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CONTENTS

The molecular basis of hypertension

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SUMMARY: Toka HR. The molecular basis of hypertension. Turk J Pediatr 2002; 44: 183-193.

Hypertension is a substantial public health problem affecting about 25% of the population in industrialized societies. The disorder is responsible for many common causes of morbidity and mortality. Despite the important role of hypertension as a cause of disease, its pathogenesis remains largely unknown. The application of genetic approaches to rare monogenic (Mendelian) forms of hypertension and hypotension has begun to delineate molecular pathways underlying human blood pressure variation, defining disease pathogenesis and identifying targets for therapeutic intervention. In all cases the pathophysiology is altered net renal salt reabsorption. Mutations are either affecting circulating mineralocorticoid hormones or renal ion channels and transporters. Examples are glucocorticoid-remediable aldosteronism (GRA), Liddle's syndrome, the syndrome of hypertension exacerbated in pregnancy, and apparent mineralocorticoid-excess (AME). Recently, alterations in genes of a novel serine-threonine kinase family (WNK1 and WNK4) were identified causing pseudohypoaldosteronism type II. The molecular pathway of this syndrome remains unclear. Additionally, there is the syndrome of hypertension associated with brachydactyly type E (Bilginturan's syndrome), for which the molecular mechanism has yet to be identified.

Key words: hypertension, molecular basis.

Hypertension is a substantial public health problem affecting 25% of the adult population in industrialized societies[1]. It is a major risk factor for many causes of morbidity and mortality in the general population, including stroke, myocardial infarction, congestive heart failure and end-stage renal disease[2]. Despite the important role of hypertension as a cause of disease, its pathogenesis remains largely unknown. From extensive investigations over the last decades it is known that hypertension has a multifactorial determination. These factors include demographic, dietary and genetic factors. Known demographic factors are age, gender and body mass[3]. Dietary factors include e.g. salt, potassium and calcium intake[4]. The influence of genetic factors are known from twin studies[5] and studies of biological versus adopted siblings[6]. Monozygotic twins show greater concordance of blood pressure than dizygotic twins, and biological siblings show higher similarity of blood pressure values than adopted siblings[7].

The identification of genes underlying hypertension has the capacity to define primary physiologic mechanisms and thereby clarify disease mechanisms and pathways. Different approaches have been made to study the genetics of hypertension. One of these approaches is the investigation of Mendelian (monogenic) forms of blood pressure variation, where single genes have a large effect on blood pressure[8]. The most progress in the research of the molecular mechanisms of hypertension has been made by investigations in monogenic forms of blood pressure variation. Mutations in 19 genes have been identified as causing abnormal blood pressure variation. Mutations in 10 genes cause monogenic forms of hypertension and mutations in 9 genes cause monogenic forms of hypotension. Numerous disease mechanisms have been defined[9].

In the following report, six syndromes are reviewed. The molecular mechanisms of the first four syndromes have been defined. The genetic alterations in glucocorticoid-remediable

aldosteronism, Liddle's syndrome, hypertension in pregnancy and apparent mineralocorticoid-excess cause increased renal salt and volume reabsorption resulting in hypertension[9]. The mechanism of pseudohypoaldosteronism type II remains unclear, although alterations in two genes of a novel serine-threonine kinase family (WNK1 and WNK4) have been recently identified[10]. The gene(s) responsible for Bilginturan's syndrome has been mapped to chromosome 12p[11], but has yet to be identified.

Glucocorticoid-remediable aldosteronism (GRA)

Patients with glucocorticoid-remediable aldosteronism have an autosomal dominant hypertension and are usually suspected of having primary aldosteronism. They have a volume expansion and a salt-sensitive form of hypertension, tend to metabolic alkalosis with hypokalemia, and respond to both thiazide diuretics and spironolactone. The latter fact suggested that mineralocorticoid products may be involved. Patient renin values are low while the aldosterone values can be elevated (Table I). They also have 18-hydroxy- and 18- oxocortisol, steroids not normally found in urine. Recognizing these abnormal products led to solving the mystery. Prednisone replacement ameliorates the hypertension, causes the abnormal steroids to disappear, and gives the syndrome its name. The abnormal cortisol derivatives and the favorable effects of glucocorticoid treatment suggested that the zona fasciculata, which express the gene for 17 β-hydroxylase (CYP17) and is ACTH-responsive, was the source of the excess mineralocorticoids. Two distinct gene poroducts, 11-β-hydroxylase (CYP11B1) and aldosterone synthase (CYP11B2), perform the terminal steps in glucocorticoid and mineralocorticoid biosynthesis, respectively. A linkage analysis in a large pedigree localized the responsible gene to chromosome 8q, exactly at the site where the genes for 11 β-hydroxylase and aldosterone synthase also reside[12]. In affected individuals, a chimeric gene consisting of the promotor-regulatory region of 11-β-hydroxylase and the structural portion of aldosterone synthase is located between CYP11B1 and CYP11B2. The chimeric gene results from a meiotic mismatch and unequal crossing over (Fig. 1). The protein product performs all reactions required for aldosterone production: however, the protein is

Table I. Monogenic (Mendelian) forms of hypertension are compared regarding potassium (K^+), pH, renin, aldosterone (Aldo), specific treatment, gene loci and gene. In contrast to the other syndromes, the hypertension and brachydactyly syndrome (HBS) is not salt-sensitive and features normal (N) values for the shown parameters

Syndrome	K^+	pH	Renin	Aldo	Treatment	Loci	Gene
GRA	↓	↑	↓	↑	Spironolactone, Amiloride	8q	Chimeric gene (CYP11B1/ CYP11B2)
Liddle's syndrome	↓	↑	↓	↓	Amiloride	16p	β and γ subunit of ENaC
AME	↓	↑	↓	↓	Spironolactone, Amiloride	16q	11-β-HSD
MR	↓	↑	↓	↓	None, multiple drug therapy	4q	MR
PHA type II	↑	↓	↓	↓	Hydrochloro-thiazide	12p 17q 1q	WNK1 WNK4 ?
HBS	N	N	N (↓)	N	None, multiple drug therapy	12p	?

GRA: glucocorticoid-remediable aldosteronism; AME: apparent mineralocorticoid-excess; MA: mineralocorticoid receptor; PHA II: pseudohypoaldosteronism type II.

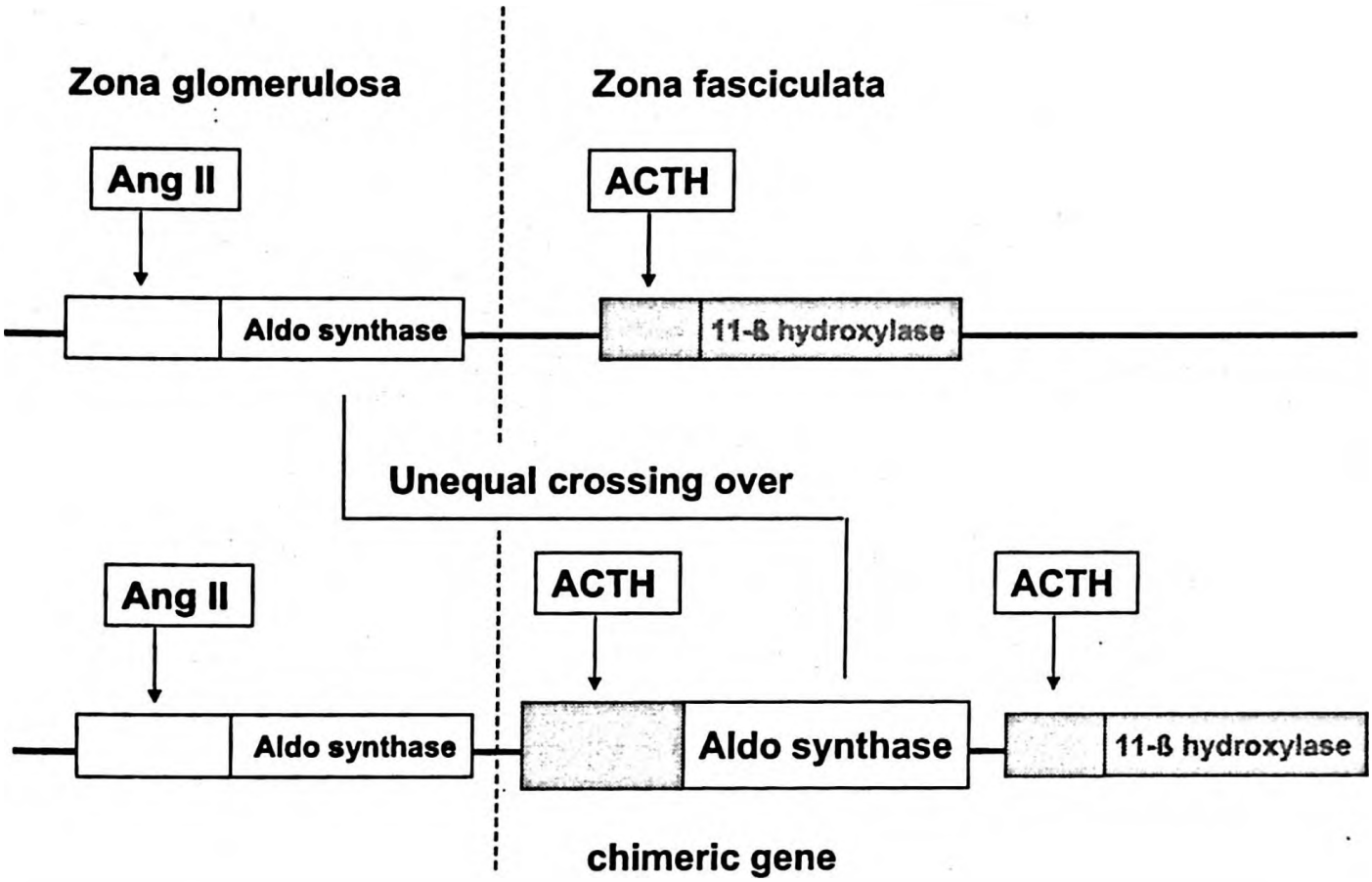

Fig. 1. A chimeric gene is formed by meiotic mismatch and unequal crossing over with the promoter region of the 11-β-hydroxylase gene (dark box) and the coding region of the aldosterone synthase gene (white box). As a result, the aldosterone synthase gene is under control of ACTH in the zona fasciculata. Ang II = angiotension II; aldo: aldosterone; ACTH: adrenocorticotropic hormone.

ACTH rather than angiotensin II-dependent. Ectopic expression of this protein in the zone fasciculata permits the formation of 18-hydroxy- and 18-oxocortisol, the biochemical hallmarks of GRA. Finally, suppressing steroid genesis in the zona fasciculata with exogenous glucocorticoids alleviates the hypertension.

Liddle's syndrome

Grant Liddle described patients with autosomal dominant monogenic hypertension who also tended to have metabolic alkalosis with hypokalemia. His patients had low renin and low aldosterone values, and did not respond to spironolactone, while thiazides and triamterene reduced the blood pressure (Table I). This observation suggested that they probably did not have a form of mineralocorticoid excess. Liddle speculated that they would show a distal tubular defect of enhanced sodium and chloride reabsorption. A renal transplant performed on a patient with Liddle's syndrome who developed renal failure cured the disease, providing strong evidence that the problem resided within the kidneys rather than in a regulatory system[13]. Shimkets et al.[14] subsequently localized the responsible gene of a family with Liddle's syndrome to chromosome 16p, and were able to show that the gene encodes for the β-subunit of the epithelial sodium channel (ENaC). The channel is amiloride-and triamterene-sensitive, explaining the efficacy of these drugs in the syndrome. The channel remains inappropriately permeable even in the face of high salt intake, thereby explaining the salt-sensitive hypertension. Subsequently, a mutation in the γ-subunit of ENaC has been found, which can also result in Liddle's syndrome[15]. The molecular mechanisms of Liddle's syndrome involve missense mutations or deletions in the cytoplasmic tails of β- or γ-subunits of ENaC. As a consequence, the channels are not internalized (clathrin-coated pits pathway) or degraded (ubiquitination by WW domain containing proteins), and instead remain activated on the cell surface[16]. Figure 2 shows a schematic illustration of ENaC removal from the cell surface.

Apparent mineralocorticoid-excess (AME)

Apparent mineralocorticoid-excess resembles the syndrome observed in persons ingesting large amounts of licorice. Licorice gluttony and treatment with carbenoxolone both cause a volume expansion, low renin, low aldosterone and a salt-sensitive form of hypertension, which may also feature metabolic alkalosis and hypokalemia. Interestingly, the hypertension responds to both thiazide and spironolactone, but no abnormal steroid products are present in the urine. Both licorice and carbenoxolone contain glycyrrhetinic acid, which was found to inhibit the enzyme 11-β-hydroxysteroid dehydrogenase (11-β-HSD). 11-β-hydroxysteroid dehydrogenase is responsible for converting cortisol to cortisone (Fig. 3). In the distal renal tubule, this step is crucial for protecting the mineralocorticoid receptor, which has the same affinity for cortisol as it does for aldosterone. This step protects us all from developing AME. Inhibition of 11-β-HSD results in AME. Interestingly, AME may also occur as a rare, autosomal recessive form of hypertension. Needless to say, the 11-β-HSD gene, which has a renal-specific isoform, was a good candidate gene for this condition.

The clinical clues helful in resolving this condition were: volume dependent salt-sensitive hypertension, tendency to hypokalemia and metabolic alkalosis, low renin and low aldosterone values, responsiveness to both thiazides and spironolactone despite absence of aldosterone or any abnormal mineralocorticoid products, and resemblance to licorice gluttony (Table I). Mune et al.[17] solved the mystery. In eight of nine families, mutations in the renal-specific isoform gene for 11-β-HSD were found,

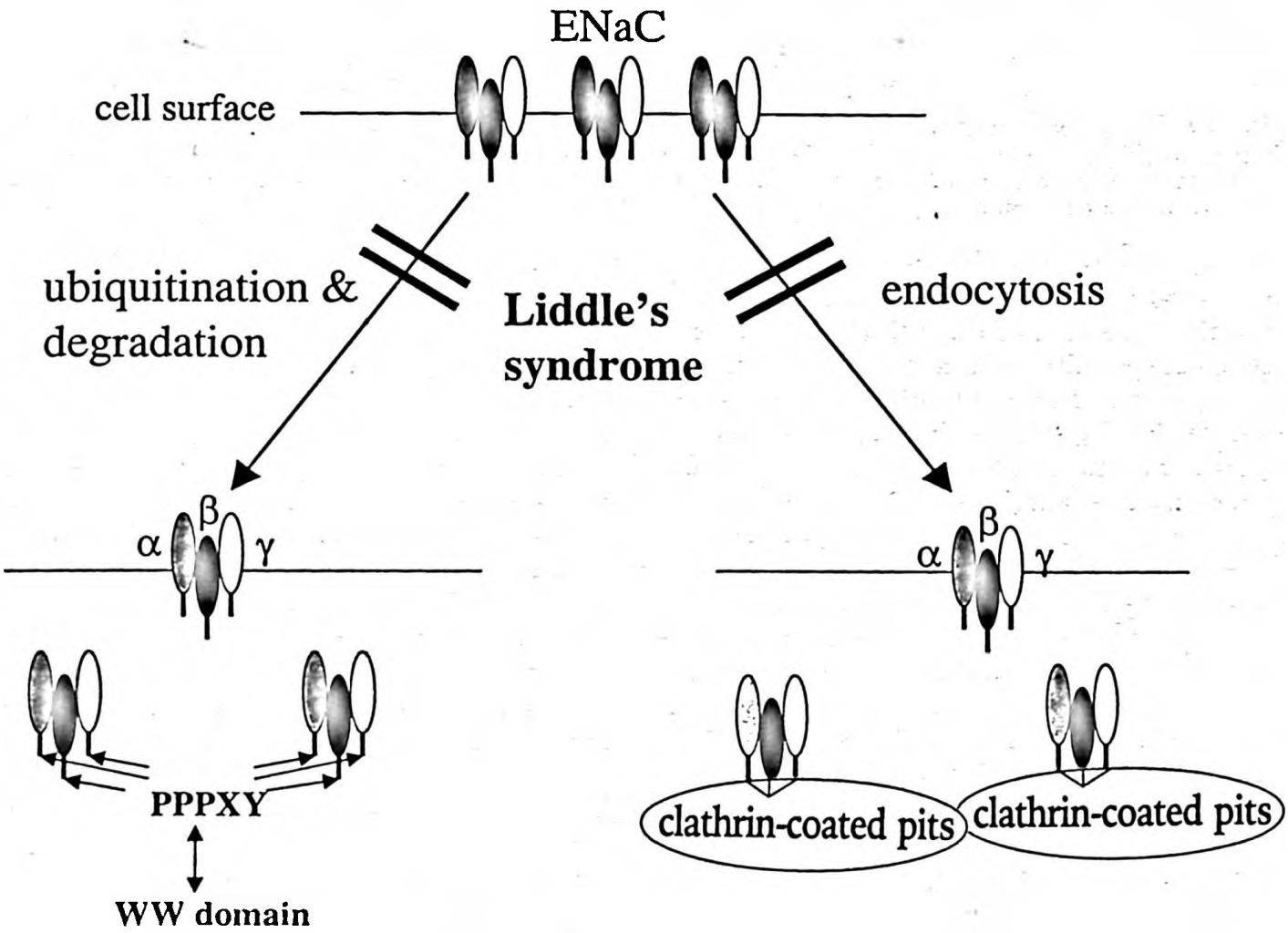

Fig. 2. Two pathways are shown for the removal of the epithelial sodium channel ENaC from the cell surface. One pathway is endocytosis by clathrin-coated pits. The other one is ubiquitination and degradation by WW-domain containing proteins specifically interacting with an amino acid sequence at the C-termini of the α-, β- and γ-subunits of ENaC. This amino acid sequence is called PY motif (PPPXY). In Liddle's syndrome missense mutations in the PY motif or deletions of the C-termini of the β- or γ-subunits cause Liddle's syndrome, inhibiting both pathways.

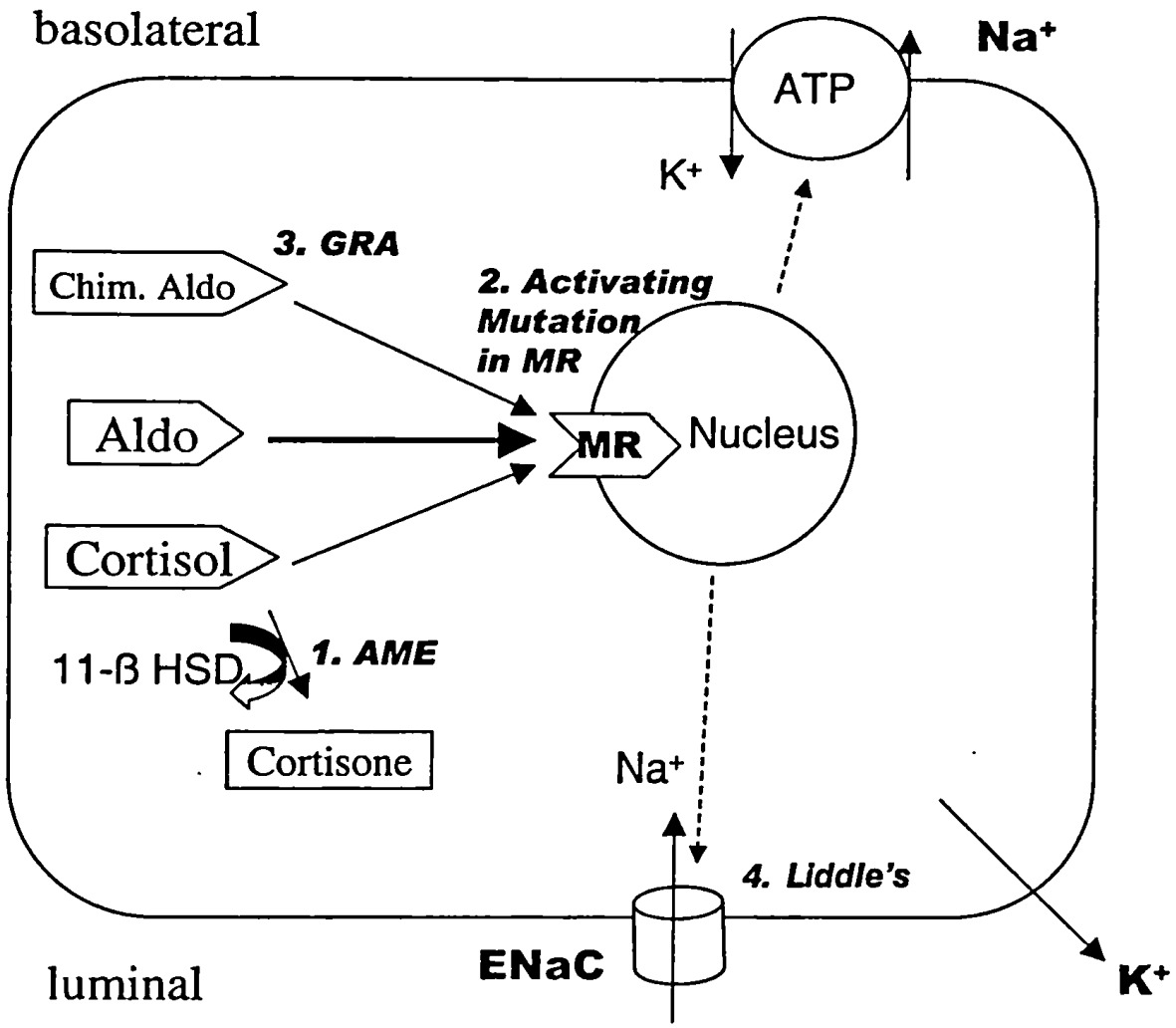

Fig. 3. A schematic illustration of a cortical collecting duct cell is shown. The mineralocorticoid receptor (MR) has the same affinity for cortisol as for aldosterone (aldo). The enzyme 11-β-hydroxysteroid dehydrogenase (11-β-HSD) "protects" the MR by metabolizing cortisol to cortisone, which has no affinity. A mutated or an inhibited enzyme results in an intracellular concentration of cortisol and an increased activation of the MR (1). Molecular mechanisms of the other syndromes are also shown. A mutated MR can result in an altered configuration and activation by steroids lacking a 21-hydroxyl group (2). A chimeric gene product (chim. aldo) in GRA causes an Ang II-independent activation of the MR (3). The increased MR activity causes enhanced Na^+ reabsorption (ENaC, Na-K-ATPase) and K^+ excretion. An increased presence and activity of ENaC at the cell surface in Liddle's syndrome has the same effect (4). GRA: glucocorticoid-remediable aldosteronism; AME: apparent mineralocorticoid-excess.

which indeed rendered the product incapable of converting cortisol to cortisone. Thus, the mineralocorticoid receptor is unprotected from cortisol in these patients and cortisol functions to occupy the mineralocorticoid receptor.

Activating mutations in the mineralocorticoid receptor (hypertension in pregnancy)

Geller et al.[18] recently presented a new Mendelian form of hypertension caused by an activating mutation in the mineralocorticoid receptor. The investigators screened for mutations in the mineralocorticoid receptor in seven unrelated patients referred for possible monogenic hypertension with the single-strand conformation polymorphism (SSCP) technique. One patient had a heterozygous mutation at codon 810 in the mineralocorticoid receptor gene, resulting in a leucine for serine substitution. This residue lies in the hormone-binding domain. The index case had severe hypertension, as did four relatives. Four other relatives had no hypertension. Affected persons all exhibited the leucine for serine substitutions, had low plasma renin activities, and low aldosterone concentrations. Since the phenotype resembles Liddle's syndrome (Table I), the investigators ruled out the presence of ENaC mutations. The authors speculate that the mineralocorticoid receptor gene mutation is an activating mutation in the receptor.

Interestingly, affected women exhibit a worsening of hypertension during pregnancy, suggesting that progesterone occupancy of the receptor results in activation rather than inhibition of aldosterone-like effects (Fig. 4). Similarly, spironolactone makes the blood pressure elevation worse, rather than better.

Geller et al.[18] were successful in elucidating the mechanism of the mutation. Their work is a good example of a successful cooperation between molecular genetics and structural proteomics. The MR-S810L mutation allows mineralocorticoid receptor activation by steroids lacking 21-hydroxyl groups. The L810 residue in helix 5 of the ligand-binding domain makes a new van der Waals interaction with alanine (A) at position 773 in helix 3. This interaction eliminates the requirement for the 21-hydroxyl group of aldosterone to interact with asparagine (N) at position 770 in helix 3. The modification explains why compounds that are normally antagonists now are agonists for the receptor.

Pseudohypoaldosteronism type II (PHA II)

PHA II features familial hypertension with hyperkalemia, normal glomerular filtration rate, suppressed plasma renin activity, normal or elevated aldosterone levels and metabolic acidosis[19]. Thiazide diuretics are highly effective in this syndrome, commensurate with salt sensitivity (Table I). The hypertension is chloride-dependent because exchange of sodium bicarbonate or sodium citrate infusion for sodium chloride improves blood pressure[20]. PHA II is a heterogeneous disease. Three gene loci were mapped to the chromosomes 1q, 12p and 17[21,22]. Two genes in which alterations cause PHA II have been recently identified. WNK1 (#12p) an WNK4 (#17q) belong to a novel serine-threonine kinase family in which lysine (K) in the catalytic domain is substituted by cysteine (with no lysine = WNK)[23].

Wilson et al.[10] identified large intronic deletions in intron 1 of WNK1 in two families (Fig. 5A).

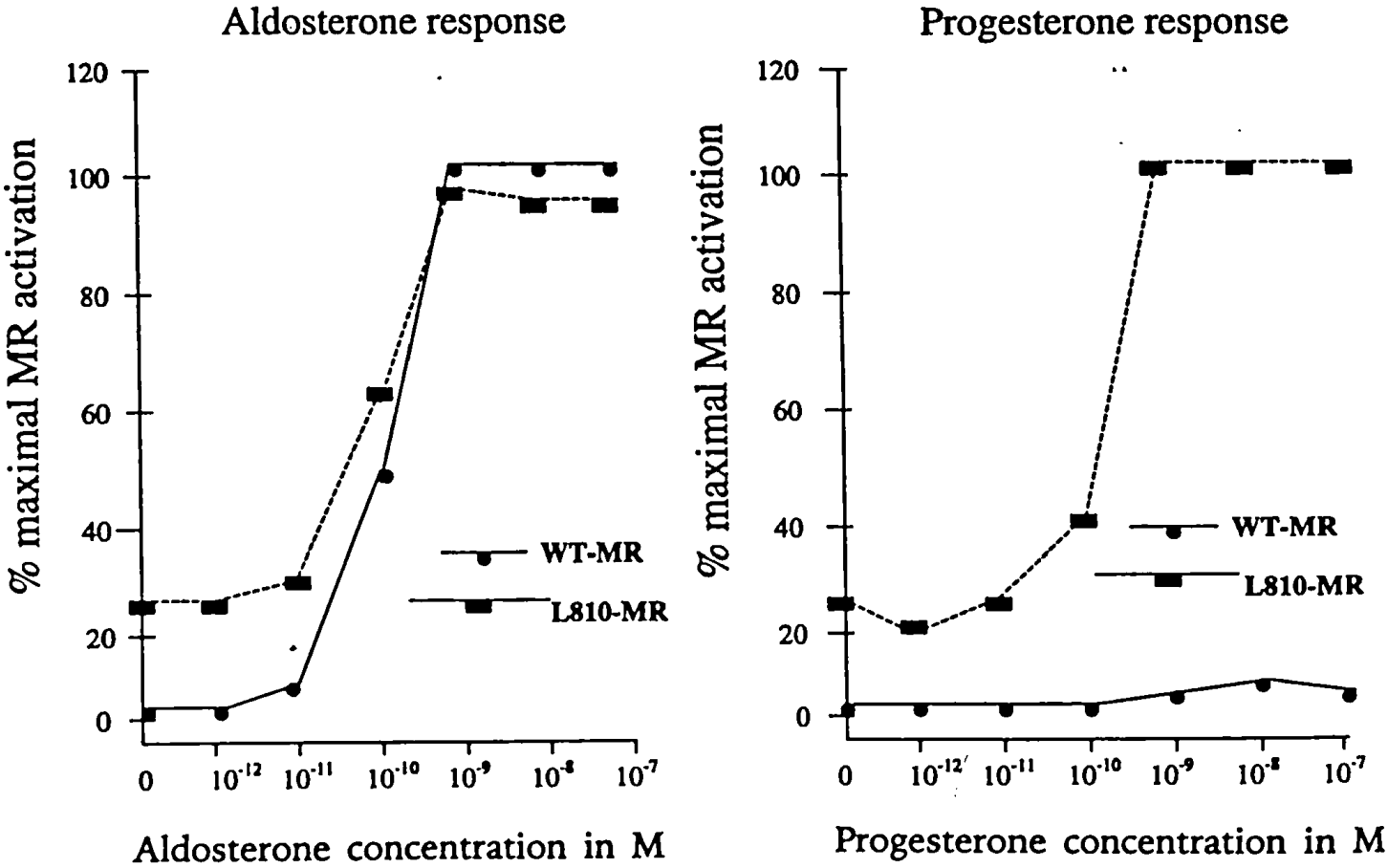

Fig. 4. Dose-response curves of the mutant MR and ML810S versus wildtype (WT) MR are shown. Activation of the MR was measured by induction of luciferase. The mutant MR shows a constitutive activation without stimulation. Otherwise, the response to increasing concentrations of aldosterone is similar to the WT MR. The WT MR shows no activation with progesterone lacking the 21-hydroxy group. The mutant MR ML810S is activated by progesterone with no difference to aldosterone response. MR: mineralocorticoid receptor.

Quantitative RT-PCR from blood leukocytes showed some evidence for gain-of-function mechanism. Patients showed a five-fold increased expression compared to intrafamilial controls (Fig. 5B). A 10 kilobase transcript is highly expressed in the kidney. Immunohistochemistry reveals that WNK1 localizes to the distal convoluted tubule (DCT) and cortical collecting duct (CCD) in the distal nephron of the kidney, and is expressed throughout the cytoplasm.

Missense mutations in WNK4 were identified in four families. The charge-changing mutations cluster in a span of four amino acids which are highly conserved among the WNK family. WNK4 is smaller than WNK1 (16 versus 156 kilobases) and shares 76% identity with WNK1 in the kinase domain and first coil-domain. WNK4 is exclusively expressed in the kidney, in intercellular junctions in the DCT and CCD, and is part of the tight junction complex.

The mechanism of these alterations in the kinases causing PHA II is unclear. The authors speculate that the action of the altered kinases increases paracellular chloride conductance in the CCD, thereby increase salt reabsorption and vascular volume, while concomitantly dissipating the electrical gradient and diminishing potassium and proton secretion[10].

Bilginturan's syndrome

Bilginturan et al.[24] described in 1974 a family with autosomal dominant hypertension associated with type E brachydactyly (Fig. 6). Affected family members had a dramatic increase in blood pressure with age and died before the age of 50 years by multiple strokes. The Turkish kindred were re-examined in 1994[25]. The hypertension can be easily distinguished from other monogenic hypertensive syndromes described thus far. The patients are not salt-sensitive and have normal renin, angiotensin, aldosterone and catecholamine responses. By measuring plasma renin activity (PRA) and plasma aldosterone in supine and upright positions, other conditions

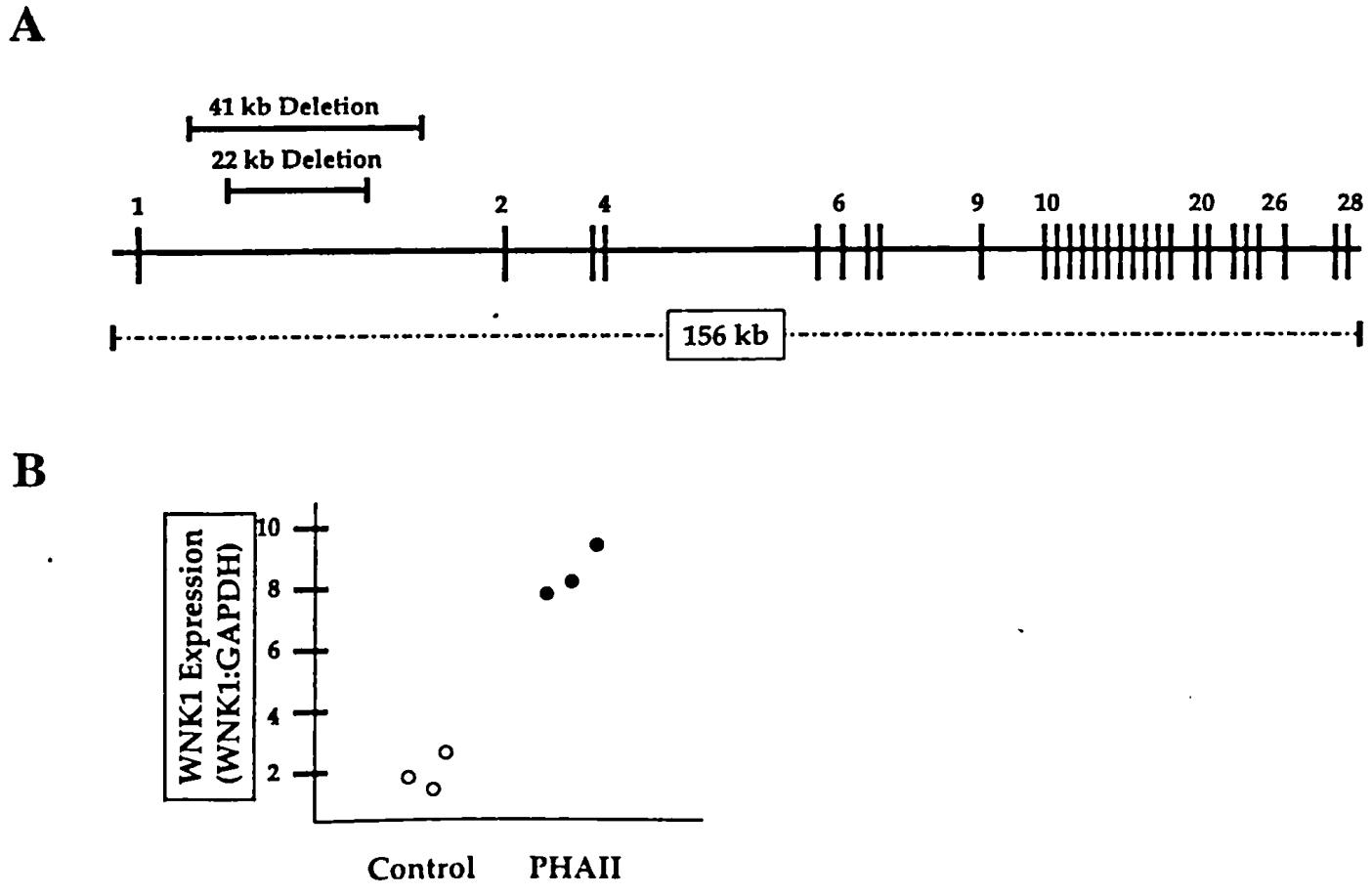

Fig. 5. (A) Genomic structure of WNK1. The intronic deletions identified in two families are located in intron 1 and are 41 or 22 kilobase respectively in size (B) RT-PCR from blood leukocytes in the 22kb deletion family shows five-fold increase in expression compared to two not affected family members and one control. PHA II: pseudohypoaldosteronism.

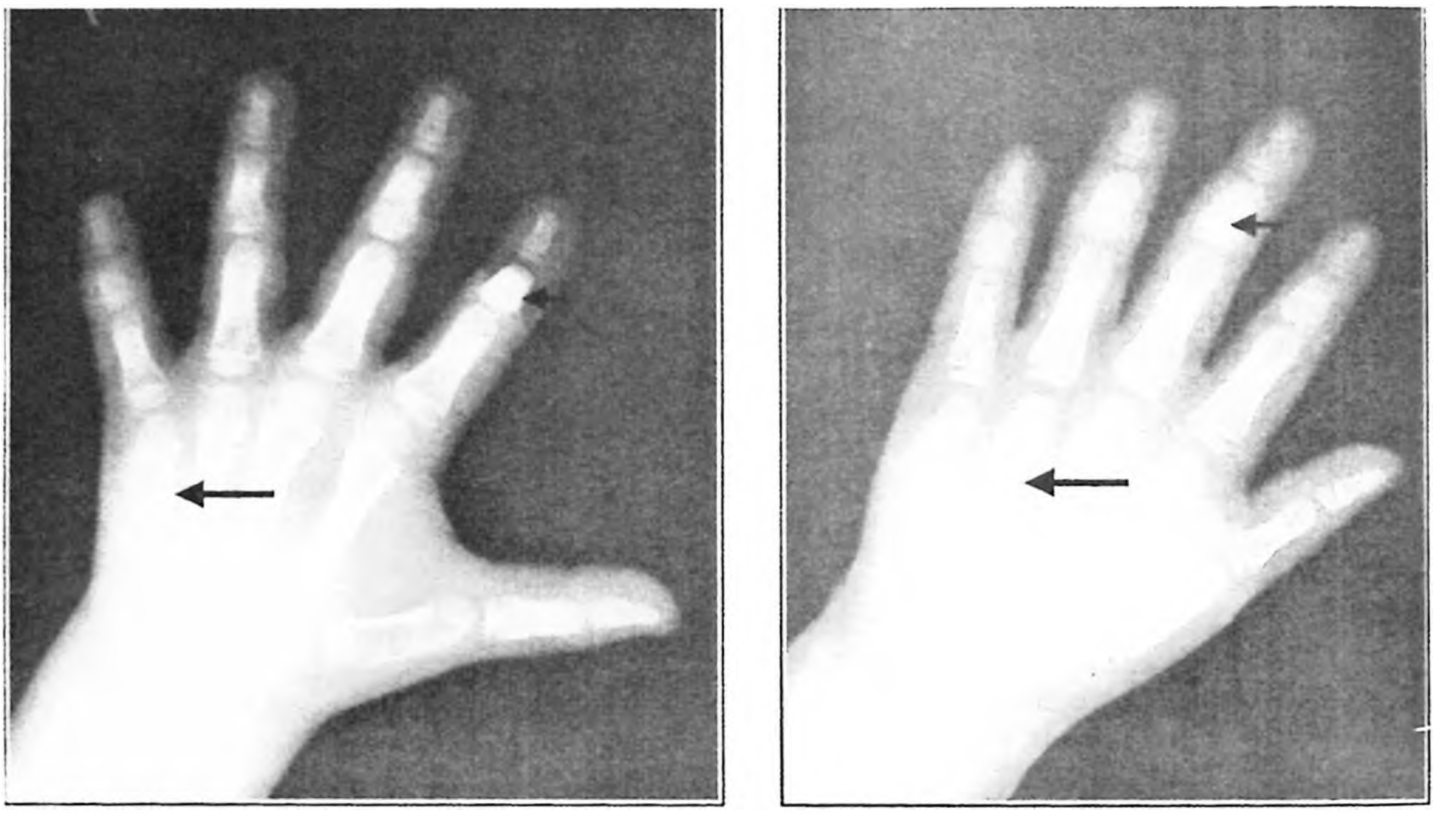

Fig. 6. Hand X-rays of a six-year-old Turkish boy and a 5 1/2-year-old Japanese boy with brachydactyly type E. The large arrows indicate the shortened metacarpal bones, which define this form of brachydactyly. The phalanges are also shortened. Additionally, cone-shaped epiphyses are present (small arrows).

can be excluded[26]. In glucocorticoid-remediable aldosteronism, PRA should be low while aldosterone concentrations are on the high normal side. In Liddle'syndrome, apparent mineralocorticoid excess, PHA II and mutations in the mineralocorticoid receptor, PRA and aldosterone levels should both be low. However, in autosomal dominant hypertension with brachydactyly, PRA and aldosterone values are normal. Table I shows the phenotypical distinction of this syndrome.

The phenotyping efforts showed that patients do not respond to any particular form of medication[27]. Beta-blocker, calcium antagonists, alpha-blocker and ACE inhibitor all improve blood pressure without significant difference. A multi-drug therapy is required for the treatment of patients.

The mechanism of the hypertension is unknown. However, an additional phenotype was discovered, which may provide a clue. Intra-operative observations[28,29], anatomical studies[30], and magnetic resonance imaging (MRI)[31] have demonstrated a posterior fossa neurovascular anomaly in patients with essential hypertension. This anomaly is believed to represent neurovascular compression (NVC) of the left ventrolateral medulla oblongata.

To test the hypothesis of whether NVC is present in patients with Bilginturan's syndrome, MRI was performed in 27 family members. All 15 affected family members had evidence for NVC. All had left sided PICA (posterior inferior cerebellar artery) or vertebral artery loops, while six had bilateral NVC. None of the nonaffected family members had NVC. These MRI data suggest NVC at the left ventrolateral medulla oblongata as an intermediate phenotype of this syndrome[32].

Based on these results, detailed autonomic testing was performed[33]. In young patients with monogenic hypertension, the hypotheses of whether or not the hypertension was mediated through sympathetic activation and of whether changes in increased sympathetic nerve traffic, vascular sensitivity, or impaired baroreflex buffering would contribute to the phenotype were tested. The average blood pressure during complete ganglionic blockade with trimethaphan was 139/83 mmHg and 90/50 mmHg in patients and controls, respectively.

However, sympathetic stimuli like cold pressor, hand-grup testing, and upright posture all increased blood pressure excessively. In contrast, muscle sympathetic nerve activity (tested by microneurography) was not increased at rest or during cold pressor test. The dose of the alpha-agonist phenylephrine that increased systolic blood pressure 12.5 mmHg was 8 μg in patients and 135 μg in control subjects before ganglionic blockade and 5 μg in patients and 13 μg in control subjects during ganglionic blockade (Fig. 7). Patients reacted with 16.9-fold increased sensitivity to phenylephrine at baseline compared to controls. During ganglionic blockade (baroreceptor reflex blocked) this difference was diminished to 2.6-fold.

These results suggest that in patients with Bilginturan's syndrome, basal blood pressure is increased independent of autonomic activity. However, sympathetic stimuli cause an excessive increase in blood pressure. Increased sympathetic nerve traffic or increased vascular sensitivity cannot explain this excessive response. A possible explanation is that the ability of the baroreflex to buffer changes in vascular tone is severely impaired. The hypertension could be related to abnormal baroreceptor reflex function.

A genome wide screen was performed to identify the responsible gene(s). The gene for Bilginturan's syndrome was mapped to the short arm of chromosome 12[34]. Additional families with the same syndrome and a chromosome 12p deletion syndrome in a Japanese child narrowed down the critical area[35,36]. The chromosomal region of interest is completely cloned and candidate genes are investigated.

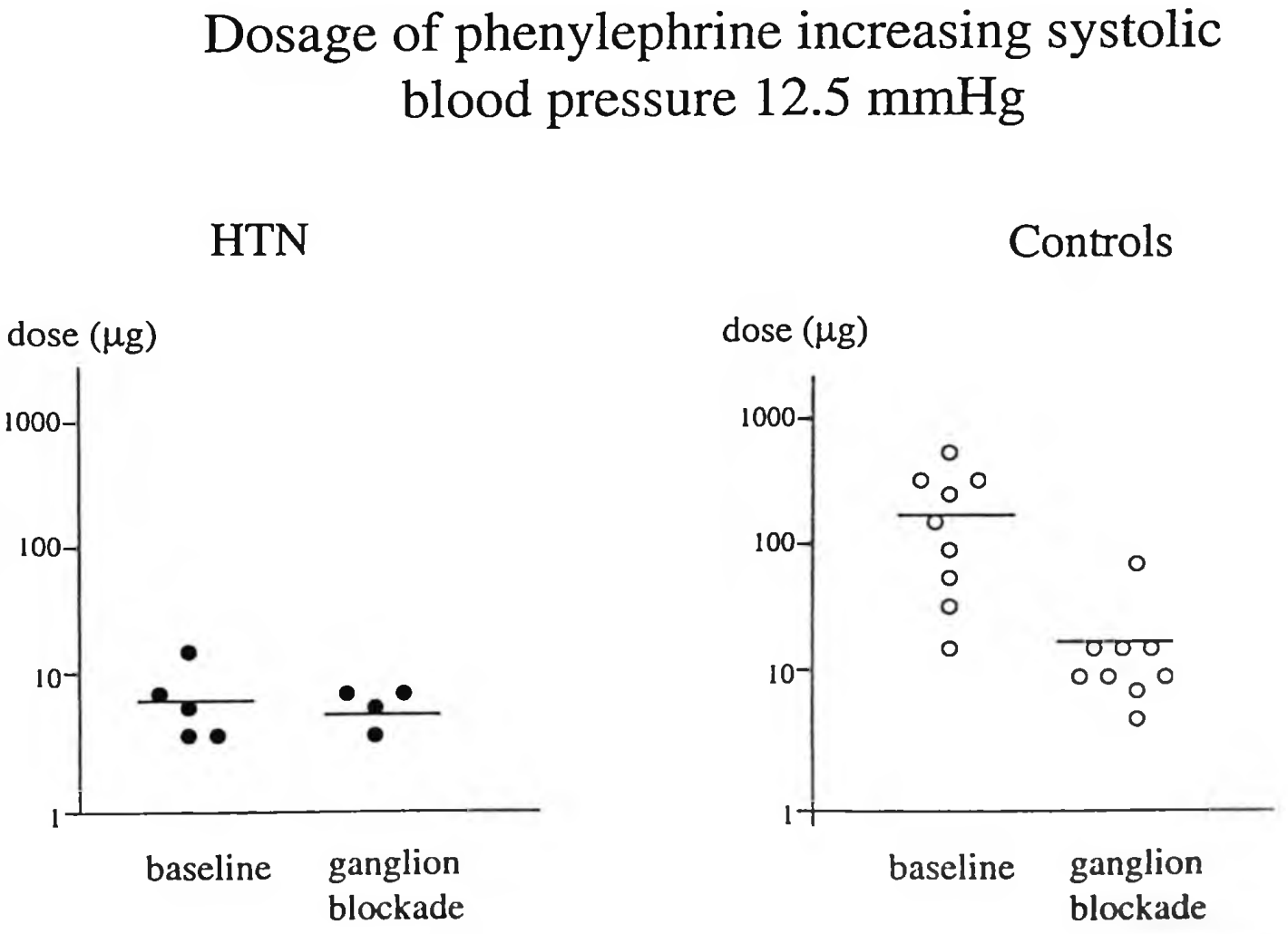

Fig. 7. Doses of phenylephrine, which increase blood pressure 12.5 mmHg before and during ganglion blockade with trimethaphan. The sensitivity to the alpha-agonist phenylephrine at baseline significantly higher (16.9-fold) in patients (HTN, black symbols) compared to controls. After interruption of the baroreflex during ganglion blockade this difference is diminished (2.6-fold).

Summary

The focus of this review was on Mendelian forms of hypertension. However, much is to be learned from Mendelian causes of hypotension. Lifton and colleagues have elucidated mutations in the ENaC alpha-subunit causing pseudohypoaldosteronism type I, three mutations involving transporters in the loop of Henle causing Bartter's syndrome, and mutations in the sodium chloride cotransporter causing Gitelman's syndrome. These conditions also speak to the issue of hypertension because they address problems in sodium handling, volume homeostasis and blood pressure regulation. Similarly, a mutation in the norepinephrine transporter has been described causing orthostatic hypotension, tachycardia, and syncope[37]. The lessons learned from these Mendelian syndromes of human blood pressure variation have been profound. They may lead us to understand the primary physiology of blood pressure regulation and disease mechanisms involved in hypertension of the general population. This progress may allow us to diagnose hypertension earlier and perhaps treat it better than we do today.

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Television Viewing and its Effect on Physical Health of Schoolage Children

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SUMMARY: Toyran M, Özmert E, Yurdakök K. Television viewing and its effect on physical health of schoolage children. Turk J Pediatr 2002; 44: 194-203.

Obesity is an increasing health problem all over the world. In addition to genetic and many environmental factors, television is also thought to be a risk factor. This study examined the effects of television viewing on obesity and other physical complaints among Turkish children. From two different socioeconomic class primary schools, 886 second- and third-grade children were visited at their schools, and their weight, height and triceps skin fold thickness (TST) were measured and body mass index (BMI) calculated. Television viewing behavior of the children, parental weight and height, and physical complaints of children were investigated by a questionnaire sent to parents. A subgroup of children was also called to the hospital, and their blood lipid profile and visual acuity were measured. According to the questionnaires, children were found to watch television 2.1 ± 1.2 hours/day (hr/d) during the weekdays, 3.4 ± 2.1 hr/d at the weekend and 2.5 ± 1.3 hr/d generally. Children were also grouped according to the amount of time they watch television. Group 1 (n=298) children watched television less than 2 hr/d, Group 2 (n=323) watched 2-4 hr/d, and Group 3 (n=68) more than 4 hr/d. The prevalence of obesity was 10.9% according to BMI, 11.8% according to TST and 6.4% according to both criteria. Obese girls were found to watch television longer than their peers (2.9 ± 1.2 hr/d vs 2.3 ± 1.3 hr/d, respectively, p=0.034), but no other relation was found between television viewing and obesity. Headache, back pain, eye symptoms and sleep problems were found to be more often among children who watched television longer ($p<0.05$).

It was concluded that television viewing is related to many physical complaints, which may have lifelong consequences (obesity). Thus, pediatricians should give appropriate guidance to families about television habits and health consequences.

Key words: television, children, obesity, health.

Nowadays watching television is an important part of daily life. After sleep, it is the activity that takes the greatest part of our children's time[1]. Because children are so intensely subjected to television, possible health effects is an important topic of investigation. The most well known and studied physical effect is obesity. Both decreased energy expenditure and increased intake of energy by eating "junk food" while watching television increase the risk of obesity[2-8]. Also television viewing has been related to an increased risk of hypercholesterolemia[9], hypertension[10], back pain[11], and eye[12] and sleep problems[13]. Although there are several studies about television viewing and health, still there is no consensus about the results.

The effect of television on health is difficult to generalize due to sociocultural differences among television-viewing habits, television programs and child-rearing activities. As far as we know, the effects of television viewing on obesity and other health problems have not been studied previously in Turkey. The aim of this study was to examine the effect of television viewing on obesity and some other physical health parameters among school age children.

Material and Methods

This study was performed in two primary schools in Ankara. Subjects were 886 second and third grade students, 472 from low-income and 414 from high-income primary schools. Students were visited at their school and their weight, height and triceps skin fold thickness (TST) were measured. Weight was measured with a standard portable scale, with children wearing their standard school clothes and without shoes. Height was measured with standard measuring tape, children without shoes and with heels together. TST was measured with a calliper, and the tips of the acromial process and the olecranon were palpated and a point halfway between marked on the skin. The skin fold was picked up over the posterior surface of the triceps muscle on a vertical line passing upward from the olecranon in the axis of the limb, and the calliper jaws were applied at the marked level[14]. Obesity was defined as body mass index (BMI) (weight divided by height square) being over 95 percentile and TST being over 85 percentile for the age group[15].

A questionnaire was sent to the parents of the students. The questionnaire included questions on the parents' weight and height, the child's and their parents' television viewing habits, and the time the child spent watching television versus other daily activities. There were also questions about television advertisements: whether the child wanted the products advertised, what kind of products he wanted most and whether the parents bought them. Parents were also asked whether their children had symptoms like headaches, back pain, eye strain or sleep problems and whether they used eyeglasses.

To assess the physical activity of the child, we inquired as to the number of vigorous exercises the child performs in a week. Children who performed three or more were defined as 'active' and those who performed less than three activities were defined as 'not active enough'[8].

According to the television viewing time reported in the questionnaires, children were separated into three groups: Group 1, children watching television two hours or less; Group 2, children watching more than two but less than four hours; and Group 3, children watching more than four hours a day. Thirty children from each group were called for further examination at the hospital. Their parents' weight and height were measured. Physical examination of the child was performed and blood pressure measured. Visual acuity was assessed by a Snellen visual acuity chart. Blood was taken for very low-density lipoprotein (VLDL), low-density lipoprotein (LDL), high-density lipoprotein (HDL) and triglyceride assessment. Parents were also given a diary containing seven pages, each for one specific day of the week. Days were divided into hours. Parents were requested to note what the child was doing each hour of the day.

The data was analyzed by Student's t test, χ^2 test and one way ANOVA test. Correlations were tested by Pearson's test. The tests were performed by using SPSS v9.0 program.

Results

Parents of 886 students (445 female, 441 male), 472 from low and 414 from high socioeconomic class schools, answered the questionnaires. Mean age of the students was 7.95 ± 0.77 years (Table I).

Of the parents, 689 answered the question about their child's television viewing time; 298 children (47%) were included in Group 1, 323 (46.9%) in Group 2 and only 68 (9.1%) in Group 3. Mean daily viewing time was 2.1 ± 1.2 hours during the week, 3.4 ± 2.1 hours on weekends and 2.5 ± 1.3 hours overall (Table II). It was found that older children spent more time watching television ($r=0.11$, $p=0.005$). Boys seemed to spend more time watching television during the weekdays but this difference disappeared on weekend. Television viewing time did not differ between high and low income groups (Table III).

Of 886 children, 100 were found to be obese (10.9%) when defined as BMI being over 95th percentile, and 109 were found to be obese (11.8%) when defined as TST being over 85th percentile. Sixty children (6.4%) satisfied both criteria. Obesity was found to be more prevalent among boys than girls and among students of high socioeconomic class school than of their low income peers (Table IV).

Mean television viewing time of obese and nonobese children was not different (Table V). Obesity prevalence among groups that were separated according to television viewing time

Table I. Age, gender and socioeconomic status of children

	Group 1 (n=298)	Group 2 (n=323)	Group 3 (n=68)	p
Age	7.9 ± 0.7	8.1 ± 0.8	7.9 ± 0.7	<0.001*
Female/Male	1.2	0.8	1.1	0.048†
Low/High income	0.9	0.9	0.7	0.756

* The difference was between Group 1 and Group 2, and between Group 2 and Group 3.
† The difference was between Group 1 and 2.

Table II. Time allocated for daily activities (hours/day)

	Watching television	Studying	Reading	Playing	Helping parents	Video games
Weekdays	2.1 ± 1.2	2.3 ± 1.7	0.7 ± 0.7	1.8 ± 1.2	0.2 ± 0.4	0.2 ± 0.5
Weekends	3.4 ± 2.1	2.9 ± 1.5	1.1 ± 0.8	3.4 ± 1.8	0.3 ± 0.6	0.3 ± 0.7
Daily	2.5 ± 1.3	2.4 ± 1.4	0.8 ± 0.6	2.3 ± 1.1	0.2 ± 0.4	02 ± 0.5

Table III. Mean television viewing time (hours/day) of children according to socioeconomic status and gender

		Weekdays	Weekend	Daily
High income	(n=415)	2.0 ± 1.3	3.2 ± 1.9	2.4 ± 1.3
Low income	(n=470)	2.1 ± 1.2	3.4 ± 2.0	2.5 ± 1.2
p		0.142	0.363	0.197
Girls	(n=444)	2.0 ± 1.2	3.3 ± 2.1	2.4 ± 1.3
Boys	(n=441)	2.2 ± 1.2	3.3 ± 1.8	2.5 ± 1.2
p		0.061	0.984	0.262

Table IV. Obesity according to socioeconomic status and gender

		BMI > 95 p		TST > 85 p		Both criteria satisfied	
		n	%	n	%	n	%
High income	(n=415)	53	12.9	60	14.6	37	9.0
Low income	(n=470)	43	9.2	43	9.3	19	4.1
p		0.104		0.020		0.004	
Girls	(n=444)	37	8.2	30	6.7	20	4.4
Boys	(n=441)	63	13.9	79	17.7	40	9.0
p		0.009		<0.0001		0.005	

BMI: body mass index; TST: triceps skinfold thickness.

Table V. Mean television viewing time (hours/day) of obese and nonobese children

	Normal	Obese	p
According to BMI	2.4 ± 1.3	2.5 ± 1.2	0.618
According to TST	2.4 ± 1.2	2.6 ± 1.3	0.289
Both criteria satisfied	2.4 ± 1.3	2.5 ± 1.2	0.795

BMI: body mass index; TST: triceps skinfold thickness.

was also not found to be different (Table VI).

Because both television viewing time and obesity prevalence was significantly different between boys and girls, the relation between television and obesity was also examined among these two groups. Among girls, mean daily television viewing time of children was found to be longer for obese girls, but this difference was not present for boys (Table VII).

Snacking while watching television was found to be more often among obese children (56.7% of obese [51/90] and 40.1% of nonobese children [285/713], p=0.003).

According to the questionnaire results, 64.6% (488/756) of children demanded the products that were advertised on television; 37% (159/430) preferred toys, 21.4% (92/430) preferred sweet food and 24.4% (105/430) demanded both toys and food. The total percent of children demanding food products was 61.9% and only 0.7% (3/430) of this was for nutritious food such as yogurt. Of the parents, 73.8% (596/808) reported that they bought these products sometimes and 3.8% (31/808) bought them frequently. Obesity according to TST was found to be more often among children of parents who bought the products their children demanded (12.5% [78/623] compared with 6.7% [12/179], respectively, p=0.031). Mean daily television viewing time of children who demanded the adversited products was found to be higher than of their peers (2.5 ± 1.2 hours and 2.3 ± 1.2 hours, respectively, p=0.011). Mean daily viewing time was also longer for children who demanded food products (not the nutritious ones) (2.8 ± 1.3 hours and 2.4 ± 1.9 hours, respectively, p=0.035).

The mean number of vigorous physical activities performed by children was found to be 2.7 ± 2.4 times per week; 42.8% (295/690) of children were classified as 'active' (performed 3 or more vigorous activities per week). Boys were found to be more active than girls. Their mean number of activities was 3.4 ± 2.5 times per week versus 2.1 ± 2.2 times per week for girls (p<0.001). Mean number of physical activities was found to have a weak positive correlation with obesity (according to BMI, p=0.002 and r=0.119, according to TST, p=0.001 and r=0.122, according to both criteria p<0.0001 and r=0.137), and being 'active' was found to be more often among children who were obese according to both criteria. The mean television viewing time of children who were and were not 'active' enough did not differ (2.5 ± 1.3 hours/day and 2.5 ± 1.2 hours/day, respectively, p>0.05). There was also not any difference in the mean number of vigorous physical activities performed weekly between groups of children that were separated according to television viewing time (2.8 ± 2.4

Table VI. Obesity frequency among groups separated according to television viewing time

	Group 1 n=298		Group 2 n=323		Group 3 n=68		
	n	%	n	%	n	%	p
BMI > 95th percentile	30	10.1	39	12.1	6	8.8	0.603
TST > 85th percentile	33	11.1	37	11.6	9	13.2	0.887
Both criteria satisfied	19	6.4	23	7.2	4	5.9	0.883

BMI: body mass index; TST: triceps skinfold thickness.

Table VII. Mean television viewing time (hours/day) of obese and nonobese boys and girls

	BMI			TST			Both criteria		
	Normal	Obese	p	Normal	Obese	p	Normal	Obese	p
Boys	n=304	n=46		n=287	n=59		n=316	n=30	
	2.5 ± 1.2	2.3 ± 1.1	0.183	2.5 ± 1.2	2.4 ± 1.2	0.613	2.5 ± 1.2	2.1 ± 1.0	0.068
Girls	n=313	n=29		n=322	n=20		n=326	n=16	
	2.3 ± 1.3	2.9 ± 1.2	0.034	2.3 ± 1.3	3.0 ± 1.3	0.029	2.3 ± 1.3	3.2 ± 1.3	0.021

BMI: body mass index; TST: triceps skinfold thickness.

times for Group 1, 2.7 ± 2.4 times for Group 2 and 2.9 ± 2.4 times for Group 3, p>0.05).

Forty percent of the parents reported that their children had headache sometimes and 5.7% had this complaint often. Children with reported headaches were found to have longer television viewing times on weekdays and in general (p=0.016 and p=0.010) (Table VIII).

Back pain was reported to be present for 20.6% of the children; these children had television viewing times longer than those who did not have this complaint on weekdays and in general (p=0.040 and p=0.041) (Table VIII). Back pain was found more often among children who watched television more than two hours: 17.1% (51/298) of the children who watched less than two hours had back pain compared with 66.3 (201/596) of the children who watched television longer (p=0.018).

Thirty-three percent of the children were reported to have complaints about their eyes sometimes and 3.2% were reported to have such complaints often. The group who had such complaints was found to have longer television viewing times than their peers on weekdays, weekends and in general (p=0.001, p=0.012 and p=0.008) (Table VIII). Eye complaints were more often in children in Group 3 than in those in Groups 1 and 2 (p=0.006 and p=0.018) (Table IX)

Eyeglasses were used by 10.9% of the children. The frequency of having glasses was not found to be different between groups according to television viewing time (Table IX) nor was television viewing time of children who had or did not have glasses (Table VIII).

Sleep problems were reported by 14.8% of parents. Nine percent had difficulty with sleep onset (73/807), 3.5% had nightmares (28/807), 1.5% had night waking (12/807), 0.4% had somnambulism (3/807) and 0.4% had other problems (3/807). Children who had sleep problems were found to watch television longer than their peers on weekdays, weekends and in general (p=0.009, p=0.001 and p=0.039) (Table VIII). Sleep problems were found to be more often among children from Groups 2 and 3 than Group 1 (p=0.024, p=0.040) (Table IX). Children who watched television later than 21:00 had sleep problems more often (36.7% [120/327]) than their peers (15.6% [86/567]) (p<0.0001). Children who had a television set in their bedroom were also found to have more sleep problems than other children (24%[25/104] compared with 13.8% [97/703]) (p=0.007).

Table VIII. Television viewing times (hours/day) of children according to physical complaints

			Television viewing time		
		n	Weekdays	Weekends	Daily
Headache	+	324	2.6 ± 1.3	3.4 ± 2.0	2.2 ± 1.3
	–	365	2.3 ± 1.2	3.2 ± 2.0	2.1 ± 1.0
	p		0.016	0.162	0.010
Back pain	+	139	2.6 ± 1.4	3.5 ± 2.1	2.3 ± 1.4
	–	550	2.4 ± 1.2	3.3 ± 2.0	2.0 ± 1.2
	p		0.040	0.198	0.041
Eye complaints	+	247	2.6 ± 1.3	3.6 ± 2.2	2.2 ± 1.2
	–	442	2.3 ± 1.2	3.2 ± 1.8	2.0 ± 1.2
	P		0.001	0.012	0.008
Using eye glasses	+	81	2.3 ± 1.7	3.1 ± 1.7	2.5 ± 1.4
	–	608	2.1 ± 1.1	3.3 ± 2.0	2.4 ± 1.2
	p		0.109	0.325	0.477
Sleep problems	+	111	2.8 ± 1.5	4.0 ± 2.3	2.4 ± 1.5
	–	578	2.4 ± 1.2	3.2 ± 1.9	2.0 ± 1.1
	p		0.009	0.001	0.039

+ : child with complaint
– : child without complaint

Table IX. Physical complaints among groups according to television viewing times

	Group 1 n=298	Group 2 n=323	Group 3 n=68	p
Headache	134 (45.0)	150 (46.4)	40 (58.8)	0.113
Back pain	51 (17.1)	68 (21.1)	20 (29.4)	0.064
Eye complaints	98 (32.9)	114 (35.3)	35 (51.5)	0.017*
Using eye glasses	37 (12.6)	34 (10.6)	10 (14.7)	0.558
Sleep problems	36 (12.1)	59 (18.3)	16 (23.5)	0.006†

* The difference is between Group 2 and Group 3 (p=0.018) and between Group 1 and Group 3 (p=0.006).
† The difference is between Group 1 and Group 2 (p=0.04) and between Group 1 and Group 3 (p=0.024).

Thirty children from each group were called for examination at the hospital. Thirty children from Group 1, 29 children from Group 2 and 25 children from Group 3 came for the examination. Parents of these children were given a one week diary. According to the diaries, mean television viewing time was 2.5 ± 1.3 hours/day. The television viewing times reported in the questionnaires and in the diaries were compared and they were found to show good correlation ($p<0.001$ and $r=0.6$).

The children's as well as their parents' weight and height were measured again. Mean television viewing time of obese (2.2 ± 1.1 h/d) and nonobese children (2.5 ± 1.3 h/d) assessed from diaries did not show a significant difference ($p>0.05$). The frequency of being obese was also not different between groups separated according to television viewing time.

Visual acuity of children was assessed using a Snellen visual acuity chart. Frequency of visual problems was not found to be different between groups according to television viewing time, and the mean television viewing times of children who did or did not have problems were similar. We could not find any correlation between distance from the television set and presence of visual problems (Table X).

Arterial blood pressure was measured for each child at the hospital. Mean systolic blood pressure was 99.9 ± 11.1 mmHg, and mean diastolic blood pressure was 67.2 ± 9.8 mmHg. Of the children, 11.4% (9/77) had systolic blood pressure and 22.1% (17/77) had diastolic blood pressure over 95th percentile for their age group. Mean television viewing time of these children was not different from their peers whose blood pressures were normal (2.4 ± 1.3 h for children who had normal systolic blood pressure, 2.7 ± 1.5 h for children who had high systolic blood pressure, 2.4 ± 1.2 h for children who had normal diastolic blood pressure, 2.7 ± 1.7 h for children who had high diastolic blood pressure, $p>0.05$). Mean blood pressures of children from groups that were separated according to television viewing time also did not show any difference (98.7 ± 13.0/66.4 ± 14.6 mmHg for Group 1, 99.8 ± 10.6/65.8 ± 10.0 mmHg for Group 2 and 99.5 ± 13.1/66.3 ± 12.5 mmHg for Group 3, $p>0.05$). There was no correlation with television viewing time and blood pressure measurements.

Blood lipid profiles were assessed for children who were examined at the hospital. Mean serum lipid levels were: cholesterol (ch) 16.3 ± 26.3 mg/dl, triglyceride (tg) 108.5 ± 68.9 mg/dl, HDL 52.6 ± 11.7 mg/dl, LDL 87.6 ± 22.1 mg/dl and VLDL 21.9 ± 13.9 mg/dl. BMI was found to be positively correlated with ch, tg and VLDL levels ($r=0.33$ and $p=0.008$, $r=0.48$ and $p<0.0001$, $r=0.48$ and $p<0.0001$, respectively). Systolic blood pressures also had a weak positive correlation with ch, tg and VLDL ($r=0.36$ and $p=0.005$, respectively). A similar correlation was present for diastolic blood pressure ($r=0.30$ and $p=0.018$, $r=0.38$ and $p=0.002$, and $r=0.37$ and $p=0.003$, respectively). Television viewing time did not have any correlation with any of these blood lipid measurements. There was no difference in mean levels of blood lipids between groups that were separated according to television viewing time ($p>0.05$) (Table XI).

Discussion

Television, as an important part of our lives, is affecting our children in many ways. It is taking the time children should spend with other activities, creating instead a sedentary lifestyle.

Table X. Mean television viewing times (hours/day) and viewing distances (meters) according to visual problems

Visual problems	Present n=87	Not present n=712	p
Viewing time	2.5 ± 1.5	2.5 ± 1.3	0.967
Viewing distance	2.5 ± 0.9	2.5 ± 1.1	0.849

Table XI. Mean blood lipid levels (mg/dl) of children from groups according to television viewing time

	Group 1	Group 2	Group 3	p
Cholesterol	155.5 ± 26.2	166.9 ± 27.6	155.8 ± 17.5	0.249
Triglyceride	105.8 ± 58.5	120.4 ± 86.3	85.4 ± 34.4	0.442
HDL	52.6 ± 12.4	51.7 ± 10.8	54.1 ± 14.2	0.878
LDL	81.7 ± 18.6	92.6 ± 23.8	84.6 ± 23.1	0.182
VLDL	21.2 ± 11.7	24.5 ± 17.4	17.0 ± 6.9	0.393

HDL: high-density lipoprotein; LDL: low-density lipoprotein; VLDL: very low-density lipoprotein.

The effect of television viewing on obesity is a fact of debate. Dietz et al.[2], studying over 6,000 children, suggested that the prevalence of obesity increases by approximately 2% for each additional hour of television viewing per day. Most of the studies support the hypothesis that television causes obesity but these studies widely differ in their method of gathering anthropometric data (some use only the data from questionnaires), in their definition of obesity, and in their means of acquiring information about television viewing time[2-7]. To our knowledge, there is no report about the effect of television viewing on obesity among Turkish children.

The two well known studies that found no relationship between television and obesity have important special methodological features. One of them is the study of Robinson et al.[16], in which the researchers had the chance to examine 279 children at 7, 14 and 24 months of the study and who did not find a meaningful association between adiposity and television viewing. The other study performed by DuRant et al.[17], was special in that it did not rely on self reporting but rather collected data about television viewing by observing the children in their houses.

In our study, the anthropometric data was obtained by measurement, and obesity was defined using BMI and TST, which are reported to be correlated to direct measures of body fat. Information about television viewing time was obtained via questionnaires and diaries. Diaries are reported to give results similar to that obtained by video recordings of the family and are more reliable than questionnaires[18]. We could not determine a relation between television viewing time and obesity (for any definition) in our study, neither using the data from questionnaires nor from the diaries. As a matter of fact, the data from the diaries was well correlated with data from the questionnaires. The latest study supporting our findings came from the United States. Mc Murray et al.[19] analyzed data of 2,389 children and concluded that after adjusting for ethnicity and socioeconomic status, there were no significant effects of television viewing on BMI and TST.

Although we could not find any relation between obesity and television viewing for the whole study group, mean daily television viewing times of obese (by all definitions) girls were found to be longer than for their nonobese peers. Supporting our findings, Crawford et al.[20] reported BMI and television to be related for women but not for men; however, there are also researchers reporting the contrary[10,21]. To find different results about a television-obesity relation for girls and boys was not a surprise in our study because both television viewing time and obesity prevalence were different between the two groups. The two groups were also different in their 'activity' level. Boys were found to be more active than girls and perhaps

girls who are already not active enough are more readily affected by a sedentary life.

Television viewing is cited as affecting both ends of the energy balance in favor of obesity. One end is energy intake. Supporting the findings of Taras et al. and others[22-24], we found that most children demanded products advertised on television (especially food that is not nutritious but rich in fat and sugar), and that children who watch television longer make their parents purchase these products more frequently. Additionally, snacking while viewing television was found to be more frequent among children who watched television longer. Both snacking while viewing and demanding the advertised food products are shown to be more frequent among obese children. Thus, as the earlier reports suggested, television has a negative effect on our children's feeding behavior.

The other end of the balance is energy expenditure. We could not reveal any correlation between television viewing time and time dedicated to sports or the number of vigorous physical activities performed by the child. In fact the relation between physical activity and obesity is itself a subject of debate. There are reports relating obesity and physical activity both in a negative[25,26] and positive[27] way (as was the case in our study), while others do not mention any relation at all[28]. Measuring physical activity and examining the complicated relation between activity-obesity and television and other sedentary activities is not easy, but we must keep in mind that at least for the time the child watches television, he is in a state of very low metabolic rate (lower than basal metabolic rate[29]). A study performed among 8-12 year-old children revealed that decreasing sedentary behavior was more successful than increasing physical activity in decreasing the frequency of being overweight[30].

Obesity is an important health problem because it is a risk factor for many childhood and adult diseases. Hypertension and hyperlipidemia are two examples[31]. The relation between television and these two health problems was also examined. A study from Belgium reported a correlation between television viewing time and systolic blood pressure of boys in their study group[20]. In our study, we could not determine any correlation between viewing time with either systolic or diastolic blood pressure. Being hypertensive also did not differ among groups divided according to television viewing time. Wong et al.[9], studying 1,081 children, reported television viewing time to be the most important risk factor for hypercholesterolemia. We studied lipid profiles (LDL, VLDL, HDL, tg, chl) of 63 children and could not find a correlation between television viewing time with any of the blood lipids examined.

Although television viewing did not seem to be directly related to obesity among our children, the results for female children in this study group concerning the effect of television viewing on feeding behavior, and reports from other countries are serious enough to take measures regarding the appropriate amount of television viewing.

Another important point here is that obesity is not the only suspected negative effect of television on physical health. Watching television is believed to cause visual problems. The only study supporting this belief reported that juvenile myopia was correlated with television viewing distance[12]. We could not demonstrate any such correlation neither as a result of television viewing time nor viewing distance, based on information from patient-reported questionnaires. Although not directly related to visual acuity, we found that watching television longer was related to eye complaints. Perhaps the continuous accommodation and convergence while watching television causes eye fatigue.

Some physical complaints such as back pain and headache were found to be more often among children who watched television longer. Vincent et al.[32], revealed that watching television caused headache in 6.4% and worsened it in 27.7% of a group of patients who had chronic headache. In this study, we found that television viewing time of children who had headaches was significantly longer than that of their peers. Troussier et al.[11] reported television viewing time to be a risk factor for back pain. Although the study of Gunzburg et al.[33] did not support this finding, we found that back pain was more frequent in Group 3 than Groups 1 and 2, and also that television viewing time of children with back pain was longer than of those without.

Sleep problems may also be related to television viewing behavior. Gupta et al.[34] observed 250

children for nine months after their initial introduction to television, and showed that 24% of the children had sleep problems although they had had none previously. Owens et al.[13] reported that television viewing time, watching television right before bedtime and presence of a television inside the child's bedroom were all risk factors for sleep problems. In this study, we also found that children who watch television longer, who continue to watch after 21:00 and who have a television set in their bedroom have sleep problems more often than their peers.

The American Academy of Pediatrics advises limiting children's viewing time to one to two hours per day[35]. The mean television viewing time in this study was over this range, and 53% of our children watched television more than two hours per day. As pediatricians, we must be familiar with the possible physical effects of television viewing in addition to psychological effects. Acquiring information about the viewing behavior of the child must be a part of the medical history, especially when the concern is one of these suggested effects (obesity, headache, back pain, sleep problems, etc). We must inform parents that they should limit their children's viewing time and not place a television set in the child's bedroom. Less sedentary and more creative activities shared with parents and friends should take the place of television viewing for the physical and psychosocial health of our children.

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Hepatitis A seroprevalence in a random sample of the Turkish population by simultaneous EPI cluster and comparison with surveys in Turkey

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This study was conducted to determine the hepatitis A virus (HAV) seroprevalence in nine provinces representative of Turkey as a whole. These provinces are representative of the country's geographical location, and demographic, economic and social characteristics. In each province, sample sizes were determined using published data on HAV seroprevalence, and sample sizes for each province and for the cluster were calculated for each group of subjects under the age of 30 for seroprevalence estimates within a 95% confidence interval. The samples were selected by a cluster method, and the planned recruitment was a total of 4,800 subjects, including 600 subjects each from five large provinces (İstanbul, Ankara, İzmir, Adana, Diyarbakır) and 450 subjects from each of the remaining four provinces (Samsun, Erzurum, Trabzon, Edirne). These numbers were distributed in accordance with the percentages for age groups in five-year increments starting from age five for the population under the age of 30 living in the rural and urban areas in each province. This study of 4,462 subjects under the age of 30 in nine provinces of Turkey identified an overall HAV seroprevalence rate of 71.3%. The distribution of HAV seroprevalences by age showed a steady increase from one year of age from 42.7% to 91.1% at 25-29 years of age. HAV seroprevalence was slightly higher in female subjects (73%) than in male subjects (69.3%). By educational status, seroprevalences were comparable except in young children under age six. Seroprevalence was notably higher in large families with six and more members (80.1%) than in small families with five or fewer members (66.7%). According to our study results, 50% of Turkish children are seropositive for HAV by the age of 10 years. We believe the date support the need for a routine primary immunization policy in Turkey and the development of effective prophylactic programs after possible exposure. Consequently, an immunization policy can be developed for each region according to its epidemiological conditions.

Key words: hepatitis A, vaccine, seroprevalence, Turkey.

Hepatitis A virus (HAV) is an endemic infectious disease caused by a picornavirus and transmitted by fecal-oral route[1].

The infectious spectrum of the disease is broad. Jaundice, the most important symptom, is absent or mild, leading to underdiagnosis or missed diagnosis in young children[1]. Moreover, the Ministry of Health often does not receive correct notification of diagnosed HAV cases; the Ministry also includes all types of hepatitis under one title in the list of diseases requiring notification. Thus, the actual number of hepatitis A cases in Turkey is not known.

Various studies about hepatitis A seroprevalence have been conducted in Turkey, However, these studies included only a limited number of patients in small localization, not representing the entire country. In a study by Coşkun et al.[2] that included 287 subjects in İzmir, anti-HAV seroprevalence was found to be 96% in the general population and 97.4% in those above age 15. In a study with 468 subjects living in İstanbul, Babacan et al.[3] found prevalence rates of 67% in the general population and 73.7% in those above age 15, respectively. In another study, Taşyaran et al.[4] demonstrated that anti-HAV seroprevalence was 33.3% in children between 3-6 years, 78.6% in those of 7-10 years, and 77.5% in the age group of 11-14 years in the province of Erzurum. Also, Badur et al.[5] reported a 98.3% HAV seroprevalence rate among blood donors in Diyarbakır.

The lack of a nationwide study identifying the HAV seroprevalence in the general population in Turkey impedes public health planning of a vaccine program and prophylactic measures after possible contact. We conducted this study to determine HAV seroprevalence in nine provinces representative of Turkey, as a whole.

Material and Methods

This HAV seroprevalence study was conducted in nine provinces of Turkey, taking into account the urban and rural areas of each province. These provinces are representative of the country's geographical location and demographic, economic and social characteristics. One-third of Turkey's population live in these nine provinces. Moreover, the population in these areas also includes a high number of residents who have migrated from neighboring and outlying provinces. The selected provinces were İstanbul, Ankara, İzmir, Adana, Diyarbakır, Samsun, Trabzon, Erzurum and Edirne.

We obtained the population distribution by rural and urban areas in each province from the results of the 1997 General Census conducted by the State Institute of Statistics[6]. Considering the age-related results of various local seroprevalence studies on the housing and environmental conditions in Turkey, we decided that a study of the population under age 30 would be most appropriate for investigation seroprevalence and certain epidemiological characteristics[3-5] of HAV.

In each province, sample sizes were determined using published data on HAV seroprevalence, and sample sizes for each province and for the cluster were calculated for each group of subjects under age 30 for seroprevalence estimates within a 95% confidence interval[7]. The planned recruitment was a total of 4,800 subjects, which included 600 subjects each from five large provinces (İstanbul, Ankara, İzmir, Adana, Diyarbakır) and 450 subjects from each of the remaining four provinces (Samsun, Erzurum, Trabzon, Edirne). These numbers were distributed in accordance with the percentages for age groups in five-year increments for the population under the age of 30 living in the rural and urban areas in each province. The study was conducted between February and December 1998. The sampling method of 30 clusters recommended for field studies by the World Health Organization was used. This provided a practical method for selecting subjects of a pre-determined number in the rural and urban areas in each province[8]. A total of 60 clusters were chosen, equally divided between urban and rural areas.

All subjects who were interviewed and who provided blood samples completed a written informed consent form. To obtain epidemiological data, subjects completed a questionnaire on housing conditions and several economic variables. Blood samples obtained from each subject were centrifuged and serum samples were stored at –20 °C. In each center, investigators were appropriately trained on issues such as the selection of subjects, obtaining informed consent, applying the questionnaire, taking blood samples, and collecting, storing and transporting sera for the

serum analysis in order to provide a standardized practice. Additionally, the authorized Ethics Committee in each center approved the seroprevalence study and the Central Ethics Committee of the Ministry of Health approved the entire study.

Serum samples were obtained and transported to the related laboratory in accordance with the principles of cold chain. For each serum sample, a quantitative investigation for anti-HAV-IgG antibodies was performed using Dade-Behring micro-ELISA kits (Dade Behring Marburgh, Germany).

All serum samples including controls and references were diluted by 1/10 and added to two separate aliquots, one containing viral antigen and the other containing control antigen. Following an incubation period of 60 minutes at 37 °C, aliquots were irrigated three times so that the unbounded materials were removed, then peroxidase-labelled anti-human conjugate (100 μl) was added. Following an incubation period of 60 minutes at 37 °C, aliquots were irrigated again, and the chromogen substrate was added. The reaction occurring in ELISA plates stored at room temperature for 30 minutes was terminated by adding 100 μl of stopper buffer solution to each aliquot. Subsequently, absorbency value for each aliquot was detected by reading at 450 nm. By considering the absorbency values for aliquot covered with or without antigen and using α-method, anti-HAV-IgG level was quantitatively determined for each serum sample.

As this is a descriptive study, no statistical analysis was performed and only the percentages were given.

Results

Although 4,800 subjects were planned, only 4,462 (93%) subjects were interviewed and underwent blood sampling. The overall HAV seroprevalence rate among these subjects was 71.3% Table I shows the distribution of subjects by province who completed the questionnaire and underwent blood sampling.

In Ankara, İzmir and Erzurum, investigators questioned and obtained blood samples from more subjects than the suggested target sample size. Seroprevalence could not be determined in 7% of selected subjects and 5.1% of questioned subjects. Blood samples could not be obtained from some children under the age of one year due to the difficulty of obtaining blood sample.

Table II shows the demographic characteristics of the subjects and also shows the overall distribution of HAV seroprevalences by age groups, steadily increasing from one year of age from 42.7% to 91.1% at 25-29 years of age. The majority of those living in the study provinces had been infected with HAV before age 20. HAV seroprevalence was slightly higher in female subjects (73%) than in male subjects (69%), but the difference was not significant. By educational status, seroprevalences were comparable except in young children under age 6 (Table II).

Table I. Distribution of subjects from nine provinces selected for sampling, who were interviewed and underwent blood analysis (Turkey 1998)

Provinces	Number of sampled subjects	Number of interviewed subjects		Number of subjects who underwent blood sampling	
		Number	%*	Number	%**
İstanbul	600	563	93.8	558	99.1
Ankara	600	636	106.0	624	98.1
İzmir	600	627	104.5	617	97.6
Adana	600	570	95.0	547	96.0
Diyarbakır	600	540	90.0	470	87.0
Samsun	450	430	95.6	347	80.1
Erzurum	450	569	126.4	564	99.1
Trabzon	450	387	86.0	376	97.2
Edirne	450	379	84.2	359	94.7
Total	4800	4701	97.9	4462	94.9

* Percentages calculated for the number of sampled subjects in each province.
** Percentages calculated for the number of interviewed subjects in each province.

Table II. Distribution of subjects under the age of 30 from nine provinces by severel demographic characteristics (Turkey 1998)

Characteristic	Number	Percentage	HAV Seroprevalence
Age			
0	61	1.3	70.2
1-4	727	15.5	42.7
5-9	875	18.6	57.0
10-14	902	19.1	70.6
15-19	798	17.0	82.5
20-24	670	14.3	90.9
25-29	595	12.7	91.1
Unknown	73	1.5	87.3
Sex			
Male	2260	48.1	69.2
Female	2441	51.9	73.1
Education			
Child under 6	1025	21.8	49.7
Student	1581	33.7	85.8
Literate*	90	1.9	94.0
Primary School	899	19.4	85.6
Secondary-High school	783	16.9	85.6
University	95	2.1	87.9
Unknown	197	4.2	73.9
Type of Location			
Urban	3074	65.7	69.9
Suburban**	300	2.1	67.3
Unknown	4		
Family size			
≤ 5	3081	65.5	66.7
Six and more ≥ 6	1620	34.5	80.1
Total	4701	100.0	

* Able to read and write.
** Residential areas around the cities and beyond the official municipality boundries.
HAV: hepatitis A virus

Family size did have a significant impact on HAV seroprevalence (Table II). Seroprevalence was notably higher in large families with six and more members (80.1%) than in small families with five or fewer members (66.7%). Seroprevalence also differed with housing conditions. Subjects living in houses with tap water (70.0%) or toilet (70.1%) had a significantly lower rate of seroprevalence than in those without these facilities (84.3% in houses with no tap water and 77.1% in houses with no indoor toilet).

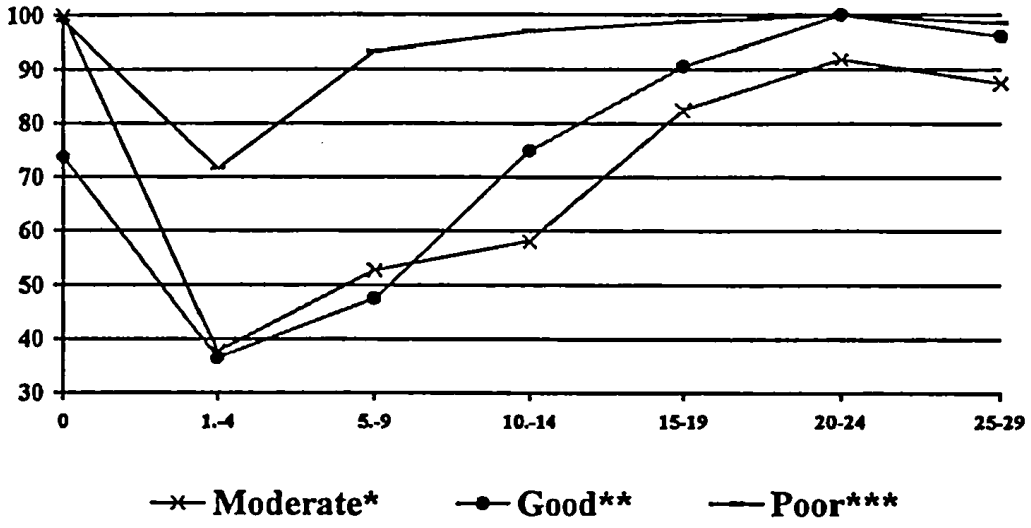
Figure 1 shows the distribution of seroprevalence rates by age. Except for Edirne, seroprevalence showed an increase from the age of five years up to age 20, whereas such increase declined as natural immunity developed in the population at later ages. Seroprevalence was also higher in adolescents in Eastern rather than Western provinces. In Turkey, economic conditions are better in the west than the east. In the relatively richer portion of Turkey, HAV seropositivity developed later, more profoundly in the adolescent age group.

Discussion

Hepatitis A infection is more likely to be asymptomatic during childhood; infection at an older age increases the likelihood of symptom development of clinical diseases, especially jaundice[9].

Anti-hepatitis A virus IgG (anti-HAV IgG) has been accepted as a marker for previous hepatitis A infection and provides immunity against the disease[9-1].

Results from epidemiological studies conducted in other countries demonstrate that the presence of hepatitis A antibody can vary



* Adana, Edirne, Trabzon, Samsun.
** Ankara, İstanbul, İzmir.
*** Erzurum, Diyarbakır.
HAV: hepatitis A virus.

Fig. 1. Age-specific HAV seroprevalence in Turkey according to socioeconomic condition of the provinces.

between different regions and ages[10,13,14]. Independent of sex and race, these differences may be due to local conditions. Size and heterogeneity of the study groups also may influence results. Representative seroepidemiological data is needed to establish preventive vaccination programs as well as a post-exposure prophylactic therapy regimen[11].

This is the first large seroprevalence study in Turkey. Most other studies were conducted with a limited number of subjects who were blood donors or had been admitted to the hospital[10,11,13-16]. Based on the population demographics of the 1997 general census, our study subjects served as a representative cross sample for the entire population under the age of 30 in Turkey.

Our study included a total of 4,462 subjects under the age of 30 from different provinces, with 93% of the targeted sample size being reached. This is the largest seroprevalence study in Turkey. The overall seroprevalence of hepatitis A was found to be 71.3%.

As HAV seroprevalence was 70.2% in infants under one year of age and 73.2% in women under the age of 30, we concluded that the transmission of maternal antibodies occurs at a high rate. Although the sample size was small, this finding supports our findings from earlier studies where seroprevalence was determined to be high[10,11,13-14]. The fact that the seroprevalence rate decreased to 42% between the ages of 1-4 years despite contact with hepatitis A suggests that the high level of HAV seroprevalence is caused by maternal antibodies in children under one year of age. Such a high level will cause a decrease in the success rate of vaccination during the first year, as demonstrated by Kanra et al[17].

The high level of maternal antibodies (up to 70%) in the first year of life and the strong possibility of a high rate of contact with hepatitis A due to the high level of endemicity must be considered when planning a vaccination program. For example, in the U.S. hepatitis A vaccination after 24 months as been recommended since the year 2000 in states with a high incidence rate of hepatitis A[18].

In our study, HAV seroprevalence increased in subjects from ages one to four years, and the increase continued during the adolescent period. These results demonstrated a high risk of hepatitis A infection in schoolage children and adolescents in Turkey.

Crowded conditions and close personal contact are also important risk factors for hepatitis A infection and are common in schools.

Our study showed no difference in HAV between the sexes, as supported by other studies[12,13,15,16].

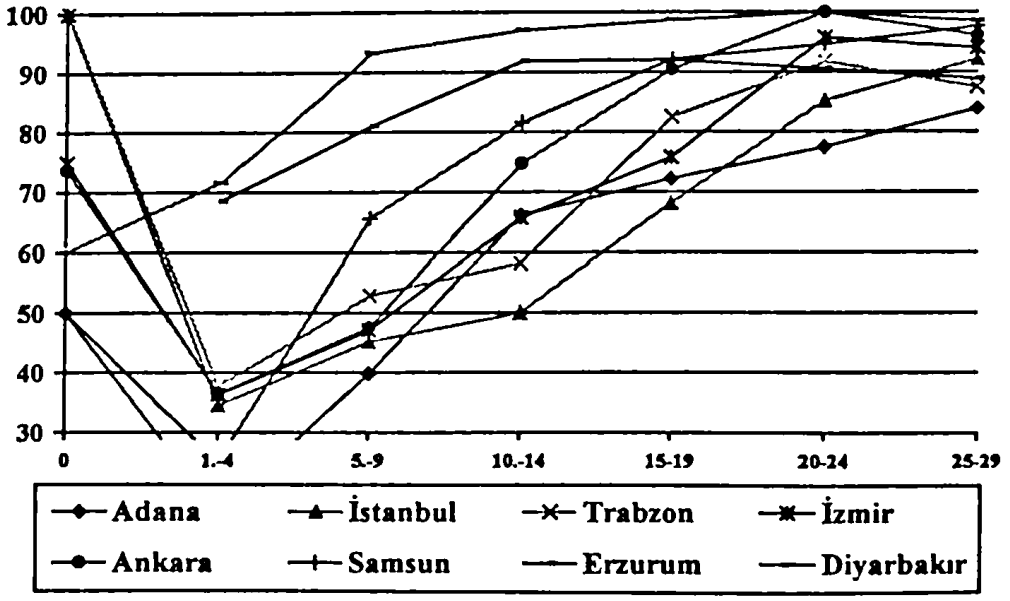
In the study by Szmuness et al[16]. in New York City, the level of hepatitis A antibodies was shown to be two- or three-fold higher in subjects with lower socioeconomic conditions than in those with a higher level of welfare and better living conditions.

In comparison of provinces, seropositivity was significantly lower in Adana (56.7%) with a high level of wealth and in Edirne (60.7%) with a high level of education and socioeconomic development than in the poor provinces of Diyarbakır (91.9%), Erzurum (85.1%) and Samsun (83.6%) (Fig. 2). The higher seropositivity in these provinces may be due to rapid, unplanned development with poor infrastructure. These provinces also have a high level of migration from the rural areas or neighboring provinces. Seropositivity was generally lower in subjects living in houses with tap water and toilet than in those without these facilities, suggesting that unplanned development without adequate sanitary infrastructure may be a risk factor for the disease[15]. As expected, contact with hepatitis A seemed more likely in large families. This is not surprising if we accept that the higher number of family members is inversely correlated with the welfare level and socio-cultural development of the family. In Ankara, İstanbul and İzmir, however, where infrastructure services are relatively sufficient, even in the suburbs, the family size had no effect on the seropositivity.

The first step in preventing hepatitis A infection is to improve the personal hygiene and infrastructure across the country. The results show that hepatitis A is moderately endemic in Turkey although seroprevalence differs from one region to another. The World Health Organization (WHO) defines, in general, moderately endemic countries as those developing, having a transitional economy, and having industrialized regions. In these countries, children are infected with hepatitis A at early ages. Additionally, viral spread is high, and the infection is more frequently seen in adolescents and young adults. The infection may be spread through personal contact, although outbreaks traced to contaminated water and food may result from inadequate infrastructure. The disease follows a course of successive cycles, and outbreaks occur when a sufficient number of sensitive people are reached, and thus almost all the people are at risk.

Turkey fits the WHO profile of a developing country where HAV exposure begins during childhood and increases with age. Studies have shown that vaccination plays an important role in preventing outbreaks in these countries.

According to our study results, 50% of Turkish children are seropositive for HAV by the age of



HAV: hepatitis A virus.

Fig. 2. HAV seroprevalence according to age throughout Turkey.

10 years. In addition, seropositivity is not similar across provinces of Turkey. HAV vaccine is recommended in areas with high endemicity in some developed countries. In the year 2001, the routine immunization schedule included HAV vaccine in six states in the U.S. Since there is a big difference in seroprevalence between the provinces in Turkey, a similar program may be recommended in here.

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Leptin levels in children with insulin dependent diabetes mellitus

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SUMMARY: Bideci A, Cinaz P, Ezgü FS. Leptin levels in children with insulin dependent diabetes mellitus. Turk J Pediatr 2002; 44: 211-214.

Leptin, a product of the *ob* gene, is a polypeptide hormone produced in adipose tissue that informs the brain about the amount of energy storage of body fat. It has very important effects on neuroendocrine functions and energy expenditure. The aim of our study was to determine leptin levels of children with insulin dependent diabetes mellitus (IDDM), which is known to affect body metabolism, and to investigate the relationship between duration of the disease, insulin dosage, HbA1c levels, body mass index (BMI), serum lipids and IGF-1 levels. Sixteen patients with IDDM (chronological age 13.8 ± 2.6 years) whose HbA1c levels were 10.2 ± 1.9 %, BMI 21.2. ± 2.7 kg/m^2, insulin dosage 0.9 ± 0.4 U/kg/day and duration of the disease 6.7 ± 2.6 years, and 12 healthy controls (13.4 ± 2.6 years) were included in the study. Fasting plasma leptin levels were measured by radioimmunoassay method. The mean plasma leptin levels of the patient and the control groups were 19.1 ± 7.6 ng/ml and 6.1 ± 2.9 ng/ml, respectively, and significant difference was found between the two groups ($p<0.05$). No correlation was found between leptin values and IGF-1, cholesterol, HDL-cholesterol, LDL-cholesterol, triglyceride levels, atherogenic index, insulin dosage or HbA1c levels in the patient group. A weak statistical correlation was determined between BMI and leptin levels in the IDDM group ($r=0.28$, $p<0.05$). A positive correlation was also found between leptin levels and the duration of the disease ($r=49$, $p<0.05$). As a result, it seems that leptin levels of children with IDDM differed from the levels of the control group significantly, and that the duration of insulin therapy was responsible for this difference.

Key words: leptin, insulin dependent diabetes mellitus, children.

Leptin, a satiety factor and the product of the *ob* gene, is produced in the adipose tissue and its expression is stimulated by insulin[1-3]. Serum leptin concentrations in humans are shown to be positively correlated with body fat ratio, body mass index (BMI) and serum insulin and cortisol levels[2-5]. Leptin as a satiety factor is thought to reduce food intake, stimulate energy expenditure, inhibit insulin secretion from the pancreas, increase glucose utilization, induce lipolysis and affect triglyceride synthesis[3,5].

We planned to investigate leptin levels and the possible relation with disease duration, insulin dose, HbA1c levels, serum lipids and IGF-1 levels in children with insulin dependent diabetes mellitus (IDDM).

Material and Methods

The local ethics committee approved the study, and informed consent was taken from all parents and the patients.

Sixteen children (8 girls, 8 boys) with IDDM whose ages were between 8-16 years were involved in the study. The control group consisted of 20 age-matched, healthy children. All the cases with IDDM had received mixture insulin (consists of regular and NPH insulins) two times a day and a diabetic diet. In all subjects duration of diabetes, insulin doses and HbA1c levels were measured. The characteristics of the cases are shown in Table I. None of the patients had an acute or chronic illness apart from IDDM, high blood pressure or

Table I. Anthropometric measurements of patient and control groups

	IDDM group	Control group
Chronological age (years)	13.8 ± 2.6	13.4 ± 1.9
Height (cm)	144.9 ± 10.9	151.2 ± 11.3
Weight (kg)	39.6 ± 11.3	41.3 ± 9.8
BMI (kg/m^2)	21.2 ± 2.7	22.3 ± 2.2
Insulin dosage (U/kg/day)	0.9 ± 0.4	-
Duration of disease (years)	6.7 ± 2.6	-
HbA1c levels (%)	10.2 ± 1.9	-

IDDM: insulin dependent diabetes mellitus; BMI: body mass index.

microalbuminuria, and none had been taking medication other than insulin. Neyzi's growth and developmental norms for children were used for the evaluation of heights and weights[6]. Genital examination and pubertal staging were performed according to the staging system of Tanner[7,8]. Bone ages were determined using the atlas of Greulich and Pyle[9].

Serum leptin levels were measured after an overnight fast, between 07:30 and 08:00, before the first insulin administration of the morning. When blood samples were taken, plasma glucose levels were determined by glucose-oxidase method using a glucose analyzer. Leptin concentrations were determined in plasma using a commercially available kit (Rinco Research IM). IGF-1 levels were determined by radioimmunoassay method.

HbA1c levels were measured using a spectrophotometer. Serum levels of total cholesterol, triglycerides and HDL-cholesterol (HDL-C) were measured by Technicon ra-xt device through colorimetric method. LDL-cholesterol (LDL-C) levels were found with Friedewaled's formula. Atherogenic index was calculated by the formula [(Total cholesterol-HDL-cholesterol)/HDL-cholesterol].

Anthropometric data of the study population are given as mean ± SD. Data was analyzed using Student's test, Mann-Whitney U and Pearson's correlation method. A p value below 0.05 was accepted as significant. All analyses were two-tailed and performed with the SPSS Software Version 7.0 Windows.

Results

The mean plasma leptin levels of the patient and control groups were 19.1 ± 7.6 ng/ml and 6.1 ± 2.9 ng/ml, respectively, and significant difference was found between the two groups ($p<0.05$). There was no difference between the two groups for IGF-1 levels ($p>0.05$). Nor was a significant difference found between the two groups regarding total cholesterol, triglycerides, HDL-C and LDL-C levels and atherogenic index (Table II). No correlation was found between leptin values and IGF-1, total cholesterol, triglycerides, HDL-C and LDL-C levels, atherogenic index, insulin dose or HbA1c levels in the patient group. A weak statistical correlation was determined between BMI and leptin levels in the IDDM group ($r=0.28$, $p<0.05$). A positive correlation was found between leptin levels and the duration of the diseases ($r=0.49$, $p<0.01$).

Discussion

The recent isolation and characterization of the obese (*ob*) gene and its gene product leptin has made a great contribution to the pathophysiology of obesity and weight homeostasis[2,3]. Leptin is thought to signal satiety and filling of peripheral fat stores to the brain, acting through specific receptors in the hypothalamus[2-4]. Serum leptin concentrations in humans are known to be positively associated with body fat percentage, BMI and serum insulin concentration[5,10]. In addition, leptin production by adipose tissue seems to be under neuroendocrine control[2]. In humans and animals, factors involved in glucose metabolism are glucose itself, insulin and glucocorticoids, and a variety of cytokines have been found to be potent regulators of leptin expression[4,5]. Especially in the newly diagnosed IDDM patients leptin levels were found to be lower, a finding related to low insulin levels[10-13]. Streptozocin-treated diabetic mice have reduced leptin mRNA levels which are partially restored

Table II. Lipid profile and IGF-1 levels of patient and control groups

	IDDM group	Control group	p values
IGF-1 (ng/ml)	200.1 ± 41.3	224.3 ± 29.2	>0.05
Cholesterol (mg/dl)	191.4 ± 32.1	164.2 ± 37.7	>0.05
LDL-Cholesterol (mg/dl)	105.4 ± 16.4	98.7 ± 20.3	>0.05
HDL-Cholesterol (mg/dl)	50.1 ± 12.6	51.9 ± 10.7	>0.05
Triglycerides (mg/dl)	114.3 ± 21.6	118.0 ± 23.4	>0.05
Atherogenic index	2.8 ± 1.0	2.3 ± 0.98	>0.05

IDDM: insulin dependent diabetes mellitus.

by insulin treatment[11]. Tuominen et al.[13] found fasting plasma leptin levels to be higher in patients with IDDM than in controls. These authors suggested that this difference may be due to chronically high insulin concentrations in diabetic patients. In our study, a positive correlation was found between disease duration and leptin levels. This finding was related to the long duration of insulin treatment. The relation between poor metabolic control and leptin levels has been stated in previous studies[10,12-14], however, leptin levels in patients with IDDM have given contradictory results. The higher leptin levels in patients with IDDM were related to the relatively higher insulin doses given and the subsequent large amount of adipose tissue[11]. However, in our study the higher leptin levels in IDDM patients seems to have been related to the duration of the disease rather than BMIs, as there was no significant difference in terms of BMI between the two groups. In addition, this difference could not be attributed to insulin doses, as our IDDM patients were receiving injections only two times daily rather than intensive therapy. The higher leptin levels could somehow be related to the relatively higher plasma glucose levels in our IDDM patients, due to their poor control of their diabetes. In previous studies in patients with IDDM, a low and deteriorated growth hormone-IGF axis was shown[15-17]. We did not find any difference between the IDDM and control groups in terms of IGF-I levels in our study. The possible correlation between leptin and IGF-1 levels was investigated, as the relation between insulin resistance and IGF-1 levels was known; however, we were unable to show any correlation. Although there are some studies in the literature showing a correlation between serum leptin levels and lipids, we were not able to show such a correlation.

As a result, it seems that leptin levels of children with IDDM differ from the levels of the control group significantly, and that the duration of insulin therapy rather than the amount of adipose tissue creates this difference.

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Serum insulin-like growth factor-I (IGF-I) and IGF-binding protein-3 levels in severe iodine deficiency

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SUMMARY: Alikaşifoğlu A, Özön A, Yordam N. Serum insulin-like growth factor-I (IGF-I) and IGF-binding protein-3 levels in severe iodine deficiency. Turk J Pediatr 2002; 44: 215-218.

Iodine deficiency is an important public health problem worldwide. It is well known that it has severe consequences such as brain damage, developmental delay, deficits in hearing and learning and lower intellectual attainment. It also has a negative impact on growth. In this study, we aimed to address this issue and we assessed height standard deviation scores of children living in an area of severe iodine deficiency in comparison to those living in a mild iodine deficiency area. Serum levels of insulin-like growth factor-I (IGF-I), IGF-binding protein-3 (IGFBP-3), thyroxine (T_4), and thyroid stimulating hormone (TSH) were also analyzed to investigate the mechanisms by which iodine depletion leads to growth failure. Pubertal children in a severe iodine deficient SID area had lower height standard deviation scores (HSDS), IGF-I and IGFBP-3 levels than those living in mild iodine deficient MID area. Similar findings could not be elucidated in the prepubertal age group. The major determinants of HSDS were age, IGF-I, IGFBP-3 and TSH. IGF-I and IGFBP-3 were negatively correlated with T_4. These findings suggest that iodine deficiency has a negative impact on growth, as well as IGF-I and IGFBP-3 levels. This effect seems to be due to the derangements in thyroid hormone economy arising from iodine depletion. The degree of this impact may be related to the duration of iodine depletion or may be dependent on the developmental stage of the organism at the time of iodine depletion.

Key words: iodine deficiency, insulin-like growth factor-I, insulin-like growth factor-binding protein-3.

Normal growth and development in children are dependent on a number of factors, including growth hormone, the growth hormone insulin-like growth factor axis, thyroid hormones and nutritional status. The complex relationship between thyroid hormones and the growth hormone – insulin-like growth factor axis has not yet been completely understood. Although the mechanism of action has not been fully elucidated, thyroid hormones probably regulate expression of insulin-like growth factor-I (IGF-I) receptors and its binding protein[1]. In previous studies low levels of serum IGF-I and the major binding protein IGF-binding protein-3 (IGFBP-3) were reported in primary hypothyroidism[2-5]. The low IGF-I and IGFBP-3 levels in hypothyroidism both in humans and animals returned to normal with thyroxine replacement[1,5-6]. Iodine as a trace element is an important substrate for thyroid hormone synthesis. Although the thyroid gland can tolerate a wide range of iodine intake with only minute changes in thyroid hormone status, iodine is still an important factor for normal growth. This is proven in the case of cretenism or mild-to-moderate growth failure seen in areas of moderate-to-severe iodine deficiency.

In this study, we assessed serum levels of IGF-I, IGFBP-3, thyroxine (T_4), and thyroid stimulating hormone (TSH) in patients with severe iodine deficiency in various age groups and compared them with age-matched controls with mild iodine deficiency.

Material and Methods

A total of 78 children, aged 7-12 years, from a mountain village in the central part of Turkey (Büyükçakır-Kayseri) with severe iodine deficiency (SID) were included in the study. The

children were assessed anthropometrically. Height standard deviation scores (HSDS) were calculated using the formula below:

$$HSDS = (X - \bar{X}) / SD$$

where X: height measurement, and $\bar{X}$ and SD the mean and standard deviation for the height appropriate for age and sex[7]. Levels of serum IGF-I, IGFBP-3 and urinary iodine were measured and compared to 75 age-matched controls living in a mild iodine deficient (MID) area in Ankara.

Urinary iodine was determined in randomly collected urine samples using the Sandell-Kolthoff reaction[8]. Urine was first digested with hydrochloric acid in a heating block and iodine was determined from its catalytic reduction of ceric ammonium sulfate in the presence of arsenious acid. Median urinary iodine/creatinine (μg/g creatinine) was used as a criteria of iodine status[9-11].

Serum IGF-I level was determined by coated tube IRMA (Diagnostic Systems Laboratories, Webster, TX, USA). The extraction procedure was performed after acidifying the serum to dissociate IGF-I from its binding proteins. Serum IGFBP-3 was measured using a double antibody radioimmunoassay (RIA) (Diagnositc Systems Laboratories, Webster, TX, USA).

Serum T_4 and TSH were measured using standard RIA and IRMA kits (ICN Pharmaceuticals, Costa Mesa, CA, USA; BRAHMS Diagnostica, Berlin, Germany).

Statistical evaluation was made using Statistical Package for Social Sciences (SPSS). Serum IGF-I and IGFBP-3 levels showed when logarithmic transformation was carried out. Student's t-test, Kruskal-Wallis and Mann-Whitney U tests were used in the comparisons. Correlation analysis and linear regression model was used where appropriate. $P<0.05$ was accepted as significant.

Results

The study group consisted of 78 children (43 boys, 35 girls), aged 7-12 years (9.3 ± 1.7 years, mean ± SD) living in an SID area (median iodine/creatinine: 19.7 μg/g creatinine). Their HSDS and IGF-I, IGFBP-3 levels were compared to 75 age-matched controls (40 boys, 35 girls) living in an area with MID (median iodine/creatinine: 60.8 μg/g creatinine).

In the prepubertal age group (7-9 years) HSDS, and serum IGF-I and IGFBP-3 levels did not differ between the children living in the SID and MID areas. In the pubertal age group, however, all parameters were significantly lower in children from the SID area than in those living in an MID area (Table I, $p<0.0001$).

IGF-I and IGFBP-3 correlated significantly with the HSDS of the children ($r=0.52$, $p<0.0001$, and $r=0.57$, $p<0.0001$, respectively). Serum IGF-I showed significant negative correlation to T_4 ($r=-0.42$, $p<0.0001$), whereas IGFBP-3 was only weakly correlated to T_4 ($r=-0.23$, $p=0.044$). There was negative correlation between T_4 and TSH as expected, although the correlation was not strong ($r=-0.34$, $p=0.003$).

Factors influencing HSDS were analyzed by multiple regression analysis. In the regression

Table I. Urinary iodine/creatinine, serum IGF-I, IGFBP-3 levels, and height standard deviation scores (HSDS) in children from mild and severe iodine deficient (ID) areas

	I/Creatinine (μg/g)*	IGF-I (ng/ml)	IGFBP-3 (mg/ml)	HSDS
Severe ID Area				
7-9 years (45)	18.1†	131.8 ± 14.4	2.8 ± 0.1	0.2 ± 0.4
10-12 years (33)	31.3‡	108.6 ± 19.3††	2.6 ± 0.1‡‡	-3.2 ± 0.4§
Mild ID Area				
7-9 years (28)	53.6†	108.1 ± 16.1	3.3 ± 0.3	0.0 ± 0.2
10-12 years (47)	64.6‡	337.8 ± 33.4††	3.4 ± 0.2‡‡	0.3 ± 0.1§

* Urinary iodine/creatinine ratio is given as median values; all other parameters are given as mean ± SEM
† $p<0.0001$ iodine/creatinine levels of MID vs SID area at the age of 7-9 years
‡ $p=0.005$ iodine/creatinine levels of MID ve SID area at the age of 10-12 years
†† $p<0.0001$ IGF-I levels of children in MID area were significantly higher than in children from SID area
‡‡ $p<0.0001$ IGFBP-3 levels of children in MID area were significantly higher than in children from SID area
§ $p<0.0001$ HSDS of children in MID area were significantly higher than in children from SID area
IGF-1: insulin-like growth factor-I; IGFBP-3: IGF-binding protein-3; SEM: standard error of the mean.

equation age, IGFBP-3, IGF-I, and TSH levels predicted the HSDS of the children in the SID area (R^2=0.67, $p<0.0001$).

Discussion

Iodine deficiency is an important public health problem for almost all countries worldwide. Turkey has long been known as a mild iodine deficiency area according to previous epidemiological studies. Urgancioğlu and Hatemi[12] reported an overal goitre prevalence of 30.5%, and visible goitre was 6.7% in their study involving 73,757 subjects throughout Turkey. Our previous study revealed severe iodine deficiency in a mountain village in the central part of Turkey, and the prevalence of goitre was more than 90% in that study[13]. These results disclosed the presence of severe iodine deficient regions in Turkey in addition to mild-to-moderate iodine deficient areas. It is well known that iodine deficiency has severe consequences such as brain damage, developmental delay, deficits in hearing, and learning and lower intellectual attainment[9,14].Hypothyroidism is the major factor responsible for these consequences. The fundamental role that thyroid hormones play in normal growth and development is well established. In experimental studies, it has been shown that thyroid hormones play an important role in the regulation of insulin-like growth factors and their binding proteins[15]. Diminished serum IGF-I and IGFBP-3 concentrations have been reported in hypothyroidism and they returned to normal with thyroxine replacement[1,5-6]. There is much research investigating the impact of thyroid hormone status on IGF-I and IGFBP-3. On the other hand, research on the association of iodine status with IGF-I and IGFBP-3 is scarce, despite the well known relation between iodine status and growth. Nazaimoon et al.[16] investigated the effects of iodine depletion on these growth factors and growth in a group of children living in a SID area. But their study involved malnourished children who may have had other problems affecting their growth.

In this study, pubertal children from a SID area had significantly lower HSDS and serum IGF-I and IGFBP-3 levels when compared to those living in a MID area. This finding suggests that growth failure seen in iodine deficiency. may be mediated by IGF-I and IGFBP-3 directly. The same difference could not be elucidated in the prepubertal age group, however. HSDS, as well as IGF-I and IGFBP-3 levels of prepubertal children living in a SID area were similar to controls. This may be explained either by the longer duration of iodine depletion in pubertal children leading to more severe or long-standing derangements in thyroid hormone status, or it may be related to the specific age period. Puberty is a stage of childhood where growth accelerates, and daily iodine requirements also increase. Iodine depletion at this stage of childhood may have more serious consequences on growth than in early childhood.

A strong correlation between serum IGF-I and IGFBP-3 levels with HSDS in this group of children supports the hypothesis that in these children growth is closely regulated by these growth factors. On the other hand, both IGF-I and IGFBP-3 levels were negatively correlated to serum T_4 levels. Also, on multiple regression analysis, the predictors of HSDS in addition to age were IGF-I, IGFBP-3 and TSH levels. These findings may support the hypothesis that the negative influence of iodine depletion on IGF-I and IGFBP-3 may be related to the derangements in thyroid hormone economy resulting from iodine deficiency.

In conclusion, our findings suggest that iodine deficiency has a negative impact on growth, as well as on IGF-I and IGFBP-3 levels. This effect seems to be due to the derangements in thyroid hormone economy arising from iodine depletion. The degree of this impact may be related to the duration of iodine depletion or to the age of the patient.

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Incidence of dysrhythmias in congenitally corrected transposition of the great arteries

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We reviewed hospital records of 45 children with corrected transposition of the great arteries (c-TGA) to determine the incidence and outcome of congenital and postoperative dysrhythmias seen in this congenital anomaly.

Our study comprised 45 patients (12 girls, 33 boys). The mean age of the patients at initial evaluation was 3.4 ± 3.7 years, and they were followed for a mean period of 3.5 ± 4 years.

Forty-three patients (95%) with c-TGA had associated intracardiac defects. Two patients (5%) did not have any cardiac defects. In 31 (69%) of the 45 patients, ventricular septal defect (VSD) was present, while the remaining 14 patients (31%) had intact ventricular septum. VSD repair was done in 17 of 31 patients.

Different types of dysrhythmias were detected in 19 of 45 patients. Six patients (13%) presented initially with congenital complete atrioventricular block (AVB) and five patients with postoperative complete ve AVB. Pacemaker implantation was required for 11 patients with complete AVB. In eight patients, ventricular and supraventricular ectopic beats, left bundle-branch block (LBBB) and first-degree AVB were determined but therapy was not required.

Twenty-five (58%) of 43 patients with intracardiac defects underwent different surgical procedures. Permanent pacemaker implantation was required for five patients (29%) after VSD repair (17 patients) due to postoperative complete AVB. The incidence of congenital AVB in 14 patients with intact ventricular septum was found to be high (29%) in comparison to the group with VSD (6%).

Patients diagnosed as c-TGA with or without cardiac defects should be followed carefully during their clinical course to identify and treat different types of dysrhythmias that can appear at any time.

Key words: corrected transposition, complete heart block, ventricular septal defect.

In congenitally corrected transposition of the great arteries (c-TGA), there is a discordant atrioventricular connection (right atrium to left ventricle and left atrium to right ventricle), and a discordant ventriculoarterial connection (left ventricle to pulmonary artery and right ventricle to aorta). Since it is physiologically a corrected transposition, the associated anomalies [ventricular septal defect (VSD), single ventricle, pulmonary stenosis (PS), left atrioventricular valve malformations] and conduction defects determine the prognosis.

Ventricular inversion frequently is associated with conduction disturbances ranging from first-degree atrioventricular block (AVB) to complete AVB. Complete AVB may appear spontaneously or during surgical treatment of associated defects. Approximately 10% of the patients present initially with complete AVB. First-degree or second-degree AVBs also have the tendency to progress to complete AVB with increasing age. In postoperative complete AVB, pacemaker therapy is always indicated. Congenital complete AVB may also not be well

tolerated; pacemaker therapy is recommended early after the recognition of complete AVB[1-3]. Atrial arrhythmias and Wolff-Parkinson-White syndrome are occasionally present[4-6].

In this study, we reviewed our patients with c-TGA with regard to associated intracardiac defects and their surgical management, types of dysrhythmias and follow-up results. We stress the importance of close follow-up in all patients with or without cardiac defects, to recognize and treat the different types of dysrhythmias which can appear at any time.

Material and Methods

In this study, 45 children (12 girls, 33 boys) diagnosed as c-TGA between January 1989 and December 1999 at Hacettepe Children's Hospital, Department of Pediatric Cardiology were retrospectively evaluated. The diagnosis of c-TGA was made in all patients by both two-dimensional and Doppler echocardiography, and then cardiac catheterization and biplane angiography were performed in 31 patients. All the patients were evaluated regarding dysrhythmia by 12-lead surface electrocardiogram and 24-hour ambulatory electrocardiographic monitoring at intervals of six to 12 months. The ages of the patients at the time of diagnosis ranged from 2 days to 11 years (mean 3.4 ± 3.7 years) and they were followed for a mean period of 3.5 ± 4 years (range 3 days to 12 years). In all patients, the following parameters were evaluated: a) cardiac defects and their surgical management, b) types of dysrhythmias, c) follow-up results of dysrhythmia.

Of 45 patients with c-TGA, 43 (95%) had associated intracardiac defects (Table I). Two patients (5%) did not have any cardiac defect. One of these patients had dextrocardia and the other had a history of chest pain.

Twenty-five (58%) of 43 patients with intracardiac defects underwent different surgical procedures (Table II). The mean age of these patients at operation was 4.4 ± 4.2 years (range 2 months to 14 years). VSD was present in 31 (69%) of the 45 patients while 14 patients (31%) had intact ventricular septum. VSD repair was done in 17 (55%) of the 31 patients. Because of secondary pulmonary hypertension, pulmonary artery banding was also performed in five (2 patients had Ebstein's anomaly) of

Table I. Associated intracardiac lesions in 45 patients with corrected transposition of the great arteries

Intracardiac lesions	n	%
Ventricular septal defect	31	69
Left AV valve regurgitation	30	66
Pulmonary stenosis	14	31
Right AV valve regurgitation	8	17
Ebstein's anomaly	6	13
Atrial septal defect	5	11
Dextrocardia	5	11

AV: atrioventricular

Table II. Surgical procedures in 25 patients with corrected transposition of the great arteries

Surgical procedures	n
Ventricular septal defect repair	17
Left AV valve replacement	6
Atrial septal defect repair	5
Pulmonary artery banding	5
Pulmonary commissurotomy	3
Blalock-Taussig shunt	3
Left ventricle-pulmonary artery conduit	1

AV: atrioventricular

17 patients with VSD repair. Left AV valve replacement was performed in six (29%) (2 patients had Ebstein's anomaly) of 30 patients due to the left AV valve regurgitation. In 14 patients with PS, pulmonary commissurotomy (3 patients), Blalock-Taussig shunt (3 patients) and left ventricle-pulmonary artery conduit (1 patient) were done. Atrial septal defect repair was performed in five patients. All the patients were examined at intervals of six to 12 months for dysrhythmia.

Different types of dysrhythmias were determined in 19 of 45 patients (Table III). Ventricular and supraventricular ectopic beats, left bundle-branch block (LBBB) and first-degree AVB were determined in eight patients who had no complaint related to dysrhythmia and normal screening with 12-lead surface electrocardiogram. They were followed without requiring any treatment in their follow-up period.

Six patients had congenitally complete AVB when first seen. Three of them had a history of syncope and/or fatigue and one patient had fetal bradycardia. The ages of six patients (13%)

Table III. Dysrhythmias in 19 of 45 patients with corrected transposition of the great arteries c-TGA

Types of dysrythmia	Patient (n: 19)
First degree AVB + supraventricular ectopic beats	1
Supraventricular ectopic beats + left bundle-branch block	1
Left bundle-branch block	1
Supraventricular ectopic beats	2
Ventricular ectopic beats	3
Postoperative AVB	5
Congenital AVB	6

AVB: atrioventricular block

with congenitally complete AVB at the time of diagnosis ranged from 2 months to 11 years (mean 2.8 ± 4.2 years). Two of them had VSD and pulmonary hypertension for which pulmonary artery banding was performed and four had intact ventricular septum. One of the patients with intact ventricular septum had ASD which was repaired. Three other patients had left AV valve regurgitation, for which one had undergone valve replacement.

Postoperatively complete AVB developed in five (29%) of the 17 patients with VSD repair, and their mean age at the operation time was 4.9 ± 5.4 years (range 5 months to 14 years). Two of five patients had undergone both pulmonary commissurotomy procedure and VSD repair. Eleven patients with congenital (6 patients) and postoperative complete AV block (5 patients) underwent permanent pacemaker implantation.

The incidence of congenitally complete AVB in the patients with intact ventricular septum was found to be higher (29%) in comparison to the group with VSD (6%) (Table IV). The incidence of normal sinus rhythm among patients with VSD was found to be higher than among those with intact ventricular septum (94% and 71%, respectively).

Follow-up: An eight-year-old patient with the diagnosis of Eisenmenger syndrome as a result of VSD and pulmonary hypertension was followed with only drug therapy. A newborn patient with Ebstein's anomaly and VSD died of sepsis.

Two patients who had undergone VSD repair died suddenly on the postoperative first day because of probable dysrhythmia. One of the patients had also undergone left ventricle-pulmonary artery conduit procedure.

At the time of last follow-up, 41 of 45 patients were in New York Heart Association Functional Class I - Class II.

Discussion

Ventricular inversion with L-transposition of the great arteries occurs in 1.4% of congenital cardiac defects[2]. The most commonly associated intracardiac defects are VSD (50-80%), PS (45-53%) and left atrioventricular valve regurgitation (18-90%)[1-3,7-9]. In our study, we found incidence of VSD as 69%, incidence of PS as 31% and incidence of left AV valve regurgitation as 66%.

In c-TGA, usually the posterior AV node fails to connect to His' bundle. An accessory anterior AV node is present, anteriorly adjacent to the pulmonary and mitral annuli. This node gives rise to the bundle of His, which penetrates the mitral annulus and then passes into the anterior aspect of the roof of the pulmonary outflow tract and reaches the ventricular septum. In the specimens with intact septum. His' bundle is

Table IV. Classification of 11 patients with congenitally complete AVB according to VSD

	n	Sinus rhythm n (%)	Congenital AVB n (%)
VSD	31	29 (94%)	2 (6%)
Intact ventricular septum	14	10 (71%)	4 (29%)
Total	45	39 (87%)	6 (13%)

AVB: atrioventricular block; VSD: Ventricular septal defect

anterior to the membranous septum and intervenes between the pulmonary outflow tract and left-sided ventricle. In the specimens with defects, the bundle is related to the right side of the anterior rim of the defect and bifurcates to give rise to inverted bundle branches[10-11]. Avoidance of these areas in surgical repair of VSDS and correction of subvalvar pulmonary stenosis in such cases should reduce the risk of traumatic heart block.

Furthermore, as a result of developing fibrosis in this precariously positioned AV bundle, congenital AV conduction abnormalities may occur with increasing age. Huhta et al.[12] reported that the risk of complete AVB increased linearly with age at a range of approximately 2% per year. The incidence of complete AVB in the median 10 year follow-up period is as high as 30%[12,13]. The patients reported previously had been followed from childhood to late adulthood. Congenital complete AVB in our series was 13% in the median 3.5 years (range 3 days to 12 years). The incidence of congenital complete AVB in patients with intact ventricular septum was higher than in those with VSD (29% and 6%, respectively). Similar results were also reported by Huhta et al.[12] and Daliento et al[13]. These results may be due to the longer life expectancy in these patients than in those with complicated c-TGA or to the greater mechanical stress exerted on the conduction system when the ventricular septum is intact[10,12,13].

The incidence of postoperative complete AVB in 17 patients who had VSD repair was 29% (5 patients). Two of five patients with VSD repair also underwent pulmonary commissurotomy. Previous studies have reported incidence of postoperative complete AVB as 24-26% in patients with VSD repair[12,14]. Furthermore, McGrath et al.14 observed that older age at repair was a risk factor for the development of heart block in patients with ventriculoarterial connections other than discordant ventricouloarterial connection, in which atrioventricular valve chordae may straddle or attach to the edge of the VSD. This may be due to a morphologic variability in the location of the AV node and His' bundle that makes patients with c-TGA less likely to develop complete heart block.

In congenitally c-TGA, first-and second-degree AV block may precede complete AV block, as histologic study has revealed that fibrosis of the His bundle is a typical finding of acquired complete AV block[1,12,13]. Therefore, first-and second-degree blocks in patients with c-TGA must be followed carefully. One patient had first-degree AV block and was followed up without progressing to complete AV block.

In congenitally c-TGA, atrial arrhythmias and Wolff-Parkinson-White syndrome are occasionally present[4,6]. We observed ventricular and supraventricular ectopic beats in seven of 19 patients with dysrhythmia. Ventricular ectopic beats were fewer than 10 to 20 per hour, and were evaluated as infrequent[15]; no treatment was necessary for them.

We conclude that patients with c-TGA are at increased risk of developing complete AV block throughout their lives. Careful follow-up of these patients may be benefical in preventing poor prognosis resulting from dysrhythmia. Indication for the implantation of a permanent pacemaker should be considered in symptomatic children because of the high incidence of sudden cardiac deaths.

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Early physiotherapy intervention in premature infants

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SUMMARY: Yiğit Ş, Kerem M, Livanelioğlu A, Oran O, Erdem G, Mutlu A, Turanlı G, Tekinalp G, Yurdakök M. Early physiotherapy intervention in premature infants. Turk J Pediatr 2002; 44: 224-229.

Preterm infants are more likely to have disabling cerebral palsy (CP) than term infants. It has been reported that early therapeutic approaches may be appropriate for infants at risk of neuromotor dysfunction, to minimize the degree of future handicaps. Two hundred and twenty-nine infants born at less than 34 weeks' gestation, with birth weight ≤2,000 g, cared for in the neonatal intensive care unit of Hacettepe University Hospital between January 1997-June 1999 were included in this study. Of the 229 infants initially included, 39 (17%) were dropped from the study within the first 12 months' assessment, due to lack of participation from the families. Thirty of the remaining 190 infants were found to have perinatal hypoxia or abnormal neurosonography, and were taken as the group at risk of development of CP, thus receiving early intervention therapy; these are listed as "premature at risk". The study group consisted of 160 infants not considered at risk. These were randomly paired into two groups of 80 infants, one that was given early interventional therapy, and the control group that received no program. Eleven of the 30 infants at risk, 2 of the 80 infants from the intervention group, and 4 of the 80 from the control group were diagnosed as having CP within the first six months of life.

There was no difference in the age of loss or acquisition of reflexes and general abilities between the intervention and control groups. There was no difference in the prevalence of CP between the intervention and control groups. In conclusion this study showed no effect of early intervention in premature babies without risk of CP other than prematurity.

Key words: physiotherapy, early intervention, premature.

Preterm infants are more likely to have disabling cerebral palsy (CP) than term infants. Early exposure to the extra-uterine environment may impact on motor development in these infants, increasing length of exposure and impacting differentially on motor development according to gestational age at birth. Certain aspects of motor maturation may be delayed by early birth, while others may be accelerated by the extra-uterine experience[1]. Motor development is an important area for monitoring of preterm infants since one-third of all cases of CP occur in children born prematurely[2]. Physical therapy has been the treatment of choice for children suffering from neuromotor disorders such as CP[3]. It has been reported that early therapeutic approaches may be appropriate for infants at risk of neuromotor dysfunction, to minimize the degree of future handicaps. However, affected children are often not identifiable at birth, thus making early treatment impossible. Twenty-seven studies of early intervention programs found that 93% of all studies reported successful interventions; however, these were often based on subjective reports and observations. Reviewers found statistical support for effectiveness in only 48% of the studies[4]. In another study[3], designed to show prevention of CP by early intervention, no statistically significant difference in the neurologic status or motor and overall development was found after 12 months of

treatment. The current study is designed to assess the effects of early interventional therapy in preterm infants.

Material and Methods

Two hundred and twenty-nine infants born at less than 34 weeks' gestation, with birth weight ≤2,000 g, cared for in the neonatal intensive care unit of Hacettepe University Hospital between January 1997-June 1999 were included in this study. Patients were registered for the study before discharge from hospital. Infants with severe congenital malformation, chromosomal abnormalities or metabolic diseases were excluded from the study. Gestational age was determined according to the last menstrual period and/or early ultrasound, and confirmed by New Ballard Score[5]. Full details of the pregnancy, birth history, Apgar scores and neonatal course (including details of nutrition, bilirubin levels, oxygen supplementation, and ventilatory support) were collected prospectively. Perinatal hypoxia diagnosis was made for the following infants: 1) with Apgar score of 5 or less at five minutes, 2) with cord blood pH lower than 7, and 3) when required bag and mask ventilation for more than three minutes immediately after birth. Cranial ultrasonography was performed on all infants, while cranial tomography or magnetic resonance imaging was performed in infants with abnormal neurosonography findings. For the first nine months, all study infants were seen monthly by the same physical therapist, then once every three months until 18-24 months old. Infants were also assessed by a neonatologist and a pediatric neurologist.

Assessment was made, recording age at acquisition of general abilities (e.g. head control, rolling, crawling, sitting and walking) and reflexes (e.g. protective extension, corrective reaction, equilibrium), and age at loss of primitive reflexes [e.g. Moro, symmetrical tonic neck reflex (STNR), asymmetrical tonic neck reflex (ATNR), and positive support][6]. Ages of acquisition of general abilities or of loss of primitive reflexes are given at chronologic and corrected ages.

Infants with perinatal hypoxia or abnormal neurosonography findings were included in the group at risk of development of CP and taken into early intervention therapy. Infants without any risk other than prematurity were assigned to intervention and non-intervention subgroups. Infant in the intervention group, like the children in the at risk group, were treated in hospital according to techniques previously described[7-10]. In addition they were given a home exercise program.

The diagnosis of CP was based on persistently abnormal neurological examination (spasticity and/or variable tone and/or persistent primitive and pathologic reflexes) and functional impairment (including abnormal quality of movement). Data are presented as means (SD). Differences among groups were tested using Student's t test, one-way analysis of variance and chi-square analysis.

Results

Of the 229 infants initially included, 39 (17%) were dropped from the study within the first 12 months' assessment, due to lack of participation from the families. Thirty of the remaining 190 infants were found to have perinatal hypoxia or abnormal neurosonography, and were taken as the group at risk of development of CP thus receiving early intervention therapy; these are listed as "premature at risk". The study group consisted of 160 infants not considered at risk. These were randomly paired into two groups of 80 infants, one that was given early interventional therapy (listed as "study group"), and the control group that received no program (listed as "control group"). Eleven of the 30 infants at risk, 2 of the 80 infants from the intervention group, and 4 of the 80 from the control group were diagnosed as having CP within the first six months of life. As soon as diagnosis was made; all 17 infants were given specific therapy[11] appropriate to their condition and were considered as a fourth study group, namely CP. Table I shows mean birth weight, gestational age, gestational height, Apgar scores, gender, parental education levels and relevant hospital data for the four groups. Birth weights and birth heights of children in the at risk group were lower than for the other babies. Hospitalization and ventilation times of babies with CP were significantly longer than for babies in the other groups. Table II shows age of loss of primitive reflexes and age of acquisition of general abilities for intervention, non-intervention and risk groups. There was no difference in the ages of loss or acquisition of reflexes and general abilities between the study and control groups other than for Moro reflex.

Table I. Characteristics of the patients

		Study group Exercise (+) N=78		Control group Exercise (-) N=76		Premature at risk N=19		Cerebral palsy N=17	
Characteristics		Mean±SD		Mean±SD		Mean±SD		Mean±SD	
Gestational age (weeks)		31.27±2.18		31.98±1.60		31.31±1.85		30.68±3.18	
Birth weight (g)		1543±54±411.24		1578.79±410.85		1356.27±429.25*		1517.25±654.08	
Birth height (cm)		40.48±3.57		40.80±5.46		38.66±3.63*		40.46±4.32	
Apgar (5 min.)		7.56±1.60		7.67±1.62		6.26±2.68		6.66±1.41	
Hospitalization time (days)		17.70±10.70		16.05±9.29		24.78±14.26		34.11±32.72**	
Ventilation time (days)		4.05±2.74		3.50±2.28		4.23±2.74		7.57±1.52**	
Mother's age (years)		30.18±5.19		29.88±4.96		28.89±5.44		32.00±6.94	
		N	%	N	%	N	%	N	%
Gender	Girl	38	48.7	33	43.4	7	36.8	8	52.9
	Boy	40	51.3	43	56.6	12	63.2	9	47.1
Labor	Cesarean	67	85.9	58	76.5	17	89.5	15	88.2
	Normal	11	14.1	18	23.5	2	10.5	2	11.8
Pregnancy	Single	50	64.1	52	68.4	16	84.2	15	88.2
	Multiple	28	35.9	24	31.6	3	15	2	11.8
Parental Education Level									
Primary School	Mother	23	29.5	30	39.5	7	36.8	6	35.3
	Father	12	15.4	13	17.1	4	21.0	5	29.4
High School or University									
	Mother	55	70.5	46	60.5	12	63.2	11	64.7
	Father	66	84.6	63	82.9	15	79.0	12	70.6

* $p<0.05$
** $p<0.01$

Age of loss of Moro reflex was slightly lower in the control group than in the study group. Acquisition age of protective extension reflex was higher in babies at risk than in the other groups. Chronological ages of loss of primitive reflexes seen in both study and control groups were compatible with generally accepted ages for term babies, while corrected ages of acquisition of general abilities seen in both study and control groups were also compatible with generally accepted ages for term babies[12].

Five of 78 babies from the study group showed mild spasticity and hyperreflexia within the first two months of life. These symptoms were virtually resolved by the time the babies reached four months of corrected age. Table III gives medical diagnosis of the study and control groups during hospitalization, showing no difference between the study and control groups. Table IV shows age of loss of primitive reflexes and age of acquisition of general abilities for babies diagnosed as CP versus the control group. Age of loss of Moro reflex and motor developmental levels were very different from the control group.

Discussion

Preterm birth is associated with a clear increase in risk of CP[13,14]. Several hypotheses have been proposed to explain the origins of CP in preterm babies. It may be result of ischemic insult in utero, leading to both preterm birth and damage to white matter[13] or, it may be that immature babies, who are vulnerable to cerebral hemorrhage and ischemia, sustain injury as a result of intrapartum and neonatal complications[15]. The stress and medical complications associated with preterm birth are presumed to have a negative influence on development, resulting in the differences seen between preterm and fullterm infants[2].

Early intervention strategies for premature babies for the prevention of CP were first developed in 1980. One of these studies, conducted by Piper et al[3]., failed to show any

Table II. Age of loss primitive reflexes and age of acquisition of general abilities for intervention. Non-intervention and risk groups

	Study group		Control group		Premature at risk	
	Corrected age	Chronologic age	Corrected age	Chronologic age	Corrected age	Chronologic age
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD
Moro	3.40±1.00	5.32±0.94	3.04±1.49*	4.90±1.46*	3.66±1.35	5.66±1.23
STNR	2.79±1.17	4.63±1.80	2.77±1.15	4.66±1.12	3.15±0.87	4.73±1.09
ATNR	2.95±1.12	4.78±1.06	2.67±1.18	4.42±1.09	2.92±1.23	4.57±1.34
(+) Support	2.29±1.29	4.23±1.23	2.03±1.54	3.84±1.77	2.91±1.02	4.78±0.89
Protective extension	5.98±1.24	7.94±1.25	5.95±1.04	7.55±1.10	6.27±1.09*	8.00±1.56*
Corrective reaction	4.87±1.27	6.72±1.23	5.31±0.95	5.35±1.00	7.40±0.84	
Equilibrium	6.03±1.09	8.00±0.98	5.71±1.22	7.52±1.03	6.38±0.76	8.44±0.72
Motor Developmental Levels						
Head control	2.20±1.09	4.07±1.02	2.29±1.32	4.17±1.38	2.67±0.85	4.66±0.90
Rolling	4.91±1.21	6.85±1.21	4.91±1.17	6.76±1.21	4.79±0.94	6.77±0.93
Sitting	7.10±1.58	9.02±1.56	6.54±1.53	8.33±1.59	6.10±1.69	8.10±1.59
Crawling	8.70±1.59	10.48±1.63	8.52±1.74	10.19±1.69	9.35±1.21	11.14±1.21
Walking	12.47±2.25	14.41±2.18	12.18±3.10	13.91±3.18	13.72±3.61	15.63±3.55

* $p<0.05$ STNR symmetrical tonic neck reflex ATNR asymmetrical tonic neck reflex

improvement in the early intervention group when compared to the control group. In another study, researchers found no differences between neurodevelopment treatment and control groups at one year of age[16]. A six-year follow up by this group reported no long-term effects of early intervention in the prevention of CP[17]. In 1990, the Pediatric Section of the American Physical Therapy Association concluded that there was no evidence that physical therapy reduces muscle tone or primitive reflexes, although some current evidence claimed positive effects of physical therapy on postural control[18]. Quantitative analysis of the treatment effects of 49 studies of early intervention showed poor statistical validity[19]. Another quantative analysis, looking at 91 effects from 31 early intervention studies, determined that the data showed moderate positive effects of treatment[20].

Table III. Medical diagnosis of the study and control groups

	Study group		Control group	
Medical problems	N	%	N	%
Sepsis	6	7.7	3	3.9
Pneumonia	2	2.6	1	1.3
SGA	6	7.7	7	9.2
RDS	7	9.0	7	9.2
Hypoglycemia	1	1.3	5	6.6
Hypocalcemia	3	3.8	3	3.9
NEC	5	6.4	4	5.2

The current study was also unable to show any clear effect of early physiotherapy on motor functions in preterm infants with birth weight ≤2,000 g. This study confirms the lack of response to hospital and home intervention in either the at-risk or normal premature groups compared with controls, showing no clear effect. It is possible that our early intervention therapy may have brought benefits not measured in this study. Early intervention might have been effective for the five infants from the intervention group showing hypertonicity and hyperreflexia in the early weeks of life. The highest rate of CP was found in the group accepted as at risk (36%). This shows that criteria used for determining infants at risk of developing CP were efficient. Although there was no statistical difference between study and control groups for incidence of CP, higher CP prevalence was found in control group (2 versus 4). The rate of CP for preterm infants below 34 weeks gestational age varied from 2.4-9%[21,22]. The CP rate found in this study (8.9%) is in accordance with these values. Although no term control group was included in this study, it is interesting to see that in both study and control groups age of loss of primitive reflexes was in accordance with term babies for chronological age while age of acquisition of general abilities was compatible with generally accepted ages for term babies for corrected age.

Table IV. Ages of loss of primitive reflexes and of acquisition of general abilities for babies diagnosed as CP versus the control group

	Cerebral palsy (CP)		Control	
Reflex	Corrected age Mean±SD	Chronological age Mean±SD	Corrected age Mean±SD	Chronological age Mean±SD
Moro	3.87±1.72*	6.08±1.83*	3.04±1.49*	4.90±1.46*
STNR	3.45±1.42	5.81±1.77	2.77±1.15	4.66±1.12
ATNR	4.04±1.23	6.16±1.46	2.67±1.18	4.42±1.09
(+) Support	2.57±1.33	4.92±1.38	2.03±1.54	3.84±1.77
Protective extension	7.92±1.17	10.14±1.34	5.95±1.04	7.55±1.10
Corrective reaction	5.27±1.78	7.66±0.58	5.31±0.95	7.14±0.99
Equilibrium	7.07±1.01	9.28±1.11	5.71±1.22	7.52±1.03
Motor developmental levels				
Head control (n=17)	2.55±1.31	4.90±1.41	2.29±1.32	4.17±1.38
Rolling (n=17)	7.25±4.26*	9.58±4.14*	4.91±1.17*	6.76±1.21*
Sitting (n=14)	10.23±4.37**	12.69±4.40**	6.54±1.53**	8.33±1.59**
Crawling (n=12)	13.33±6.29*	15.88±6.58*	8.52±1.74*	10.19±1.69*
Walking (n=10)	22.25±8.42**	24.62±8.76**	12.18±3.10**	13.91±3.18**
Clinical type	N	%		
Spastic Diplegia	12	70.6		
Spastic Tetraplegia	3	17.7		
Spastic Hemiplegia	2	11.7		

* $p<0.05$

** $p<0.01$

STNR symmetrical tonic neck reflex ATNR asymmetrical tonic neck reflex

The patients diagnosed as CP were given neurodevelopmental therapy, as it is one of the most common approaches for infants presenting mild-to-moderate neurological dysfunction. In this study most of the infants with CP were diagnosed around the age of six months. One of the benefits of the study was the establishment of the importance of a routine follow-up program for all infants diagnosed as at risk of developing CP. In conclusion, this study showed no effect of early intervention in premature babies without risk of CP other than prematurity.

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Risk factors of early childhood caries in Turkish children

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SUMMARY: Ölmez S, Uzamış M. Risk factors of early childhood caries in Turkish children. Turk J Pediatr 2002; 44: 230-236.

This study was performed to determine the relationship between infant feeding habits, oral hygiene patterns, parents' education level and early childhood caries (ECC) in nine-to 59-month-old Turkish children. Clinical examinations were carried out by a pediatric dentist using dmft indices, and the dmft was found to be 5.8. In the other part of the study, the mothers completed questionnaires for information related to risk factors. Father's education level and fluoride consumption showed statistical associations with caries. Breast - bottle-feeding together was more common, and these children had a higher prevalence of caries than the children who were only breast-fed. Also, children who were bottle-fed at night developed more caries lesions. Frequent consumption of sugar-containing beverages was a common habit among children. Brushing habit did not have any effect on carious development in this study. Based on these associations it is concluded that ECC is a risk factor for general health of children in Turkey.

Key words: early childhood caries, risk factors.

Early childhood caries (ECC) is a specific form of rampant caries attributed to the prolonged use of a nursing bottle containing fermentable carbohydrate liquids. Not only bottle abuse but also prolonged breast-feeding is considered to be a contributing factor to the development of caries in early childhood[2-7]. This condition is also attributed to frequent use of sweetened medicaments[8,9] and to sweetened pacifier usage[10].

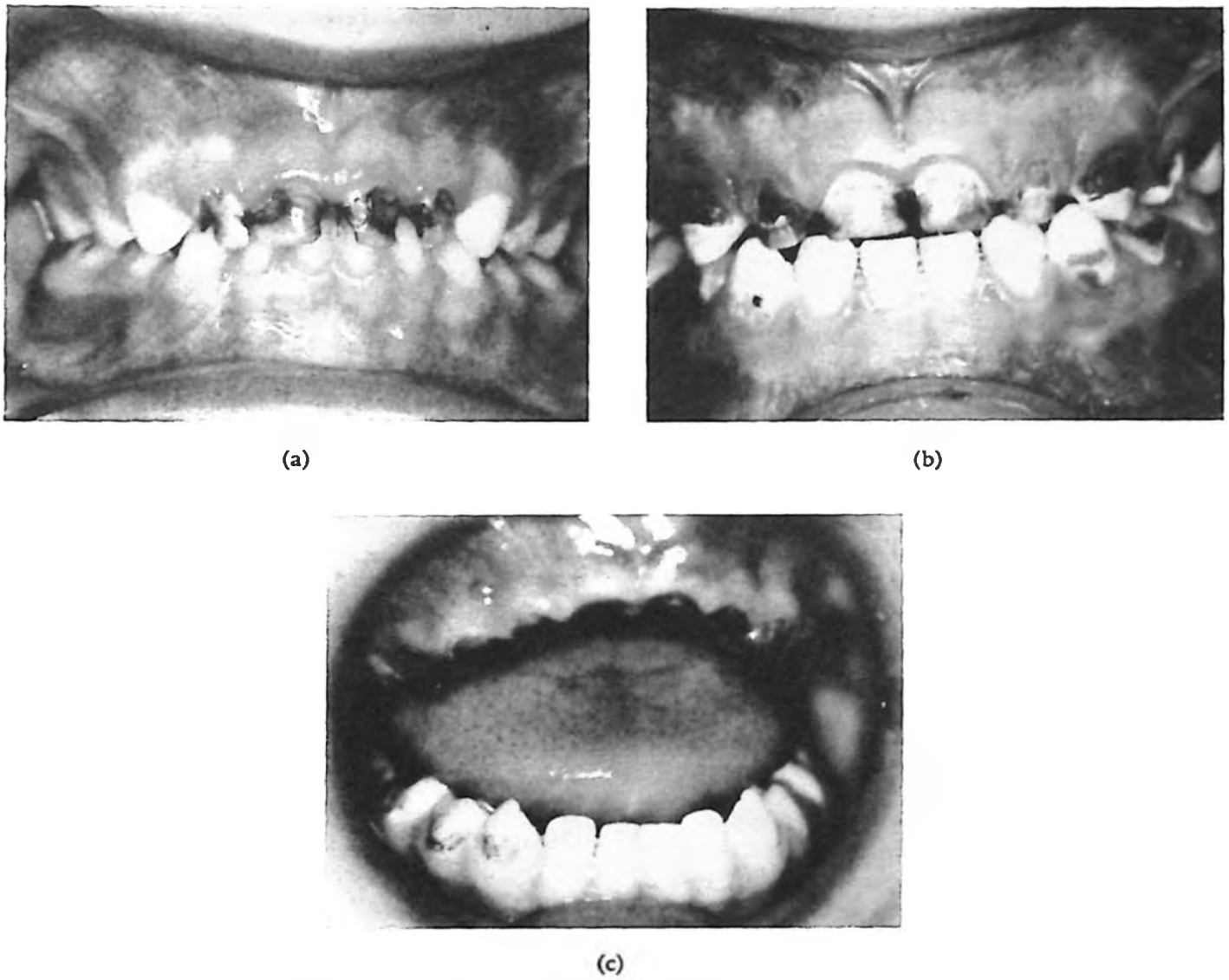
The syndrome has been characterized as first affecting the labial and lingual surfaces of the four maxillary incisors followed by maxillary molars, mandibular molars and, rarely, mandibular incisors [10](Fig. 1a, b, c). More extensive patterns of caries are observed in toddlers with prolonged nursing habits and lack of oral hygiene.

Despite considerable advances in the prevention of dental caries, it is still a problem among infants and toddlers living in poor economic circumstances in both developing and industrialized countries in which undernutrition is common[1]. The number of children suffering from this form of dental decay ranges between 1-70% among different cultural and ethnic groups[11]. In industrialized countries the prevalence, severity and patterns of caries are thought to relate to determinants that include social and educational background, and dietary and oral hygiene practices[12,13]. These factors may not affect caries development in the same way in developing countries. The prevalence of ECC in Turkey has been determined as 8% in a population of high socio-economic groups and might be high as 10% for the country as a whole[14].

A child who has poor oral health is not a healthy child, and any efforts to improve child health which do not address oral health are certain to fail[15]. An understanding of the relationship between etiological factors and ECC is necessary to better comprehend the situation and to develop new public health programs. The purpose of this study therefore, was to evaluate factors related to ECC to find out successful solutions to the public health challenges.

Material and Methods

One hundred and twenty children aged nine to 59 months and their parents who were seen in our clinic in Ankara were eligible to participate in this study. The participants live in the area



(a) (b)

(c)

Fig. 1 a, b, c. Intraoral view showing early childhood caries.

where the fluoride level in the drinking water is less that 0.3 ppm. In the first part of the study the mothers were asked to complete a questionnaire comprised four sections. The first section covered general information concerning the health condition of the child and the ages and education levels of the parents. The second section was devoted to aspects concerning the child's teeth. In the third section all suspect nutritional habits that might have contributed to the condition of the teeth were recorded. The last section of the questionnaire concerned the prevention of oral infections through brushing, and the use of fluoride by topical or systemic administration.

In the second part of the study one pediatric dentist examined the children using # 23 explorers, front surface mirrors and flashlights. Before the clinical examination, the dentist brushed the child's teeth. Any remaining plaque was cleaned with a sterile gauze during the examination. For each child the number and location of caries teeth were recorded. When two or more maxillary teeth were affected by dentine caries and the caries in the other teeth followed the pattern of caries with regards to the time of eruption, the caries was considered to be ECC[3].

The relationships between the variables of the questionnaire were analyzed using the two-way chi-square test statistics.

Results

Of the total 120 children included in this study 58 were boys (48.3%) and 62 were girls (51.7%). Early childhood caries was seen in 83 (69.1%) children. The mean dmft was 5.8 per child. Seventeen children (14.1%) showed caries in four maxillary incisors. The more extensive

Table I. Number and percentage of children (n=120) with caries experience and relation to children's age and gender

	Total		Caries-free		With caries	
	n	n%	n	n%	n	n%
9-24 months	49	40.8%	28	57.1%	21	42.9%
25-59 months	71	59.2%	9	12.7%	62	87.3%
Gender						
Boys	58	48.3%	16	27.6%	42	72.4%
Girls	62	51.7%	21	33.9%	41	66.1%

patterns of caries involving incisors and/or canines and primary molars were seen in 50.8% (n=61) of the children. Only five children had less than two caries (Table I).

Prevalence of caries in relation to age and gender is shown in Table I. Caries was seen in 21 (42.9%) of the 9 to 24-month-old children and in 62 (87.3%) of the 25 to 59-month-old children. Analysis using the chi square test confirmed differences with age to be statistically significant (x^2=26.88, p=0.000) (Table I).

The relation between education level of the parents and caries is shown in Figure 2. The education level of the sample showed that while 76 (63.3%) of the mothers and 63 (44.2%) of the fathers were either illiterate or had finished primary school, 44 (36.6%) of the mothers and 67 (55.8%) of the fathers were educated at high school or university level. Analysis using the chi-square test showed differences between father's education level and prevalence of caries to be statistically significant (x^2=9.294, p=0.002). However, mothers' education level and prevalence of caries did not confirm differences to be statistically significant. In accordance with findings in relation to fathers' education, children whose fathers were educated at the high school or university level showed more nursing caries than children whose fathers were educated at a lower level (Fig. 2).

The pattern of basic factors in ECC formation, i.e. weaning habits, consumption of sugar-containing beverages, use of sugar-containing medication, tooth-brushing habit and fluoride consumption, is shown in Figures 3, 4 and 5. Thirty-eight children had been solely breast-fed and 82 had been fed using both breast and bottle. There were two children who had been only bottle-fed. For those who were breast-fed, 73.6% of the children continued breast-feeding beyond one year of age. The duration of breast-feeding and bottle usage was not significantly associated with caries development, but both breast- and bottle-feeding was a risk factor when used for one year or more. Sixty-eight children were using the bottle most often at night, and 73.5% of these children on avaerage, who used bottle at nighttime, suffered from caries.

According to replies in the questionnaires, 65.8% of the children with ECC were still being

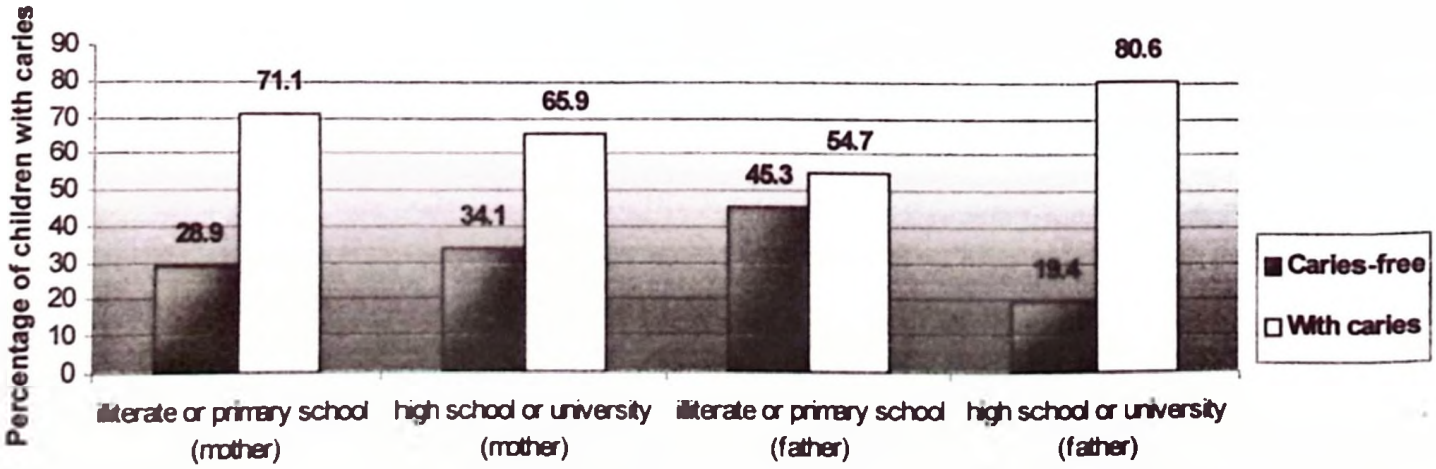


Fig. 2. Percentage of children with caries experience according to education level of the parents.

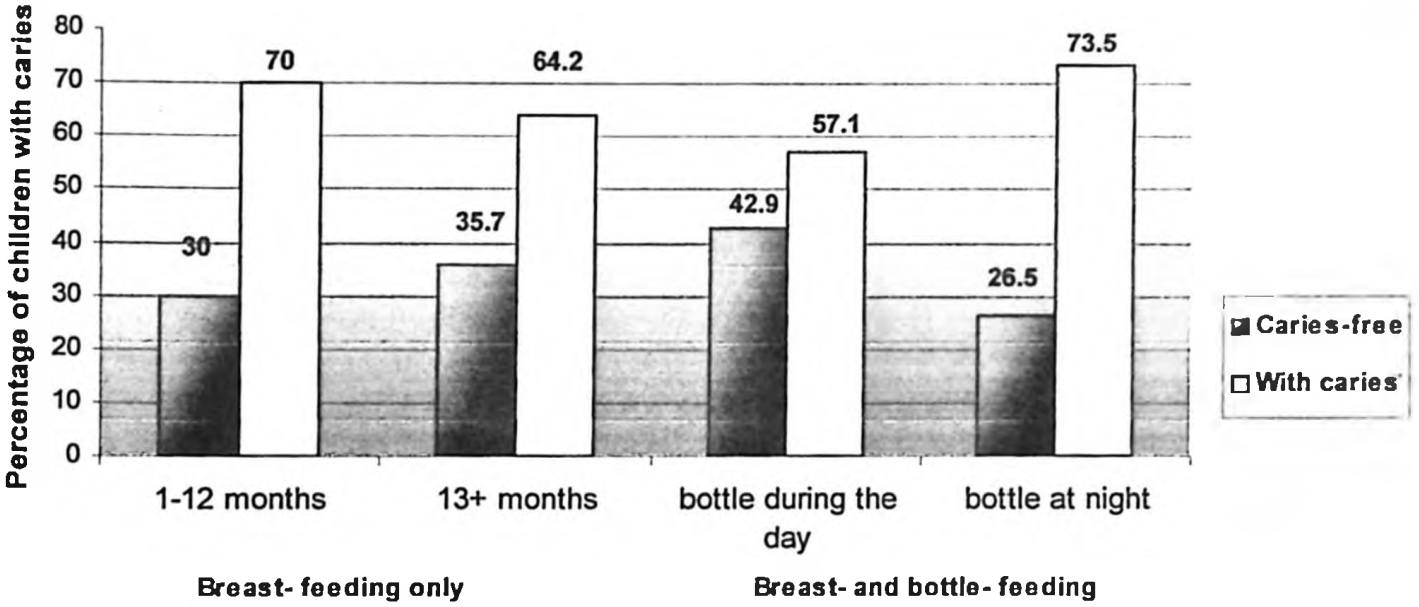


Fig. 3. Percentage of children with caries experience according to nursing habits.

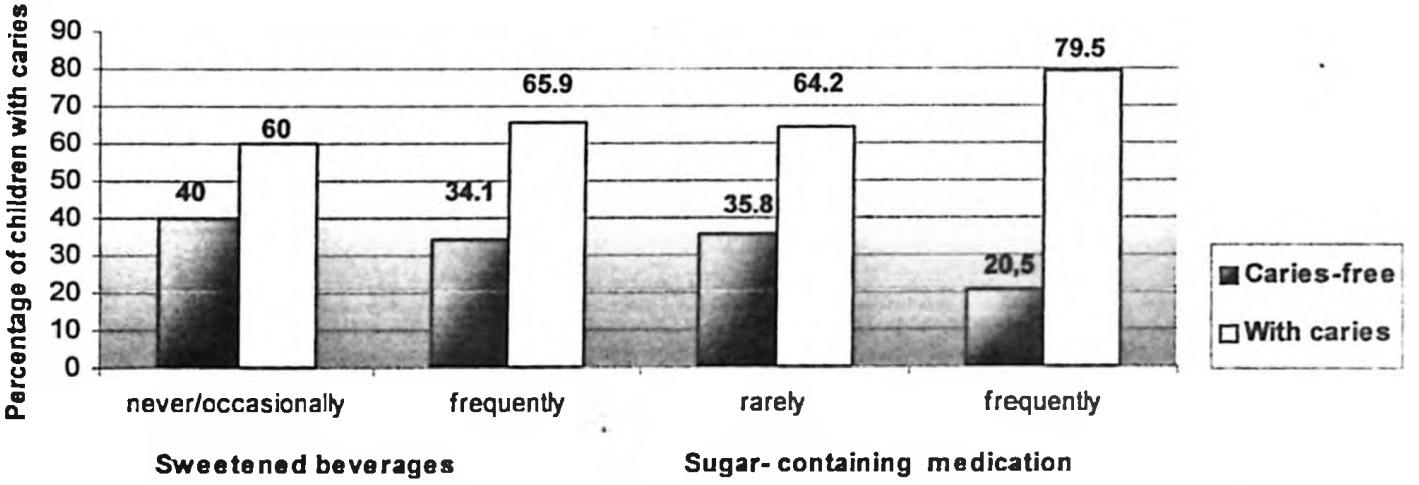


Fig. 4. Percentage of children with caries experience according to sweetened beverages and sugar-containing medication intake.

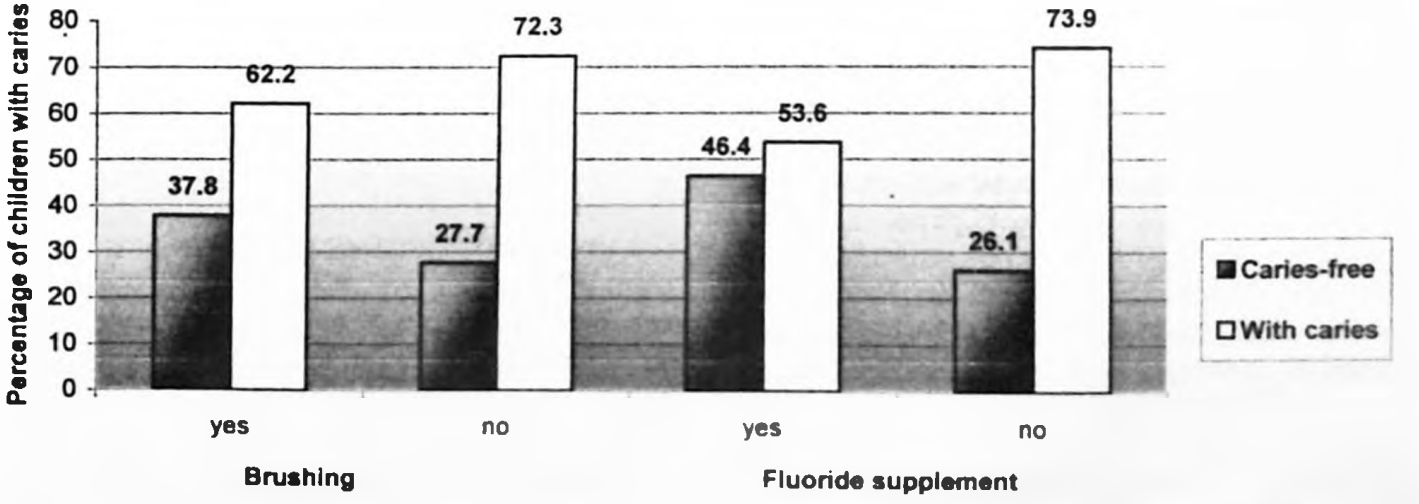


Fig. 5. Percentage of children with caries experience according to brushing and fluoride supplement usage.

given milk in an infant bottle with sugar, honey or other sweet items added, two or more times a day. Children who never/occasionally or frequently used sweetened beverages in the bottle developed caries lesions at rates of 60% and 65.9%, respectively. Although sweetened beverages are a risk factor for caries development, there was no statistically significant relationship between consumption frequency of sweetened beverages and ECC.

No significant association between the usage of sugar containing medicine and development of caries was found in our study.

An examination of brushing habit revealed that 30.8% of children brushed their teeth with fluoridated toothpaste. Of these children 62.2% developed ECC, while 72.3% of the non-users developed ECC. The brushing habit did not show differences in nursing caries development statistically ($x^2=1231$, $p=0.267$).

Finally, 73.9% of the children with ECC had never taken fluoride supplement. The difference between the fluoride supplement consumption and caries development was significant ($x^2=4.163$, $p=0.041$).

Discussion

This study considered prevalence of ECC and association with caries risk factors in nine-to-59-month old Turkish children. The mean dmft of this population was 5.8. According to three other studies conducted in our country, the mean or percentage of dmft of preschool children were found to be 1.08[16] 0.68[17] 16,5[18]. The mean dmft in this study was found to be higher than the other studies, perhaps because as the study group was chosen from the patients who applied to our clinic.

Appropriate breastfeeding is well recognized as the best diet for infants. However, both uptake and duration of breast-feeding varies within and between countries and depends on several factors, such as medical professionals' guidelines, traditions, and cultural and social contexts[12]. For example, 31.6% of the children in this study had been soleley breast-fed and 73.6% of them had been breastfeeding beyond 13 months. In a Swedish study, only 7% of the Swedish infants were breastfed at twelve months[19]. The average duration of breast-feeding among Jordan children is 8.9 months[13]. Under normal dietary conditions, milk is not considered to be cariogenic agent, but repeated and prolonged exposure leads to a larger decrease in plaque pH[20]. Although both plaque and enamel dissolutions are less for bovine and human milk compared to lactose and sucrose solutions, it was found that in comparison to bovine milk, more enamel dissolution was caused by human milk[21].

From the reported findings, the impression may be gained that breastfeeding is undesirable. However, the clinical reports attributable to on-demand breastfeeding are extremely rare, and the benefits of breastfeeding overweight any possible harmful effects. Simple preventive measures such as tooth cleaning from an early age should do much to prevent onset and development of breastmilk caries[22].

In this study, 73.6% of the children were breast-fed beyond 13 months. Duration of breast-feeding did not significantly relate to the presence of caries, and the mean caries scores were high in all groups. Like some other authors, we concluded that it is not the breast-feeding necessarily that causes dental caries, but rather other caries-promoting habits like poor oral hygiene, intake of sugar-containing beverages or low fluoride consumption[23-27].

According to the results of the study, breast-feeding and bottle usage together was more common among children. Children who were using a bottle at night developed more caries lesions than those the others who only a used bottle during the day.

Reports on the subject have shown that the manner in which a child falls asleep is the most important factor in ECC development[28]. The mouth volume of milk obtained from the artificial nipple is not enough to stimulate the swallowing reflex. Thus, in bottle feeding the milk accumulates in the mouth around the teeth until the swallowing reflex is stimulated[25]. This finding supports the basic theoretical mechanism of why bottle feeding at night is a risk factor of ECC. Because usage of a bottle containing sweetened milk and/or beverages is the main risk factor, it is recommended to substitute a cup for the bottle by 12 months of age[29].

Studies in many parts of the world have consistently recorded that caries was higher among children of mothers with the lowest

levels of education[12,13]. According to our study, mothers' education level had no effect on the percentage of ECC. This might be due to the lack of oral health education among Turkish mothers. Another interesting finding is that the higher the education level of the father, the higher the incidence of the caries. Generally, mothers are the primary promoters of oral hygiene practices, and they have a major influence on the dietary habits and food choices of infants, toddlers and children[30-34]. An education program should be developed in order to change the parents' and especially mothers' attitudes and behaviors towards dental hygiene of their children in our country.

According to Horowitz[29], children who receive frequent exposure to sugar containing antibiotics are at risk of ECC. According to the results of our questionnaire, 81% of the children were using sugar containing medicine; however, a significant association between sugar-containing medicine usage and caries development was not found.

It is recommended that parents clean their children's teeth with a sterile gauze daily and begin brushing their teeth by the age of one year without using a dentifrice[35]. A fluoridated dentifrice should be used by the age of three. Although a high percentage of children (69.2%) did not brush their teeth, there was no significant difference between brushing habit and caries development. We concluded that the brushing was not done after each feeding, thus allowing early caries lesions to form. These results are in accordance with the findings of Muller[8], who defined poor oral hygiene as one of the risk factors of ECC. Ankara is a non-fluoridated area. According to İsmail[31], children who live in non-fluoridated communities may benefit from professional fluoride applications as well as the use of fluoride tablets and drops. However, both topical application and fluoride supplement usage are very rare in Turkey. Our study confirms this finding, as 23.3% of the children benefited from the effect of fluoride.

As a result, we conclude that EEC is a risk factor for Turkish children. Very young children who are unable to cooperate when receiving restorative care for the most part require costly treatment in a hospital under sedation or general anesthesia[36,37]. Unfortunately, it is impossible to treat every child suffering from ECC in such conditions[38]. Since prevention rather than treatment is the best solution of ECC, the education and training of parents about healthy dietary feeding and oral hygiene habits before the eruption of the first teeth and treatment of infants diagnosed with early signs of ECC are essential to prevent ECC.

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A hospital outbreak of aseptic meningitis due to echovirus type 30 in Antalya, Turkey

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SUMMARY: Akman S, Özkaya E, Çolak D, Daloğlu M. A hospital outbreak of aseptic meningitis due to Echovirus type 30 in Antalya, Turkey. Turk J Pediatr 2002; 44: 237-239.

We analyzed clinical and laboratory findings of 23 hospitalized patients with aseptic meningitis in the Department of Pediatrics, Akdeniz University Hospital. The patients presented with the classic symptoms and signs of aseptic meningitis. Protein levels of the cerebrospinal fluid (CSF) samples ranged from 18 to 99 mg/dl, with a mean of 36.5±4.9 mg/dl. The mean ratio of CSF glucose compared to blood samples was 0.73. Echovirus type 30 was identified in CSF and/or stool samples of 19 patients. Four patients had negative virus culture. The outcome was favorable in all patients. We thought that this outbreak of aseptic meningitis in our department might denote a summer outbreak in the city. However, this remained unproven since field investigations could not be completed. Advances in virus culture or polymerase chain reaction techniques and satisfactory medical records may help patient care by promoting early diagnosis and by eliminating unnecessary antibiotic therapy, allowing epidemiological studies.

Key words: aseptic meningitis, echovirus type 30.

Acute aseptic meningitis is characterized by fever, vomiting, headache, weakness, diarrhea, and pain in the neck, back and legs, and by cerebrospinal fluid (CSF) pleocytosis in the absence of bacteria or fungi[1,2].

The echoviruses and group B Coxsackieviruses as members of the genus Enterovirus cause more than 90% of cases[1-3]. Echovirus type 30 was first isolated in Scotland in 1959 from cases of aseptic meningitis[4]. Echovirus 30 meningitis outbreaks have previously been reported in Switzerland, the United States, Japan and German[3,5-8].

We summarize herein the clinical, laboratory and epidemiological findings of the 1999 outbreak of Echovirus type 30 in the Department of Pediatrics, Akdeniz University Hospital.

Material and Methods

Between July and September 1999, 43 patients with clinically suspected aseptic meningitis were admitted to our department. For detecting the existence of an epidemic, the numbers of observed and estimated cases were determined for every month of 1999. The observed cases in August (n=25) and September (n=13) were prominently more than monthly estimated cases (n=5.9).

Because of technical and financial problems, CSF and stool samples of only 23 patients could be sent to the reference laboratory; thus, clinical and laboratory data presented includes only these 23 patients.

During this outbreak, the patients had been admitted with fever, vomiting, headache, and signs of meningeal irritation. Lumbar punctures on patients, with the exception of one with brain edema, were all done within one day of onset of illness. The diagnosis was supported by examination of the CSF, which included leukocyte count, measurement of protein and glucose levels, Gram's stain, and culture for viruses, bacteria and fungi.

Viral culture: 34 samples (11 CSF and 23 stool) from 23 patients were collected in sterile containers, and frozen at -70°C until analyses. The stool culture for all patients was done,

whereas the CSF culture could not be done in 12 patients. All specimens were transported to laboratory in dry ice. Virus isolations were performed in Virology Laboratory of the Refik Saydam Center of Hıfzıssıhha in Ankara. CSF was cultured directly. Ten percent stool suspensions in phosphate-buffered saline were centrifuged, and the supernatants were used for inoculation of virus culture.

Virus culture was inoculated with a minimum of 0.2 ml of specimen and incubated at 35°C. Inoculation was performed into tube monolayer cultures of Hep 2 and RD cells. The tubes were observed daily for cytopathic effect (CPE). Cultures showing CPE were passaged onto fresh cells. Positive isolates were typed by micro neutralization with the use of intersecting pools of hyperimmune sera supplied by the European Reference Center for Poliomyelitis, Bilthoven, The Netherlands.

Results

Mean age of 23 patients was 6.2 years (range 16 months to 12 years, 14 male, 9 female). Fever (91%, n=21), which ranged from 38 to 40°C, headache (91%, n=21) and vomiting (87%, n=20) were the most significant symptoms associated with infection. Other common symptoms/signs included weakness (30%, n=7), abdominal pain (17%, n=4), leg pain (17%, n=4), diarrhea (n=1), confusion (n=1) and macular rash (n=1). At least one of the meningeal irritation signs, such as stiff neck (n=21), (n=10) or Brudzinski (n=17) signs, was positive in all patients. Leukocyte counts of CSF ranged from 0 to 570 cells/mm^3, with a mean of 175±176.7 cells. The majority of the cells were lymphocytes in 17 out of 23 CSF samples (74%). Protein levels of the CSF samples ranged from 18 to 99 mg/dl, with a mean of 36.5±4.9 mg/dl. Glucose levels of the CSF ranged from 45 to 77 mg/dl, with a mean of 58.5±12 mg/dl. The mean ratio of CSF glucose compared to blood samples was 0.73.

Patients with positive virus culture:

The virus isolation was performed positively in 28 of 34 samples. Echovirus type 30 was identified in nine CSF and 19 stool stamples of 19 patients. Six 6 samples (2 CSF and 4 stool) of four patients were negative for virus culture. Finally, 19 patients had positive virus culture while four patients had negative virus cultures.

Follow-up:

Only one patient experienced complication. Computerized tomography of this patient with brain edema was normal at tenth day of hospitalization. All patients had recovered completely at follow-up.

Epidemic aseptic meningitis due to Echovirus 30 has been reported in a few studies. The presently described outbreak in our hospital occurred at the same time as the previously reported outbreak in 15 patients in Ankara[9]. Limited data from other Echovirus 30 outbreaks suggest that Echovirus 30 is associated with a high attack rate, particularly among children. The cases recognized can be accepted as "tip of a very large iceberg" of Echovirus 30 infections. Infection may appear after an incubation period of only five 5 days, although acute illness occurs only in about half of all infected persons. Viral excretion begins with the onset of illness and appears acutely in pharyngeal secretions, but it can continue in the feces for weeks[10]. In temperate regions, transmission and disease are more common in the summer, often occurring only each summer. In tropical areas, transmission occurs year round, and more people become infected at a younger age[1,2]. Comparison of reported outbreaks in Switzerland, the United States, Japan and Germany in children reveals a number of aspects of difference. In Germany and in Alaska the first cases were found in May and the peak incidence was during June, while in New York and our department, the peak incidence was during August[5,7,8]. In all these epidemics, the reported cases tended to concentrate in more populated areas like commercial centers or large apartment buildings, a factor known to promote enteroviral transmission. Antalya serves as the economic, transportation, medical and tourism center for the Mediterranean area. This outbreak of aseptic meningitis in our department may have denoted a summer outbreak in the city. However, the estimated cases for Antalya could not be determined because of the absence of a satisfactory medical record about aseptic meningitis or gastroenteritis cases for adults and children in other hospitals. The initial field investigations could not be completed because of technical and financial failure. Prevention of transmission can be accomplished by elimination of close personal contact with infected persons, but since so many infected

persons are asymptomatic, this is virtually impossible[10].

Interesting similarities were observed in the distributions of cases by age and gender in some epidemics. The younger (<6 years old) males predominated in our department, and in the New York, Germany, Alaska, Ankara and San Diego epidemics[5,7,8,9,11].

Reintjes et al.[7] showed that children in an outbreak who had contact with an ill household member, who attended day care or who used playgrounds were three to six times more likely to become ill than those without those risk factors.

The clinical characteristics of aseptic meningitis were similar in reported epidemics and our department epidemic. However, we noted that the most prominent symptom in our department was fever (91%), while it was noted in only 40% of patients in Alaska, 76% in Germany and 66% in San Diego[5,7,11]. The CSF findings were similar to those previously described. Interestingly, two patients had no pleocytosis as those in the New York, San Diego and Alaska epidemics[5,8,11]. One patient had high WBC count in CSF sample (570/mm^3) as in the Germany epidemic[7]. Early in the disease, the cells are often polymorphonuclear; later, mononuclear cells predominate. This change in cellular type is often demonstrated in CSF samples obtained as little as 8-12 hours apart[1]. We found predominating lymphocytes (74%) within the first 24 hours. The severity of meningeal symptoms and other signs of neurologic involvement among children with aseptic meningitis vary widely. Complications such as febrile seizures, complex seizures, brain edema, lethargy, coma, and movement disorders occur early in the course in 5-10% of patients[2]. Only one of our patients experienced complication. Computerized tomography of this patient with brain edema was also normal at tenth day of hospitalization.

Our isolation percentages of the virus from nine of 11 CSF samples and 19 of 23 stool samples were higher than in the Alaska (5/19 for CSF samples and 14/25 for stool samples) and San Diego epidemics (12/27 for CSF samples), and was similar to that in the Germany epidemic (10/12 for stool samples).

Twenty-one patients had received parenteral antibiotic therapy for ten days since the differential diagnosis of viral meningitis could not be done on the grounds of clinical presentation or laboratory findings, and virological techniques failed for early diagnosis. Parenteral antibiotic therapy was administered to two patients with characteristic findings of aseptic meningitis until a bacterial cause was excluded by culture of CSF.

We diagnosed aseptic meningitis due to Echovirus 30 after hospital discharge of patients. Therefore, some patients with positive CSF and stool cultures for Echovirus took unnecessary medication. Advances in virus culture or polymerase chain reaction techniques may help patient care by promoting early diagnosis, eliminating unnecessary antibiotic therapy, allowing early hospital discharge and diminishing health-care costs.

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Familial vesicoureteral reflux in asymptomatic siblings

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A prospective study was established to identify the incidence of vesicoureteral reflux in the asymptomatic siblings of patients with reflux in our region. Of 32 patients with reflux, 37 siblings were screened with urine analysis, urine culture and contrast voiding cystourethrograms, and six (16.2%) were found to have reflux. Renal scan revealed scarring in five. We concluded that siblings of children with vesicoureteral reflux are at high risk, and must be screened so that renal damage and associated morbidity secondary to reflux might be minimized.

Key words: vesicoureteral reflux, sibling relations, hereditary diseases.

Primary vesicoureteral reflux (VUR) is the most common urological anomaly in children[1-3]. Reflux nephropathy is the cause of end stage renal failure in 3-25% of children and in 10-15% of adult patients[3-11]. Incidence of VUR is less than 1% in the general population[2,12,13]. Familial tendency of VUR detected in twins was first described by Stephens in 1955[14]. Studies performed in recent years found the incidence of VUR in siblings between 8-46%[1-3,8,15-17]. Screening of siblings for reflux has become a well accepted practice in many developed centers. Since the role of familial characteristics of reflux is known, racial differences may be present. There is not sufficient data in the literature about sibling reflux among Turkish children apart from the study of Şahin et al.[18]. A prospective study was designed to find the incidence of VUR in asymptomatic siblings of index patients with VUR in our region.

Material and Methods

With parental consent, siblings of the index patients, having no previous urological symptoms, were evaluated with routine urine analysis, urine culture and contrast voiding cystourethrograms (VCUG). Siblings positive for reflux at the end of these investigations were managed as patients with primary VUR. Siblings and patients with neurogenic bladder, posterior urethral valve, ureterocele or other congenital anomalies causing secondary reflux were not included in the study.

Results

Thirty-seven siblings (16 female/21 male) of 32 patients were studied (Table I). The ages of patients ranged from 18 months to 16 years (mean, 7.9 years). There were no previous urological symptoms in any of the siblings, and none of the families had a history of other members with VUR.

Urine analysis revealed pyuria in two siblings. One of these had unilateral low-grade (I°) reflux accompanying bilateral incomplete duplex systems. The other sibling with infection cultured E. coli, and this four-years-old male had unilateral renal scar without detectable

Table I. Sex and age distribution of siblings

Age (year)	F	M	Total
<1	–	–	–
1-2	–	2	2
3-5	2	6	8
6-10	9	10	19
>10	5	3	8
Total	16	21	37

F: female, M: male

Table II. Findings in asymptomatic siblings

	Age (year)	Sex	VCUG (side/grade)	USG	DMSA (scar)	Management	Follow-up
1♦	4	M	–	Normal	R+	conservative	w/o symptoms
2	6	M	L/2	Normal	–	conservative	VUR disappeared
3*	6	F	R/1	Normal	–	conservative	VUR disappeared
4	7	M	L/4	Left pelvicaliectasis	L+	UNS	VUR disappeared
5	9	F	L/5	Left pelvicaliectasis	L+	UNS	VUR disappeared
6	10	F	R/3	Normal	R+	UNS	VUR disappeared

VUR: vesicoureteral reflux; VCUG: voiding cystourethrogram; M: male; F: female; R: right; L: left; Bil: bilateral; UNS: ureteroneocystostomy; USG: ultrasonography.

♦ DMSA renal scan revealed scarring on the right but no detectable reflux was found.

* Bilateral incomplete duplication was detected.

reflux. VUR was noted in six siblings (16.2%) with an equal sex distribution (3M/3F). Reflux was grade I to II in two siblings. Grade III to V reflux was present in four patients, and one of them was bilateral. DMSA renal scan revealed reflux nephropathy in the latter four siblings, and all were treated surgically. The former two siblings with low-grade reflux were followed conservatively, and reflux resolved in both. All siblings with VUR were followed up without further deterioration (Table II).

Discussion

Vesicoureteral reflux is a common abnormality seen in children with urinary tract infections. Reflux of the infected urine to the upper tract may cause renal scarring and nephropathy. Unless treated promptly, 30-60% of patients with VUR have radiographic evidence of renal scarring[19], and hypertension develops in 11-20%. Twenty percent of renal transplantations are done in patients with reflux nephropathy[20]. At present, 40% of children on hemodialysis are cases that have end stage renal failure due to reflux nephropathy. Noe et al.[6] detected VUR in as many as 66% of children whose mothers had VUR previously. Succeeding reports instituted a familial aspect of vesicoureteric reflux disease. Puri et al.[3] reported the incidence of reflux as 13.6% in 624 siblings with much higher grade and reflux nephropathy incidence. Because of high incidences of both VUR and renal scarring at the time of diagnosis, early evaluation has been suggested in siblings of index patients[2]. The incidence of reflux and associated findings in our study group were high so as to support the present data in the literature.

There is a familial tendency or trait in the etiology of VUR, although special features of inheritance are still controversial. Some investigators proposed an autosomal dominant type of inheritance[21]. Sengar et al.[22] suggested a linkage with the major HLA complex located on the sixth pair of human chromosomes. Middleton et al.[23] proposed that it was sex linked. Others suggest polygenic type of inheritance[1,24,25]. Eccles et al.[26] presented evidence that this common disorder may be caused by mutations in the developmental pathway of which the PAX2 gene forms a part, but this is not a major cause of primary familial reflux[27]. Further investigations are required for clear explanation of inheritance of reflux.

The likelihood of reflux resolution, especially in siblings of index patients, has been reported to be around 58%, and this possibility is 28% per year[9,11,12]. Kenda et al.[2] reported VUR incidence as 50% in siblings under one year old, and it is 9% in patients over two years of age. The resolution of reflux with conservative treatment was somewhat low in our series. However, the ages of the patients with persistent reflux were between 7 and 14, whereas two siblings at six years of age were devoid of reflux after a period of conservative treatment. Nevertheless, the reflux grades of these cases might have also affected the spontaneous resolution chance, as they were lower compared to those of nonresponders to conservative follow-up. It is not possible to suggest a unique behavior for the reflux in siblings looking at the results of this relatively small series, but such a difference was not defined in the published studies either.

In previously reported studies, the incidence of reflux between male and female siblings was similar, except for Noe's report[4], in which there was a higher incidence in females. In the present study, there was also no correlation or similarity between reflux grades, sex distribution, or renal scarring, when index patients were compared to siblings with reflux.

In a four-year-old sibling in our series, DMSA renogram detected scarring in the absence of reflux. This situation suggests a possible spontaneous resolution of an asymptomatic reflux and unrecognized infection in the course. Reflux may resolve spontaneously if patients can be prevented from infection, as a result of long-term follow-up. But being unaware of ongoing reflux puts the patient at risk for an unexpected, and at times undiagnosed, pyelonephritis. Noe proposed that VCUG should be performed in all female and male siblings up to three years of age, because of higher incidence of VUR in this group, and in all female and male siblings between 3 to 5 years of age who have a history of urinary tract infection. Ultrasonography may be sufficient in asymptomatic male siblings over three years, and in female siblings over five years of age[4].

One of the main concerns related to routine sibling screening is the unavailability of a single reliable, noninvasive, and readily performed test. Indirect radionuclide cystography is a good alternative for VCUG, but only in children over five years of age[2,5,10,16]. Despite its disadvantages, VCUG is still the screening test of choice for most siblings. Nevertheless, a single DMSA scan in siblings over five years of age may suffice for screening purposes. A normal result can rule out complicated reflux reliably in most cases. Positive findings will indicate further evaluation including cystography.

In conclusion, detection and management of siblings for VUR is of vital importance due to the high incidence of renal damaging. Asymptomatic siblings may have previously undetected renal scars either with or without reflux. In this respect, families of children with VUR should be told about its familial trait. All asymptomatic siblings should be first evaluated by urine sampling, urine culture, urinary ultrasonography and contrast VCUG regardless of age or sex. Symptomatic siblings should be evaluated as a patient and contrast VCUG should be done, followed by a DMSA renal scan.

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Malignant pleural mesothelioma in a child: long-term survival with ICE-WAC chemotherapy regimen

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Malignant mesothelioma is a very rare tumor in childhood. Presently, treatment of this disease continues to be frustrating and prognosis remains poor. We here report a pediatric case of malignant pleural mesothelioma who gave a complete response to ICE-VAC chemotherapy regimen and achieved a long-term survival. An eight-year-old girl underwent exploratory thoracotomy and decortication because of a unilateral loculated and multicystic pleural effusion. Histopathological diagnosis was sarcomatoid pleural malignant mesothelioma. After decortication, chemotherapy with ICE (ifosfamide, carboplatin, etoposide) - VAC (vincristine, adriamycin, cyclophosphamide) combination was started. Six courses of chemotherapy resulted in complete clinical and radiological tumor response. She did not receive any further therapy and remains disease-free three years after the first remission. ICE-VAC chemotherapy combination resulted in a complete tumor response and a long-term disease-free survival for the presented case. The efficacy of this chemotherapy regimen in malignant mesothelioma needs to be documented in future trials.

Key words: malignant mesothelioma, ICE, ICE-VAC, chemotherapy, rare tumors.

Malignant mesothelioma (MM) is a very rare tumor of childhood, accounting for fewer than 0.07% of childhood malignancies[1,2]. Presently, treatment of this disease continues to be frustrating and prognosis remains poor. The overall prognosis of MM in childhood appears to be as unfavorable as the adult counterpart, but some pediatric cases with MM with long-term survival have been reported[3,4]. We describe a case of pleural MM in a child with long-term survival who gave a complete response to ICE (ifosfamide, carboplatin, etoposide) - VAC (vincristine, adriamycin, cyclophosphamide) chemotherapy regimen.

Case Report

An eight-year-old girl presented in March 1997 with fever, cough, shortness of breath, and left-sided chest pain of 15 days' duration. She had been previously well except for weight loss of one kilogram during the last month. Her past and family history were both unremarkable.

On admission, physical examination revealed tachypnea, dyspnea, markedly decreased breath sounds and dullness to percussion at the left middle and basal lung regions. Complete blood count findings were consistent with slight anemia and leukocytosis. She had an erythrocyte sedimentation rate of 130 mm/h and serum fibrinogen level of 7 g/dl (normal range 2-4 g/dl). Renal and liver function tests were within normal limits, except for the albumin level which was low (2.5 g/dl). Chest X-ray showed a large left-sided pleural effusion. An attempt at thoracentesis failed to obtain fluid. Thoracal USG (ultrasonography) showed no free fluid but revealed multiloculated cystic lesions occupying the pleural space. Using USG-guided thoracentesis, some pleural fluid was aspirated which was straw-colored with a specific gravity of 1010 and a LDH of 7,200 mg/dl. Cytological examination of the pleural fluid yielded 1,200 leukocytes/mm^3 with 74% lymphocytes and 26% polymorphonuclear leukocytes, and

negative results for malignancy. Chest computed tomography (CT) revealed a large loculated pleural effusion, areas of pleural thickening and passive atelectasis (Fig. 1). Cultures gave negative results for non-specific agents and mycobacterium tuberculosis. No improvement was obtained with an empirical antibiotic combination. It was decided to proceed to exploratory thoracotomoy and open biopsy since the unilateral pleural effusion was unresponsive to antibacterial therapy and since the massive effusion could not be drained because of loculated and multicystic characteristics of pleural lesions. Intraoperative findings disclosed fibrous white plaques occupying the entire left lung surface. Left pleura showed extensive adherence but cleavage was made along the lung tissue and successful decortication was performed. Decortication material consisted of

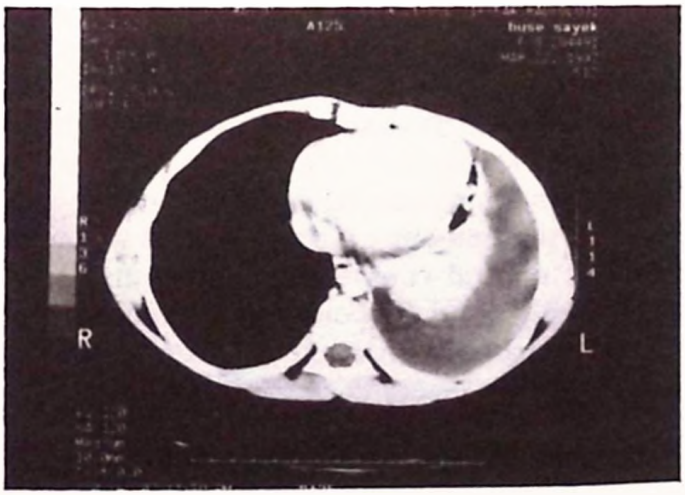

Fig. 1. Axial computed tomography scan shows a large left-sided pleural effusion and passive atelectasis.

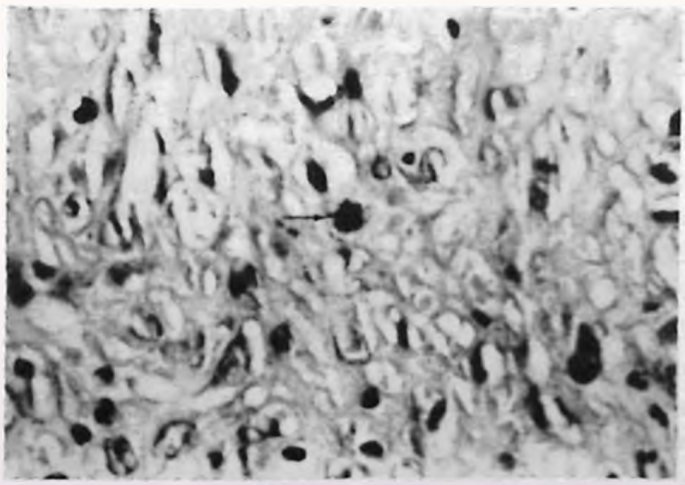

Fig. 2. Photomicrograph of the malignant mesothelioma with atypic, oval to elongated cells and an atypic mitotic figure (arrow) (H.E. stain, original magnification × 400).

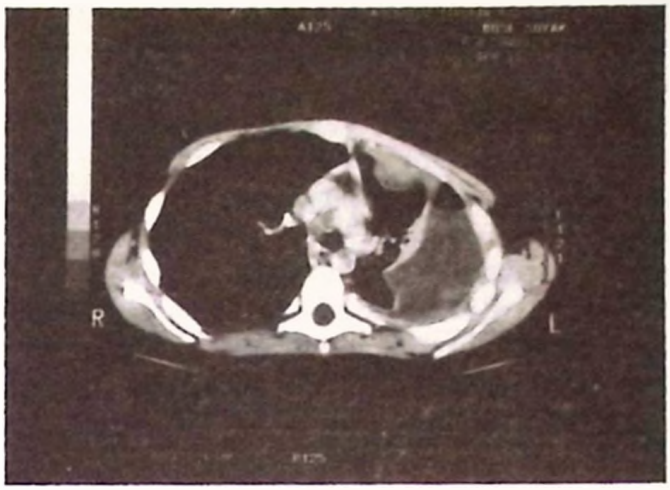

Fig. 3. Post-surgical computed tomography scan demonstrates a new pleural based solid mass of 2 cm in anterior chest wall accompanying the pleural effusion in the left hemithorax.

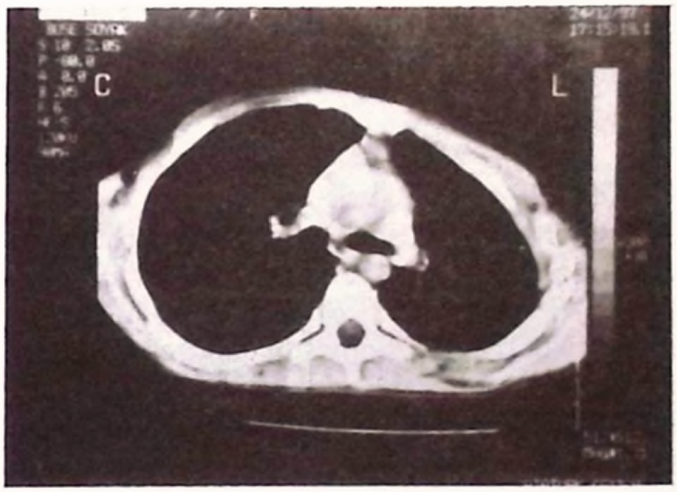

Fig. 4. Chest computed tomography showing only minimal pleural thickening on the left.

grayish-white, firm tissue covered with fibrin on one surface, measuring 14×5×0.8 cm. Microscopic examination showed the entire pleura to be thickened by neoplastic process. The tumor was highly cellular, made up of interwoven bundles of spindle cells which were immunohistochemically positive for both vimentin and keratin. Neoplastic cells showed nuclear atypia and occasional mitotic figures (Fig. 2). Histopathological diagnosis was sarcomatoid malignant mesothelioma. No history of environmental asbestos or another unusual exposure could be obtained either for the patient or for the family with subsequent questioning.

Postoperative CT showed a new 2 cm pleural based solid mass adjacent to the chest wall at the level of the carina. Again noted were large

loculated fluid collections in the left hemithorax (Fig. 3). After decortication, combination chemotherapy was started with ICE (ifosfamide 1.5 gr/m² + MESNA day 1-3; carboplatin 500 mg/m² day 3; etoposide 100 mg/m² day 1-3) alternating with VAC (vincristine 2 mg/m²; adriamycin 60 mg/m²; cyclophosphamide 600 mg/m² on day 1) with three-week intervals. The first course (ICE-VAC) resulted in significant clinical improvement in terms of dyspnea and tachypnea, and control CT showed a marked regression in the amount of effusion and disappearance of the extrapleural solid mass. A complete clinical and radiological response was obtained with six courses of chemotherapy; chest CT revealed only minimal diffuse pleural thickening at the level of left upper lobe (Fig. 4). The patient received no further therapy, and has been monitored with close clinical and radiological examination. Total follow-up period reached 36 months after discontinuation of therapy without any disease recurrence.

Discussion

Malignant mesothelioma rarely occurs in childhood; only an estimated 2-5% of all cases present in the first two decades of life[5]. The majority of mesotheliomas in children originate in the pleura as in the adult cases[2,4-6]; however, some less frequently encountered sites have also been reported, including the peritoneum[3,7], pericardium[8] and tunica vaginalis[9]. In contrast to the adult MM, there is little information concerning MM of childhood, and the etiology, epidemiology, natural course of the disease and optimal treatment strategies for this rare tumor of childhood are not well known. For the presented case, no history of exposure to asbestos or any other hazardous material in the patient's environment was obtained. Although there is a wealth of evidence supporting a strong association between asbestos exposure and MM in adults, no such clear causal association has been documented in MM of childhood[2,5,6]. A recent study on genetic epidemiology of malignant mesothelioma suggested an autosomal dominant pattern of inheritance for this tumor[10]. The family history of the presented case did not reveal any individual with mesothelioma.

Treatment of pleural MM in adults continues to be frustrating regardless of the modality employed. It is unresponsive to most chemotherapy and radiotherapy regimens, and it typically recurs even after the most aggressive attempts at surgical resection[11,12]. The outlook for pediatric patients with diffuse MM remains poor as in the adult patients. In localized tumors, resection is curative, but diffuse or invasive MMs, as seen in our patient, show poor prognosis since complete surgical resection is usually not possible. Brenner et al.[4] reported seven pediatric cases of MM and concluded that surgery and radiotherapy were not effective in controlling the disease in most of the cases.

Malignant mesothelioma was not a presumptive diagnosis for this patient while discussing thoracotomy since this tumor is extremely rare in this age group. The patient underwent exploratory thoracotomy and decortication with both diagnostic and therapeutic intent. After histopathologic diagnosis of MM, a second operation including pneumonectomy and also radiation therapy were discussed but, in an attempt to avoid the potential morbidity in a very young child, it was decided to employ these treatment modalities only in case of therapy failure. Systemic chemotherapy was the choice for this patient since some tumors show a different natural course in children and give surprisingly good response to chemotherapy when compared with adult counterparts.

Numerous trials of chemotherapeutic agents have been performed, but no chemotherapy regimen has yet emerged as an effective treatment for pleural MM[12]. However, among the chemotherapy agents that have been tested in adults, the anthracyclines, platinum compounds, and alkylating agents have demonstrated small but real activity against mesothelioma[11,13]. Although MM usually gives poor response to chemotherapy, some cases with response to adriamycin or to a combination containing adriamycin and cisplatin have been reported[11-13]. A few pediatric cases who gave a complete response to chemotherapy have been reported with vincristine, adriamycin, cyclophosphamide combination[4], and with ifosfamide[14]. Varan et al.[15] reported an adolescent boy with pleural MM who gave a very good response to a combination regimen containing vincristine, adriamycin, ifosfamide and cisplatin.

We combined ICE regimen with VAC regimen. The former combination has been shown to be

effective in resistant and relapsed solid tumors of childhood[16,17]. While the latter is a well documented combination for its efficacy in various malignant soft tissue tumors of childhood.

In conclusion, we obtained a complete response and a long-term survival with this combination. The efficacy of ICE-VAC regimen in MM merits further evaluation. Because of the very small number of pediatric patients with MM at each institution, multi-institutional trials are necessary to approach this rare tumor of childhood in an efficient manner.

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Hemolytic disease of the newborn due to isoimmunization with anti-E antibodies: a case report*

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SUMMARY: Sarıcı SÜ, Alpay F, Yeşilkaya E, Özcan O, Gökçay E. Hemolytic disease of the newborn due to isoimmunization with anti-E antibodies: a case report. Turk J Pediatr 2001; 248-250.

Minor blood group hemolytic disease is extremely rare, since the overall potency of minor blood groups in inducing antibodies is significantly lower when compared with that of Rh (D) antigen. We hereby report a very rare case of severe neonatal anti-E hemolytic disease due to E minor blood group incompatibility. A term newborn born to a 27-year-old, gravida 3, para 3 mother was referred due to a high and increasing serum bilirubin level despite phototherapy on the 4th day of life. On admission physical examination was normal except for the jaundice, and results of the laboratory investigation demonstrated a moderate-to-severe anemia (hemoglobin 7.8 g/dl) and a severe hemolytic hyperbilirubinemia (serum total and indirect bilirubin levels 36 mg/dl and 32.8 mg/dl, respectively; reticulocyte count 15%; and a positive direct antiglobulin test). As there was no apparent cause of the hemolytic disease such as Rh or ABO incompatibilities, further investigation (a positive indirect antiglobulin test and a positive irregular anti-E antibody in both the patient and mother, and minor blood group antigen profiles in family members compatible with E minor blood group isoimmunization) revealed the presence of anti-E hemolytic disease due to E minor blood group incompatibility. Two exchange transfusions with a 12-hour-interval were performed with minor blood group compatible fresh whole blood, and the patient was discharged in a healthy condition on the 10th postnatal day. If the most common causes of severe neonatal hemolytic disease such as Rh and ABO incompatibilities cannot be demonstrated in a newborn with significant hemolytic hyperbilirubinemia, anti-E hemolytic disease should strongly be considered in differential diagnosis. It should be kept in mind that a very severe from of minor group antibody hemolytic disease characterized by anemia and severe hyperbilirubinemia many exchange transfusions may be encountered during the course of the disease.

Key words: anti-E hemolytic disease, E minor blood group isoimmunization, hyperbilirubinemia, minor blood group incompatibility, newborn.

Hemolytic disease of the newborn due to minor blood group incompatibilities has been a greater problem since the decline of Rh (D) hemolytic disease with widespread use of prophylactic anti-D gamma globulin therapy. Of these minor blood groups, Kell, Duffy, Diego, Kidd, MNS, P, C, c and E in particular may cause neonatal hyperbilirubinemia[1]. Minor blood group hemolytic disease is extremely rare, as the overall potency of these minor groups in inducing antibodies is significantly lower when compared with that of Rh (D) antigen[1,2]. In this article a very rare case of severe neonatal hemolytic disease due to anti-E antibodies is presented and discussed.

Case Report

A 4,000 g male newborn was born at 40 weeks' gestation to a 27-year-old, gravida 3, para 3 mother by spontaneous vaginal delivery at a peripheral hospital. The baby was referred to our Division of Newborn Medicine due to increasing serum bilirubin level despite a

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phototherapy treatment of 50 hours at 72 hours of life.

In detailed family history the parents and first sibling were normal whereas the second sibling and undergone three exchange transfusions because of high (>35 mg/dl) serum bilirubin levels in the first 72 hours of life. Physical examination of the baby on admission at 90 hours of life was normal except for the jaundice. His weight was 3,830 g, and his length and circumference were 50 cm and 34.5 cm, respectively. Renal function tests, transaminases, and serum electrolyte and blood sugar levels were within normal limits. Serum total and direct bilirubin levels were 36 mg/dl and 3.2 mg/dl, respectively. Results of the complete blood count were hemoglobin 7.8 g/dl, hematocrit 23.6%, white blood cell $10.1\times10^3/\mu l$, and platelets $347\times10^3/\mu l$, and reticulocyte count was 15%. Further investigation to determine the exact etiology of the neonatal hemolytic disease revealed the following: blood groups of 0 Rh (+) and B Rh (+), respectively, in the patient and mother, a positive direct antiglobulin test in the patient, and a positive indirect antiglobulin test and a positive irregular antibody (anti-E) in both the patient and mother. To confirm the type of the hemolytic disease in the patient, minor blood group antigen profiles were studied in family members, and were as follows: CcEeCw(–) Kell(–) in the patient, CceeCw(–)Kell(–) in the mother, ccEECw(–)Kell(–) in the father, ccEeCw(–)Kell(–) in the first sibling, and ccEeCw(–)Kell(–) in the second sibling. Anti-E hemolytic disease due to E minor blood group incompatibility was diagnosed in view of the clinical and laboratory findings. Two exchange transfusions with a 12-hour-interval were performed with minor blood group compatible E(–) fresh whole blood. The case was discharged in a healthy condition on the 10th postnatal day.

Discussion

The most common causes of red blood cell hemolysis in the fetus and newborn are Rh (D) and ABO blood group incompatibilities. In cases of isoimmune hemolytic hyperbilirubinemia in which neither of these incompatibilities can be demonstrated in the etiology, the diagnosis of a minor blood group incompatibility should strongly be suspected[1,2]. We excluded other causes of both early neonatal hyperbilirubinemia and anemia such as infection, sepsis, and autoimmune diseases based on the clinical findings and results of laboratory investigations, and finally established the diagnosis of an isoimmune minor blood group incompatibility in our case.

The pathophysiology of fetal and neonatal isoimmunization in minor blood group incompatibilities is very similar to that in Rh (D) incompatibility and erythroblastosis fetalis. Initial maternal antibodies appearing in response to antigenic stimulation are primarily immunoglobulin-M (IgM) antibodies, and these are of no importance in the pathogenesis of hemolytic disease of the newborn since they cannot cross the placenta to enter the fetal circulation. Following repetitive antigenic stimulations as in subsequent antigen-positive pregnancies, however, the titer of immunoglobulin-G (IgG) antibodies increases, and these antibodies cause a positive indirect antiglobulin test in the mother can cross the placenta, thus leading to a hemolytic disease in varying degrees in the fetus and newborn[2,3]. The indirect antiglobulin test positivity in the mother of our case is due to the irregular antibody (anti-E) titration in maternal circulation. That the first sibling of the family with "E" minor blood group incompatibility has not had, but the second and third (present case) siblings have had a severe neonatal hemolytic disease is also in accordance with the pathophysiology of minor blood group isoimmunization.

The majority of minor blood group incompatibilities causing a significant hemolytic disease occur with anti-c, anti-E, or anti-Kell antibodies[4,7]. Minor blood group incompatibilities usually cause a neonatal hemolytic disease with slight-to-moderate severity[1,2,8], and of the minor group antibodies, anti-c causes virtually the most severe form of hemolytic disease of the newborn[1,4]. Even though our case did not have the classical findings of hydrops fetalis such as ascites, edema, and effusions, anemia and severe hemolytic hyperbilirubinemia requiring two exchange transfusions were in favor of the presence of a very severe form of a minor group antibody (anti-E) hemolytic disease. Severe

forms of fetal and neonatal anti-E hemolytic disease requring intrauterine transfusions are rare in the literature[8-11]. Transfusion of E antigen negative blood products in treatment of anti-E hemolytic disease would help in preventing further hemolysis that might be caused by transfusion of E (+) red blood cells.

If neither Rh (D) nor ABO incompatibilities can be demonstrated as the cause of anemia and hemolytic hyperbilirubinemia in a newborn, anti-E isoimmune hemolytic disease should strongly be considered in the differential diagnosis. It should be kept in mind that the pathophysiology of E minor blood group isoimmunization is very similar to that of Rh (D) incompatibility. A very severe form of minor group antibody hemolytic disease characterized by anemia and severe hyperbilirubinemia requiring many exchange transfusions may be encountered during the course of the disease.

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Utility of dobutamine stress echocardiography in Kawasaki disease: a case report and review of the literature

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SUMMARY: Ökçün B, Özhan H, Baran T, Saltık L, Mutlu H, Üner S, Küçükoğlu MS. Utility of dobutamine stress echocardiography in Kawasaki disease: a case report and review of the literature. Turk J Pediatr 2001; 251-253.

Dobutamine stress echocardiography (DSE) has become widely accepted in the evaluation of adult patients with coronary heart disease. There are new challenges about the use of DSE in the pediatric age group to document ischemia. DSE can demonstrate ischemia noninvasively in Kawasaki disease (KD) patients who are candidates for coronary angiography. We wanted to assess the feasibility and the physiologic responses of DSE in a KD patient with coronary aneurysm. The patient had no ischemia in DSE, which was confirmed by coronary angiography showing no stenosis. The literature about DSE use in KD is reviewed.

Key words: dobutamine stress echocardiography, Kawasaki disease.

Dobutamine stress echocardiography (DSE) has become a diagnostic tool for the evaluation of coronary artery disease and the detection of myocardial viability. In the diagnosis of significant coronary artery disease, it provides similar accuracy to exercise stress thallium-201 myocardial perfusion scintigraphy. Dobutamine stress echocardiography is also a promising modality for predicting the recovery of hibernating myocardium from contractile dysfunction after coronary angioplasty or bypass surgery. Recently, quite a number of studies have been done with DSE in the pediatric population[1-3]. Kawasaki disease (KD), heart transplant patients and children taking anthracycline therapy were especially investigated[1]. We report a case of a six-month-old Kawasaki disease patient complicated with coronary artery aneurysm. DSE was performed the first such pediatric case in our institute, to evaluate ischemia presence and the result was compared with coronary artery angiography, the gold standard for detecting stenotic lesions causing ischemia.

Case Report

A six-month-old male patient was admitted to a university hospital due to resistant fever and was diagnosed as Kawasaki disease. He was referred to our clinic for transthoracic echocardiography (TTE) to reveal any coronary artery aneurysms. There were aneurysms of 12×16 mm and 6×15 mm in diameter in his left and right coronary artery, respectively. TTE was normal otherwise.

In order to determine if the underlying lesions caused any ischemia, DSE was performed. Prior to dobutamine infusion, rest electrocardiogram, parasternal short- and long-axis, and apical 4-2 chamber views were recorded. There were no left ventricular or valve function abnormalities. Ejection fraction was 70%. Dobutamine was started at a dose of 5 μg/kg/min. The dose was increased 5 μg/kg/min every three minutes, until the maximum dose of 40 μg/kg/min was reached. Heart rate and blood pressure were recorded at each step, and electrocardiograms were recorded before and at the end of the perfusion. During DSE no wall motion abnormality was seen. The test was negative for ischemia (Figs. 1a and 1b). Coronary angiography showed aneurysmal dilatations without any stenosis, in both right and left coronaries (Figs. 2a and 2b).

Discussion

Kawasaki disease has a risk of coronary artery inflammation and aneurysm formation in 5-20%

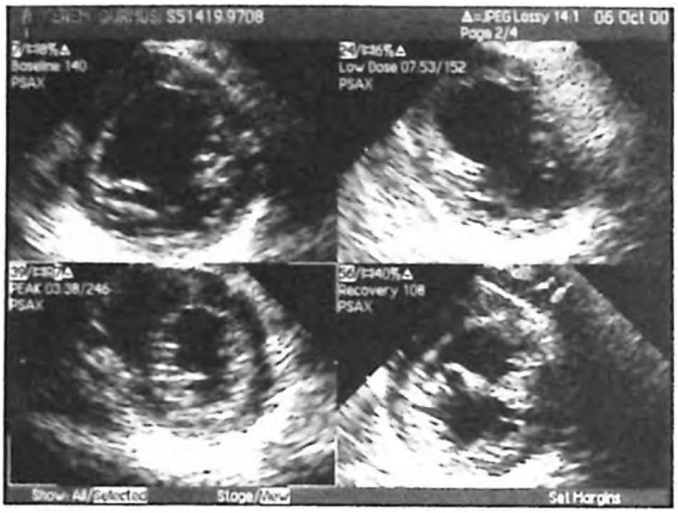

Fig. 1a. Dobutamine stress echocardiography parasternal short-axis views at the beginning of study, at low dose (5 μg/kg/min) dobutamine infusion, at maximum dose (40 μg/kg/min) infusion and at the end of recovery period. No wall motion abnormality can be seen.

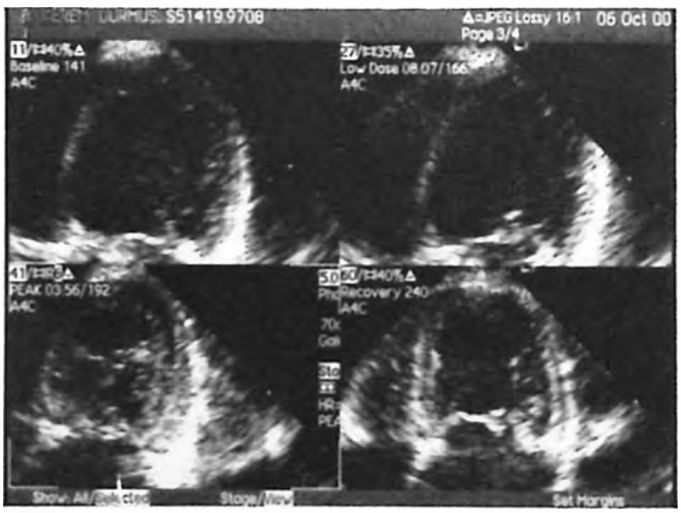

Fig. 1b. Dobutamine stress echocardiography apical four-chamber views at the beginning of study, at low dose (5 μg/kg/min) dobutamine infusion, at maximum dose (40 μg/kg/min) infusion and at the end of recovery period. No wall motion abnormality can be seen.

of patients. The most common cause of death is due to cardiac complications. Children under one year of age appear to be at particularly high risk for development of coronary abnormalities. In a study from Japan, from January 1973 through December 1992, a total of 302 patients (183 males, 119 females) with KD underwent coronary angiography. Coronary abnormalities were confirmed in 71 (23.5%) of 302 cases. Serial angiographic evaluation of 42 cases revealed different progressions in coronary abnormalities[4]. The sensitivity of two-dimensional echocardiography is 100% in detecting aneurysms in the proximal portions of both the right and left coronary arteries, and is useful in selecting patients for invasive investigation with selective coronary arteriography[5]. In a recent study of 594 patients with KD, 24.6% were diagnosed as having coronary aneurysms, and during follow-up, ischemic heart disease developed in 4.7% and myocardial infarction in 1.9%. Death occurred in 0.8%. The 448 patients with normal findings at the first angiogram subsequently never developed any abnormal cardiac findings[6]. It is important to treat the localized stenosis in preventing myocardial infarction in the chronic phase of KD. Serial angiographic observation is indicated for those patients who develop large coronary aneurysms during the acute phase of KD. Since coronary angiography is an invasive

Fig. 2a. Coronary artery angiography demonstrating aneurysm formation in left anterior descending artery without any stenotic lesion.

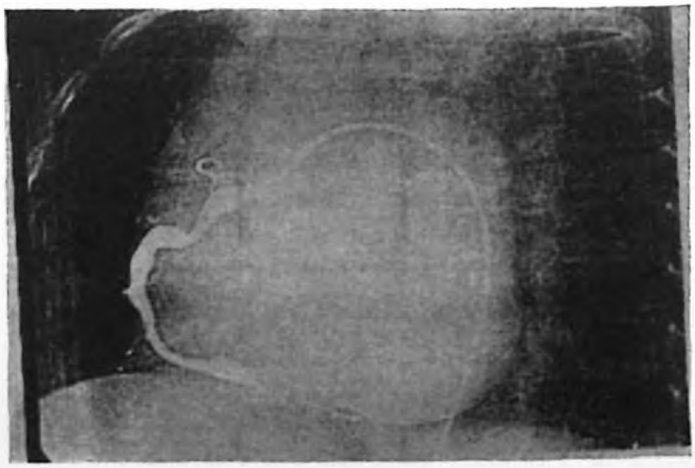

Fig. 2b. Coronary artery angiography demonstrating aneurysm formation in the right coronary artery without any stenotic lesion.

procedure, DSE was recently investigated as a non-invasive screening test in these patients, to document ischemia[1].

Another study designed to determine the feasibility of performing exercise stress echocardiography in children diagnosed with coronary abnormalities secondary to KD was performed involving 28 children aged 6 to 16 years. All had acute KD one to 10 years before the study, and coronary artery abnormalities were identified during previous echocardiographic imaging. Two patients developed new exercise-induced wall motion abnormalities that corresponded to angiographically defined critical stenosis of the left anterior descending coronary artery, meaning that among patients with coronary artery involvement resulting from KD, exercise stress echocardiography is a safe, noninvasive procedure and may identify children with myocardial ischemia previously detected with ECG stress test alone[7].

In conclusion, DSE appears to be a feasible, safe, and useful modality for the noninvasive assessment of flow-limiting stenosis in the pediatric population and can be used serially in the routine follow-up and risk stratification in children at risk for coronary events[1]. DSE has some limitations in discriminating particular regions of ischemia when multiple ventricular segments are involved and when the imaging is suboptimal. It can be applied using minimal additional resources in an otherwise functioning echocardiography laboratory and, with appropriate training, can achieve clinical results comparable with those of large-scale multicenter trials. Ongoing improvements in technology and the development of new reagents such as myocardial contrast agents hold promise for further advancements in the near future[8].

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Dissection of aorta: a pediatric case report

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SUMMARY: Serdaroğlu G, Levent E, Yurtsever S, Çalkavur T, Yünten N, Aydoğdu S. Dissection of aorta: a pediatric case report. Turk J Pediatr 2001; 254-257.

We present a 15-year-old boy who developed sudden walking disability and sensory loss. He could not stand up on his feet and had no feeling following a sudden fall while playing basketball. He had been referred to a local hospital with these symptoms. In his physical examination absence of deep tendon reflexes and sensory loss were noted. His arterial blood pressure was 210/160 mmHg. He was transferred to our hospital with these findings and diagnosis of Guillain-Barré syndrome and hypertensive encephalopathy. There was sudden onset of sensory loss, walking disability and history of trauma. In the following hours hematuria, back pain and lower extremity ischemia developed. We suspected spinal artery injury based on the findings. Dissection of descending aorta was established with the help of magnetic resonance imaging of spinal region and contrasted aortography. The patient went to surgery immediately. He was lost on the second day after operation because of malperfusion. We report this case because dissecting aorta is very rare in the pediatric age group. High index of suspicion and early aortography are needed to diagnose aorta dissection.

Key words: aorta dissection, childhood, hypertension.

Dissection of the aorta is characterized by separation of the layers of the media by a column of circulating blood. This acute event is not associated with the presence of an aneurysm. The incidence is approximately 5.2 per million per year. It is seen in all age groups but it is rare in the extremes of life[1]. Although the etiology of aortic dissections is not well defined, hypertension, connective tissue disorders, aortic stenosis, coarctation of the aorta, iatrogenic trauma and pregnancy are the common causes. Clinically dissections seen within the first two weeks following onset of symptoms are considered acute and beyond this period chronic. The acute mortality in the critical first two weeks varies from 57% to 89%[2]. De Bakey[3] classification simplified the dissections into three basic types: Type 1 is a dissection starting in the ascending aorta and involving the entire length of the aorta; type 2 is limited to the ascending aorta; and type 3 starts distal to the left subclavian artery, but spares the ascending aorta and the arch. Male/female ratio has been reported as 2:1 or 3:1. Average age is 50-70 years. Acute mortality is 60-90% in type 1 and type 2, but 15-40% in type 3 dissections.

Case Report

15-year-old boy was referred to the hospital with the symptoms of walking disability and sensory loss. His symptoms had started when he was playing basketball. He had jumped up and fallen down suddenly, and immediately thereafter noticed that he had no feeling his feet and could not walk. He was referred to a local hospital: his arterial blood pressure was 210/160 mmHg. Absence of deep tendon reflexes and sensory loss of distal part of extremities were noticed. He was transferred to our hospital with these findings and a diagnosis of Guillain-Barré syndrome and hypertensive encephalopathy. His past and familial history revealed no remarkable findings. In his physical examination, weight was 90 kg ($<97^{th}$ percentile), height 180 cm ($>97^{th}$ percentile), and body mass index was 27.7 kg/m^2 (overweight). Cardiovascular and respiratory system examination was normal. Arterial blood pressure was 150/90 mmHg (90^{th} percentile).

Anti-hypertensive agent was given at the first hospital to which he was referred in the following hours his blood pressure was difficult to control. In neurologic examination he was conscious and cooperative, cranial nerves were intact, and muscle strength and tonus were normal in upper extremities, but significantly depressed in distal. Deep tendon reflexes were normal in upper extremities but absent in distal. Sensory loss was bilateral significant up to 10 cm over his knees. The other system findings were normal. Laboratory investigations included white blood cell count 22,300/mm^2, red blood cell count 4.58×10^6/mm^3, hemoglobin 10.9 g/dl, hematocrit 33.6%, platelets 295,000/mm^3 and normal urine examination in the first hour. At the sixth hour macroscopic hematuria started and significant erythrocyturia was found. Liver and kidney function tests, blood glucose, serum ions and prothrombin time were normal. At the sixth hour blood chemistry revealed: SGOT: 932 IU/L, SGPT: 341 IU/L, CPK: 1318 mg/dl, CPK-MB: 45 mg/dl, and LDH: 624 IU/L. Cholesterol and lipid values were normal. He was transferred to our hospital with initial diagnosis of Guillain-Barré syndrome and hypertensive encephalopathy. We thought this diagnosis was inlikely because symptoms of our patient appeared suddenly, did not show progression and there was no prodromal period. We were also doubtful of hypertensive encephalopathy, because he did not have clinical findings of encephalopathy. He had a history of sudden trauma and had serious hypertension. Lumbosacral X-ray and cranial tomography were normal. Chest X-ray showed widening of mediastinum (Fig. 1). His extremities were pulseless and became cold at about the seventh hour and he started to complain of back pain. We suspected spinal cord and artery injury with these clinical signs. Magnetic resonance imaging (MRI) of spinal region was done and showed pathology of the aorta, and type 3 dissection was defined (Fig. 2). The patient went to operation immediately and graft disposition was performed; he was last at the 48th hour after operation because of malperfusion.

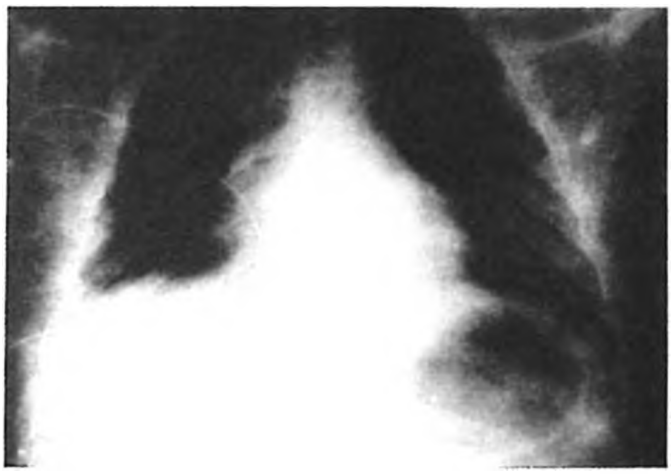

Fig. 1. Antero-posterior chest X-ray showed mediastinal broadening.

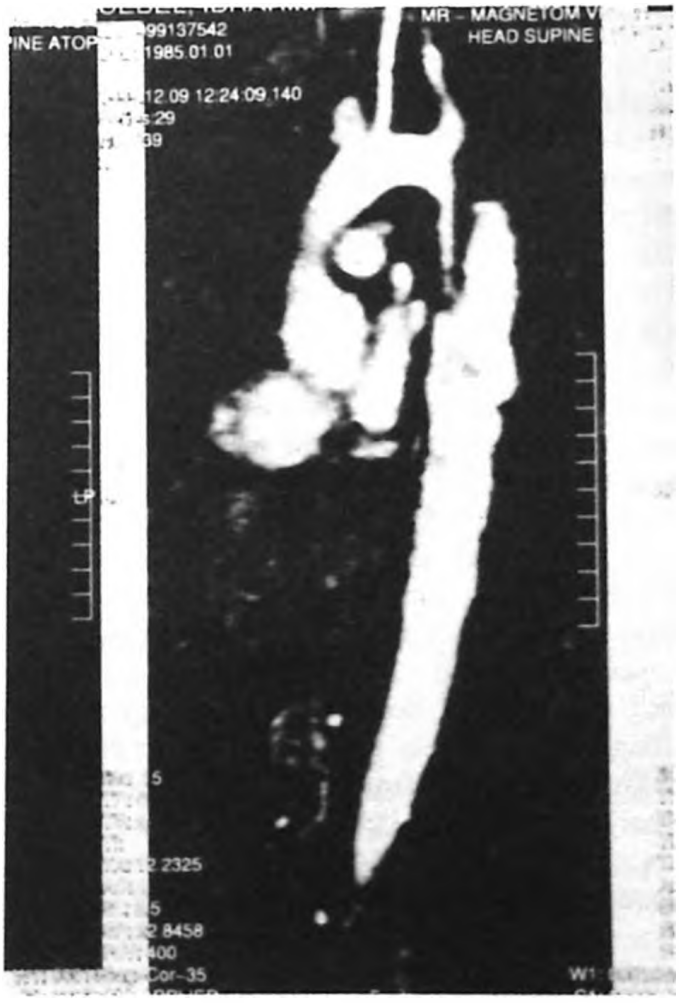

Fig. 2. 3D contrast magnetic resonance aortography showed dissection located at the proximal part of the descending aorta starting distally to the left subclavian artery.

Discussion

Acute dissection of the aorta is the most frequent catastrophic disease involving the aorta and remains the leading cause of death from aortic pathology. This pathology is very rare in pediatric age groups especially in children who do not have any predisposing risk factors. Etiology of aortic dissections is not well defined, but hypertension, heredity, connective tissue disorders, Marfan's syndrome, aortic stenosis and coarctation of the aorta are the predisposing

conditions[4]. Our patient was not evaluated before, so he and his family did not know whether he had hypertension or not. He was overweight and had serious hypertension when he was referred to the hospital. Sudden hypertensive attack might have occurred at the time of trauma during his sudden fall. Incidence of hypertension in acute dissections is about 75%[2]. The presence of hypertension is more common among patients with type 3 dissections[2]. Vogt et al.[5] reported four patients aged 14 to 21 years who developed acute aortic dissection. All four patients had systemic hypertension related to chronic renal insufficiency. The role of heredity in aortic dissections in the general population is poorly defined except for patients with connective tissue disorders like Ehlers-Danlos syndrome and Marfan's syndrome. Familial occurrence of dissections and annuloaortic ectasia in association with a mutation in the gene for type III procollagen has been reported[6]. Aorta-related complications, especially acute dissections, are the leading cause of death in Marfan's syndrome. Dilatation of the ascending aorta and a family history of acute dissection are associated with an increased risk of dissection in this syndrome[7,8]. There was no history of aortic dissection or sudden death in our patient's family. Aortic stenosis and coarctation, which are other etiologies of aortic dissection, were not determined during operation in our case. A review of the literature revealed many reported many of aortic aneurysms in childhood but very few of cases with aortic dissection. Dissection of aorta was reported in two cases with Turner's syndrome. They were 10- and 9-year-old girls and both had aorta coarctation repaired previously[9]. Teien et al.[10] reported a case of spontaneous dissection in a 12-year-old boy whose half brother had an idiopathic dilated aorta and whose mother had also required surgery for dissection of a dilated aorta. No features of connective tissue disorder were presented in any family member. Panja et al.[11] presented a nine-year-old girl with chest pain and dyspnea of sudden onset. She also did not have Marfanoid features and had normal aortic valve on echocardiography. The diagnosis of dissecting aneurysm of ascending aorta was established with the help of aortagraphy. Nitsuya et al.[12] reported that aortic wall dissection in young patients might be etiologically associated with increased acid mucopolysaccharide accumulation in the aortic media. Clinical features of aorta dissection change due to the type of dissection. Sudden or accelerated death may be the presentation and the diagnosis can be made only at autopsy. Pain is the most dramatic symptom. Back pain started in our case in the follow-up period. Neurologic manifestation such as temporary blindness, degrees of hemi- or paraparesis or plegia, or deep coma may be seen on presentation[1]. Our case presented with paraparesis and lower extremity ischemia. The blood pressure on admission is normal or high in over 80% of the patients. The blood pressure was difficult to control in our case. The severe hypertensive response may have been related to renal ischemia primary hypertension may have been present have in our case. Limb ischemia signs are present in about 40% patients at admission[2]. Hematuria and oliguria are signs of renal involvement. Hematuria started at the sixth hour in our case but urine volume as adequate (3 ml/kg/h). Abnormalities seen in the serum chemistries are related to severity of the accompanying organ dysfunction. Chest X-rays show widening of the mediastinum and blurring of the aortic knob in over 80% of the patients. Because diagnosis can be made only with computed tomography, magnetic resonance imaging or aortography[11], pediatric cases may be undiagnosed. Suspicion is essential to diagnose the disorder. We must consider dissection in children, especially with predisposing risk factors, in the presence of sudden onset of pain, dyspnea, syncope, hypertension, limb ischemia symptoms and hemiparesis.

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Severe iron deficiency anemia in a child with idiopathic pulmonary hemosiderosis: a case report

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SUMMARY: Derbent M, Özçay F, Saatçi Ü, Özbek N. Severe iron deficiency anemia in a child with idiopathic pulmonary hemosiderosis: a case report. Turk J Pediatr 2002; 44: 258-260.

We report a case of idiopathic pulmonary hemosiderosis (IPH) in a three-year-old male patient who presented with severe iron deficiency anemia. The child had been diagnosed with iron deficiency anemia nine months earlier and had received multiple blood transfusions, but the cause of his anemia had not been established. The diagnosis of IPH was made after a biopsy of the left lung showed large numbers of hemosiderin-filled macrophages in the alveoli. He did not respond to standard dose corticosteroid (CS) treatment (2 mg/kg/d). However, high-dose short-term CS treatment was successful in two episodes of acute respiratory hemorrhage in this patient. We conclude that IPH should always be considered when investigating the cause of iron deficiency anemia. A more rapid diagnosis in this case could have prevented unnecessary investigations and blood transfusions. We also suggest that high-dose short-term CS treatment should be kept in mind, especially in patients who do not respond to a standard dose.

Key words: idiopathic pulmonary hemosiderosis, high-dose corticosteroids, iron deficiency anemia.

Idiopathic pulmonary hemosiderosis (IPH) is a rare disorder of unknown etiology that is manifest by iron deficiency anemia, recurrent or chronic pulmonary symptoms such as cough and hemoptysis, and diffuse pulmonary infiltrates[1]. The incidence of IPH is reported to range from 0.24 to 1.23 cases per million[2]. Although its specific cause is unknown, the disease is considered to be an immune-mediated condition[2]. The clinical course of IPH is highly variable, and most patients continue to experience episodes of pulmonary hemorrhage despite treatment. Affected individuals often present with anemia, coughing and radiological evidence of pulmonary infiltrates. Symptoms such as fever, respiratory distress and clubbing are usually seen at later stages of the disease, but may also be the first signs observed[2,3].

In this report, we describe a pediatric patient with IPH who presented with severe iron deficiency anemia.

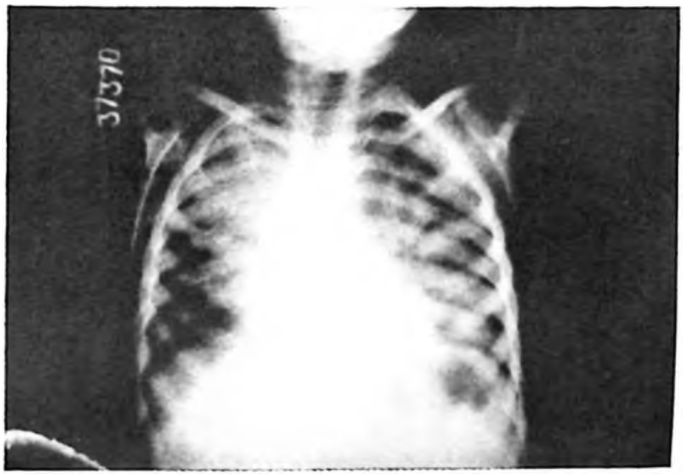
Case Report

A three-year-old male patient was referred to our hospital for severe anemia of unknown cause. He had a nine-month history of pallor and fatigue that had gradually worsened with time, and was suffering from severe fatigue at presentation. There was no history of hemoptysis or dyspnea. The patient's anemia had been investigated at a number of other hospitals. These work-ups had revealed iron deficiency anemia and the child had received multiple blood transfusions, but the underlying problem could not be determined.

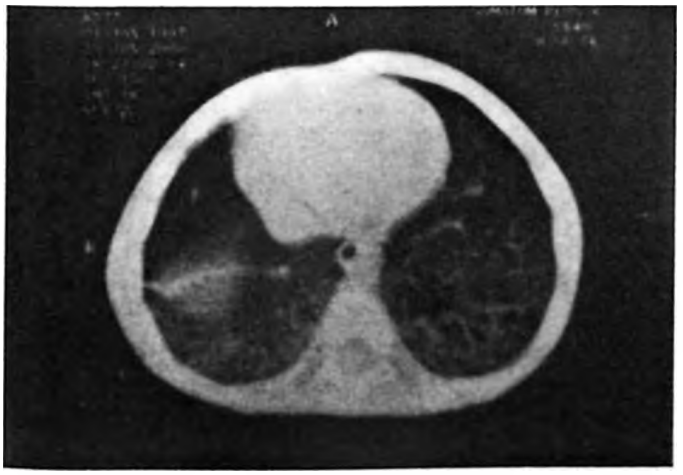
Physical examination at our center revealed marked palor, dyspnea, tachycardia, ronchi, a symmetrical pattern of decreased breath sounds over both lung fields and clubbing of the fingers. The child's size and weight were within normal limits for his age. The laboratory findings were as follows: hemoglobin 4.6 g/dl, hematocrit 14.6%, leukocyte count 12.4×10^9/L (differential

This study was presented at the IVth National Hematology Congress, 1-4 November 2000, İzmir, Turkey

85% polymorphonuclear leukocytes, 15% lymphocytes), platelet count 240x10^9/L, reticulocyte count 4.6%, serum iron 28 μg/dl (normal, 50-140 μg/dl), serum iron binding capacity 410 μg/dl (normal 130-350 μg/dl), and ferritin 293 ng/ml (normal, 15-300 ng/ml). A chest X-ray (Fig. 1a) and thoracic computed tomography (Fig. 1b) demonstrated a symmetrical diffuse pattern of pulmonary infiltrates bilaterally. Examination of gastric aspirate specimens showed no hemosiderin in the macrophages present, but biopsy of the left lung revealed large numbers of hemosiderin-filled macrophages in the alveoli (Fig. 2). A direct Coombs' test, and testing for cold agglutinins, antinuclear antibody, anti-DNA antibody and glomerular basement membrane antibody were all negative. Complement 3 and 4 levels and urine analysis were normal. A radioallergosorbent test (RAST) for cow's milk indicated the patient was sensitive to milk protein.



(a)



(b)

Fig. 1a and 1b. The patient's chest X-ray (1a) and computed tomography (1b) show a symmetrical diffuse pattern of pulmonary infiltrates bilaterally.

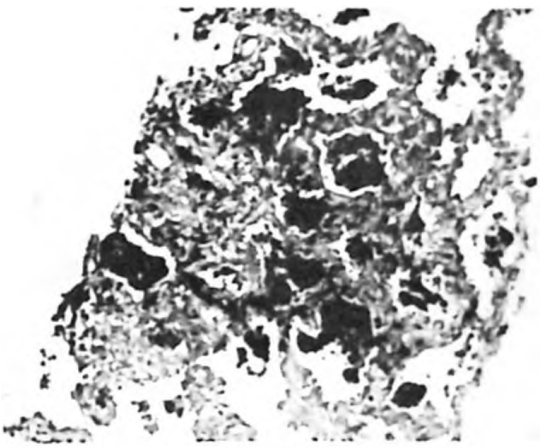


Fig. 2. Biopsy of the left lung showed the large numbers of hemosiderin-filled macrophages in the alveoli (Prussian blue, x 115).

Once the diagnosis of IPH was confirmed by the lung biopsy and other findings, we initiated a course of standard-dose corticosteroid (CS) treatment (2 mg/kg/d). Since the patient's RAST for cow's milk was positive, dietary restriction of milk and milk products was another important element of treatment. However, the patient encountered two episodes of acute respiratory hemorrhage and distress under this treatment regimen. On both occasions, he responded to high-dose short-term methylprednisolone, given as 30 mg/kg for 3 days, 20 mg/kg for 4 days, and tapered to a 2 mg/kg maintenance dose.

Discussion

Idiopathic pulmonary hemosiderosis is a disorder of unknown etiology that is characterized by recurrent or chronic hemorrhage and accumulation of hemosiderin in the lung alveoli. The disease can affect individuals of any age, from neonates through to adults, and occurs with equal frequency in males and females[3,4]. The many experimental, morphologic, and ultrastructural studies that have been done of IPH have not revealed the mechanisms behind this condition[3]. The response to immunosuppressive therapy in some patients suggests that the disease may have an immunological basis[2,5]. In addition, some familial cases have been reported, and Kiper and colleagues[3] found that 43% of their IPH patients had consanguineous parents, indicating a possible genetic component as well[2,6].

The three main findings associated with IPH are as follows: 1) iron deficiency anemia of no other apparent cause; 2) pulmonary symptoms,

including cough, dyspnea and hemoptysis; and 3) transient diffuse pulmonary infiltrates or a miliary pattern on the chest radiograph. Diagnosis of IPH is established only when hemosiderin-filled macrophages are identified in multiple gastric aspirate specimens and/or on histological examination of a lung biopsy[3]. Our patient presented with severe iron deficiency anemia, and the diagnosis of IPH was confirmed by the finding of hemosiderin-filled macrophages in lung biopsy material (Fig. 2). We ruled out other causes of pulmonary hemorrhage, including rheumatological diseases, with appropriate laboratory testing. Goodpasture's syndrome was also excluded based on a negative test for antibody to be glomerular basement membrane and on normal urinalysis.

Diagnosis tends to be more difficult in cases of insidious onset. Kiper and associates[3] studied 23 children with IPH between 1979-1994, and noted there was often a long delay (range, 4 months to 10 years) between the start of symptoms and the time when the correct diagnosis was made. We attribute the nine-month delay in our case to the fact that the patient exhibited no respiratory symptoms of hemoptysis, cough or dyspnea in the earlier stages.

Interestingly, reports have noted a connection between IPH and sensitivity to cow's milk[2]. Individuals with IPH who exhibit this form of sensitivity have a better prognosis than those who do not have milk protein sensitivity. The former category of patients may not need long-term immunosuppression. Saeed and coauthors[2] reported one patient who was successfully treated with a milk-free diet only, without any medication. Still, it is not known what role milk precipitins play in the pathogenesis of IPH[2].

Studies indicate that patients show varied response to immunosuppressants such as corticosteroids, azathioprine, cyclophosphamide, and hydroxychloroquine. Recent work has revealed that long-term, low-dose CS therapy prevents respiratory crises and prolongs survival in most cases[2]. Based on these findings, we initially prescribed standard-dose CS combined with dietary milk restriction for our patient. However, standard-doses of CS were insufficient in this case, and he responded well to treatment with higher doses of CS.

We wish to emphasize that IPH should always be considered a possible cause of iron deficiency anemia, especially in patients who require multiple blood transfusions and exhibit reticulocytosis. Our case is important in that it exemplifies how the diagnosis can be overlooked, and how this can lead to serious deterioration. We would like to suggest high-dose short-term CS treatment as one form of therapy, especially in patients who do not respond to standard-dose CS treatment.

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Complete heart block in thalassemia major: a case report

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SUMMARY: Küçükosmanoğlu O, Özbarlas N, Şaşmaz İ. Complete heart block in thalassemia major: a case report. Turk J Pediatr 2002; 44: 261-262.

Cardiac complications of iron overload are the most common cause of death in patients with thalassemia major. These complications include recurrent pericarditis, refractory congestive heart failure and rhythm disorders. The usual rhythm disturbances are supraventricular or ventricular premature contractions and first-or second-degree heart block. Complete heart block is a very rare complication of thalassemia major. Herein, we report a case of complete heart block with thalassemia major. The patient also had serious congestive heart failure. Management of the heart block with pacemaker brought no clinical improvement, and she died in the second month of hospitalization.

Key words: thalassemia major, complete heart block, endocardial pacemaker.

The cardiac complications of iron overload are the most common causes of death in patients with thalassemia major[1]. These complications include recurrent pericarditis, refractory congestive heart failure, supraventricular or ventricular premature contractions and various forms of heart block Although many authors mentioned "various forms" of heart block, first- and second-degree block are the most common types. Complete heart block is a very rare condition in patients with thalassemia major[2-5].

In this paper, we report a 15-year-old girl with complete atrioventricular block and severe congestive heart failure due to cardiac hemosiderosis who died in spite of medical therapy and pacemaker implantation.

Case Report

A 15-year-old girl was referred to the Pediatric Cardiology Department with generalized edema, dyspnea, fatigue and generalized weakness. She had been followed at the Pediatric Hematology Department with the diagnosis of thalassemia major since her neonatal period, and she had received many blood transfusions and irregular deferoxamine therapy. Physical examination revealed a regular pulse of 60 bpm and blood pressure of 120/70 mmHg. She had generalized edema, ascites, marked hepatosplenomegaly and chromatic skin discoloration. Her hemoglobin level was 10.2 g/dl and ferritin level 4,520 ng/ml. Heart sounds were normal. Chest X-ray showed marked cardiomegaly with a cardiothoracic index of 0.62. Echocardiography showed severe systolic dysfunction (ejection fraction 38%, fractional shortening 18%) and dilatation of cardiac chambers. Twelve-lead ECG showed complete atrioventricular block. Holter recording revealed complete atrioventricular block with a ventricular rate of 50-60 bpm, frequent multiform ventricular premature complexes and slow, nonsustained (3-11 beats) idioventricular rhythm episodes (Figs. 1a and 1b). Decongestive therapy was

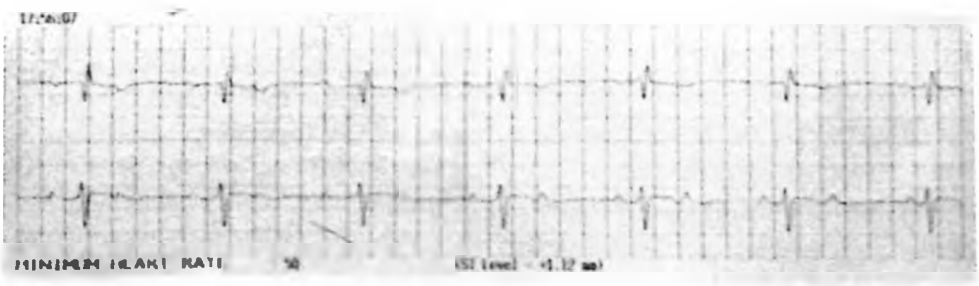

Fig. 1. Holter electrocardiogram obtained before pacemaker implantation, with a) complete heart block and,

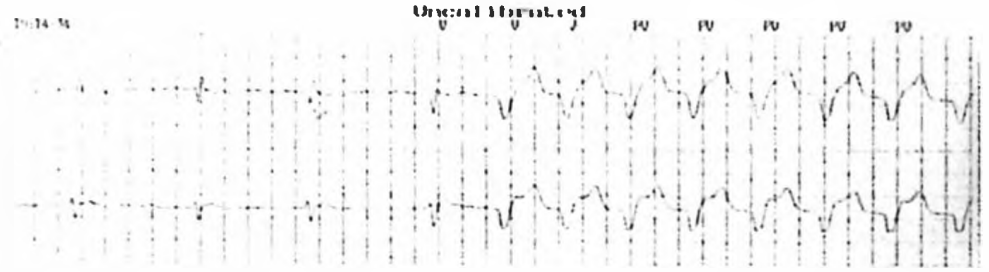

Fig. 1. Holter electrocardiogram obtained before pacemaker implantation, with b) idioventricular rhythm episode.

given and an endocardial DDD pacemaker was implanted successfully. She was discharged a week after pacemaker implantation with ejection fraction of 48% and fractional shotening of 24%. However, four days later she admitted to hospital with worsening symptoms of heart failure. The pacemaker functions were found normal. In spite of further intensive medical therapy, she died in the second month of hospitalization.

Discussion

Repeated blood transfusions to prevent severe anemia are necessary in patients with thalassemia major. But these frequent transfusions lead to chronic iron overload and related cardiac complications. Extent of cardiac impairment mostly depends on the quantity of iron deposition in the ventricular myocardium. When clinical findings of cardiac failure become apparent, patients with thalassemia major have a poor prognosis with a short life expectancy from six months to one year[6-7]. However, in a recent study, Kremastinos et al.[2] found that the five-year survival rate in patients with thalassemia and heart failure was greater (48%) than previously reported. Regular subcutaneous deferoxamine infusion therapy may protect patients from iron overload and related cardiac toxicity. Nevertheless, patients who receive deferoxamine are not entirely risk-free of cardiac iron deposition[5]. Serum ferritin levels are not correlated with survival in patients with thalassemia major and cardiac involvement[2]. Besides ventricular and atrial myocardium, conduction tissue is another site of iron deposition. The usual cardiac rhythm disturbances are supraventricular or ventricular premature contractions, and first-or second-degree heart block. Engle et al.[3] reported two cases of complete heart block due to hemochromatosis in the pre-deferoxamine era. Kremastinos et al.[2] reported that one of 52 patients who received iron chelation therapy with deferoxamine before the age of five years had complete heart block, and they emphasized that patients with rhythm disorders had poor prognosis. In our patient, heart block was an additional cause of congestive cardiac failure, but the management of the heart block with pacemaker brought no clinical improvement and she died in the second month of hospitalization. Insufficient iron chelation therapy was the main reason for the severe cardiac involvement. High-dose continuous deferoxamine infusion could be effective in decreasing the serum ferritin level, but this does not provide clinical improvement in patients with established clinical findings of heart failure[1,2].

We conclude that complete atrioventricular block may develop in the terminal stage of thalassemia major and that pacemaker therapy may not be effective in this condition because of the severe involvement of the myocardium. Regular cardiovascular evaluation of the patients and timely diagnosis of cardiac involvement may be beneficial in the management of thalassemia major.

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Hypodipsia-hypernatremia syndrome associated with holoprosencephaly in a child: a case report

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SUMMARY: Karabay-Bayazıt A, Hergüner Ö, Altunbaşak Ş, Noyan A, Yüksel B, Anarat A. Hypodipsia-hypernatremia syndrome associated with holoprosencephaly in a child. Turk J Pediatr 2002; 44: 263-266.

We report a child with diabetes insipidus and hypodipsia associated with holoprosencephaly. A two-year-old girl with the history of several admittances to hospital during and after the newborn period with hypernatremic dehydration, acute renal failure and convulsions is presented. The patient had hypodipsia, hypernatremia, microcephaly, failure to thrive, and unilateral cleft lip and palate. Magnetic resonance imaging revealed lobar type holoprosencephaly. Increased plasma osmolality and decreased urinary osmolality were detected. Her urine ADH level was 10 ng/day. Plasma osmolality levels returned to normal after hydration and administration of a vasopressin analogue. These findings suggest that in children with hypernatremia-hypodipsia syndrome, the possibility of cerebral malformations should always be kept in mind.

Key words: hypodipsia, hypernatremia, holoprosencephaly.

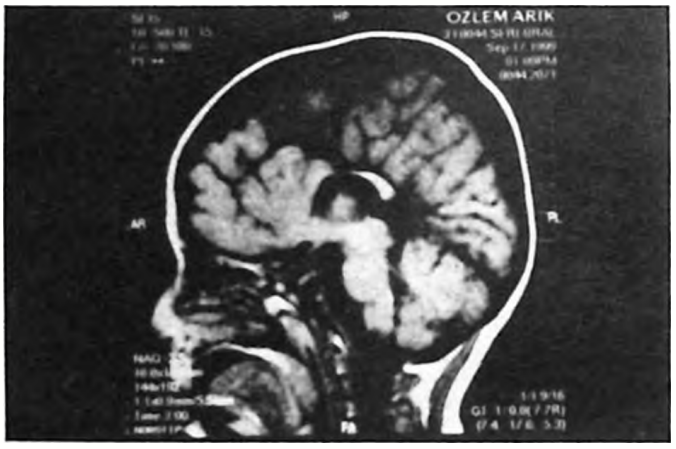
Adipsia or hypodipsia as an isolated defect of the thirst center is extremely rare and most often occurs in patients with hypothalamic disorders, congenital malformations and microcephaly[1]. One of the causes of hypernatremia is hypodipsia-hypernatremia syndrome, and its association with median structures of the brain and face is known[2]. We present here a child with facial abnormalities, which included unilateral cleft lip and plate, flat nose, and orbital hypertelorism associated with lobar holoprosencephaly, and diabetes insipidus.

Case Report

A 2 ½-year-old female was hospitalized because of hypodipsia, convulsions, unconsciousness, hypernatremic dehydration and acute renal failure. She was born after eight months of pregnancy by cesarean operation because of her mother's diabetes. Due to unilateral cleft lip and palate and prematurity, she had been hospitalized for one month in neonatal period. She had been re-admitted several times there after because of hypernatremic dehydration. She had history of convulsions when she was six- and twenty-months-old, and also had an operation to repair cleft lip at 1 ½ years. She had two cousins with cleft lip and palate in her family history. The parents also mentioned a significant adipsia and retardation of development in the patient. On physical examination, she was lethargic. Her tongue and buccal mucosa were excessively dry. She had anuria for eight hours preceding admission. Her height, weight and head circumference were under the third percentile for age. She had abnormal facial appearance with cleft palate, operated cleft lip, flat nose and hypertelorism. The following laboratory data were obtained: BUN, 80 mg/dl; creatinine 3.4 mg/dl; Na, 186 mEq/L; uric acid, 18 mg/dl; anion gap, 15; serum osmolality, 449 mOsm/kg; and urine osmolality 78 mOsm/kg. Blood counts- Hct, 41.4%; white blood cell count, 8,100/mm^3; platelet count, 176,000/mm^3; urinalysis –pH, 5; specific gravity, 1010; and 3-4 erythrocytes in the sediment.

She was severely dehydrated. The deficit was replaced uniformly within 48 hours with a solution of 0.2% saline with dextrose, so as to minimize the risk of central nervous system

dysfunction. Renal function tests returned to normal after hydration. Her cerebral magnetic resonance imaging revealed dysgenesis of corpus callosum, agenesis of septum pellucidum, hypoplasia of falx and sella turcica. Lobar holoprosencephaly was diagnosed (Fig. 1). Her chromosome analysis was found as 46, XX. Water deprivation test was performed over a two-hour period. The patient was closely observed to avoid severe rapid development of dehydration. At the beginning of the test, blood and timed urine were obtained from the child for serum and urinary antidiuretic hormone (ADH) levels, then 10 mg desmopressin was given intranasally. ADH administration led to a decrease in urine flow and increase in urinary concentration and urinary osmolality. The results of the test supported our diagnosis of central diabetes insipidus (Table I). A nasogastric feeding tube was placed in and her family warned about the importance of giving water to the child.



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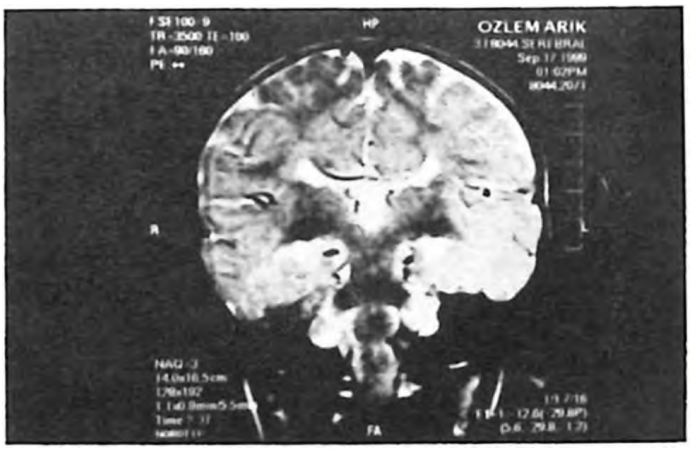

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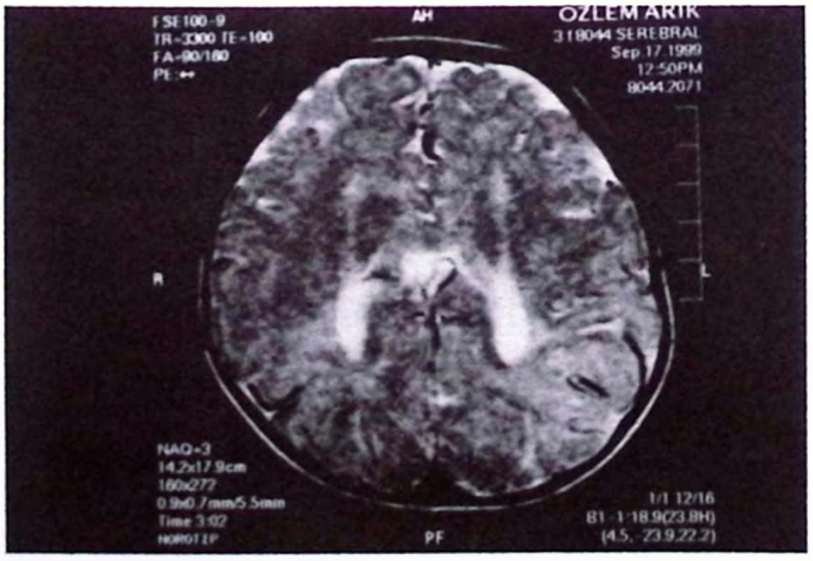

(c)

Fig. 1. Dysgeensis of corpus callosum, hypoplasia of falx, sella turcica and agenesis of septum pellucidum are seen.
a) sagittal T1-weighted section;
b) coronal T2-weighted section;
c) axial T2-weighted section.

Table I. Results of Water Deprivation Test

	Before AVP	After AVP
Maximum U_{OSM}/S_{OSM}	61/335 mosm/L	591/336 mosm/L
Serum ADH	3.5 pg/ml	—
Urinary ADH	<10 ng/day	not performed

ADH: antidiuretic hormone.

Discussion

Two important mechanisms are responsible to prevent hyperosmolality in normal individuals: water intake is increased and the release and action of ADH is also increased to produce a concentrated urine[1]. Central diabetes insipidus may evolve from various problems that lead to a deficiency of ADH secretion from the posterior pituitary gland[3]. There is close communication among neural centers regulating thirst and water conservation, and intrinsic central nervous system (CNS) disease may occasionally manifest with symptoms of disordered thirst in association with impaired ADH secretion. This finding has been observed in a group of disorders loosely termed adipsia/hypernatremia[3]. These patients usually have a central lesion that impairs the thirst and ADH release centers, causing their destruction[4]. Adipsia-hypodipsia and recurrent hypernatremia are usually manifestations of structural abnormalities of the hypothalamic-pituitary area[5]. Also, dysfunction of the anterior pituitary lobe, obesity, abnormal regulation of body temperature, psychomotor dysregulation and episodic muscular weakness could be encountered in these patients[6]. A decreased release of thyroid stimulating hormone (TSH), prolactin and growth hormone may be detected[7]. In our patient, thyroxine, triiodothyronine and TSH levels were normal, and a rate of growth of 0.5 cm/month documented in the last four months. Her body percentiles were below the third percentile.

These patients have recurrent or persistent hypernatremia without thirst. History of convulsions, polyuria, hypodipsia, and recurrent hypernatremia attacks and midfacial defects led us to suspect a central pathology associated with diabetes insipidus in our patient. Holoprosencephaly results from failure of separation of the embryonic forebrain, or prosencephalon, into symmetric cerebral hemispheres[8]. It was detected on the patient's cerebral magnetic resonance imaging. Holoprosencephaly involves forebrain and facial malformations that can range from mild to severe and it occurs more commonly in infants born to diabetic mothers[8,9], as was the case in our patient. It has been demonstrated that chromosomal abnormalities detected in some patients with holoprosencephaly include trisomies 13 and 18, deletions 18p- and 13q-, ring 18, the "pseudo-trisomy 13 syndrome", and triploidy[8,9]. Our patient's chromosomal analysis was found as 46, XX.

Holoprosencephaly and its association with hypernatremia and diabetes insipidus has been reported rarely in the literature[10-12]. Ohtake et al.[10] reported two young children with chronic hypernatremia, midline facial defects and holoprosencephaly. Kappy et al.[11] had restored serum electrolytes to normal with desmopressin acetate in a three-month-old child with holoprosencephaly and central diabetes insipidus. Arranz Gomez et al[12]. reported the clinical and neuroradiological findings in a case of semilobar holoprosencephaly associated with hypernatremia behaving like diabetes insipidus. In our patient, defective ADH release was shown with water deprivation test. It is known that defective synthesis or release of ADH will impair renal concentrating capacity and these patients will have a risk of hypernatremia. Because of the defective thirst mechanism caused by holoprosencephaly, our patient could not maintain the necessary high water intake, and hypernatremic episodes occurred.

In conclusion, if recurrent hypernatremic dehydration attacks with hypodipsia and convulsion are seen in a young child, CNS abnormalities associated with diabetes insipidus should always be searched.

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Presentation of a case with Salmonella glomerulonephritis

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SUMMARY: Dönmez O, Başdemir G. Presentation of a case with Salmonella glomerulonephritis. Turk J Pediatr 2002; 44: 267-268.

Salmonella infection is frequently encountered in childhood, but it is rarely associated with glomerulonephritis. We present in this report a case with Salmonella glomerulonephritis, which is infrequent in children. His general condition was found moderate, and temperature and blood pressure were 38 °C and 150/90 mmHg, respectively. The whole blood counts were as follows: white blood cell count 3,800/mm^3, hemoglobin 6.3 g/dl and platelet count 240,000/mm^3. Serum urea was 140 mg/dl, albumin 2.5 g/dl and complement (C_3) 23.6 mg/dl. Both Salmonella type O and Salmonella typhi H were detected positive (1/800 titer). In view of these findings, the case was considered as Salmonella glomerulonephritis; his clinical and laboratory recovery were achieved by supportive therapy.

Key words: children, typhoid fever, glomerulonephritis, salmonella.

Many etiologic agents have been implicated in acute post-infectious glomerulonephritis. The identification of an etiologic agent requires the temporal association with an illness in which a specific agent has been isolated, a serologic response to that agent that can be documented by rising antibody titers, and/or identification of the antigen or its antibody in the glomerulus[1,2]. Typhoid fever is relatively common but is rarely associated with glomerulonephritis[2]. Glomerular involvement has been described as being either in mesangial proliferative glomerulonephritis or diffuse proliferative glomerulonephritis form[3,4]. In this report, a nine-year-old male patient was presented who was diagnosed as Salmonella glomerulonephritis.

Case Report

A nine-year-old boy was admitted to our clinic because of macroscopic hematuria, oliguria, edema, hypertension and high fever persisting for two weeks. On physical examination he was found in moderate condition, with pallor, periorbital and pretibial edema and hepatosplenomegaly. His body temperature, pulse rate and blood pressure were 38°C, 108 beat/min and 150/90 mmHg, respectively. The whole blood counts were as follows: white blood cells 3,800/mm^3, hemoglobin (Hb) 6.3 g/dl and platelets 240,000/mm^3. Urine analysis revealed severe proteinuria with a specific gravity of 1020. Urine protein loss was 52 mg/m^2 per hour. Serum urea was 140 mg/dl, creatinine 1.8 mg/dl, aspartate aminotransferase 66 U/L, alanine aminotransferase 59 U/L and serum complement (C_3) 23.6 mg/dl. His serum total protein was 5 g/dl and albumin 2.5 g/dl, and serum immune globulins were normal. Renal biopsy was performed because of heavy proteinuria. Irregular, coarse granular mesangial accumulation of C_3 (+++) and IgG (+) was detected by immuno-fluorescence microscopy. Histopathological findings were in agreement with diffuse proliferative glomerulonephritis. Agglutination tests were performed due to persisting high fever. Both Salmonella typhi O and Salmonella typhi H were detected positive (1/800 titer). ANA and Anti ds-DNA were found negative. According to these findings, Salmonella glomerulonephritis was considered in this case. Ceftriaxone treatment along with supportive therapy were given. The clinical findings improved and urine protein became negative following the treatment. Serum complement level also returned to normal within eight weeks.

Discussion

Salmonella infections can be diagnosed easily when presenting with classical symptoms. In contrast, in those cases presenting with atypical

symptoms, difficulty in diagnosis might occur[3]. Renal involvement in typhoid fever might manifest as cystitis or pyelonephritis[2,5]. Acute tubulointerstitial nephritis was also reported as a rare cause of acute renal dysfunction during Salmonella typhimurium infections[6,7]. In addition, glomerular involvement has been described as a rare complication of typhoid fever[2,3]. In patients with glomerular involvement, microscopic and occasionally macroscopic hematuria, associated with moderate proteinuria and normal or slightly diminished renal function, could be found at the first stage of the disease. Clinical findings of Salmonella glomerulonephritis are different from those of poststreptococcal glomerulonephritis (PSGN)[5]. Although the cause has not been accurately explained, edema may last more than four weeks in some cases with Salmonella glomerulonephritis[2,3]. Persisting high fever, increased transminases and splenomegaly are also found in these cases. In addition, serum C_3 level decreases to a lesser degree than in cases with PSGN[2,3,5].

Our case was admitted to the clinic because of high fever lasting for two weeks, hematuria, oliguria, edema and hypertension. His physical findings revealed high fever, hypertension, edema, pallor, oliguria, splenomegaly and hepatomegaly. Laboratory results showed elevated serum urea, creatinine, and transaminase and decreased C_3 levels. In addition, hematuria and proteinuria were present. Glomerulonephritis was considered on the basis of these findings. Renal biopsy was performed due to continuous severe proteinuria, and diffuse proliferative glomerulonephritis was detected. It was reported that biopsy results of glomerular involvement in typhoid glomerulonephritis might be found in such forms as diffuse mesangial proliferation, IgA nephropathy or acute diffuse proliferative glomerulonephritis[1-5]. Sitprija et al.[4] detected Salmonella Vi antigen in the renal biopsy of patients with typhoid glomerulonephritis. Diagnostic difficulties can be experienced in Salmonella glomerulonephritis since it is not seen as frequently as PSGN and because the clinical symptoms of Salmonella glomerulonephritis are not well described. In this case, Salmonella glomerulonephritis was diagnosed based on both clinical and renal biopsy findings. Edema, macroscopic hematuria, oliguria, and hypertension were the striking symptoms along with positive group agglutination test and diminished serum C_3 level. However, serum complement levels returned to normal following the antibiotic treatment. This also supported the diagnosis of Salmonella glomerulonephritis. Our patient is now in follow-up, and his clinical and laboratory findings have improved.

In conclusion, immune-mediated glomerulonephritis must be considered as a rare cause of oliguria, hypertension, hematuria and decreased serum complement (C_3) during Salmonella typhimurium infection.

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Cerebro-oculo-facio-skeletal syndrome: report of two cases from Turkey with postmortem findings

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SUMMARY: Semerci CN, Onat N, Günçe S, Demirel N, Becer M, Yılmazer Y, Öznur İ, Türkyılmaz C, Balcı S. Cerebro-oculo-facio-skeletal syndrome: report of two cases from Turkey with postmortem findings. Turk J Pediatr 2002; 44: 269-273.

We describe two cases of COFS (cerebro-oculo-facio-skeletal) syndrome in two newborn females of consanguineous parents. The clinical, radiological and pathological features of the patients are presented. One of the two cases had 11 pairs of ribs (Case 1) and the other had three-lobed left lung (Case 2), neither of which has been described in COFS syndrome previously . To our knowledge, these are the first reported cases of COFS syndrome from Turkey.

Key words: cerebro-oculo-facio-skeletal syndrome, microcephaly, contractures of the extremities.

Cerebro-oculo-facio-skeletal (COFS) syndrome, or Pena-Shokeir syndrome type II, was first described by Pena and Shokeir[1] in 1974. COFS syndrome is an autosomal recessive disorder characterized by hypotonia, microcephaly, microphthalmia, cataracts, blepharophimosis, large auricles, prominence of the nasal bridge, micrognathia, widely set nipples, camptodactyly, flexion contractures on the elbows and knees, generalized osteoporosis, dysplastic acetabula, coxa valga and rocker-bottom feet[1-3]. We report the clinical and postmortem findings of two newborn girls with COFS syndrome having some new abnormalities in addition to the ones reported previously.

Case Report

Case 1

A female infant was born at 38 weeks of gestation by cesarean section because of transverse position. Unfortunately her mother had never admitted to hospital for obstetric examination during pregnancy. The mother (36 years old) and the father (42 years old) were first cousins. The previous obstetric history included four surviving children, a premature delivery who had died at 18 days and two induced abortions.

Birth weight was 2,200 g (<10th percentile), length was 43 cm (<10th percentile), Clinical examination showed bilateral microphthalmia, nystagmus, blepharophimosis, prominent nasal bridge, high and narrow palate, micrognathia, overhanging upper lip, low set and large auricles, hirsutism, short neck, camptodactyly, flexion contractures of the lower limbs, and rocker-bottom feet (Fig. 1). Laboratory tests showed normal levels of serum biochemical values, and karyotype was 46, XX. Radiological findings included eleven ribs, bilaterally flexion contractures of the proximal interphalangeal joints bilaterally, ulnar deviation of the hands (Fig. 2), and congenital vertical talus deformity of the foot (rocker-bottom feet) bilaterally (Fig. 3). The patient died at the 8th day of age exhibiting feeding and breathing difficulties. Before the postmortem examination, brain magnetic resonance imaging (MR) was performed, which demonstrated overall decrease in white matter of both cerebral hemispheres, marked dilatation of the left and slight dilatation of the right lateral ventricle, and choroid plexus hemorrhage in both lateral ventricles (Fig. 4). The genu of corpus callosum was present; however, its body and splenium could not be demonstrated.

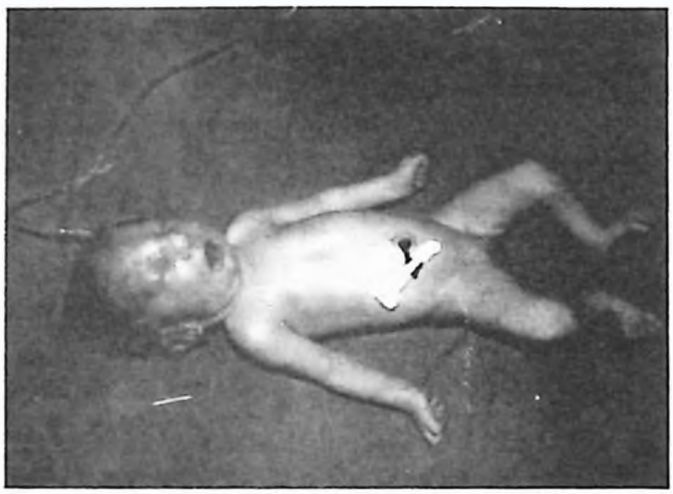

Fig. 1. General apearance of Case 1.

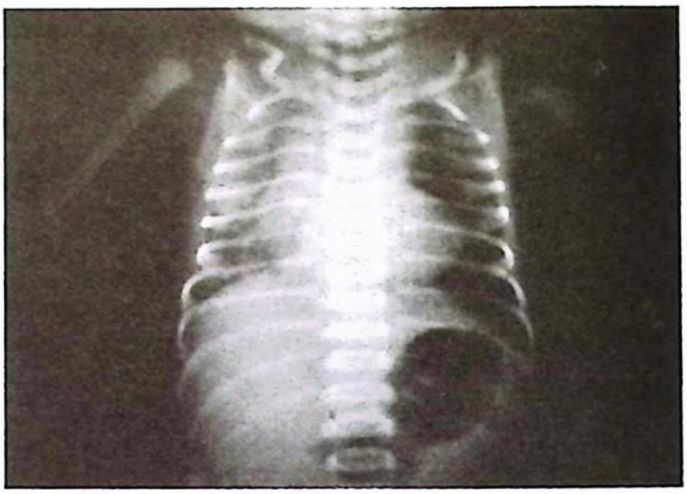

Fig. 2. X-ray: eleven pairs of ribs and ulnar deviation of the hands (Case 1).

Fig. 3. X-ray: dorsoflexion of the hands and camptodactyly, flexion contractures of the lower limbs, and vertical talus deformity (Case 1).

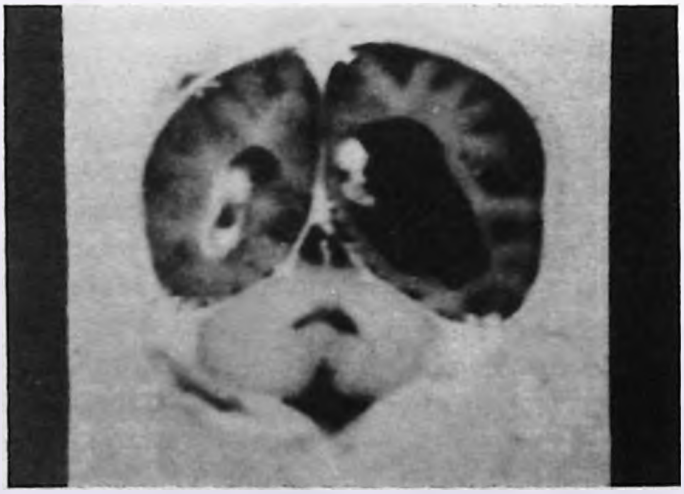

Fig. 4. Cranial MRI showing marked dilatation of left lateral ventricle and choroid plexus hemorrhage in both ventricles. White matter is decreased on both sides (Note. The superior sagittal sinus is hyperintense due to postmortem imaging) (Case 1).

Autopsy findings showed craniosynostosis, decrease in white matter of cerebral hemispheres, choroids plexus hemorrhage in both ventricles and pneumonia.

Case 2

Our second case was a four-day-old female infant. She had a healthy male sib. Her female sib, who had died at two days of age, had the same phenotype as the patient. The mother (25 years old) and the father (35 years old) were first cousins. Before delivery, ventriculomegaly, rocker-bottom feet and polyhydramnios were detected at 22 weeks of gestation by ultrasonography, but the parents did not accept to terminate this pregnancy. At birth, weight was 2,100 g (<10th percentile), length was 45 cm (<10th percentile) and head circumference was 31 cm (<10th percentile). Physical examination revealed microcephaly, micrognathia, prominent and large nasal bridge, low-set ears, overhanging upper lip, hairy frontal region, widely set nipples and camptodactyly (Fig. 5). The hips and knees showed severe flexion contractures. There was bilateral talipes equinovarus deformity (Fig. 6). Neurological examination revealed generalized mild hypotonia. Chromosome analysis revealed 46, XX, inv (9) (p11;q13). She had difficulty in breathing and feeding as in the first case, and died at the 9th day of life.

At autopsy, ventriculomegaly and a three-lobed left lung were found. On microscopic examination there were generalized gliosis and congestion in the brain and bronchopneumonia.

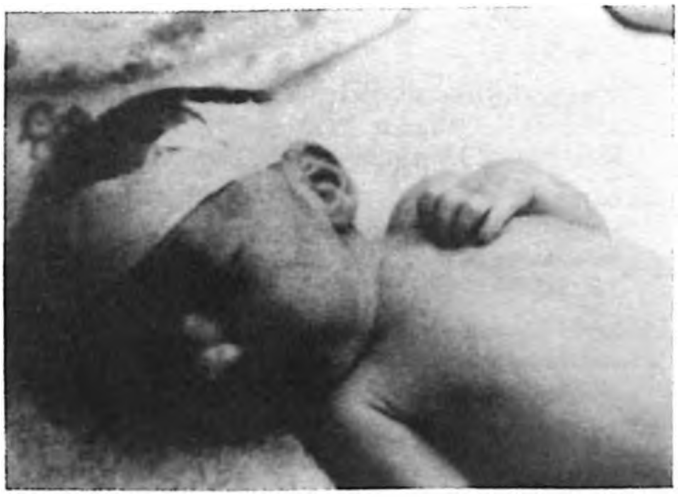

Fig. 5. Note prominent and large nasal bridge, micrognathia, widely set nipples and camptodactyly (Case 2).

Fig. 6. Flexion contractures of the lower limbs and talipes equinovarus deformity are seen (Case 2).

Discussion

Cerebro-oculo-facio-skeletal syndrome was first described by Pena and Shokeir[1] in 1974. This syndrome is caharcterized by neurogenic arthrogryposis, microcephaly, microphthalmia, cataracts, prominent root of nose, overlapping upper lip, rocker-bottom feet, hirsutism, camptodactyly, osteoporosis and osteopetrosis[1-3]. The diagnosis of COFS syndrome is difficult because it is variable even within a family and has many variants. The mode of inheritence of this rare syndrome is autosomal recessive, but X-linked recessive form may also present[4-7]. While our patients had the most characteristic features of this syndrome, Case 1 also had eleven pairs of ribs and Case 2 a three-lobed left lung.

In COFS syndrome, may skeletal anomalies are observed, such as camptodactyly, limb contractures, rocker-bottom feet, kyphoscoliosis, longitudinal foot groove, hip dysplasia, craniosynostosis, osteoporosis and osteopetrosis[1-3,8]. The 11 pairs of ribs found in Case 1 had previously been reported in trisomy 18, trisomy 21, femoral hypoplasia-unusual facies syndrome, Ritscher-Schinzel syndrome, spondylocostal dysostoses, and cerebro-costo-mandibular syndrome[9-10], but never in association with COFS syndrome.

Postmortem examination of Case 2 showed bilateral three-lobed lungs. Abnormalities of lung lobation have been reported in asplenia/polysplenia syndrome[11] but not in COFS syndrome previously.

Other important findings in COFS syndrome are those related to the central nervous system. These are microcephaly, callosal agenesis,

polymicrogyria, neuronal heterotopia, white matter hypoplasia, optic tract abnormalities, small pons, reduced myelination and hypoplastic dentate nucleus[1,2,8,12-16]. In our cases, microcephaly, partial agenesis of corpus callosum, white matter hypoplasia and ventriculomegaly were present.

Pulmonary infections and degenerative changes of spinal cord are the main causes of death in children with COFS syndrome as in the presented cases[17]. However, the etiology of COFS syndrome has not been clearly understood. Temtamy et al.[18] described an Egyptian girl with phenotypic abnormalities of COFS syndrome who had balanced translocation of 46, XX,t (1;16) (q23;q13) in all cells, and thus suggested that the gene for COFS syndrome may be located on chromosome 1q23 or 16q13. We described heterozygous pericentric inversion of chromosome 9 in Case 2. Pericentric inversion of chromosome 9 is a commonly observed structural variation in many healthy people[19]. At the same time, this inversion has also been reported in some patients with different phenotype and ophthalmological abnormalities, mental retardation, psychiatric problems and schizophrenia. Recently, Baltacı et al.[20] reported homozygous pericentric inversion 9 in a case with Walker-Warburg syndrome. They reported that further observations were needed in order to explain the causal association of these two conditions.

Patton et al.[21] and later Hamel et al.[22] noticed for the first time that there are some phenotypic similarities between early-onset Cockayne's (CS) syndrome and COFS syndrome. Recent molecular studies by Meira et al.[23] in COFS syndrome demonstrated a mutation identical to the one detected in Cockayne's syndrome group B (CSB). They suggested that COFS syndrome and CS might share a common pathogenesis.

Well known clinical findings of COFS syndrome can facilitate early prenatal diagnosis. Paladini et al.[24] were the first to prenatally diagnose a case of COFS syndrome, at 21 weeks of gestational age by ultrasonography. They demonstrated that the fetus had micrognathia, multiple joint contractures and rocker-bottom feet. The diagnosis was also confirmed on the basis of postmortem findings after termination of the pregnancy. In our second case, ventriculomegaly and rocker-bottom feet were prenatally diagnosed by ultrasonography at 22 weeks of gestation, but the parents refused termination of the pregnancy.

In conclusion, this report presents the first two cases of COFS syndrome from Turkey. The eleven pairs of ribs and three-lobed lungs have not previously been described in this syndrome.

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Megalocornea, macrocephaly, mental and motor retardation: MMMM syndrome (Neuhäuser syndrome) in two sisters with hypoplastic corpus callosum

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SUMMARY: Balcı S, Tekşam Ö, Gedik Ş. Megalocornea, macrocephaly, mental and motor retardation: MMMM syndrome (Neuhäuser syndrome) in two sisters with hyoplastic corpus callosum. Turk J Pediatr 2002; 44: 274-277.

We report two sisters with Neuhäuser [megalocornea, macrocephaly, mental and motor retardation MMMM] syndrome. They also had hypotonia, incomplete cleft palate, bifid uvula, depressed nasal bridge, epicanthal folds, hypoplastic labia major, micrognathia and pectus excavatum. Their brain magnetic resonance imaging showed cortical atrophy, large fourth ventricle and hypoplasia of corpus callosum. These findings have not been reported before in MMMM syndrome. Prenatal sonography could have been helpful if the mother had asked for genetic counseling given the presence of hypoplasia of corpus callosum and Dandy-Walker variant.

Key words: megalocornea, macrocephaly, mental retardation, hypotomia, Neuhäuser syndrome, posterior cleft palate, hypoplastic corpus callosum, MMMM syndrome.

The association of megalocornea, mental-motor retardation and macrocephaly (MMMM) is a rare autosomal recessive syndrome and a well delineated clinical entity. This syndrome was first described by Neuhäuser et al.[1] in 1975. Later, similar cases with variable expression were reported by Schmidt and Rapin et al.[2], Del Giudice et al.[3], Rass-Rothschild et al.[4], Santolaya et al.[5] and finally Verloes et al.[6]. We describe two sisters with MMMM syndrome or Neuhäuser syndrome who are different from the previously reported cases with findings such as hypoplasia of the corpus callosum. These findings have not been described before and, we believe, they are very important, especially in the differential diagnosis of MMMM syndrome during early prenatal diagnosis.

Case Reports

Case 1

A 10-month-old female patient was admitted to our hospital with chief complaints of mental-motor retardation, hypotonia, megalocornea and incomplete cleft palate. The parents were first-degree relatives. Our patient was the third child of the family. The first male child had died at 15 days, possibly from meconium aspiration. The second child was a nine-year-old healthy male. On physical examination of the patient, head circumference and length were 49 cm (>95th percentile) and 68 cm (10th-25th percentile), respectively. The weight was 6,700 g (<5th percentile). She had motor retardation, hypotonia, depressed nasal bridge, incomplete cleft palate, bifid uvula and micrognathia. Skull and vertebral x-rays, abdominal sonography, chromosome analysis (46, XX), urine and blood amino acid chromatography were normal. TORCH serology was negative. Brain magnetic resonance imaging (MRI) showed large cisterna magna and fourth ventricle. Corpus callosum was hypoplastic. Ophthalmologic examination revealed bilateral megalocornea (corneal diameter: 15 mm). Unfortunately, the patient died in the first year of life.

Case 2 (Sister of Case 1)

Case 2 was a 14-month-old girl who was the fourth child of the family. Unfortunately, the mother did not ask for genetic counseling during the pregnancy. The patient was first admitted to our department when she was 14-months-

old. On physical examination, the weight was 12 kg (95th percentile), and length was 78 cm (75th percentile). The head circumference was 51 cm (>95th percentile) (Fig. 1). She had severe mental-motor retardation, hypotonia, epicanthal folds, depressed nasal bridge, sparse and blonde hair, low-set ears, incomplete cleft palate, bifid uvula, hemangioma on the neck, short columella and philtrum, pectus excavatum, and hypoplastic labia major. Urine and blood amino acid chromatography, chromosome analysis (46 XX), and echocardiogram were normal. Cranial MRI and computed tomography (CT) showed hypoplasia of corpus callosum and cerebellum, large fourth ventricle, frontal-temporal cortical atrophy and Dandy-Walker variant (Fig. 2). Ophthalmologic examination showed megalocornea (diameter: 16 mm). Iris, anterior segment and intraocular pressure were normal.

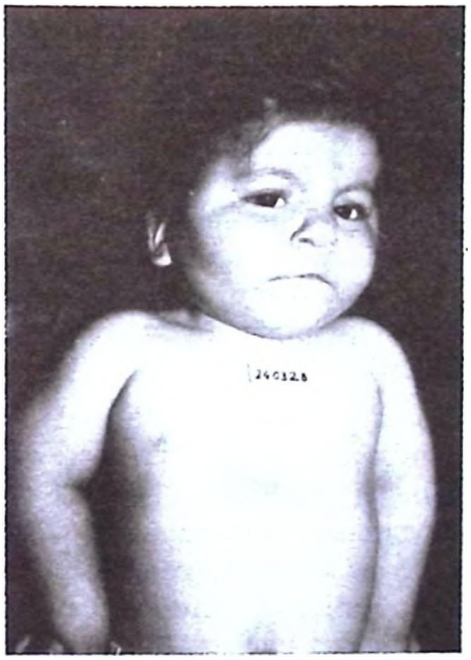

Fig. 1a: The 14-month-old girl (Case 2) with megalocornea, hypotonia, and epicanthal folds.

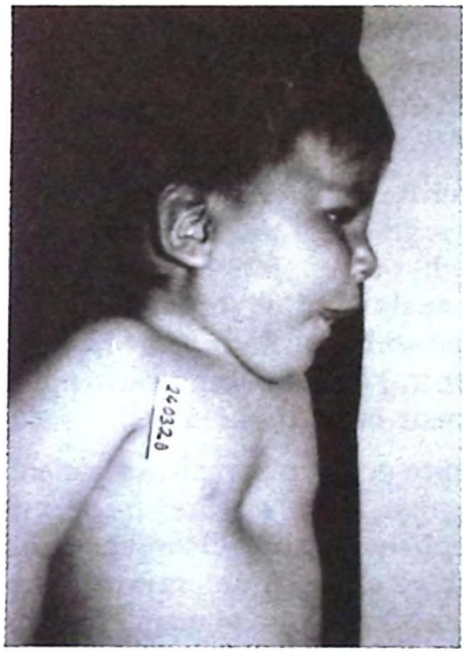

Fig. 1b: Case 2: Note depressed nasal bridge, low-set ears and pectus excavatum.

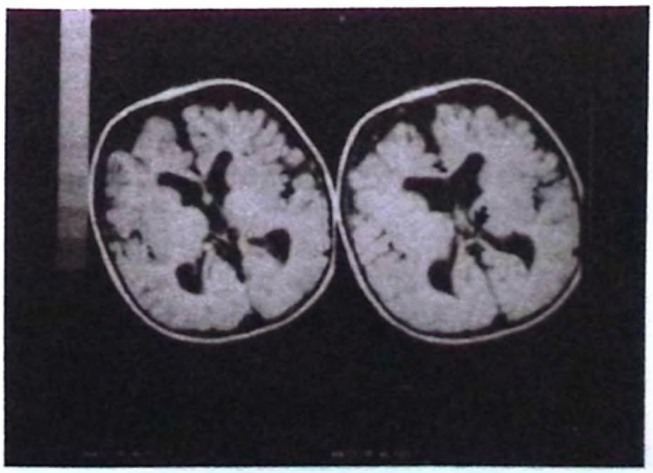

Fig. 2a: Brain magnetic resonance imaging (MRI) of Case 2 dmonstrates cortical atrophy, and hypoplasia of corpus callosum (arrow).

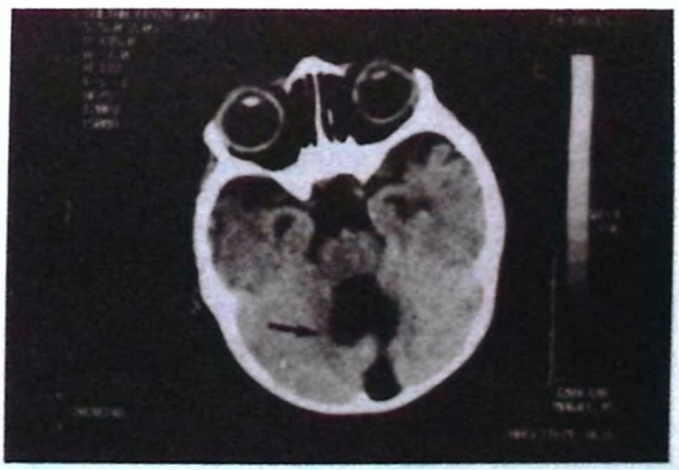

Fig. 2b: Brain computed tomography (CT) demonstrates large fourth ventricle with hypoplasia of vermis indicating Dandy-Walker variant (arrow).

Discussion

Neuhäuser et al.[1] reported an autosomal recessive entity characterized by mental retardation, seizures, muscular hypotonia and megalocornea in 1975. All of their patients (3 siblings and 4 sporadic cases) were moderately to severely retarded and had delayed motor development and megalocornea. Seizures and abnormal EEG recordings were reported in four of seven patients. Santolaya et al.[5] thought that congenital hypotonia might be another major sign of the Neuhäuser syndrome. Santolaya et al.[5] and Raas-Rothschild et al.[4] revealed that mental retardation and megalocornea are nonspecific findings. They suggested that hypotonia is an additional finding in MMMM syndrome.

Megalocornea is a developmental anomaly of the anterior segment of the globe without signs of ocular hypertension[1]. Iris hypoplasia, iridodonesis and myopia are frequently associated with megalocornea. Megalocornea is greater than 12.5 mm of corneal diameter[7], and was present in both our cases.

Del Giudice et al.[3] reported two patients. They thought that short stature, microcephaly or macrocephaly, seizure disorder, neurological symptoms and some minor anomalies represented less common manifestations in this syndrome. They accepted mental retardation and megalocornea as the two sufficient criteria for diagnosis. Frydman et al.[8] described two patients with macrocephaly, mild mental retardation and megalocornea, as well as hypotonia, poor coordination and swallowing difficulties, suggesting that considerable clinical variability or true genetic heterogeneity may be seen in this syndrome. Verloes et al.[6] noticed the heterogeneity in megalocornea, mental-motor retardation (MMR) syndrome and they classified it into five types. Type 1 (Neuhäuser) includes iris hypoplasia, minor anomalies, variable mental retardation and seizures. Type 2 (Frank-Temtamy) is composed of megalocornea, camptodactyly, scoliosis and growth retardation. Type 3 includes normal irides, severe hypotonia, relative or absolute macrocephaly and minor anomalies. Type 4 (Frydman) includes normal irides, megalencephaly and obesity. Type 5 includes unclassifiable cases.

In our two affected sisters, severe mental-motor retardation, megalocornea, hypotonia, incomplete cleft palate, bifid uvula, depressed nasal bridge and micrognathia were present. Incomplete cleft palate can be seen as a minor finding in MMMM syndrome as seen in our cases. Palate abnormalities including high palate[1,3,8], flat palate[1] and low palate with a double convexity and a median groove[6] have been described in previous cases; however, more cases should be described to be able to define cleft palate as a specific finding in MMMM syndrome. Although it is not a specific finding, cleft palate could also be helpful in the prenatal diagnosis of this syndrome.

The significance of our cases was the additional findings of corpus callosum hypoplasia and Dandy-Walker variant (Fig. 2). In the previous reported cases, cranial CT revealed normal[5,6] or mild dilatation of the ventricles without hydrocephalus[8]. Verloes et al.[6] described a case in whom cranial CT demonstrated mild diffuse cortical atrophy. Kimura et al.[9] described a patient with primary hypothyroidism and hypomyelination on brain MRI.

Our cases may be a new recessive type of Neuhäuser syndrome with these additional abnormalities. These findings could be potentially helpful for prenatal diagnosis of this syndrome. The etiology of MMMM syndrome has not yet been described; the inheritance pattern in particular remains unclear. In our second case, prenatal ultrasonography could have been helpful if the mother had asked for genetic counseling, given the presence of hypoplasia of corpus callosum and large fourth ventricle in addition to other anomalies in the previous child. We keep DNA samples of these siblings to determine gene defect for future investigations. Finally, corpus callosum hypoplasia can be an additional finding of MMMM syndrome; however, it is not clear whether or not this association is the result of inheritance by autosomal recessive gene from consanguineous parents. More cases are necessary in order to explain the exact nature of this association.

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