone receptor studies have given no explanation for the striking female predominance[3].

The mass usually originates from the upper jaw; the maxillary alveolar ridge is affected as often as the mandible, usually in the incisor-canine region. Cases of multiple tumors on both maxilla and mandible have been reported[1].

Although it is a benign lesion, the tumor may cause feeding and respiratory problems when too large or when multiple tumors exist[1,2]. The tumor does not grow after birth and spontaneous remissions have been reported on occasion[1].

Microscopically, the tumor consists of solid sheets or clusters of large, uniform, pale-staining granular cells; the overlying mucosa is of stratified squamous epithelium without pseudoepitheliomatous hyperplasia[4]. A prominent arborizing fibrovascular network in the thin connective tissue septa is noted throughout the tumor[1].

The histogenesis of the tumor remains controversial. Recent theories of origin include epithelial cells, undifferentiated mesenchymal cells, pericytes, fibroblasts, smooth muscle cells, nerve related cells, and myofibroblasts[3].

A few cases of congenital epulis have been discovered incidentally by routine prenatal ultrasound examination[5].

The treatment is surgical excision; recurrences have not been reported[1,2]. Laser treatment (excision by laser) is another choice, also allowing rapid recovery[5].

The differential diagnosis includes hemangioma, fibroma, granuloma, embryonal rhabdomyosarcoma, malignant granular cell myoblastoma, alveolar rahbdomyosarcoma, chondrogenic and osteogenic sarcomas and schwannoma[1,2,4].

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MYELODYSPLASTIC SYNDROME IN A CHILD WITH A HISTORY OF MEDULLOBLASTOMA*

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SUMMARY: Akyüz C, Emir S, Güler N, Türker A, Büyükpamukçu M. (Oncology Unit, Department of Pediatrics and Adult Oncology Unit, Department of Internal Medicine, Hacettepe University Faculty of Medicine, Ankara, Turkey). Myelodysplastic syndrome in a child with a history of medulloblastoma. Turk J Pediatr 1998; 40: 131-134.

We present a case of myelodysplastic syndrome (MDS) following treatment for medulloblastoma. The tumor was diagnosed at 15 years of age and managed with surgery, craniospinal radiation and a triple-durg regimen [chloroethylnitrosourea (CCNU), vincristine (VCR), procarbazine]. Fifteen months after the completion of therapy, the patient developed MDS with monosomy 5 and monosomy 7 on chromosome analysis of bone marrow cells. Two weeks later, MDS evolved into acute myeloblastic leukemia (AML). Therapy-related MDS or AML may be a complication for patients with past brain tumors. Therefore, they should be carefully followed up by regular physical examinations and complete blood counts. *Key words: medulloblastoma, myelodysplastic syndrome, second malignancy, monosomy 5, monosomy 7.*

Several reports suggest that the development of leukemic disorders as a second neoplasm may be related to the treatment of the first malignancy[1,2]. This association has reported mainly for Hodgkin's disease and non-Hodgkin's lymphoma[3]. A similar association is not well recognized in children receiving chemotherapy and radiotherapy for brain tumors. We report a case who showed myelodysplastic syndrome (MDS) and acute myeloblastic leukemia (AML) following treatment for medulloblastoma because of the rarity of leukemic disorders such as these two in patients treated for brain tumors.

Case Report

In August 1991, a 15-year-old, previously healthy boy came to Hacettepe University Children's Hospital with complaints of headache, vomiting and ataxia. During the radiological evaluatilon of the patient, a posterior fossa tumor was

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recognized in the cranial computed tomography. Histopathologic diagnosis of medulloblastoma was established after the surgical removal of the tumor. Residual tumor was not present on the postoperative cranial tomography. The patient was further managed with radiotherapy (3600 cGy to the neuroaxis, 1800 cGy boost to the tumor bed) in another centre. Chemotherapy cycles consisting of chloroethylnitrosourea (CCNU), vincristine (VCR), and procarbazine were given every six weeks for one year and terminated in November 1992. At the end of the treatment, reevaluation revealed no evidence of residual or recurrent tumor. Fifteen months after the completion of therapy, the patient complained of pallor and fatigue. Complete blood count (CBC) showed Hb: 6.1 g/dl, platelet count: 77,000/mm^3, and WBC: 2,400/mm^3 with 34 percent neutrophils, 64 percent lymphocytes, and 2 percent eosinophiles. Bone marrow examination revealed hypercellularity with increased blasts (17%) and dyserythropoiesis. Bone marrow biopsy was reported as normocellular with an excess of eosinophilic leukocytes. Rare ringed sideroblasts were shown in bone marrow with the iron stain. Bone marrow synchronized cultures revealed a karyotype of 45, XY with the deletion of the fifth and seventh chromosomes and presence of marker chromosome in 18 of the 25 metaphases analyzed (45, XY, -5, -7, +mar). The diagnosis of myelodysplastic syndrome (MDS) was established. Two weeks later, MDS evolved into acute myeloblastic leukemia. The patient was treated with anti-leukemic therapy, (VCR + ARA - C + mitoxantrone + prednisolone). However, the patient did not achieve a remission and became refractory to the therapy and died with disease progression eight months after the diagnosis of MDS.

Discussion

Brain tumor is the second most common neoplasm in children after leukemia[4]. Medulloblastomas represent twenty to thirty percent of all childhood brain tumors. New therapeutic approaches have improved the outcome in medulloblastoma. Radiation to the craniospinal region and addition of multidrug regimens led to this improvement, replacing the application of local radiotherapy[5]. In general, this aggressive approach consisting of radiotherapy and chemotherapy forms the basis of the principal treatment of neoplastic disorders. In the long-term follow up of these patients, complications of this therapy have been increasingly recognized. Secondary malignancies have high morbidity and mortality. Common risk factors for the development of secondary malignancies are the primary tumor, type of chemotherapy, radiotherapy and underlying genetic diseases. The increased risk of second malignancies, most commonly AML, has been reported in treated cases of different types of tumors, especially in Hodgkin's disease[1-3]. However, few cases with a history of brain tumors have been reported to date[6-10]. In our patient, the onset of acute leukemia was preceded by a phase of myelodysplasia. Myelodysplasia preceding leukemia has been reported before[6, 8].

Myelodysplastic syndrome is rare in children. The most widely recognized classification is the one proposed by the French-American-British (FAB) Cooperative Group, and it is based on morphological findings of the peripheral blood smear and bone marrow[11]. The FAB classification for our patient was refractory anemia with excess blasts (RAEB).

Secondary MDS, due to previous toxic chemical exposure or chemoradiotherapy, may occur at all ages. This secondary form of MDS, with or without progression to AML, is emerging as a significant clinical problem, and may cause substantial morbidity and mortality. Use of more intensive treatment regimens combining high-dose chemotherapy and radiotherapy and broader utilization of adjuvant chemoirradiation in solid tumor therapy are some of the reasons for increased incidence. In secondary MDS, abnormal karyotypes are evident in virtually all patients. Multiple chromosome aberrations are the rule. Chromosomes 5 and 7 are involved in 85 percent of the secondary MDS patients[12-13]. Cytogenetic analysis of the bone marrow in our patient revealed monosomy 5 and monosomy 7, which is characteristic of therapy-related MDS and AML. Nitrosourea is one of the durgs accused causing the development of leukemias after the treatment of primary brain tumors[8-9]. In animals, nitrosoureas have a mitogenetic, carcinogenic and teratogenic action. The role played by alkylating agents in the induction of iatrogenic acute leukemia is well known.

In different studies by Baram et al.[14] and Pui et al.[15], it was reported that two cases treated with MOPP (nitrogen mustard, vincristine, prednisolone, and procarbazine) chemotherapy for brain tumor developed acute lymphocytic leukemia and MDS. In another study by Hayani et al.[16], two of eight children who survived medulloblastoma developed MDS. One of them had received MOPP chemotherapy for a brain tumor at the age of 12 months, completing a total of 24 courses, and 19 months later developed MDS with monosomy 7. The other who developed MDS was a seven-year-old boy treated with craniospinal radiation and MOPP chemotherapy. In both cases, MDS evolved into AML. Although we cannot conclude that chemotherapy with CCNU caused MDS in our patient, it is most likely that the chemotherapy played a major role in the pathogenesis of MDS. Radiation therapy may also have been a contributory factor in our patient. The time interval between the therapy and the evolution of MDS was short, a similar finding as noted in the previously reported cases. This is unlike cases involving adults where such a latent period is usually more than three years. As a major immunosuppressant, procarbazine is certainly an important factor in the induction of leukemia in Hodgkin's diseases[17]. Therefore, we must consider the possible role of procarbazine, along with CCNU, in the development of MDS and leukemia in our patient.

In conclusion, we report a case who developed myelodysplastic syndrome and acute myeloblastic leukemia after treatment for medulloblastoma. We consider radiotherapy and chemotherapy responsible for this complication. Those children who have been treated with radiotherapy and chemotherapy need to be closely followed up with regular physical examinations and peripheral blood counts. Bone marrow examination including cytogenetic analysis should be performed when peripheral cytopenia is detected.

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BILATERAL PROPTOSIS CAUSED BY ORBITAL MYOSITIS*
A Case Report

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SUMMARY: Aydın K, Narin N, Erkılıç K, Kurtoğlu S, Hallaç İK, Poyrazoğlu MH. (Departments of Pediatrics and Ophthalmology, Erciyes University Faculty of Medicine, Kayseri, Turkey). Bilateral proptosis caused by orbital myositis: a case report. Turk J Pediatr 1998; 40: 135-138.

Proptosis, unilateral or bilateral, is a frequent indication for medical evaluation and orbital computed tomography. The most common cause of proptosis in adults and children is inflammatory disorders. Orbital myositis is a subgroup of the orbital pseudotumor syndrome in which one or more of the extraocular muscles are primarily infiltrated by an inflammatory process. Computed tomography and ultrasonography showed enlargement of one or more extraocular muscles in orbital myositis.

In our case, we observed clinically and by orbital computed tomography, evidence of isolated bilateral extraocular muscle swelling after upper respiratory tract infection. Proptosis and other findings were spontaneously and completely resolved after twenty days. Because proptosis caused by orbital myositis is extremely rare in children and there is limited information in the literature, this case was reported.
Key words: proptosis, orbital myositis, childhood.

Protrusion of the eyeball is called proptosis or exophthalmos and is the result of the expansion of tissue within the orbital cavity. Expansive lesions may be inflammatory, neoplastic, cystic or vascular. Bilateral involvement generally indicates a systemic disease, such as Graves' disease[1]. Orbital myositis is a subgroup of the orbital pseudotumor syndrome, the latter term being applied to inflammatilon of any orbital soft tissues, including fat, lacrimal gland, connective tissue and muscles[2]. Initial features of acute orbital myositis may include pain, proptosis, diplopia and conjunctival chemosis[2-6]. Cases of orbital myositis caused by upper respiratory tract infections have recently been reported[2-6].

Case Report

A six-year-old boy developed acute bilateral proptosis, pain, conjunctival chemosis and eyelid swelling. There was a history of upper respiratory infection ten days previously. On examination, bilateral proptosis of six mm, chemosis and eyelid swelling were found (Fig. 1). Fundoscopic examination and visual

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acuity were normal. The patient was afebrile and otherwise healthy. The white blood cell counts were 7400/mm^3, erythrocyte sedimentation rate 17 mm/h and C-reactive protein 5 mg/L. The other laboratory findings included antinuclear, antimicrosomal and antithyroglobulin antibody; total and free T3, T4 and TSH were normal. The first creatine kinase level was 271 U/L and after twenty days 64 U/L. Cranial computed tomography (CT) was normal and orbital CT showed bilateral diffuse enlargement of all the extraocular muscles (Figs. 2 and 3). Proptosis and other findings were spontaneously and completely resolved after twenty days without treatment (Fig. 4). The measurements (width) of the extraocular muscles on the first and 20th day are shown in Table I.

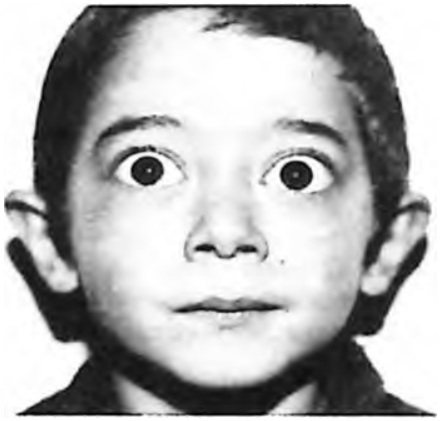

Fig. 1: Bilateral proptosis and eyelid swelling are seen.

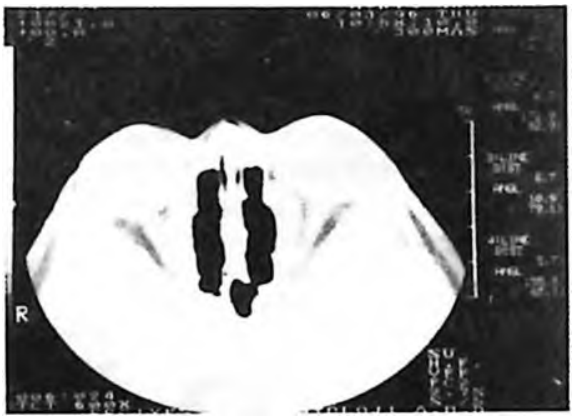

Fig. 2: Orbital CT showed bilateral extraocular muscle enlargement.

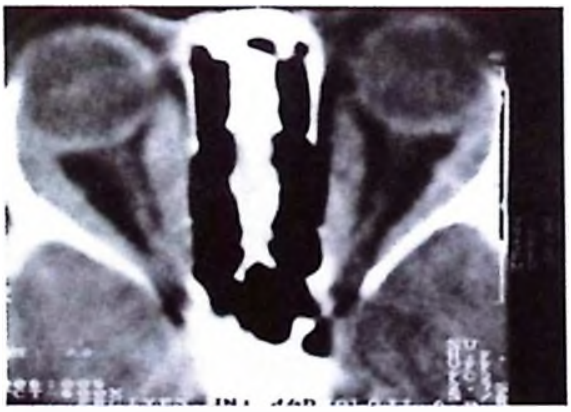

Fig. 3: Orbital CT showed bilateral extraocular muscle enlargement.

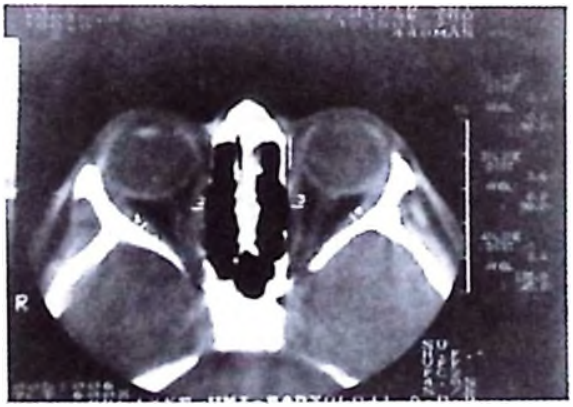

Fig. 4: Orbital CT was normal after twenty days.

Table I: Width of the Extraocular Muscles (mm)

	Onset	After Twenty Days
Right lateral rectus	5.5	3.2
Right medial rectus	6.2	3.4
Left lateral rectus	5.7	3.4
Left medial rectus	6.7	3.6

Discussion

A frequent cause of proptosis in adults and children is inflammatory pseudotumor. This entity consists of a heterogenous group of inflammatory diseases of unknown cause[1]. The site of inflammation is usually diffuse, onset is usually rapid and pain is often present[1,2]. Pulsating proptosis reflects the pulse of an orbital vascular malformation; varices produce intermittent proptosis[1]. Proptosis and periorbital edema due to diltiazem treatment have been reported in adults[7]. Orbital cellulitis is the most common cause of proptosis in children. The diagnosis is not difficult, because the clinical findings are characteristic[1]. Bilateral involvement generally indicates a systemic disease, such as Graves' disease[1]. Severe Graves' ophthalmopathy is uncommon in children. Proptosis occurs in more than half of the patients with childhood Graves' disease[8], while unilateral or bilateral proptosis in adults is due almost always to Graves' disease[1,9,12]. The extraocular muscles may swell up to eight times their normal size in Graves' disease[12]. Some degree of ophthalmopathy occurs in a high percentage of hyperthyroid patients. However, ophthalmopathy can also occur with hypothyroidism or with no detectable thyroid abnormality[1]. There was no thyroid abnormality in our case.

Idiopathic orbital myositis is a subgroup of inflammatory orbital pseudotumor. Initial features of acute orbital myositis may include pain, proptosis, diplopia and conjunctival chemosis[1,7-9,13]. While in children multiple extraocular muscles are usually involved, in adult patients only a single muscle is involved[13]. Computed tomography showed enlargement of one or more extraocular muscles in orbital myositis[2-4,6]. In our case, there was proptosis, chemosis and eyelid swelling and orbital CT showed bilateral diffuse enlargement of all the extraocular muscles. The differential diagnosis of extraocular muscle enlargement includes Graves' disease, idiopathic inflammation, systemic lupus erythematosus (SLE), Wegener granulomatosis, arteriovenous (A-V) malformation, carotid-cavernous fistula and metastasis[1-3,5].

Graves' ophthalmopathy and idiopathic ophthalmic inflammation are easily distinguished on clinical grounds: idiopathic ophthalmic inflammation is usually characterized by the acute onset of deep orbital pain and by an often dramatically rapid resolution, either spontaneous by or after oral administration of corticosteroids[2].

The extraocular muscles may be involved in cysticercosis. Computed tomography scan shows an orbital mass with an area of lucency and a spot of higher density that suggests a calcified Cysticercus[13]. In our case, there was no tomographic sign of cysticercosis. Some cases of orbital myositis are associated with orbital hemorrhage and ecchymosis[3]. However, acute orbital myositis should be included in the differential diagnosis of conditions that may be associated with spontaneous orbital hemorrhage and eyelid ecchymosis. Orbital myositis may be acute, subacute or recurrent. The acute form responds well to high doses

of oral corticosteroids. The subacute form of the disease responds to a lesser degree[2,4]. Orbital myositis caused by upper respiratory tract infections has recently been reported[2,6], as has orbital myositis secondary to lyme disease[14]. There was a history of upper respiratory tract infection in our case ten days prior to our examination. We have obtained with clinical and laboratory findings evidence of bilateral orbital myositis. Proptosis and the other findings were completely resolved without treatment after twenty days and there was no recurrence observed in the following six months.

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DIPLOID – TRIPLOID AND TETRAPLOID MOSAICISM IN A CHILD WITH CRYPTOGENIC CIRRHOSIS AND MEMBRANOUS GLOMERULONEPHRITIS: A CAUSAL RELATIONSHIP OR COINCIDENTAL ASSOCIATION?*

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SUMMARY: Topaloğlu R, Aktaş D, Bakkaloğlu A, Balcı S, Doğru D, Öztürk R. (Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Diploid-triploid and tetraploid mosaicism in a child with cryptogenic cirrhosis and membranous glomerulonephritis: a causal relationship or coincidental association? Turk J Pediatr 1998; 40: 139-143.

We present a seven-year-old boy with cryptogenic cirrhosis, membranous glomerulonephritis, mild mental retardation and mild dysmorphic changes. Chromosomal analysis showed diploid, triploid and tetraploid mosaicism which was detected both by cytogenetic study and flow cytometric analysis of nuclear DNA content. Complete tetraploidy and triploidy, usually lethal, are rare chromosomal disorders. This is the first reported case of diploid-triploid-tetraploid mosaicism with cryptogenic cirrhosis and membranous glomerulonephritis. *Key words: triploidy, tetraploidy, mosaicism, cryptogenic cirrhosis, membranous glomerulonephritis.*

Tetraploidy and triploidy are relatively common chromosomal disorders in spontaneously aborted fetuses[1-3]. Only a few dysmorphic infants have been described with complete and mosaic tetraploidy. In complete triploidy, the longest postnatal survival is five months[4-6]. Prolonged survival has only been reported with diploid-triploid mixoploid cases[7,8]. Dysmorphic findings and multiple congenital anomalies are common[7,8]. We present a seven-year-old boy who had diploid-triploid-tetraploid mosaicism without severe dysmorphic findings but with cryptogenic cirrhosis and membranous glomerulonephritis (MGN).

Case Report

A seven-year-old boy was referred to our hospital with hepatomegaly which was found on routine physical examination. He was born following a full-term pregnancy, as the fourth child of a 33-year-old mother and 38-year-old father. Parents were

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first degree cousins. There was no family history of spontaneous abortions, congenital malformations, mental retardation, cirrhosis or nephrotic syndrome.

On admission, his blood pressure was 150-100 mmHg. He had flat occiput, short palpebral fissures, low set ears, bilateral simian lines, short thumbs and grade III/VI systolic ejection murmur on the left parasternal area (Figs. 1, 2). His liver was palpable 4 cm under the costal margin in the mildclavicular line and 5 cm under xiphoid, with moderate ascites, and a 3+ pedal edema was present.

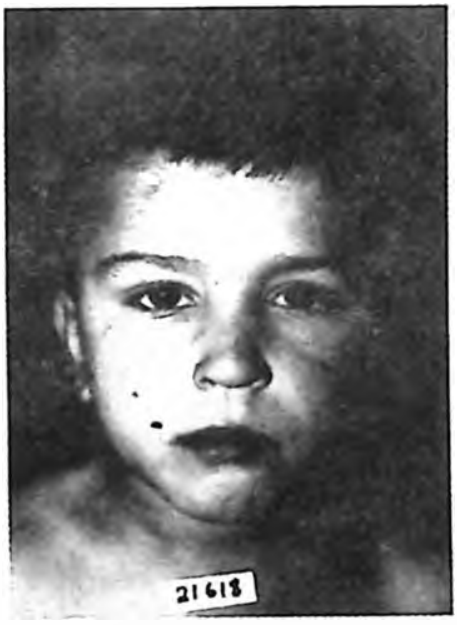

Fig. 1: Note the short palpebral fissures and low set ears of the patient.

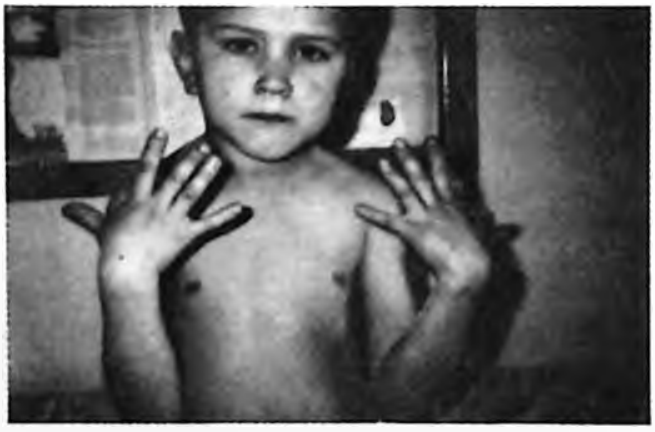

Fig. 2: Note the short thumbs of the patient.

Laboratory findings were as follows: 4+ proteinuria (150 mg/m^2/hour), microscopic hematuria with no pyuria, creatinine clearance 76 ml/min/1.73m^2, total serum protein 5.7 g/dl, serum albumin 2.2 g/dl, alanine aminotransferase (ALT) 55 IU/L, aspartate aminotransferase (AST) 87 IU/L and alkaline phosphatase 247 IU/L. An

abdominal ultrasonography study revealed parenchymal disease of liver and kidney. The following laboratory examinations were normal: serum ceruloplasmin, serum copper, sweat chloride test, serum and urinary amino acids, alpha-1-antitrypsin, antistreptolysin O titer, C-reactive protein, serum complements (C3, C4), circulating immune complex, serum immunoglobulins, cryoglobulins, antinuclear antibodies (ANA), anti-doublestranded deoxyribonucleic acid (anti-ds DNA) and myeloperoxidase-antineutrophil cytoplasmic antibodies (MPO-ANCA). His hepatitis markers (HBs, Anti HBs, HCV Ab, anti HAV) were negative and remained negative during the two year follow-up period.

His liver biopsy was reported as cirrihosis. A needle kidney biopsy was performed and found to be membranous glomerulonephritis (MGN) stage III.

Urine analysis, serum proteins and transaminases were normal in parents and siblings.

Cytogenetic studies

Peripheral venous blood samples were obtained and lymphocyte cultures were set up. For chromosome preparation the standard technique was followed. Slides were stained for Giemsa-banding and QM-banding. In these studies, 58 percent of the cells showed a normal male karyotype (46, XY), 7 percent were triploid (69, XXY) and 35 percent were tetraploid (92, XXXY) (Figs. 3-5). The karyotypes of parents

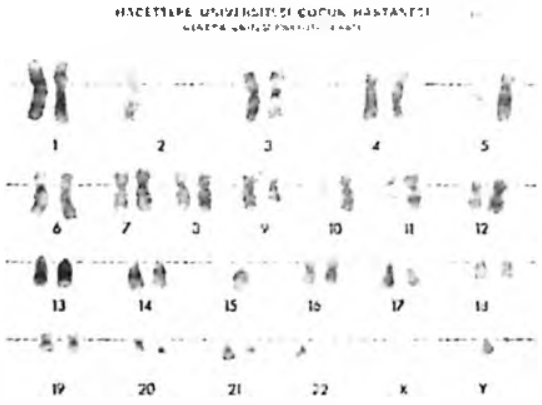

Fig. 3: A normal male karyotype (46, XY) presented in 58% of cells.

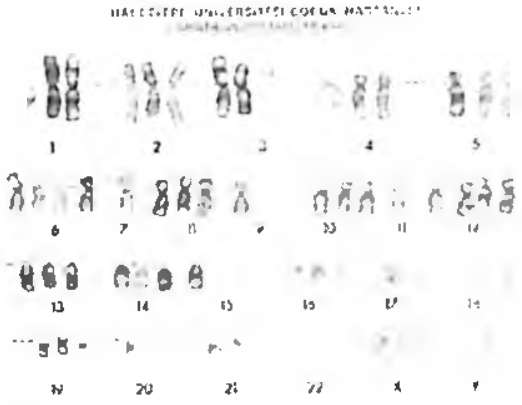

Fig. 4: A triploid karyotype (69, XXY) presented in 7% of cells.

Fig. 5: A tetraploid karyotype (92, XXXY) presented in 35% of cells.

and all three siblings were normal. DNA content in peripheral blood lymphocytes of the index patient was studied with flow cytometer, and was found to be increased to a value of 2.8 percent (normal 1%), which is compatible with mosaicism.

Discussion

Triploidy and tetraploidy frequently cause early spontaneous abortions[1,2]. Triploidy associated with molar changes of the placenta is one of the major causes for loss of triploid pregnancies. A few cases of the full triploidy without placental hydatidiform changes have survived the neonatal period but died during infancy. Prolonged postnatal survival has only been noted with diploid-triploid mixoploidy with severe dysmorphic changes[1]. Complete tetraploidy and tetraploid mosaicism appeared to be very rare (1.1%).

Cardinal findings of triploidy syndrome are characterized by syndactyly of the third and fourth fingers and severe intrauterine growth retardation[9]. In our patient, both cytogenetic and flow cytometric DNA analysis revealed the diploid-triploid-tetraploid mosaicism. Some associated features have been noticed in mosaic cases. Rojanasakul et al.[10] noted tetraploidy mosaicism in two sisters with polycystic ovary syndrome. Near triploidy, near tetraploidy and near diploidy have been reported in pediatric solid tumors and in Hodgkin's disease[11]. Kidney malformations, such as horseshoe kidney, cystic dysplasia, membranoproliferative glomerulonephritis, amyloidosis and immunotactoid glomerulonephritis may be associated with chromosomal anomalies, particularly with Down syndrome[12-14]. In complete triploidy, cystic dysplastic kidneys have been noted[15].

Our patient exhibited cryptogenic cirrhosis and MGN. Glomerular morphologic abnormalities may be seen in more than 50 percent of cirrhotic livers on necropsy or biopsy. This has been the first asociation of MGN related to cryptogenic cirrhosis with diploid, triploid and tetraploid mosaicism.

Although a coincidental relation cannot be excluded, a disturbance of the mitotic process expressed in an increased frequency of polypoidy might well have temporal pathogenetic significance. The disturbance of the mitotic process could be due to an underlying gene defect which may also predispose to cryptogenic cirrhosis and related glomerulopathy.

We think more reports of similar cases are needed to clarify the nature of the association of mixoploidy with coexisting diseases.

Acknowledgement

We thank Dr. Altan Yalçıner for his help with the flow cytometric analysis of the patient.

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BALLOON DILATION OF STENOTIC NONVALVED CONDUITS AFTER FONTAN OPERATION*

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SUMMARY: Alehan D, Çeliker A, Ceviz N. (Cardiology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Balloon dilation of stenotic nonvalved conduits after Fontan operation. Turk J Pediatr 1998; 40: 145-149.

The Fontan operation is used to supply a ventriculo-arterial connection in patients with tricuspid atresia. An important complication is the obstruction of the conduit that may necessitate reoperation. In these patients balloon dilation of the conduit stenosis has been advocated as a method to relieve the obstruction and postpone surgical replacement. While there are several reports about the balloon dilation of stenotic valved conduits, we do not have enough information about the results of balloon dilation of nonvalved conduits. We performed successful balloon dilations in two patients with tricuspid atresia who underwent the Fontan operation and had stenotic nonvalved conduits. In the first patient, the stenosis was relieved but recurred. A second balloon dilation procedure was performed, and the patient has been symptom free for one year. In the second patient, the stenosis was relieved but recurred. Our preliminary results suggest that balloon dilation is an efficient method to relieve the obstruction in stenotic nonvalved conduits and can be repeated successfully if the stenosis recurs. *Key words: balloon angioplasty, stenotic nonvalved conduits.*

At present, a definitive operation for tricuspid atresia is offered by either the Fontan or Kreutzer procedures. In the Fontan operation, a ventriculo-arterial connection is supplied by either a valved conduit between the right atrium (RA) and pulmonary trunk, connection of the RA to right ventricle (RV) with a conduit, or by direct anastomosis of the right atrial appendage to the RV. Complications of these procedures in the intermediate and long-term include interatrial and interventricular shunts and conduit obstruction due to "peel" or thrombosis. These complications may necessitate reoperation[1] which is more traumatic, increases hospital stay, and possibly has a higher mortality. Balloon dilation of the conduit stenosis has been advocated as a method to relieve the obstruction and postpone surgical replacement[2]. To contribute to the data about the benefit of balloon dilation of stenotic conduits, we report our short-term experience with balloon dilation of nonvalved stenotic conduits between the RA and the pulmonary artery (PA) in one patient and between the RA and RV in another patient, both of whom underwent the Fontan operation due to tricuspid atresia.

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Case Reports

Case 1

A two-month-old boy was referred to the Pediatric Cardiology Unit of Hacettepe University for evaluation of cyanosis, and was diagnosed as having tricuspid atresia, atrial septal defect (ASD) and ventricular septal defect (VSD). A left Blalock-Taussig shunt operation was performed at 32 months of age. Five years later, he underwent a modified Fontan operation and a nonvalved conduit was placed between the right atrial auricula and the in fundibulum of the RV. In addition, the ASD and VSD were closed.

Four years after the operation, the patient was admitted to the hospital with massive ascites, hepatomegaly and edema due to right-sided heart failure. On cardiac catheterization, mean right atrial pressure was measured as 17 mm Hg, and mean pulmonary artery pressure as 10 mm Hg. Pressure gradient between the proximal and distal parts of the conduit was 7 mmHg. Cineangiocardiography revealed stenosis of the distal part of the conduit.

To carry out a percutaneous balloon angioplasty, a 7F endhole catheter was passed to the main pulmonary artery through the stenotic conduit, and then a 0.035 inch flexible wire was advanced across the conduit into the right PA. The endhole catheter was removed, leaving the wire in place. A 10 mm angioplasty balloon catheter was advanced over the wire for two inflations of 20 sec to a maximum pressure of 12 atmospheres. Two further inflations with a 12 mm balloon were carried out. During the first angioplasty procedure disappearance of the indentation was observed. Following the inflations, mean right atrial pressure was measured as 11 mm Hg, mean pumonary artery pressure as 8 mm Hg, and the pressure gradient as 3 mm Hg. Two days later, symptoms of right heart failure disappeared and the patient was discharged. Two months after the balloon angioplasty, the patient was admitted to the hospital with recurring symptoms of right heart failure. Echocardiographic study demonstrated a pressure gradient of 16 mm Hg across the conduit. A second balloon angioplasty procedure, similar to the first one, was performed. After the second balloon angioplasty procedure, symptoms of right heart failure disappeared, and have not recurred during a follow-up period of one year. Control echocardiographic studies revealed no evidence of stenosis across the conduit.

Case 2

A nine-month-old boy was admitted to the hospital with cyanosis-tricuspid atresia, hypoplastic right ventricle, ASD and VSD were detected on echocardiographic study. The diagnosis was confirmed by cardiac catheterization. Four years after the first admission, a left-modified Blalock-Taussig shunt operation was carried

out. When the patient was 8.5 years old, he underwent a Fontan operation and a dacron graft was implanted between the right atrial appendix and main pulmonary artery. Five months later, the patient was admitted to the hospital with signs and symptoms of right-sided heart failure. Cardiac catheterization revealed a mean right atrial pressure of 21 mm Hg, mean pulmonary artery pressure of 10 mm Hg, and a pressure gradient of 11 mm Hg. Cineangiocardiography demonstrated stenosis of the distal part of the conduit (Fig. 1). Similar to the procedure carried out in Case 1, a balloon angioplasty was performed with three inflations of 20 seconds to a maximum perssure of 12 atmospheres by using a 9 mm angioplasty balloon catheter. An indentation which had been observed at the beginning of the inflation (Fig. 2a), disappeared during the angioplasty (Fig. 2b). After the procedure, the diameter of the stenosis increased from 3.6 mm to 5.3 mm

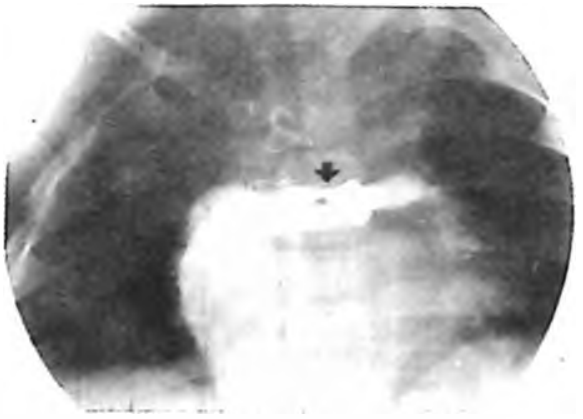
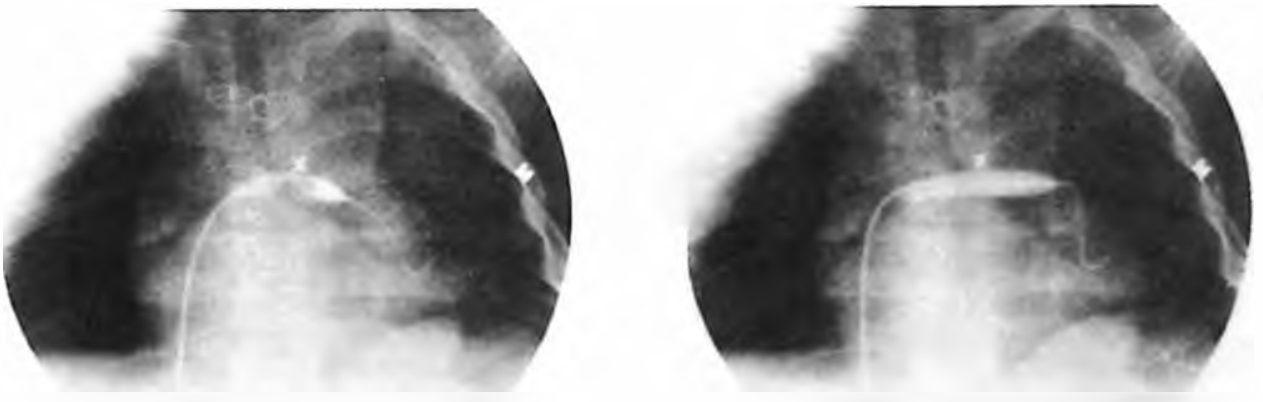


Fig. 1: Right atrial angiogram in the postero-anterior projection showing severe stenosis at the distal part of the conduit (arrow).



2a 2b

Fig. 2a: Postero-anterior view showing indentation at the stenotic part of the conduit (x). . 2b: After full inflation, indentation disappeared due to enlargement of the stenotic area.

(Fig. 3). The mean right atrial pressure was measured as 15 mm Hg and the mean pulmonary artery pressure as 12 mm Hg. Pressure gradient between the right atrium and pulmonary artery decreased from 11 mm Hg to 3 mm Hg. On the Fourth day following the angioplasty, the patient was free of the symptoms of right heart failure, and was discharged. However, three months after the balloon dilation valvuloplasty, he was admitted to the hospital with recurring symptoms of right heart failure and is now awaiting stent implantation.

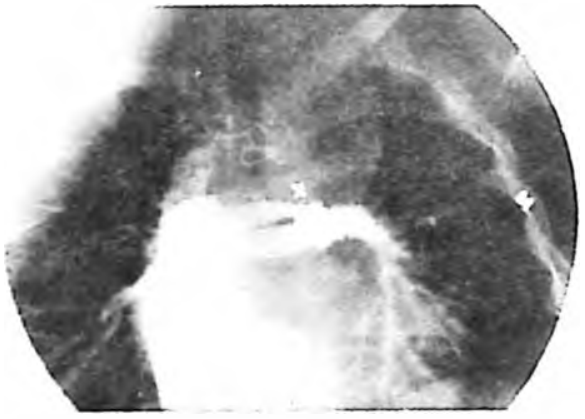


Fig. 3: The postdilation angiogram demonstrating apparent enlargement of the stenotic area.

Discussion

The extracardiac conduit operation has permitted surgical correction of a number of congenital heart diseases, but the development of progressive conduit calcification and stenosis remains a serious and nearly universal late complication[1,3]. It has been reported that the actuarial freedom from conduit replacement of the valved conduits is 81 percent at five years, 61 at seven years and 0 percent at 10 years, and that patients with nonvalved conduits are 100 percent reoperation free at four years[4]. Surgical conduit replacement can be performed at low risk[5,6], but the number of surgical conduit replacements a patient can tolerate is not unlimited. Thus, by prolonging the viable lifespan of each conduit, we may be able to extend the patient's survival. Postponement of conduit replacement is particularly advantageous in the youngest children because the increased growth between operations should aid the surgeon in placing an optimum-sized conduit without intrathoracic compression[3]. Balloon dilation angioplasty seems to be a useful procedure to postpone the need for surgical conduit replacement in patients with stenotic conduits.

Partial and transient relief of conduit obstruction by balloon dilatilon has been reported by several authors[2,3,7]. Lloyd et al.[3] reported successful balloon dilation valvuloplasty in three of six patients with stenotic valved conduits between the right ventricle and pulmonary artery. Long-term follow up results of these three

patients were not given in the paper. Sohn et al.[2] reported their experience with balloon dilation of stenotic valved conduits between the right ventricle and pulmonary artery in five patients, of valved homograft in the aortic valve position in one patient, and of non-valved conduit between the right atrium andpulmonary artery in one patient. Zeevi et al.[7] reported successful balloon dilation in three of nine patilents who had stenotic bioprosthetic valved conduits between the pulmonary ventricle and pulmonary artery. One of these three patients underwent conduit replacement less than one year after the procedure with the exception of one patient reported by Sohn et al.[7], in all these reports, balloon dilation angioplasty had been performed on valved conduits. To our knowledge, our patients are the second and third with nonvalved conduits to undergo balloon dilation. In stenotic valved conduits, balloon dilation is reported to be only partially and transiently successful, because of some limitations[2,3]. However, there is not enough data about the balloon dilation of nonvalved conduits. Sohn et al.[2] reported the only case who had a stenotic nonvalved conduit between the right atrium and pulmonary artery and underwent a balloon dilation. In this patient, a stent was implanted 19 months after the balloon dilation because of restenosis, and a repeated balloon dilation was not carried out[2]. In our first case however, a second successful balloon dilation procedure was performed, which resulted in an acceptable pressure gradient. The patient is still symptom free one year after the second dilation.

Although this is a very preliminary experience, our study suggests that in patients with nonvalved stenotic conduits, balloon dilation is a safe and feasible option for palliation of stenosis. If stenosis recurs, repeated balloon dilations may be performed to postpone the conduit replacement either to provide time for the patient's growth or to prolong the viable lifespan of each conduit.

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