Evaluation of 36 patients from Turkey with neuronal ceroid lipofuscinosis: clinical, neurophysiological, neuroradiological and histopathologic studies

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Neuronal ceroid lipofuscinosis (NCL) is one of the most common progressive neurodegenerative diseases seen in childhood. NCL is inherited as autosomal recessive trait, and is characterized by the accumulation of 'ceroid lipofuscin' in neuronal and extraneuronal cells. Clinical features include seizures, ataxia, myoclonus, loss of vision, and mental and motor deterioration. Although the disease is widely seen across the world, there seems to be an information gap in Asian countries. To date, no comprehensive and detailed studies on NCL have been carried out in Turkey. However, one could predict that the disease is rather frequent in Turkey due to high rates of consanguineous marriages. Thirty-six Turkish patients were evaluated in this study. Sixteen (44.5%) patients were girls, and 20 (55.5%) were boys. Parents were consanguineous in 25 families (80%). In five families (14%), the disease was seen in two sibs. The diagnosis was based on clinical evaluation, and neurophysiological, neuroradiologic, enzymatic, and histopathological studies. Electron microscopic study was the main diagnostic laboratory test.

Three patients were classified as infantile NCL, 11 were late infantile NCL, 5 were juvenile type NCL and 17 patients were Turkish variant NCL. In juvenile type, major initial symptom was visual impairment, whereas in all other types seizures were predominantly the first symptom at the onset of the disease. The initial symptoms of Turkish variant NCL were similar to those of late infantile type. Similar age at clinical symptoms and the presence of visual symptoms were common features of Turkish variant and juvenile NCL. Compared to late infantile NCL, Turkish variant, showed a more severe course regarding seizures. Electroencephalogram (EEG) showed abnormal features predominantly in Turkish variant, and were remarkable for occipital spikes. In patients with Turkish variant magnetic resonance imaging of the brain showed brainstem involvement, especially pons, in all patients except one; cerebral and cerebellar atrophy were seen with a slower course compared to late infantile NCL. Clinical picture of NCL in advanced stages of the disease was similar regardless of the subtype.

Key words: ***neuronal ceroid lipofuscinosis, neurophysiology, neuroradiology, histopathology, enzyme level.***

Neuronal ceroid lipofuscinosis (NCL), commonly referred to as Batten's disease, is possibly the most common group of progressive neurodegenerative disorders in children. The NCLs are autosomal recessive disorders characterized by accumulation of lipopigment such as lipofuscin and ceroid in neurons and extraneural cells[1]. Clinically, all classic childhood cases are characterized by rapid deterioration of vision, seizures, cognitive

impairment, ataxia, and regression in motor skills, which lead to a vegetative state and early death[2]. According to age of onset, and clinical and pathological findings, the NCLs are classified into four main types as infantile type (CLN1, Santavuori), late infantile type (CLN2, Jansky-Bielschowsky), juvenile type (CLN3, Batten-Spielmeyer-Vogt), and adult type (CLN4, Kufs)[3]. In addition to these main types, the NCLs include four late infantile NCL variants: Finnish variant (CLN5, fLINCL), Czech or Portuguese variant (CLN6, pLINCL), Turkish variant (CLN7, tLINCL), and progressive epilepsy with mental retardation (EPMR), also called Northern Epilepsy[4]. Clinical types of NCL, corresponding gene symbols, loci, and enzyme defects are summarized in Table I. The prevalence of different types of NCL varies depending upon race or country of origin[5-9]. The variation of prevalence or distribution of different types of NCL in various parts of the world may be due to genetic differences. However, further epidemiologic studies are necessary to clarify this genetic heterogeneity. Although the disease is widely seen across the world, there appears to be an information gap regarding NCL in Asian countries[10].

Table I. Summary of Clinical Types of NCL, Corresponding Gene Symbols, Loci and Enzyme Defects

Clinical type of NCL	Gene symbol	Locus	Enzyme activity
Infantile-Juvenile	CLN1	1p32	PPT1 deficient
Late infantile	CLN2	11p15	TPP-1 deficient
Variant late infantile	CLN6	15q21-23	?
Finnish variant late infantile	CLN5	13q22	?
Turkish variant late infantile	CLN7	?	?
Juvenile	CLN3	16p12	?
Northern epilepsy	CLN8	8p23	?
Adult	CLN4	?	?

PPT1 : Palmitoyl-protein thioesterase.
TPP-1: Tripeptidyl peptidase.

To date no, comprehensive and detailed study on Turkish patients with NCL has been done, aside from a few case reports[11,12]. However, one could predict that the disorder is rather frequent in Turkey due to high rates of consanguineous marriages. The aim of this study was to define the spectrum of the NCL phenotypes in a Turkish series, to determine the correlation between types and clinical manifestations in Turkish patients with NCL, to find out the features of the Turkish variant, and to compare them to those of other types of NCL.

Material and Methods

This study included 36 patients with NCL (from 31 families) admitted to the Hacettepe University İhsan Doğramacı Children's Hospital, Department of Pediatric Neurology between 1995-2000. The diagnosis of NCL was based on clinicial, neurophysiological, ultrastructural, histopathological, and neuroradiological findings, and enzymatic diagnostic techniques. The classification of types of NCL was done according to the age of onset and clinical-pathological findings. In some patients, determination of type of NCL was confirmed by enzyme analysis. Peripheric lymphocytes were studied in all patients to demostrate vacuolization. Magnetic resonance imaging (MRI) was obtained in 22 patients. Parents were relatives in 29 patients. All patients received antioxidant therapy following diagnosis.

Electron microscopic (EM) examination of the circulating lymphocytes as well as skin samples was the main diagnostic technique. Ten milliliter venous blood with heparin was taken from patients and lymphocytes were isolated from venous blood using Ficoll-Hypoque technique[13]. For EM examination: following one day of fixation in 2% glutaraldehyde solution, material was washed with Sorenson's phosphate buffer and portfixed in 1% osmium tetraxide. After dehydration with graded ethanols and propylene oxide, the specimens

were embedded in resin. On two-micron toluidin blue-stained sections, lymphocyte rich areas were selected for thin sections. Thin sections were stained with lead citrate and 1% uranyl acetate. JEOL JEM 100°C electron microscopy was used for examination.

Results

Clinical Findings

We identified 36 patients with NCL; the clinical data are summarized in Table II. The geographical distribution of patients with NCL is shown in Fig. 1. Patients with infantile, late infantile, juvenile, and Turkish variant NCL accounted for 3 (8.3%), 11 (30.5%), 5 (13.8%), and 17 (47.2%) cases, respectively (Fig. 2).

Infantile NCL (CLN1)

There were three unrelated cases with infantile NCL in our series (Cases 1, 2 and 3). The mean age was 4.5 years (range 2.5-10 years). All patients had palmitoyl-protein thioesterase 1 (PPT1) deficiency. Interestingly, although PPT1 level was low, case 2 showed curvilinear pattern

Table II. Summary of Clinical and Pathological Features in Patients with NCL in Turkey

Patient	Type	Sex	Age of onset	Initial symptom	C.M.	Pathology	L.V.
1	INCL	F	1.5	Motor impairment	+	GROD	–
2	INCL	M	1.5	Motor impairment	+	CVB	–
3	INCL	M	1.5	Motor impairment	+	GROD	–
4	LINCL	M	3	Seizures	+	CVB	–
5	LINCL	M	1/2	Seizures	+	CVB	–
6	LINCL	F	4	Seizures	–	CVB	–
7	LINCL	F	2.5	Seizures	+	CVB	–
8	LINCL	F	3	Motor impairment	+	CVB	–
9	LINCL	F	3	Seizures	+	CVB	
10	LINCL	M	3	Seizures	+	CVB	–
11	LINCL	F	3	Seizures	+	CVB	–
12	LINCL	F	2	Seizures	+	CVB	–
13	LINCL	M	3	Seizures	+	CVB	–
14	LINCL	M	3	Seizures	+	CVB	–
15	tLINCL	F	7	Developmental regression, ataxia	–	Solid FPP	–
16	tLINCL	F	6	Developmental regression, seizures	–	Solid FPP	–
17	tLINCL	M	3	Seizures	+	Solid FPP	–
18	tLINCL	M	4.5	Motor impairment	+	Solid FPP	–
19	tLINCL	F	7	Seizures	+	Solid FPP	–
20	tLINCL	M	5	Seizures	+	Solid FPP	–
21	tLINCL	F	5.5	Seizures	+	Solid FPP	–
22	tLINCL	M	3	Seizures	–	Solid FPP	–
23	tLINCL	M	6	Seizures	+	Solid FPP	–
24	tLINCL	F	5	Motor impairment	+	Solid FPP	–
25	tLINCL	M	6	Seizures	+	Solid FPP	–
26	tLINCL	F	4.5	Seizures	+	Solid FPP	
27	tLINCL	M	6	Visual impairment	+	Solid FPP	–
28	tLINCL	F	7	Seizures	+	Solid FPP	–
29	tLINCL	F	2	Speech impairment	–	Solid FPP	–
30	tLINCL	M	3.5	Seizures	–	Solid FPP	–
31	tLINCL	F	5.5	Seizures	+	Solid FPP	–
32	JNCL	F	7	Visual impairment	–	FPP	+
33	JNCL	M	5	Visual impairment	+	FPP	+
34	JNCL	M	8	Visual impairment	+	FPP	+
35	JNCL	M	6	Visual impairment	+	FPP	+
36	JNCL	F	5	Visual impairment	+	FPP	+

INCL: Infantile neuronal ceroid lipofuscinosis; LINCL: Late infantile neuronal ceroid lipofuscinosis; JNCL: Juvenile neuronal ceroid lipofuscinosis; tLINCL: Turkish late infantile neuronal ceroid lipofuscinosis; M: Male; F: Female; +: Present; –: Not present; ?:Unknown; GROD: Granular osmiophilic deposits; CVB: Curvilinear body; FPP: Fingerprint pattern; C.M: consanguineous marriage; L.V: Lymphocytic vacuoles.

Fig. 1. Geographical distribution of patients with NCL across Turkey.
*: INCL; Δ: LINCL; ^ : tLINCL; 0: JNCL.

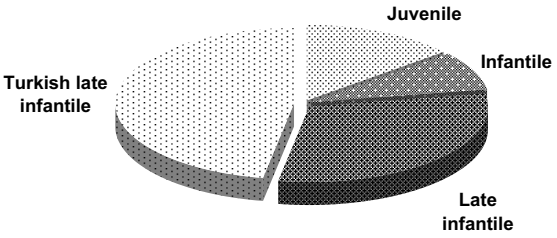

Fig. 2. Distribution of patients according to the types of NCL.

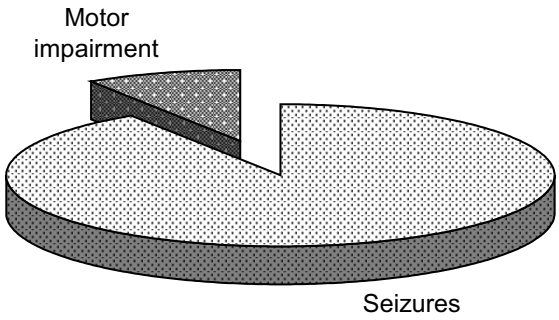

Fig. 3. Initial symptoms of patients with late infantile NCL.

on EM examination. Mean age of onset was 1.5 years (range 16-18 months). All of them presented with motor impairment as an initial symptom. Other clinical symptoms which developed during follow-up included myoclonus, personality changes, visual failure, seizures, mental deterioration and in one patient, stereotypic hand movements mimicking Rett's syndrome; two are in vegetative state.

Late Infantile NCL (CLN2)

Late infantile NCL was diagnosed in 11 cases (Cases 4 through 14). The diagnosis in six cases was confirmed by enzyme analysis. Mean age of onset was 2.9 years (range 6 months-4 years). One presented with motor impairment, the others with seizures as an initial symptom (Fig. 3). During the course of disease, they showed loss of vision, myoclonus, personality changes, mental regression and pyramidal tract signs. The latter was seen only in half of the patients. They all lost ambulation within approximately 1.5-2 years after onset of disease.

Turkish Variant NCL (CLN7, tLINCL)

Seventeen cases (cases 15 through 31) were diagnosed with Turkish variant. The mean age of onset was 5.1 years (range 2-7 years). Most of them had a clinical onset in preschool age. The characteristics of initial symptoms of Turkish variant are given in Fig. 4. The most common initial symptom was seizures, reported in 12 of 17 cases, with a more severe course compared to late infantile NCL. Two patients presented with motor impairment, one patient presented with visual impairment, one patient presented with speech impairment, and one with developmental regression and ataxia. Mental regression, myoclonus, speech impairment, loss of vision and personality disorders developed during the course of disease. In one patient, extrapyramidal signs, stereotypic hand movements and severe autistic behavior also

developed. Eleven patients lost ambulation (patients 15, 17-22, 24, 26, 29, 30) in an average of two years after onset. All patients in this group showed solid fingerprint pattern (FPP) on EM examination of circulating lymphocytes (Fig. 5).

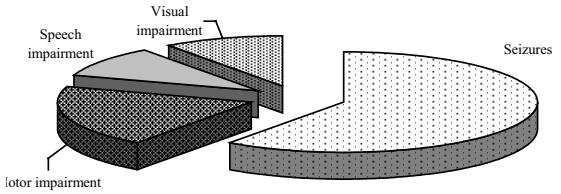

Fig. 4. Initial symptoms of Turkish variant late infantile NCL.

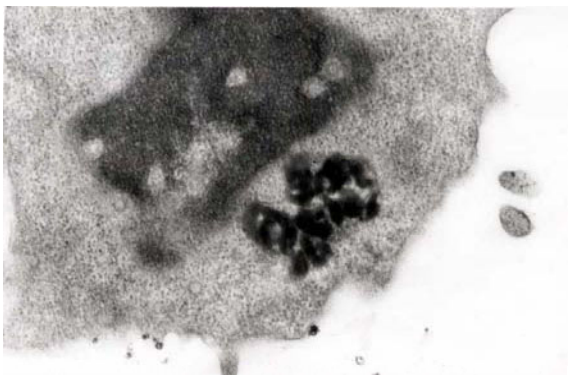

Fig. 5. Cytoplasmic inclusion in a circulating lymphocyte with the characteristic appearance of the solid fingerprint pattern in a patient with Turkish variant LINCL.

Juvenile NCL (CLN3)

Five patients were classified as juvenile NCL (cases 32 through 36). The mean age of onset was 6.2 years (range 5-8 years). The clinical picture was typical with visual impairment owing to retinitis pigmentosa in preschool age, followed by seizures, mental regression, dysarthria, sleep disorders and behavioral deterioration. One patient had typical autistic behavior. Two patients lost ambulation at nine years. Notably, most patients developed a typical facial appearance, with thin, prolonged face, sunken eyes, and prominent chin and ears. All patients in this group had vacuolized circulating lymphocytes (Fig. 6).

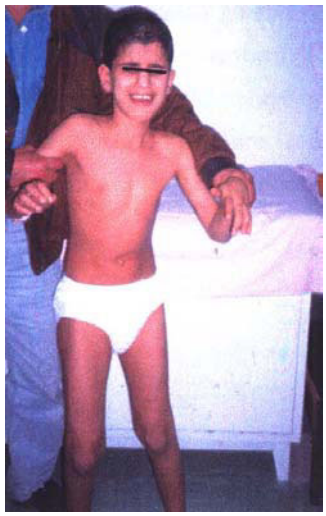

Fig. 6. A patient with juvenile NCL and typical facial features.

Neurophysiological Results

All groups showed abnormal neurophysiological findings. Most patients with juvenile NCL and Turkish variant had abnormal electroretinogram (ERG) and visual evoked potentials (VEP) (Fig. 7), whereas abnormal brainstem audiotory evoked potentials (BAEP) were seen in approximately half of the patients with Turkish variant (45%). Electroencephalography (EEG) recordings were evaluated in 11 patients. We found abnormal EEG features in all groups, including background slowing, fast spike and waves and focal epileptiform discharges. EEGs of patients with Turkish variant showed predominately occipital spikes and subcontinuous fast spike and wave activity. Furthermore, Turkish variant had more severe EEG findings than other types of NCL (Fig. 8).

Neuroradiological Results

Thirty-three MRIs from 22 patients were obtained. Table III summarizes neuroradiologic features of the patients. All patients with late

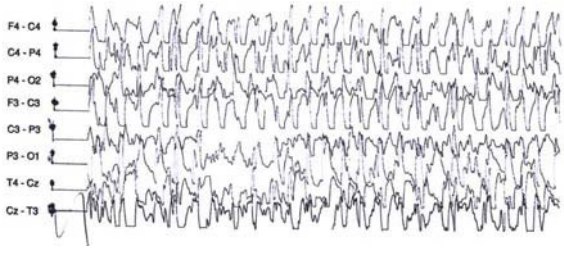

Fig. 7. EEG of a patient with tLINCL at seven years of age showing electrographical status epilepticus.

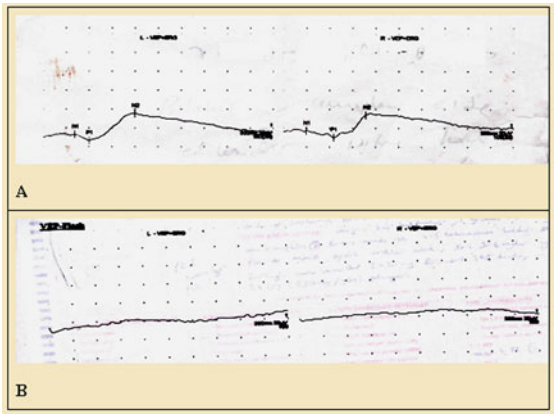

Fig. 8. a) Bilateral normal electroretinogram (ERG) responses. **b)** Extinguished ERG responses bilaterally.

infantile NCL and Turkish variant showed cerebellar atrophy on MRI. Most patients (19/22) had cerebral atrophy at various degrees. Although cerebral atrophy was severe in patients with late infantile NCL, patients with Turkish variant showed mild cerebral atrophy even two years after the onset. Brainstem, particularly pons, was affected in all patients with Turkish variant but one (Fig. 8, 9).

Discussion

We present the spectrum of the NCL phenotypes in 36 Turkish patients with NCL. Hacettepe University İhsan Doğramacı Children's Hospital is the best established tertiary referral center in

Table III. MRI features of the patients with NCL in Turkey

Patient	Type	Interval[5] (year)	Cerebellar atrophy		Brainstem	Hypointensity of thalami	Basal ganglia	PVWM	CI	CE	Cerebral atrophy	CC
			H	V								
1	INCL	0.5	0	0	+	2	–	2	1	–	1	1
2	INCL	0.8	0	1	+	2	–	2	1	–	2	2
3	LINCL	0.6	1	1	–	0	–	2	1	–	2	1
8	LINCL	2	2	2	–	0	–	2	–	–	2	1
		2.5	2	2	–	0	–	2↑	1↑	–	2	2↑
9	LINCL	2	2	2	–	1	–	1	1	+	2	1
11	LINCL	6	3	3	+	1	–	2	1	–	3	2
15	TLINCL	1	1	1	–	0	–	2	1	–	1	1
		2	1	1	–	0	–	2↑	1 S	+	2	1
		3	1	1	+	0	–	2↑	1 S	–	2	2
18	TLINCL	1.5	2	2	+	2	–	2	1	+	1	1
20	TLINCL	0.8	1	1	+	1	–	2	1	–	0	0
		1	1	1	+	1	–	2↑	1 S	–	0	0
		2	1	1	+	1	–	2	1	–	1	1
21	TLINCL	2.5	2	2	+	0	–	2	1	–	1	1
23	TLINCL	4	2	2	+	0	–	2	1	–	1	1
24	TLINCL	0.6	1	1	–	0	–	2	1	–	–	0
		1.5	2	2	+	0	–	2↑	1	–	1↑	1↑
25	TLINCL	1.5	0	1	+	2	–	2	1	–	0	1
26	TLINCL	3.5	2	2	–	0	–	2	1	+	3	2
27	TLINCL	2	1	1	+	1	–	2	1	–	1	O
28	TLINCL	2	1	1	+	2	–	2	1	–	2	1
		3.5	2	2	+	2	–	2 A	1 S	–	2↑	2↑
29	TLINCL	0.5	1	2	+	0	+*	2	1	–	1	1
30	TLINCL	2	0	0	–	2	–	2	1	–	1	0
		3.5	1	1	+	2	–	2 S	1 S	–	1	1
		5	2	2	+	+	–	2 –	1↑	+	3	2
		7	2↑	2↑	+	2	–	2 –	1↑	+	3	2
32	JNCL	2.5	1	1	+	0	–	2	1	–	1	2
		5	2↑	2↑	+	0	–	2 S	1 S	–	2	2
33	JNCL	1	0	0	–	0	–	0	0	–	0	0
34	JNCL	4	0	0	–	1	–	0	1	–	0	0
35	JNCL	8	1	1	–	1	–	1	1	–	2	2

$: Interval between initial symptom and the date of MRI; H: Hemispheric; V: Vermian; PVWM: Periventricular white matter; CC: Corpus callosum; CI: Capsula interna; CE: Capsula externa; S: Same; ↑: Increased; +: Available; –: Unavailable; 0: Not present; 1: Mild; 2: Moderate; 3: Severe; * Involvement due to chronic hepatic disorder.

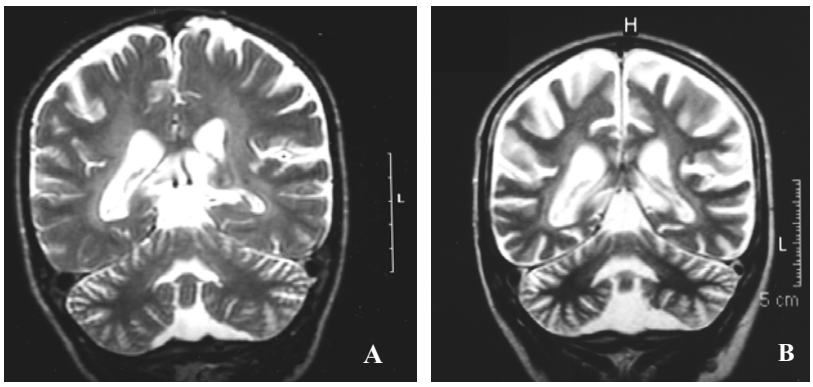

Fig. 9 a-b. In two studies obtained two years apart (A, former), T-2 weighted images at coronal section revealed diffuse hyperintensity in the periventricular white matter, and atrophy of the cerebrum and cerebellum which increased remarkably over time.

Turkey, therefore we expect that our patients reflect a general view of this rare disorder in our country. In our series late infantile NCL and Turkish variant, a variant form of late infantile NCL, were the most prevalent types of NCL, constituting 30.5% and 47% of patients, respectively. Individual pediatric types within the spectrum of the NCLs vary among countries due most probably to genetic diversity[10], with the juvenile type being most frequent in European countries including Germany, Sweden and other Scandinavian countries, and the infantile type being most frequent in Finland and Italy[5,8,9]. In a series from Argentina, late infantile NCL was the most prevalent type, with most patients of European descent[7]. The only study on Asian patients with NCL was a series of 36 cases reported by Oishi et al. in Japan[10]. The authors pointed out that late infantile and juvenile NCL were the most frequent types of NCL in Japan, and the results were consistent with that of European countries, thus indicating that the distribution of types of NCL was different in Turkey, from both European countries and Japan.

In a series from the Czech Republic, late infantile and pLINCL, a variant type of late infantile NCL, outnumbered other types of NCL, with approximately half of the patients being of Romany origin[14]. Interestingly, the majority of patients with pLINCL are people from Portugal, Pakistan, or India and from the Romany population in the Czech Republic. Furthermore, it is estimated that there is an ethnic link in the NCL subtype and that the Romany population originated from Pakistan/India[4]. The distribution of the patients with NCL in our series was similar to the Czech series.

The mean ages at the onset of clinical symptoms (infantile, late infantile, Turkish variant, and juvenile form) were 1.5, 2.9, 5.1, and 6.2 years, respectively. The results were consistent with the corresponding results reported in the United States and Japan[6,10]. Regarding initial symptoms, in patients with both late infantile NCL and Turkish variant NCL, seizures, usually generalized tonic-clonic, were the most prominent characteristic. However, the first symptom in patients with juvenile NCL was visual impairment, and in patients with infantile NCL motor impairment. In Europe, Japan, and the United States, the initial symptom in late infantile NCL is mostly seizures, and in juvenile NCL visual failure[5-9]. The mode of presentation in late infantile and juvenile forms of NCL in our series was quite similar to previous reports in the literature.

As for the Turkish variant of NCL, a subtype of late infantile type, although the major presenting symptom in the literature is seizures, initial symptom of two patients in our series (Patients 18 and 24) was motor impairment, suggesting that clinical presentation of the Turkish variant overlaps with late infantile type[15,16]. One patient (Patient 27) presented with visual impairment, and his sister (Patient 28) initially had seizures, however, the latter subsequently developed visual loss and retinopathy, which were evident on admission. The ages at the onset of the disease and visual symptoms of these siblings could be supportive of juvenile type of NCL[5-10]; however, absence of vacuolization in peripheric lymphocytes and the 'solid finger print' patern on EM examination led us to the subclassification of

Turkish variant[17,18]. Turkish variant NCL has a wider range of age of onset, the youngest age overlapping with late infantile NCL, and older ages reaching the age of onset of juvenile NCL. Seizures are the outstanding clinical feature of late infantile NCL and Turkish variant. Motor impairment is an overlapping initial symptom both for Turkish variant and late infantile NCL, whereas visual impairment is seen in both Turkish variant and juvenile NCL. Turkish variant seems to have a broader age of onset with clinical features shared by two other subtypes of NCL with distinct and widely spread ages of onset. From this clinical perspective, the Turkish variant might be considered as an intermediate form between late infantile and juvenile NCL. However, patients with Turkish variant had a more severe course regarding seizures. Eleven of 17 patients lost ambulation in an average of two years after onset. Age of onset and inital symptoms do not seem to be of predictive value for outcome. These patients showed a rapid deterioration with intractable seizures, progressive ataxia and quadriparesis. Further clinical and genetic studies are required to better define the different clinical course of patients with Turkish variant NCL. We are in the process of studying molecular genetic aspects of NCL in collaboration with Prof. Anna-Elina Lehesjoki at the University of Helsinki, Finland, to better define the clinical and genetic correlation, and to provide genetic and prenatal counseling.

Neurophysiological evaluation plays a important role in the diagnosis of NCL. Electroencephalogram (EEG) recordings were evaluated in 11 of 36 patients, and showed slowing of the background activity and presence of fast spike and waves in all types of NCL. Voltage suppression was a prominent feature in all types, except in juvenile type. Occipital spikes, subcontinuous slow spike and waves were most common in Turkish variant, and overall EEG appeared to be more pathologic compared to other types of NCL (Fig. 7). EEG findings of our patients were otherwise consistent with previous reports[19,20].

Both electroretinogram (ERG) and VEP are useful diagnostic tests, particularly in late infantile NCL[1]. In all NCL types retinal degeneration is present which leads to attenuation of ERG amplitude. Also, patients show a progressive VEP abnormality with attenuation of potentials and increased latencies[19,21]. Almost all of our patients regardless of NCL type showed abnormal ERG and/or VEP responses. We noted that in patients with late infantile NCL, VEP abnormalities became prominent after six years of age, whereas in the Turkish variant, it was present as early as one year of age. All patients with Turkish variant had diminished ERG between the ages of 4-10 years, as seen in patients with juvenile NCL (Fig. 8). BAEP was abnormal in approximately half of the patients in this group, consistent with brainstem involvement on MRI.

Magnetic resonance imaging (MRI) findings in patients with NCL include cerebral and cerebellar atrophy with variable severity, thinning of the cortex, mild hyperintensity of the periventricular white matter on T2-weighted images and decreased T2 signal in the thalami[22-25]. The MRI findings in our patients are given in Table III. These findings are neither specific nor constantly seen, however, NCL should be considered in a child with progressive encephalopathy when MRI shows such features[26]. Cerebral atrophy is one of the cardinal findings of NCL; it was observed in 19 of 22 patients regardless of the type of NCL. In both the infantile and late infantile NCL, cerebral atrophy shows a rapid progression[27,28]. However, in our study, cerebral atrophy showed a mild course developing over the first two years of the disease in patients with Turkish variant NCL (Fig. 9). Cerebellar atrophy is a more prominent feature and shows a more rapid progression in late infantile NCL than in other forms of NCL, such as infantile and juvenile forms[29]. Regarding cerebellar atrophy, our data were similar to previous reports. Another MRI feature of NCL is mild hyperintensity in the deep white matter due to gliosis and loss of myelin as demonstrated in pathological studies[30]. All our patients, except for two, had similar findings on T2-weighted images. Hypointensity of the thalami on T2-weighted images, due to probable intracellular storage of ceroid-lipofuscin pigments, may be present in some patients with late infantile and juvenile NCL[28,31]. MRI findings of the Turkish variant was most remarkable for brainstem involvement, particularly at the pons level, detected in all patients except one (Fig. 10). One other distinguishing feature was increased signal intensity in the posterior crus of the internal capsule, seen in all patients, whereas in previous reports, internal capsules were spared in NCL[24,32]. However, we anticipate that our finding might be a secondary change, and that internal capsules might be affected by wallerian degeneration as the deep white matter[33].

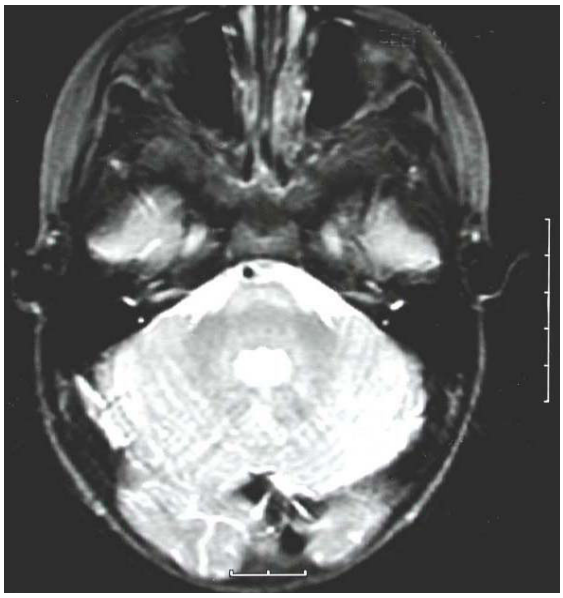

Fig. 10. T2 weighted transverse section shows increased signal intensity of anterior pons and pontine tegmentum at the level of brainstem.

The current study is the first comprehensive study on a large group of patients with NCL from Turkey, and the majority of patients belonged to the Turkish variant subgroup. In summary, the initial symptoms of Turkish variant NCL were similar to those of late infantile type. Turkish variant NCL was similar to juvenile type in terms of the age of onset and visual problems. However, patients with Turkish variant had a more severe seizure disorder compared to late infantile NCL. EEG showed abnormal features predominantly in the Turkish variant. Brain MRI showed brainstem involvement, especially pons, in all patients except one. Cerebral and cerebellar atrophy were seen with a slower course compared to late infantile NCL. Clinical picture of NCL in advanced stages of the disease is the same regardless of the subtype.

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Iodine deficiency in pregnant women and in their neonates in the central Anatolian region (Kayseri) of Turkey

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SUMMARY: Kurtoğlu S, Akcakuş M, Kocaoğlu Ç, Güneş T, Karaküçük I, Kula M, Kocakoç E. Iodine deficiency in pregnant women and in their neonates in the central Anatolia region (Kayseri) of Turkey. Turk J Pediatr 2004; 46: 11-15.

Severe iodine deficiency disorders may have been eradicated in many parts of the world, but milder forms still exist and may escape detection. The aim of this study was to assess the iodine nutritional status of pregnant women and their newborns, and the prevalence rates and severity of iodine deficiency in the Kayseri region, which has appeared to be iodine deficient in previous studies. A cross-sectional voluntary screening study was performed in the Maternity Unit of the University Hospital. Seventy pregnant women and their babies participated in this study. Iodine deficiency with high prevalence of goiter, low urinary iodine excretion and high serum thyroglobulin concentrations were recognized among pregnant women and their babies in Kayseri. Regular administration of iodine, starting at preconception or in early pregnancy and continuing during the period of nursing, is recommended in these regions.

Key words: thyroid function, thyroglobulin, thyroid volume, urinary iodine, pregnant women, newborn.

Iodine deficiency remains an important public health problem for almost all countries worldwide. An estimated one-third of the world's population is currently exposed to the risk of iodine deficiency disorders (IDD). These disorders are caused by insufficient iodine intake and, in some areas, goitrogenic factors in the diet. Their negative impact on the health of individuals and societies, and thus on national economic development as well, is tremendous[1-6].

The spectrum of health problems caused by iodine deficiency includes goiter stillbirth and hypothyroidism. However, its most severe consequence is mental retardation due to brain damage occurring during fetal development as a result of maternal hypothyroidism. Indeed, iodine deficiency is the world's greatest single cause of preventable brain damage in childhood. While cretinism is the most extreme outcome, of much greater significance are the subtler degrees of mental impairment that lead to poor school performance, reduced intellectual ability and impaired work capacity. Iodine-deficient communities have been found to score 10-15 points lower on IQ tests than iodine-replete ones. These disorders can be prevented by ensuring adequate iodine intake, which is the primary objective of the current worldwide drive to eliminate IDD[7-13]. According to the dietary allowances of iodine, as endorsed by the International Council for Control of Iodine Deficiency Disorders (ICCIDD) and the World Health Organization (WHO), the ideal iodine intake should be 150 mg/d for normal adults and 200 mg/d for pregnant (and lactating) women[14,15].

Turkey has long been known as a mild to moderate iodine deficient area according to the figures obtained from previous epidemiological studies[16-21]. It is believed that total goiter prevalence in Turkey is as high as 30.5%, and that of visible goiter 6.7%[20]. It was also shown that goiter prevalence did not fall below 2% in any region, and may increase up to 50% in some[20]. Turkey is geographically a mountainous region with volcanic properties, so lack of iodine in the soil is an expected finding underlying endemic goiter. Parameters of iodine status in Central

Anatolia (Kayseri province and mountainous region) have shown severe iodine deficiency in previous cross-sectional studies[17-21].

In this study we analyzed the iodine nutritional status of pregnant women and their babies, and the prevalence rates and severity of iodine deficiency in an area of suspected moderate to severe iodine deficiency (region of Kayseri).

Material and Methods

We enrolled 70 pregnant women and their newborns into a cross-sectional voluntary screening study. The use of iodized salt was elicited by detailed history. All the subjects were apparently healthy women and none of them gave any history of thyroid disease, nor were they taking any thyroid modifying medication. The women were admitted for delivery at Erciyes University Maternity Unit. They gave birth to apparently healthy full-term babies. The Ethical Committee of the Faculy of Medicine approved the protocol.

Thyroid volume (TV) measurements were performed by ultrasound (Toshiba, 7.5 MHz linear transducer). Each lobe of the thyroid gland was assessed separately by measuring the three main diameters, and the total volume of the thyroid was calculated by the algorithm $\pi/6$ height x width x depth[22]. In pregnant women, TV greater than 18.0 ml was considered as thyroid stimulation or hypertrophy and greater than 22.0 ml was considered as goiter[23].

The upper limit of TV in newborns is 1.5 ml[24].

The estimation of urinary iodine (UI) concentration was performed in spot urine samples obtained from all mothers and their newborns on the 5th day after delivery. Urine specimens were stored at –70°C until required for analysis. Final evaluation was done with reversed-phase high-performance liquid chromatography (HPLC)[25]. The results were expressed in terms of μg/L. Classification of the severity of IDD in mothers was according to the cut-off points of UI excretion values; thus, UI values (μg/L) less than 20 were considered severe, between 20 and 49 as moderate, between 50 and 99 as mild and greater than 100 as adequate[4]. The iodine deficiency in neonates was regarded to be mild with UI concentration between 31-50 μg/L, moderate in the range 30-15 μg/L and severe when values were less than 15 μg/L[2].

The women provided approximately 10 ml venous blood just before delivery. A doctor or a trained midwife obtained cord blood samples (10 ml) during delivery. The blood samples were allowed to coagulate at room temperature before separation of the serum by centrifugation. The serum samples were frozen within 1 h of sampling and then kept frozen at –70°C pending analysis.

Free triiodothyronine (FT3) and Free thyroxine (FT4) were measured by radioimmunoassay (Amersham UK). TSH (Amersham UK) thyroglobulin (Tg) (CIS Bio International, France) were determined using a sensitive immunoradiometric assay.

In mothers, biochemical criterion of excessive thyroid stimulation was defined as serum Tg greater than 30 ng/ml[23,26]. Cord blood normal Tg level is 2-54 ng/ml[27].

In the absence of iodine deficiency, the frequency of neonatal TSH above 5 mU/L whole blood (or 10 mU/L serum) is less than 3%. A frequency of 3%-19.9% indicates mild IDD. Frequencies of 20%-39.9% and above 40% indicate moderate and severe IDD, respectively[4,28,29].

Statistical Analysis

All data processing was done with the Statistical Package for Social Sciences SPSS 10.0 software for Windows. Commonly used statistical methods (median, proportions) were applied to analyze the data. The data were found to be not normally distributed. The level of significance in all statistical tests was set at $p \leq 0.05$. The Mann-Whitney U test and Pearson's correlation were used for independent variables.

Results

Only 23% of the mothers had access to iodized salt.

Serum Studies

The median concentrations (and ranges) of neonatal TSH, Tg, FT3 and FT4 were 7.4 (1.06-30.54) mU/L, 71.6 (7.07-598.12) μg/L, 1.3 (0.64-4.29) pg/ml, and 1.3 (0.65-2.52) ng/dl, respectively. The corresponding levels for the mothers during labor were 2.2 (0.82-4.85) mU/L, 25.7 (0.38-185.18) μg/L, 1.3 (0.72-2.74) pg/ml, and 1.2 (0.78-2.07) ng/dl, respectively (Table I).

The median neonatal serum concentrations of TSH and Tg were significantly higher than the corresponding maternal levels ($P<0.0001$,

P<0.0001, respectively). There were no significant differences between the median neonatal concentrations and corresponding maternal levels of FT3 and FT4. There was a significant correlation between the newborn and maternal levels of FT3 (r: 0.32, p<0.05) (Fig. 1).

Urinary Iodine in Mothers

The median value of UI in mothers in the first week after delivery was 30.2 μg/dl (range 3.20-171.50). There was no correlation between UI TV. Severe iodine deficiency (UI <20 μg/L) was detected in 33%, moderate deficiency (20-49 μg/L) in 33% and mild deficiency (50-99 μg/L) in 24% of the mothers. The UI excretion was normal (>100 μg/L) in 10% of these women.

Table I. Median Serum Concentrations (and Ranges) of Tg, TSH, FT3, FT4, TV and UI in Pregnant Women During Labor and in Their Neonates

Parameter	Pregnant women during labor	Neonates
Tg (ng/ml)	25.7 (0.38-185.18)	71.6 (7.07-598.12)
TSH (mU/L)	2.2 (0.82-4.85)	7.4 (1.06-30.54)
FT3 (pg/ml)	1.3 (0.72-2.74)	1.3 (0.64-4.29)
FT4 (ng/dl)	1.2 (0.78-2.07)	1.3 (0.65-2.52)
TV (ml)	15.7 (4.90-41.19)	0.8 (0.28-5.78)
UI (μg/L)	30.2 (3.20-171.50)	23.8 (3.20-95.30)

Tg: Thyroglobulin, FT3: Free triiodothyronine, FT4: Free thyroxine, TV: Thyroid volume, UI: Urinary iodine.

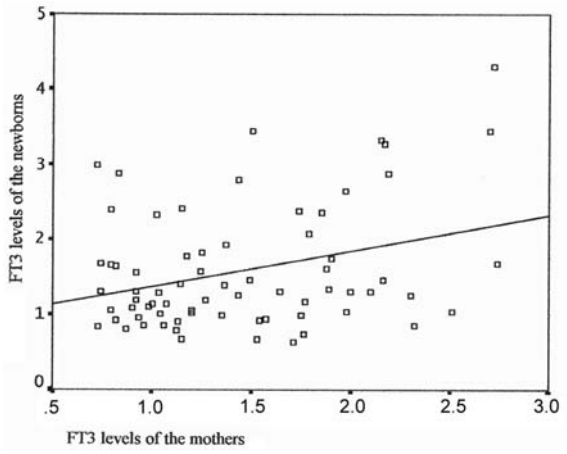

Fig. 1. Correlation between free triiodothyronine (FT3) (pg/ml) levels of the mothers and their newborns (r: 032, p<0.05).

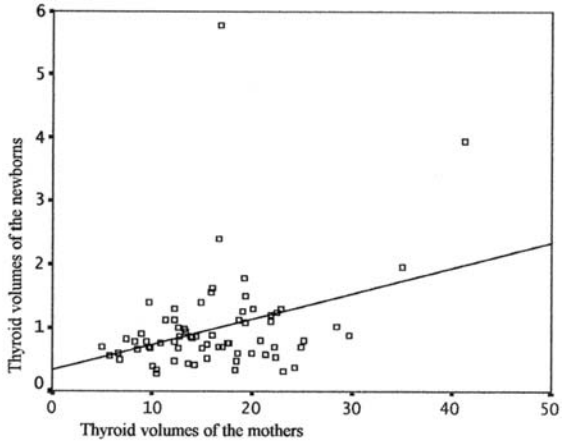

Fig. 2. Correlation between thyroid volumes (ml) of the mothers and their newborns (r: 0.34, p<0.05).

Thyroid Volumes in Mothers

In the first week after delivery, median TV found in all 70 women was 15.7 ml (range 4.90-41.19). Thyroid gland volume was in excess of the normal value of 18 ml in 37% of the women. Goiter was diagnosed in 17%.

Thyroid Volumes in Newborns

Median TV found in all 70 newborns was 0.8 ml (range 0.28-5.78). Volume >1.5 ml was found in eight newborns (11.4%). There was a significant correlation between the newborn and maternal thyroid volumes (r: 034, P<0.05) (Fig. 2).

Urinary Iodine in Newborns

In newborns, the median UI in the first week after birth was 23.8 μg/dl (range 3.20-95.30). Severe iodine deficiency (UI <15 μg/L) was detected in 27%, moderate iodine deficiency (15-30 μg/L) in 33% and mild deficiency (31-50 μg/L) in 23% of the babies. The UI excretion was normal (>50 μg/L) in 17% of these newborns.

There was a significant correlation between the newborn and maternal UI levels (r: 0.24, p<0.05) (Fig. 3).

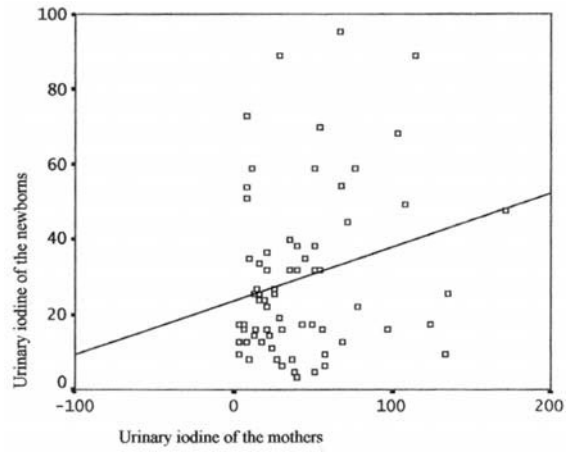

Fig. 3. Correlation between urinary iodine levels of the mothers and their newborns (0.24, p<0.05).

Discussion

Iodine deficiency causes developmental abnormalities in all age groups. These include not only goiter with impaired thyroid function but also decreased fertility, increased perinatal mortality, retarded growth, and impairment of mental development, including its extreme form, endemic cretinism[6]. The most detrimental effects of inadequate iodine intake appear in pregnant women and in children[7-9]. In 2001 alone, some 50 million children were born without any preventive measures having been taken against IDD during pregnancy[3].

Urinary iodine is an indicator to assess present iodine intake[6]. There is an agreement that spot urine samples from a representiative fraction of the population provide accurate information on the status of iodine nutrition. In our study, the UI excretion was adequate (>100 g/L) in only 10% of these mothers and in only 17% of their newborns (>50 µg/L). The median values of UI in mothers and their babies on the 5th day after delivery were 30.2 (range 3.20-171.50) and 23.8 (3.20-95.30) µg/L, respectively, supporting that Kayseri is an area of moderate iodine deficiency[4].

In this study, the median TVs of women and their babies were 15.7 ml (4.90-41.19) and 0.8 ml (0.28-5.78), respectively. In the same region, Kurtoğlu et al.[21] found a higher median TV of the newborn (1.26 ml) in 1994. The volume of the thyroid gland was in excess of the normal value of 18 ml in 37.1% and goiter was diagnosed in 17.2% of the women (TV>22 ml). Goiter (TV>1.5 ml) was diagnosed in 11.4% of the newborns. In these findings, TV of the women and their babies in the Kayseri region pointed to mild iodine deficiency.

In population studies, Tg is a sensitive marker of iodine deficiency[30,31]. Median Tg levels of the mothers and their babies were 25.7 ng/ml (range 0.38-185.18) and 71.6 ng/ml (range 7.07-598.12), respectively. In 30 newborns (42.9%), cord Tg levels were above 54 ng/dl. In 29 mothers (41.4%), serum Tg levels were above 30 ng/dl. High serum levels of Tg in both mothers and newborns reflect that Kayseri is an iodine deficiency endemic area in Turkey[17,21]. In 27.1% of newborns, cord blood TSH level was above 10 mU/L; none of the mothers had serum TSH levels above 5 mU/L. Neonatal thyroid screening appears to be a particularly sensitive index in the monitoring of iodine supply at a population level[28,29]. In our study, the frequency of cord serum TSH above 10 mU/L (5 mU/L blood) was 27.1%, indicating moderate iodine deficiency.

Salt iodization is arguably the most effective way to correct iodine deficiency in the long run[32] and is currently the preferred method for iodine repletion in Turkey. However, the circumstances leading to severe iodine deficiency in remote areas may in turn govern the success of the efforts toward correction. In Turkey, iodization of table salt was initiated in 1968 on a voluntary basis, when the use of potassium iodide was approved by the revised food codex. According to recent numbers from the Ministry of Health, iodized salt production of the major salt companies increased to 57% of their entire production in 1999. Now, whole table salt has to be iodized; however, iodization of industrial salt is not enforced. Although iodization of table salt is now legally enforced, this is in fact impossible to establish countrywide. There are more than 400 salt manufacturers in Turkey, most of which are small local producers. These local manufacturers use traditional, old-fashioned methods in salt production, and they do not have the substructure appropriate for salt iodization. In many small places like these villages, the population rely on these local manufacturers using primitive technology[16,19]. Recently, the Health Ministry started to work on a national salt iodization program to improve

iodine intake nationwide, but the level of utilization of iodized salt is far from sufficient to improve iodine status. In our study, only 23% of the mothers had access to iodized salt.

Regular administration of iodine, starting at preconception or in early pregnancy and continuing during the period of nursing, is recommended in these regions.

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Assessment of goiter prevalence, iodine status and thyroid functions in school-age children of rural Yusufeli district in eastern Turkey

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SUMMARY: Özkan B, Olgun H, Ceviz N, Polat P, Taysi S, Orbak Z, Koşan C. Assessment of goiter prevalence, iodine status and thyroid functions in school-age children of rural Yusufeli district in eastern Turkey. Turk J Pediatr 2004; 46: 16-21.

According to previous studies, Turkey has generally been accepted as a moderate endemic iodine deficient country. However, it has recently been reported that there are regions in Turkey where iodine deficiency is more severe than previously known. The current study was aimed at ascertaining the goiter prevalence by thyroid volumes, iodine status and thyroid functions in school-age children living in an area which is suspected to have moderate or severe iodine deficiency.

Overall goiter was found in 47.6% of children, in 22.8% of girls and in 24.8% of boys. Mean thyroid volumes did not differ significantly according to sex. Significant correlation was found between thyroid volume and body surface area and age. There was a negative correlation between the urinary iodine concentration and thyroid volume ($r=0.45$, $p<0.01$). Median urinary iodine concentrations in subjects with and without goiter were 20 μg/dl and 5.2 μg/dl, respectively. While median urinary iodine levels of the subjects with goiter were consistent with severe-moderate iodine deficiency, levels in subjects without goiter were comparable to moderate-mild iodine deficiency. None of the subjects had the signs or symptoms of hyper-or hypothyroidism. The differences in the mean values of thyroid hormones and TSH levels between subjects with or without goiter were not significant ($p>0.05$). No correlation was found between urinary iodine concentrations and thyroid hormone levels. A weak correlation was found between urinary iodine concentration and TSH levels ($r=0.12$, $p=0.05$).

Individuals with goiter were investigated etiologically: biochemical hypothyroidism was detected in 2%, compensated hypothyroidism in 12.6%, autoimmune thyroiditis in 2%, nodular goiter in 3% and isolated high TSH level with autoimmune thyroiditis in 0.08%.

In conclusion, although a salt iodization program has been started in Turkey, our study indicates that some regions with severe iodine deficiency are still present. This research suggests that this program should be re-evaluated for remote areas with self-contained economic systems, and should be expanded and more effectively applied nation-wide.

Key words: iodine deficiency, children, Turkey.

Iodine deficiency is still an important public health issue in Turkey. According to previous studies, Turkey has generally been accepted as a moderate endemic iodine deficiency country[1]. Although salt iodization was started in 1968, the level of utilization of iodized salt has been inadequate to control iodine deficiency. In 1995, the Health Ministry initiated a new national program including standardization of iodized salt and its use nation-wide, and legislation for mandatory iodization of household salt was passed in 1998. However, it has recently been reported that there are regions in Turkey where iodine deficiency is more severe than previously known[2,3].

An inadequate dietary supply of iodine results in the development of a variety of disorders classified under the general heading of iodine deficiency disorders. Endemic goiter is the first and most visible sign of iodine deficiency. The thyroid enlarges as an adaptation to normalize inadequate hormone levels, a reaction mediated by thyrotropin (TSH) stimulation. During this adaptation, deviation in thyroid hormone levels may occur, ranging from compensated hypothyroidism to primary hypothyroidism in respect to the severity of iodine deficiency[4].

The aims of this study were: 1) to determine goiter prevalence by ultrasonography and urinary iodine excretion in school-children aged 7-14 years in a remote area in which goiter is thought to be endemic; 2) to assess the impact of iodine deficiency on thyroid hormone levels of students with or without goiter; 3) to learn how effectively the salt iodization program has been working to improve iodine intake in this remote area.

Material and Methods

The study was performed in the mountain villages of Yusufeli, which is a town in eastern Turkey. Five hundred and eighteen school-children attend the four primary school, and come from the surrounding mountain villages. Of the 518 students, 259 were selected by using systematic sampling method to achieve a homogeneous distribution. Nine subjects were excluded: due to absence of informed consent (n=5), because serum thyroid hormones could not be measured (n=3), and because thyroid ultrasonography could not be performed (n=1). Thus, 250 school-children (126 boys) aged 7-14 years, who were born or living at least for five years in the area, were included in the study. A questionnaire was given to all students participating in the study to be filled out by their families regarding whether or not they used iodized salt in the preparation of food in their homes. All students underwent physical examination and age, gender, weight of the subjects were recorded. Body surface area (BSA in m^2) was calculated suing the formula $BSA=W^{0.425}xH^{0.725}x1.84x10^{-4}$ where W is the weight in kg and H is the height in cm[5]. Thyroid ultrasonic volume measurement was performed by the same radiologist for each student in the supine position with the neck slightly hyperextended. The dimensions of both thyroid lobes were measured with high resolution real-time portable ultrasonic scanner (Corevision, Toshiba, Japan) using a 8 MHz linear transducer (PLF-805ST, Toshiba, Japan). Longitudinal and transverse scans were performed allowing the measurement of the depth (d), the width (w) and the length (L) of each lobe. The volume of each lobe was calculated by the formula: V (ml)=0.479 x d x w x L (cm). The thyroid volume was the sum of the volumes of both lobes. The volume of the isthmus was not included. To define the goiter, thyroid volumes by ultrasound for age and gender were compared with reference thyroid volumes (percentile 97) of children born and living in areas from 12 European countries where iodine intake is normal.

Urinary iodine concentrations were measured in randomly collected urine samples by Sandhell-Kolthoff reaction. Urine was first digested with chloric acid in a heating block and iodine was determined by its catalytic reduction of ceric ammonium sulfate in the presence of arsenious acid. Mean urinary iodine excretion lower than 1.9 μg/dl was accepted as severe, levels between 2.0-4.9 μg/dl as moderate and levels between 5.0-9.9 μg/dl as mild iodine deficiency[6].

Serum free thyroxine (FT_4), total thyroxine (TT_4), free triiodothyronine (FT_3), total triiodothyronine (TT_3) and thyroid stimulating hormone (TSH) concentrations were determined by chemiluminometric method using ACS 180 (Chiron Diagnostic). Serum anti-thyroid antibodies were studied using enzyme-linked immunoassay (ELISA) method (Clark Laboratories Inc., New York, USA). The results of thyroid hormones were compared with the reference values in the same ages in the literature in which chemiluminometric method was used[7,8]. Cut-off levels for anti-thyroperoxidase and anti-microsomal antibodies were >0.527 and >0.460, respectively.

This study was approved by the Atatürk University Ethical Committee and informed consent forms were obtained from families of all children recruited for the study. Statistical analysis was carried out using the Statistical Package for Social Sciences (SPSS). Student's-t test was used in comparisons. Chi-square test was used where appropriate.

Results

According to questionnaire responses, 62.8% (158/250) of the subjects were consuming uniodized salt, termed "rock salt".

Clinical characteristics, mean and median thyroid volumes of subjects by age and sex, and the upper limits of reference thyroid volumes are shown in Table I. When compared with the upper limits of the reference thyroid volumes by ultrasonography, goiter was found in 47.6% (119/250) of all children, in 22.8% (57/250) of girls, and in 24.8% (62/250) of boys. Although goiter prevalence was slightly higher in boys, the difference was not statistically significant ($p>0.05$). Mean thyroid volumes did not differ significantly by sex ($p>0.05$). Significant correlations were found between thyroid volume and body surface area (BSA) ($r=0.99$, $p<0.05$) and age ($r=0.96$, $p<0.05$).

Median urinary iodine concentrations of subjects with and without goiter were 2.0 µg/dl and 5.2 µg/dl, respectively (Table II), and the difference was statistically significant ($p<0.05$). While median urinary iodine levels of the subjects with goiter were consistent with severe-moderate iodine deficiency, the levels in subjects without goiter were comparable to moderate-mild iodine deficiency[6]. The correlation between urinary iodine excretion and thyroid volume is depicted in Figure 1. There was a negative correlation between them ($r=0.45$, $p<0.01$).

Table III shows the serum thyroid hormone levels in subjects with and without goiter. None of the subjects had the signs or symptoms of

Table I. Characteristics of the Subjects with Goiter by Age and Sex

				Thyroid volume (ml)				
Age	Sex	N	BSA* (m^2)	Mean±SD	Range	Median	ULN** (97%)	No of subjects with goiter (%)
7	F	11	0.8	6.9±4.1	3.6-10.2	5.2	5.9	4 (36.4)
	M	5	0.8	5.7±2.0	3.6-10.6	5.4	5.7	2 (40)
8	F	11	0.9	7.2±3.0	3.9-10.5	5.8	6.9	7 (63.6)
	M	15	0.9	7.0±2.5	3.9-9.8	6.7	6.1	9 (60)
9	F	14	1.0	8.0±2.7	5.1-0.9	7.7	8.0	7 (50)
	M	14	1.0	7.4±2.1	5.1-10.4	8.1	6.8	8 (57.1)
10	F	12	1.1	9.6±2.6	5.4-11.7	8.3	9.2	6 (50)
	M	12	1.0	8.5±4.2	5.4-11.7	6.6	7.8	5 (41.7)
11	F	15	1.2	12.7±6.4	9.9-15.5	11.8	10.4	7 (46.6)
	M	23	1.1	10.7±5.9	9.9-13.0	9.0	9.0	10 (43.3)
12	F	24	1.3	13.1±8.9	10.9-15.3	10.2	11.7	9 (37.5)
	M	22	1.2	12.6±5.0	10.9-14.9	10.9	10.4	10 (45.4)
13	F	18	1.3	13.8±6.3	10.2-15.3	11.7	13.1	6 (33.3)
	M	19	1.4	13.1±7.4	10.2-15.8	11.8	12.0	8 (42.1)
14	F	19	1.4	15.6±5.4	13.1-18.1	17.1	14.6	11 (57.9)
	M	16	1.5	17.0±5.4	10.2-19.6	16.2	13.9	10 (62.5)
Total		250						119 (47.6)
	F/M	124/126						57/62 (45.9/49.2)

* Body surface area, ** Upper limit of normal thyroid volume.

Table II. Mean and Median Urinary Iodine Concentrations of Subjects with and without Goiter

		UIC* (µg/dl)		
	n	Mean±SD	Median	Range
Subjects with goiter	119	2.9±3.3	2.0	0.0-17
Subjects without goiter	131	5.9±5.5	5.2	0.0-25
Total	250	4.5±4.6	2.9	0.0-25

UIC*: Urinary iodine concentration.

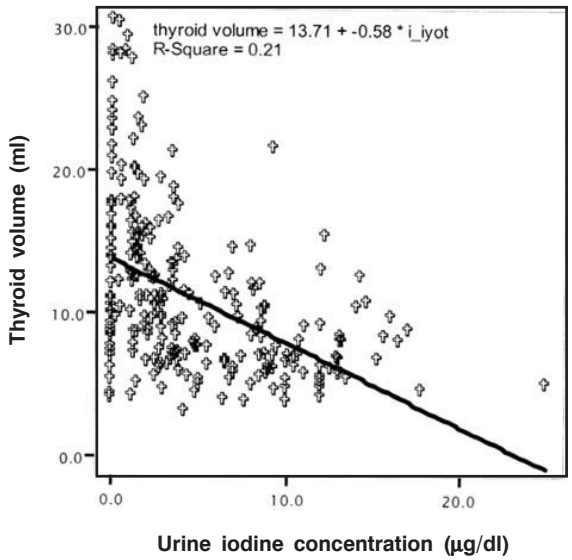

Fig. 1. Correlation between urine iodine concentration and thyroid volume (r=0.45, p<0.01).

hyper-or hypothyroidism. The differences in the mean values of thyroid hormones and TSH levels between subjects with and without goiter were not significant (p>0.05). No correlation was found between urinary iodine concentrations and thyroid hormone levels (p>0.05). A weak negative correlation was found between urine iodine concentration and TSH levels (r=0.12, p=0.05). Isolated TSH elevation was diagnosed in 15 (12.6%) subjects with goiter. Mean TSH values of the subjects having isolated TSH elevation was 7.32±1.1 (5.9-10.6) mIU/ml. Of 119 subjects with goiter, 16 (13.0%) had elevation of total T_3 and/or FT_3 levels when compared with the reference thyroid hormone values in the literature. Mean T_3/T_4 ratio between the subjects with and without goiter did not show statistical difference (p>0.05), although it was slightly higher in subjects with goiter (Table III).

Individuals with goiter were investigated etiologically: biochemical hypothyroidism was detected in 2% (3/119), autoimmune thyroiditis in 2% (3/119), nodular goiter in 3% (4/119, and isolated high TSH level with autoimmune thyroiditis in 0.08% (1/119).

Discussion

According to the World Health Organization (WHO), if more than 5% of school-age children are suffering from goiter, the area should be classified as endemic for iodine deficiency. Earlier studies concerning iodine deficiency which have been conducted in different regions of the country have indicated that Turkey is a moderately iodine deficient country. In a large survey performed by Urgancıoğlu and Hatemi[1], overall goiter prevalence by palpation was found as 30.5% nation-wide. They also reported that goiter prevalence may increase up to 50% in some regions. In 1995, a nation-wide salt iodization program implemented by the Ministry of Health was initiated to control iodine deficiency. However, Yordam et al[2]. recently reported that goiter prevalence was 92% in a remote area, which points to severe iodine deficiency. The present study was conducted in a mountain region suspected to be moderately or severely iodine deficient. Overall goiter prevalence by ultrasound was found to be 47.6%, suggesting severe iodine deficiency. Goiter prevalence tended to be higher in boys (24.8%) than in girls (22.8%), but this did not reach statistical significance. For the field studies in remote areas where no other methods are available, goiter staging by physical examination set by WHO has been used to detect goiter prevalence. Although the sensitivity of clinical examination in establishing presence of goiter increases with better training

Table III. Mean Thyroid Hormone Levels and T_3/T_4 Ratio in Subjects with and without Goiter

	Subjects with goiter		Subjects without goiter		
	Mean±SD	Range	Mean±SD	Range	P
TSH (mIU/Ml)	2.28±1.48	0.49±10.6	2.41±1.33	0.50-4.08	>0.05
TT_3 (ng/ml)	1.61±0.26	1.09-2.40	1.59±0.26	1.08-2.33	>0.05
FT_3 (pg/ml)	3.84±0.38	2.97-5.27	3.79-0.37	3.04-4.28	>0.05
TT_4 (µg/dl)	8.02±2.05	1.00-14.0	8.70±1.46	4.30-13.60	>0.05
FT_4 (ng/ml)	1.13±0.18	0.59-1.65	1.11±0.19	0.47-1.63	>0.05
TT_3/TT_4	0.20±0.05	0.15-0.45	0.18±0.02	0.10-0.29	>0.05

Reference values[7-8]: TSH: 04-4.2, TT_3: 0.97-1.95, FT_3: 1.4-4.1, TT_4: 4.4-14, FT_4: 07-2.3.
FT_3: Free triiodothyronine, FT_4: Free thyroxine, TT3: Total triiodothyronine.

of the health personnel, goiter prevalence in the studies based on clinical estimation of thyroid size may result in overestimation of small goiter, especially in children. The distinction between absence of goiter (Stage 0) and presence of small goiter (stage I) is difficult and, consequently, the overall goiter prevalence may be incorrect. Therefore, the frequency of distribution of thyroid volume measured by ultrasound is highly recommended, especially in endemic regions where visible goiter rate is low[4].

In previous studies where the correlation between thyroid volume and variables such as age, sex, weight, height and BSA were analyzed, the strongest correlation was found between the thyroid volume and BSA[9-10]. In the current study, mean thyroid volumes did not differ significantly between sexes ($p>0.05$), and there was significant correlation between thyroid volume and BSA ($r=0.99$, $p<0.05$) and age ($r=0.96$, $p<0.05$). Although thyroid volumes of the students gradually increased with age, there was a striking increase in thyroid volumes after 10 years of age in girls and after 12 years of age in boys, which is consistent with the ages of onset of puberty[4].

In our study, while mean and median urinary iodine measurements of the subjects with goiter were consistent with severe-moderate iodine deficiency, levels in subjects without goiter were consistent with mild-moderate iodine deficiency (Table II). Although some studies failed to show any correlation between the urinary iodine levels and thyroid volume[11], we found negative correlation between thyroid size and the urinary iodine levels ($r=0.45$, $p<0.01$) (Fig. 1). The lowest mean urinary iodine excretion was detected in subjects with the largest thyroid size. As in our study, a negative correlation has also been reported in other studies[1]. However, there may not be a correlation between the thyroid volume and urinary iodine level. Just as reports of normal iodine levels in subjects with goiter are present in the literature, low iodine levels have also been reported in subjects without goiter[11-13]. This situation has been explained by the fact that urinary iodine level is not the unique factor in the forming of goiter, although urinary iodine excretion is an important epidemiological factor. High goiter prevalence in these studies might also be related to environmental factors such as local natural goitrogens, water pollution, dietary minerals, or genetic thyroid hormone biosynthesis disorders[11].

The region in which we performed this study is a plentiful rainy and mountainous area with a partly self contained economy. Most of the families of the students were still consuming uniodized salt, or "rock salt". People living in this area mainly consume agricultural and animal products, which may lead to iodine deficiency. These results show that is region of mountain villages in Yusufeli in which the study was performed, is a highly endemic area due to severe iodine deficiency, comparable to some regions in Latin America, Africa and Asia.

In our study, there was no difference in mean thyroid hormone levels between the subjects with and without goiter (Table III). Mean thyroid hormone levels were comparable to the reference values[7,8]. Also, there was no correlation between the urinary iodine concentration and serum thyroid hormone levels ($p>0.05$). However, a weak negative correlation was found between urine iodine concentration and TSH levels ($p=0.05$). In some studies, significant changes in thyroid hormone levels ranging from isolated high TSH levels to biochemical hypothyroidism in subjects living in endemic regions have been reported[2,4,14,15]. In our study, 15 (12.6%) of the students had isolated high TSH (compensated hypothyroidism), and 3 had biochemical hypothyroidism due to iodine deficiency.

Although some previous studies[8,15] from the Black Sea region, which surrounds the current study area, have indicated moderate-severe iodine deficiency, severe iodine deficiency in this area was not reported before.

In conclusion, although a salt iodization program has been started in Turkey, our study indicates that some regions with severe iodine deficiency still exist. This research suggests that this program should be re-evaluated for remote areas with self-contained economic systems, and should be expanded and more effectively applied nation-wide. As previously suggested by Yordam et al.[2], to prevent the deleterious effects of severe iodine deficiency on populations living in remote areas such as in the mountain villages of Yusufeli, iodized oil and iodine tablets, which are effective in the short-term, should be urgently implemented.

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Hypercalciuria and nephrocalcinosis in cystic fibrosis patients

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The objective of this study was to determine the frequency of nephrocalcinosis and hypercalciuria in cystic fibrosis (CF) patients, and to search possible causes of this phenomenon. Forty-three CF children (24 boys, 19 girls; mean age 64.9 months, range 5 months-18 years) were included in this study. Plasma sodium, potassium, chloride, BUN, creatinine, calcium, phosphorus, magnesium, alkaline phosphatase; spot urine sodium, potassium, chloride, creatinine, calcium, magnesium; and serum 25-hydroxyvitamin-D levels were measured in all patients. Urine samples were examined for microscopic hematuria. Fractional sodium, potassium, chloride excretion and estimated glomerular filtration rate (GFR) were calculated. All patients underwent renal ultrasonography.

Hypercalciuria, nephrocalcinosis and microscopic hematuria were detected in 15 patients (34.2%), 10 patients (23.2%) and two patients (5%), respectively. There was no significant but borderline correlation between 25-hydroxyvitamin-D levels and hypercalciuria (r: 0.308, p:0.05). There were no correlations between Shwachman clinical scoring system results and hypercalciuria (r: 0.221, p: 0.148) and age and hypercalciuria (r: -0.229, p: 0.135). Patients with chronic Pseudomonas colonization showed no hypercalciuria or nephrocalcinosis. There was no difference for plasma biochemical results, renal function tests, hypercalciuria and nephrocalcinosis between CF patients who had or had not experienced pseudo Bartter's syndrome (PBS) before. There was no relation between detected CF mutations of the patients and hypercalciuria and nephrocalcinosis. These results suggested that it is a primary abnormality of calcium metabolism in the kidney.

Key words: cystic fibrosis, hypercalciuria, nephrocalcinosis, pseudo Bartter's syndrome.

Cystic fibrosis (CF) is an inherited disorder causing pancreatic, pulmonary and sinus disease in patients. It is caused by defects in the CF transmembrane conductance regulator (CFTR) gene, which encodes a protein that functions as a chloride channel and is regulated by "cyclic adenosine monophosphate" (camp) dependent protein kinase[1]. Considering the special role of the kidney for fluid and ion homeostasis, alteration of calcium metabolism would be expected in a CF kidney. There are some controversial studies about nephrocalcinosis and hypercalciuria in CF patients. Katz et al.[2] found a high frequency of nephrocalcinosis and hypercalciuria in CF patients, and they postulated that "this is a primary renal leak of calcium". On the other hand, in some other studies, hypercalciuria/nephrocalcinosis frequency was found no higher than other chronic debilitating diseases[3,4].

The objective of the present study was to determine the frequency of nephrocalcinosis and hypercalciuria in CF children, and to search for possible causes of this phenomenon.

Material and Methods

Forty-three consecutive (CF) children (24 boys, 19 girls), who came for control visits to the out patient clinic of Hacettepe University, İhsan Doğramacı Children's Hospital, Pediatric Pulmonology Division during the study period,

were included in this study. CF was diagnosed by at least two sweat chloride values higher than 60 mEq/L, along with the presence of physical and laboratory findings compatible with the disease. Mean age was 64.9 months (range 5-216 months). Mean Shwachman clinical scoring system result was 78.16 (range 40-98). Chronic Pseudomonas colonization was noted in five patients. All the patients received 3 mEq/kg extra sodium chloride and 800 IU/day vitamin D orally. Dietary calcium content was within normal range (426-1137 mg) for all patients. None of the patients received steroids or diuretics before, or aminoglycoside antibiotics during, the study period.

Pseudo Bartter syndrome (PBS) was diagnosed in the CF patients when they showed hypoelectrolytemia with alkalosis, and elevated renin and aldosterone levels in serum. In 16 patients at least one PBS attack had been diagnosed before this study. During the study period none of the patients showed PBS and mean period from their last PBS attack was 18 months (2-76 months).

Plasma sodium (138-145 mEq/L), potassium (3.4-4.7 mEq/L), chloride (95-110 mEq/L), BUN (5-18 mg/dl), creatinine (0.6-1.2 mg/dl), uric acid (3.4-7 mg/dl), calcium (8.8-10.8 mg/dl), phosphorus (4.5-5.5 mg/dl), magnesium (1.8-3 mg/dl), and alkaline phosphatase (250-1000 U/L); and spot urine sodium, potassium, chloride, creatinine, calcium, and magnesium measurements were performed in all patients by autoanalyzer (Hitachi 911 automatic analyzer). Serum 25-hydroxyvitamin-D levels were measured by RIA kit (Incstar-USA) in all patients (N: 10-40 ng/ml). Urine samples were examined for microscopic hematuria. Five or more erythrocytes in one microscopic area was accepted as hematuria. Fractional sodium, potassium, and chloride excretion were calculated using plasma and spot urine sodium, potassium, and creatinine levels. Twenty-four hour urine collection could not be performed because of the patients' age group. Therefore estimated glomerular filtration rate (GFR) was measured using plasma creatinine as described in the literature[5].

Hypercalciuria was defined as urine calcium/creatinine levels above 0.25 mg/mg creatinine, and hypermagnesuria was magnesium/creatinine levels above 0.27 mg/mg creatinine[6].

The two most common mutations of the CFTR gene in our population, delta F 508 and 1677 delTA, were tested in all 43 patients[7]. Some but not all of the untyped alleles could be sequenced to search for unidentified mutations. Patients were divided into three groups according to the genotype, as group 1: homozygous for the delta F508 mutation (n:8); group 2: compound heterozygous for delta F508 mutation (n: 15, 2 patients-dF508/1677delTA; 2 patients-dF508/2789+5G-A; each dF508/W1282X, dF508/N1303K, dF508/R1066L, dF508/4374+1 G-A, dF508/148T; 6 patients-dF508/unknown) and, group 3: other known mutations (n: 20; A96E/A96E, R347/R347H, M152V/M152V, 2183+5G-A/D1152H, W496/2181 delA, 2183A-G, G85E/R334W, 1677delTA/E92K, 621+1G-T/621+1G-T, N1303K/W1098XG-A, 1677delTA/unknown, R1162X/unknown, G85E/unknown, 8 unknown/unknown).

All patients underwent renal ultrasonography. A scoring system was used for evaluationg nephrocalcinosis sonographically. Cortical hyperechogenicity was scored as type 1, medullary hyperechogenicity as type 2, and cortical and medullary hyperechogenicity as type 3.

Informed consent was obtained from parents of all participating children.

Data are given as mean±SEM. Statistical analyses were performed by using SPSS computerized statistics program with Mann Whitney-U test and correlations with Pearson correlation test. At two-tailed p value of less than 0.05 was considered significant.

Results

Biochemical data of the patients are presented in Tables I and II. Hypercalciuria, nephrocalcinosis and microscopic hematuria were detected in 15 patients (34.2%), 10 patients (23.2%), and two patients (5%), respectively. All patients with nephrocalcinosis showed type 2 (medullary) hyperechogenicity. All 10 patients with nephrocalcinosis and two patients with hematuria also had hypercalciuria.

There was no significant, but borderline, correlation between 25-hydroxyvitamin-D levels and hypercalciuria (r: 0.308, p: 0.05) (Fig. 1). There was no correlation between Shwachman clinical scoring system results and hypercalciuria (r: 0.221; p: 0.148). Also, no correlation was

detected for age of the patients and hypercalciuria (r: -0.229; p: 0.135). Patients with chronic Pseudomonas colonization did not show hypercalciuria or nephrocalcinosis. There was no difference in plasma biochemical results, renal function tests, hypercalciuria and nephrocalcinosis between CF patients with and without PBS (Tables III and IV). No significant difference was observed for any mutation group in the CF patients with or without hypercalciuria (p: 0.194) or nephrocalcinosis (p: 0.242).

Table I. Biochemical Data in Serum of the Patients

	mean (±SD)
pH	7.35 (±0.04)
HCO_3 (mEq/L)	20.87 (±2)
Na (mEq/L)	143.53 (±3.52)
K (mEq/L)	4.63 (±0.48)
CL (mEq/L)	105.84 (±3.39)
Osmolarity (mOsm/L)	299.50 (±17.09)
BUN (mg/dl)	12.02 (±5.11)
Cre (mg/dl)	0.56 (±0.14)
Uric acid (mg/dl)	4.15 (±1.40)
Ca (mg/dl)	9.89 (±0.63)
P (mg/dl)	5.32 (±0.77)
Alkaline phosphatase (U/L)	289.58 (+98.65)
25-hydroxyvitamin-D (ng/ml)	16.93 (±7.52)

HCO_3, bicarbonate; Na, sodium; K, potassium; CL, chloride; BUN, blood urea nitrogen; Cre, creatinine; Ca, calcium; P, phosphorus.

Table II. Biochemical Data in Urine of the Patients

	mean (±SD)
pH	5.63 (±1.04)
Density	1019.23 (±6.52)
Osmolarity (mOsm/L	671.22 (±281.63)
Ca/Cr (mg/mg)	0.17 (±0.10)
Mg/Cr (mg/mg)	0.13 (±0.12)
FeNa (%)	0.78 (±0.80)
FeK (%)	18.80 (±13.51)
FeCI (%)	1.02 (±0.80)
EGFR (ml/min 1.73 m^2)	101.46 (±25.33)

Ca/Cr, calcium/creatinine; Mg/Cr, magnesium/creatinine; FeNa, fractional sodium excretion; FeK, fractional potassium excretion; FeCI, fractional chloride excretion; EGFR, estimated glomerular filtration rate.

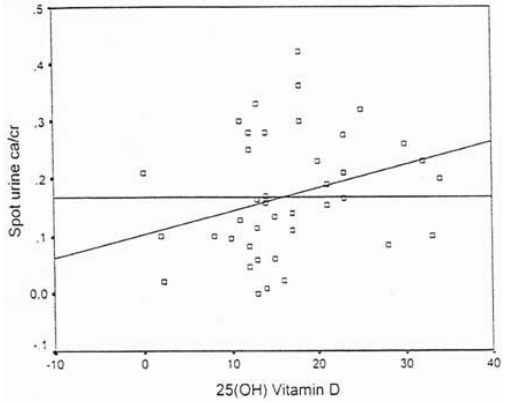

Fig. 1. Relation between spot urine calcium/creatinine levels and 25-hydroxyvitamin-D levels (r: 0.308, p: 0.05).

Table III. Comparative Biochemical Data in Serum of the Patients in Two Groups

	Group I	Group II	p
pH	7.34±0.47	7.35±0.036	0.48
HCO_3 (mEq/L)	20.18±2.38	21.28±1.64	0.09
Na (mEq/L)	143.37±3.55	143.62±3.23	0.92
K (mEq/L)	4.60±0.44	4.64±0.512	0.50
CL (mEq/L)	105.68±2.54	105.9±23.82	0.79
Osmolarity (mOsm/L)	294.64±4.06	277.37±87.22	0.13
BUN (mg/dl)	14.12±6.37	0.77±3.82	0.10
Cre (mg/dl)	0.49±0.085	0.59±0.158	0.06
Uric acid (mg/dl)	4.26±1.46	4.08±1.38	0.76
Ca (mg/dl)	9.83±0.819	9.91±0.5	0.87
P (mg/dl)	5.43±0.86	5.25±0.72	0.63
Alkaline phosphatase (U/L)	283.73±95	252.38±142	0.30
25-hydroxyvitamin-D (ng/mL)	19.25±8.29	14.67±7.2	0.16

Group I: CF patients who experienced Pseudo-Bartter's syndrome (PBS) before.
Group II: CF patients who did not experience Pseudo Bartter's syndrome (PBS) before.

HCO_3, bicarbonate; Na, sodium; K, potassium; CL, chloride; BUN, blood urea nitrogen; Cre, creatinine; Ca, calcium; P, phosphorus, $p<0.05$ is significant.

Table IV. Comparative Biochemical Data in Serum of the Patients in Two Groups

	Group I	Group II	p
pH	5.78±1.27	5.33±1.37	0.57
Density	1020.62±5.43	1018.40±7.04	0.36
Osmolarity (mOsm/L)	699.64±303.35	601.60±318	0.36
Ca/Cr (mg/mg)	0.20±0.1	0.15±0.10	0.16
Mg/Cr (mg/mg)	0.13±0.15	0.11±0.20	0.86
FeNa (%)	0.57±0.65	0.90±0.86	0.08
FeK (%)	21.07±17.94	17.44±10.19	0.95
FeCI (%)	0.82±0.68	1.14±0.85	0.14
EGFR (ml/min/1.73 m^2)	94.92±19.54	105.32±27.8	0.19

Group I: CF patients who experienced Pseudo-Bartter's syndrome before.
Group II: CF patients who did not experience Pseudo-Bartter's syndrome before.

Ca/Cr, calcium/creatinine; Mg/Cr, magnesium/creatinine; FeNa, fractional sodium excretion; FeK, fractional potassium excretion; FeCI, fractional chloride excretion, EGFR, estimated glomerular filtration rate; $p<0.05$ is significant.

Discussion

Several recent studies have been undertaken in order to evaluate whether renal calcium metabolism is altered in patients with CF. In our study we detected high frequency of hypercalciuria (34.2%) and nephrocalcinosis (23.2%) in CF patients. In 1988 Katz et al.[2] demonstrated microscopic nephrocalcinosis in 35 of 38 renal specimens obtained from autopsy of CF patients, including a baby stillborn near the time of birth, and in none of the 10 autopsy controls, all of whom died as a result of acute trauma. Also, hypercalciuria was detected in five of the 14 CF patients. On this basis they postulated that there is primary abnormality of calcium metabolism in the kidney of CF patients. On the other hand Gruskin et al.[3] found no differences in calcium excretion between CF patients and normal controls. Bentur et al.[4] detected normal urinary calcium excretion in 30 of the 34 CF patients; none of the 17 patients examined by renal ultrasonography had nephrocalcinosis. They also performed a similar study on patients who died as a result of chronic debilitating disease. Focal deposits of calcium were seen in five of the 14 CF patients, and in six of 15 control patients. They concluded that microscopic nephrocalcinosis and hypercalciuria in CF patients have, most likely, secondary epiphenomenon related to preterminal events.

It is known that many factors can alter calcium excretion in CF patients. In our study, all of the patients' glomerular and tubular functions, and plasma calcium, phosphorus and alkaline phosphatase levels were within normal limits. None of the patients used drugs that altered calcium metabolism. Dietary calcium levels were within normal limits. Another contributing factor to development of hypercalciuria and nephrocalcinosis could be vitamin D supplementation. However 25-hydroxyvitamin-D levels in our patients were detected as normal or below normal in spite of the fact that they were receiving 800 IU/day vitamin D.

One of the possible causes for the abnormal calcium excretion is high sodium intake. However, this was not so in our patients. All the patients had received 3 mEq/kg extra sodium chloride in their diet, but their serum sodium and fractional sodium excretion levels were within normal limits.

Immobilization is usually mentioned among other causes of hypercalciuria. Our patients' Shwachman clinical scores were generally high, therefore, none was immobile because of the disease, and there was no relation between clinical score results and hypercalciuria.

Patients with CF usually have essential fatty acid (EFA) deficiency. It is a well known fact that EFA deficiency in rats causes functional and morphological changes in the kidney, such as decreased urinary volume, hematuria, and nephrocalcinosis[8]. EFA measurement could not be performed on our patients.

Hypercalciuria and nephrocalcinosis have also been described in patients with PBS. Hypochloremic metabolic alkalosis with hyponatremia, hypokalemia, hypochloremia, and elevated plasma renin and aldosterone levels are the characteristic biochemical picture of Bartter's syndrome[9]. There are some other

disorders including CF, in which the metabolic findings may mimic Bartter's syndrome, called PBS[10-14]. Loss of electrolytes through sweating plays a primary role in the appearance of PBS in patients with CF[15,16]. Vomiting, diarrhea, and feeding with inadequate salt diet also contribute to development of PBS[17,18]. PBS was not uncommon in our CF patients[19]. Rodriguez-Soriano et al.[20] reported 30 patients who showed PBS because of chloride deficiency. They showed a significant elevation in the serum concentrations of calcium and phosphate with high urinary excretions of calcium and magnesium continuing, even after almost-complete recovery of the remaining biochemical disturbances due to chloride deficiency. The authors also pointed out the potential risk of developing nephrocalcinosis after dietary chloride deficiency. Nephrocalcinosis was reported in six fatal cases of chloride-depletion alkalosis related to pyloric stenosis[21]. To date, no findings have been described regarding long-term renal function and nephrocalcinosis in CF patients who experienced PBS. To find the effect of PBS on hypercalciuria and nephrocalcinosis in CF patients, we compared renal functions, plasma levels of calcium and phosphorus, hypercalciuria and nephrocalcinosis in CF patients who experienced at least one known PBS attack in their past history, with those who did not. We could not find any statistical difference, regarding hypercalciuria and nephrocalcinosis, between the two groups.

Elevated excretion of other lithogenic substances, e.g. oxalate, glycolate and uric acid, has been reported in CF patients before[22,23]. These measurements could not be performed in our patients.

Although the number of our patients was too small to reach a definitive conclusion, we did not detect any relation between a specific CF genotype and the appearance of hypercalciuria and nephrocalcinosis in our patients. This suggests that other genetic or environmental factors may influence the development of hypercalciuria or nephrocalcinosis. Recently, some studies on hypercalciuria and nephrolithiasis disorders showed the relation between these disorders and chloride channels (CLC)[24,25]. These disorders of hypercalciuric nephrolithiasis (Dent's disease, X-linked recessive nephrolithiasis, X-linked recessive hypophosphatemic rickets, idiopathic low molecular weight proteinuria associated with hypercalciuric nephrocalcinosis in Japanese children) have been established as sharing a common genetic etiology by demonstrating mutations in the renal chloride channel gene (CLCN5). It is not known, but there are some hypotheses regarding how mutations in the renal chloride channel result in low-molecular weight proteinuria and hypercalciuria. CFTR is different from other CLC, functioning as a cAMP-activating chloride channel of low conductance, but there is some evidence about the control role of CFTR on the regulation of other chloride channels[26]. With these findings we can suggest that the high incidence of hypercalciuria and nephrocalcinosis in CF patients may be the result of disregulation of CFTR expressed in kidney tubules or the effect of CFTR on the other chloride channels.

In conclusion, we detected a high frequency of hypercalciuria (34.2%) and nephrocalcinosis (23.2%) in our CF patients. There was no detected relation between these findings and possible causes of hypercalciuria and nephrocalcinosis. The results suggest that it is a primary abnormality of calcium metabolism in the kidney.

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Biochemical markers of bone turnover in the diagnosis of renal osteodystrophy in dialyzed children

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SUMMARY: Baskın E, Beşbaş N, Saatçi Ü, Hasçelik G, Topaloğlu R, Özen S, Bakkaloğlu A. Biochemical markers of bone turnover in the diagnosis of renal osteodystrophy in dialyzed children. Turk J Pediatr 2004; 46: 28-31.

In this study we investigated the value of biochemical markers of bone turnover in the diagnosis of renal osteodystrophy in dialysis patients. The study was carried out in 22 chronic renal failure patients (mean age: 16.1±4.5) being treated with chronic dialysis. There were three groups according to intact parathormone (iPTH) levels: Group I (n: 6): iPTH levels were less than 200 pg/ml; Group II (n: 9): iPTH levels were between 201 and 500 pg/ml; and Group III (n: 7). iPTH levels were higher than 501 pg/ml. We investigated iPTH, bone alkaline phosphatase, total serum alkaline phosphatase, osteocalcin, serum type 1 procollagen peptide (PICP) and insulin-like growth factor-1 (IGF-1) levels in all patients.

In group III mean bone alkaline phosphatase level (126.0±10.95) was significantly higher than in both group I and group II (52.16±22.8, 57.35±16.21) ($p<0.001$). Mean osteocalcin level (35.13±2.93) in group I was significantly lower than in group III (40.52±2.83) ($p<0.05$). Serum alkaline phosphatase, PICP and IGF-1 levels were not different between the groups ($p>0.05$). There was a significant positive correlation between bone alkaline phosphatase and iPTH ($r=0.80$, $p<0.0001$). Serum osteocalcin correlated with both bone alkaline phosphatase and iPTH (correlation) coefficients were $r=0.44$ and $r=0.51$ respectively, $p<0.05$). It is concluded that bone alkaline phosphatase and osteoocalcin combined with iPTH level seem to be useful noninvasive markers of bone metabolism in dialysis patients.

Key words: renal osteodystrophy,biochemical markers, bone alkaline phosphatase, osteocalcin, chronic dialysis.

It has been known for over 100 years that bone disease accompanies renal failure. Bone histology remains the gold standard for the diagnosis of renal osteodystrophy and the distinction between high and low bone turnover disease. However, bone biopsy is an invasive procedure accompanied by technical difficulties in the processing and studying of the specimens. For that reason, specific and sensitive serum biochemical markers are required for monitoring bone turnover in uremia. The ideal biochemical marker of bone turnover should be unique to bone and reflect total skeletal activity and be well correlated with histomorphometric and radiocalcium kinetics results[1]. Serum alkaline phosphatase has been used as a biochemical marker of bone disease for many years. But total alkaline phosphatase originates from different organs (liver, bone, intestine, placenta etc.) and sometimes lacks specificity. In the last decade it has been shown that measurement of intact parathormone (iPTH) is a useful predictor of bone histology and a noninvasive tool in distinguishing between high turnover, normal and low turnover bone disease in large patient gorups[2]. However, in an individual patient serum iPTH alone is frequently unable to distinguish adynamic bone from hyperparathyroid bone disease[3]. Combined with other biochemical markers it may be useful in solving this problem.

In this study we investigated the value of biochemical markers of bone turnover in the diagnosis of renal osteodystrophy in dialysis patients.

Material and Methods

The study was carried out in 22 chronic renal failure patients being treated with chronic dialysis. The study group included 11 girls and 11 boys, ages between 8 and 18 years (mean age 15.1±3.5). Dialysis therapy was hemodialysis for three to for hours thrice weekly in 17 patients and continuous ambulatory peritoneal dialysis in five patients. There were three groups according to iPTH levels. Group I included 6 patients (2 girls, 4 boys), and iPTH levels were less than 200 pg/ml. Group II included 9 patients (5 girls, 4 boys) and iPTH levels were between 201 and 500 pg/ml. Group III consisted of 7 patients (4 girls, 3 boys), and iPTH levels were higher than 501 pg/ml.

Phosphate binder therapy consisted of either calcium acetate or calcium carbonate. Aluminum hydroxide was not used unless hypercalcemia developed. None of the patients had clinical or biochemical evidence of liver disease. Immediately before a dialysis session, blood samples were drawn from the arterial port for the assay of iPTH, bone alkaline phosphatase, total serum alkaline phosphatase, osteocalcin and serum type 1 procollagen peptide (PICP). İPTH was determined by chemiluminescent enzyme immunometric assay (Immulite 2000, Bio DPC, USA); the normal range for this assay is 12-62 pg/ml. Serum osteocalcin was measured by ELISA (Novocalcin, Metra Biosystems, Inc., USA): the normal range is 3.40-9.10 for males and 3.70-10 for females. Total alkaline phosphatase, calcium and phosphate levels were determined by autoanalyzer (Hitachi 747). Bone alkaline phosphatase level was measured by ELISA (Alk phase-B, Metra Biosystems, Inc., USA). Serum PICP was evaluated by ELISA (Prolage-C Metra Biosystems, Inc., USA). Insulin-like growth factor-1 (IGF-1) level was measured by two-site immunoradiometric assay (DSL-5600 ACTIVE IGF-1 Coated-Tube IRMA Kit, Diagnostic System Laboratories, Inc, USA). In patients with PTH levels higher than 500 pg/ml (group III), parathyroid glands were imaged with ultrasonography and technetium-99m-sestamibi (99mTc-MIBI) for the detection of parathyroid hyperplasia or adenoma.

Statistical analysis included the evaluation of correlation matrix, one-way ANOVA, and Mann-Whitney U test. A value of $p<0.05$ was considered significant. All the results are expressed as the mean±SD.

Results

Mean ages of groups I, II and III were 14.7±4.1, 16.2±4.8 and 15.3±3.9, respectively ($p>0.05$). Mean bone alkaline phosphatase, osteocalcin, PICP, IGF-1 and total alkaline phosphatase levels are shown in Table I.

In group III patients mean bone alkaline phosphatase level (126.0±10.95 µlt) was significantly higher than in both group I (52.16±22.8 u/L) and group II (57.35±16.21 u/L) ($p<0.001$) (Table I). Mean osteocalcin level (35.13±2.93 ng/ml) in group I (iPTH levels less than 200 pg/ml) was significantly lower than in group III (40.52±2.83 ng/ml) ($p<0.05$). However, there was no significant difference between group II and group III ($p>0.05$). Group I patients had lower mean serum PICP and IGF-1 levels than group II and group III, but the difference was not significant ($p>0.05$). There was no significant correlation between PICP and bone alkaline phosphatase ($r=0.39$, $p>0.05$). Although total alkaline phosphatase level was higher in group III than in the others, there was no significant correlation between total alkaline phosphatase and iPTH ($r=0.33$), $p>0.05$) (Table II).

There was a significant positive correlation between bone alkaline phosphatase and iPTH ($r=0.80$, $p<0.0001$) (Fig. 1). Bone alkaline phosphatase also correlated with total alkaline phosphatase ($r=0.47$, $p<0.05$). Serum osteocalcin correlated with both bone alkaline phosphatase and iPTH (correlation coefficients were $r=0.44$ and $r=0.51$, respectively, $p<0.05$).

Table I. Biochemical Markers in Dialysis Patients

	Group I* (n=6)	Group II* (n=9)	Group III* (n=7)	
BAP (U/L)	52.16±22.8[t]	57.33±16.21	126±10.95[t]	[t](p: 0.0000)
Octeocalcin (ng/ml)	35.13±2.93§	39.11±3.96	40.52±2.83§	§(p: 0.027)
PICP (ng/ml)	249.80±180.12	347.31±174.71	423.20±208.63	(p: 0.27)
IGF-1 (ng/ml)	192.00±136.97	297.45±229.59	445.21±279.60	(p: 0.15)

* Mean±SD.

Table II. Biochemicla Markers and Correlation Matrix

	iPTH		BAP	
TAP	0.33	(P: 0.13)	0.47*	(P: 0.031)
Osteocalcin	0.51*	(p: 0.014)	0.44*	(p: 0.035)
PICP	0.28	(p: 0.19)	0.39	(p: 0.06)
IGF-1	0.37	(p: 0.08)	0.38	(p: 0.07)
BAP	0.80*	(p: 0.0000)		

* Significantly correlated.

PICP: type 1 procollagen peptide, BAP: bone alkaline phosphatase, TAP: total alkaline phosphatase, IGF-1: insulin-like growth Factor-1, iPTH: intact parathormone.

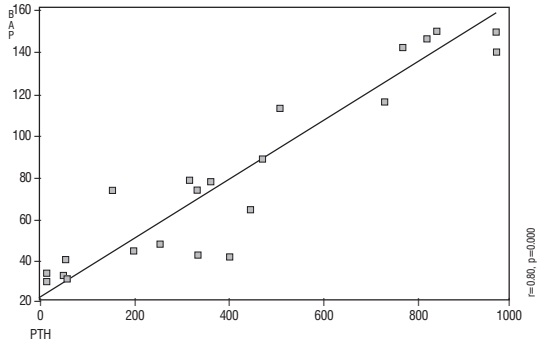

Fig. 1. Relationship between intract parathormone (iPTH) and bone specific alkaline phosphatase (BAP).

Discussion

In the last years, several enzymes and matrix proteins synthesized by osteoblasts and protein fragments released after bone matrix breakdown have been proposed as serum biochemical markers of bone formation and bone resorption. Markers of bone formation are alkaline phosphatase, bone-specific-alkaline phosphatase, osteocalcin, PICP, and IGF-1. Markers of bone resorption are tartrate-resistant acid phosphatase, PICP cross-linked telopeptide, pyridinoline and deoxypyridinoline, beta-2 microglobulin, bone sialoproteins, cytokines and growth factors[1,4,5].

In our study bone alkaline phosphatase showed significant correlation with iPTH and correlation coefficients (r) values better than those of total alkaline phosphatase and osteocalcin. Serum bone alkaline phosphatase is considered superior in determining total alkaline phosphatase activity for assessing bone metabolism, as has been previously reported[6-8]. Although optimal iPTH cut-off levels have been uncertain, iPTH of less than 100 pg/ml may strongly suggest adynamic bone disease[9]. Recently it was found that adynamic bone disease should be suspected when plasma iPTH levels were less than 150 pg/ml and bone alkaline phosphatase (BAP) levels were lower than 27 pg/ml[10]. In our patients with PTH levels less than 200 pg/ml, mean osteocalcin and BAP level were significantly lower than in group III patients. This may be associated with decreased bone formation. Therefore, low iPTH combined with low osteocalcin and BAP levels may reflect low turnover bone disease.

In our patients we did not observe a significant correlation between serum PICP and other parameters as has been previously reported[1,11,12]. It is suggested that PICP is not a sensitive marker of bone metabolism in uremia. Recently it has been reported that pyridinoline seems to be currently the most sensitive and specific marker for evaluation of bone resorption in renal osteodystrophy[11,13]. Besides these biochemical markers, serum beta-2 microglobulin, cytokines and growth factors might have a role in the noninvasive diagnosis of renal osteodystrophy[14-16]. Ferreira et al.[14] found serum beta-2 microglobulin correlated with osteocalcin, BAP and pyridinoline, and in patients with high turnover bone disease, serum beta-2 microglobulin was higher than in patients with normal and low turnover bone disease. IGF-1 might also prove to be of potential interest in evaluating bone turnover. In addition to being an indicator of nutritional status, it has been suggested that IGF-1 could serve as a bone remodeling marker as well[17]. Beşbaş et al.[17] reported that determination of IGF-1 levels in childhood hemodialysis patients in conjuction with anthropometric measurements is useful for identification of nutrition. However, other clinical studies have not confirmed a correlation between IGF-1 and serological or histological parameters of renal osteodystrophy[18]. In our patients we did not observe a significant correlation between IGF-1 and other parameters.

The evaluation of bone turnover should include a combination of different markers so that the balance between bone formation and bone resorption can be evaluated. Bone alkaline phosphatase and osteocalcin seem to be good markers for bone formation but measurement of other markers such as pyridinoline are needed to determine bone resorption[1,13].

It is concluded that BAP and osteoocalcin combined with iPTH seem to be useful noninvasive markers of bone metabolism in chronic dialysis patients both with high turnover and low turnover bone disease.

Future studies are clearly needed to better understand the value of these markers in uremic patients.

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The results of treatment with idarubicin in childhood acute nonlymphoblastic leukemia

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SUMMARY: Şaşmaz İ, Tanyeli A, Bayram İ, Antmen B, Yılmaz L, Küçükosmanoğlu O, Kılınç Y. The results of treatment with idarubicin in childhood acute nonlymphoblastic leukemia. Turk J Pediatr 2004; 46: 32-37.

Anthracycline and cytosine arabinoside are used in combination as the standard therapy for remission induction of acute nonlymphoblastic leukemia. Idarubicin, a synthetic daunorubicin analogue, shows an improved spectrum activity and diminishes acute or chronic toxicity when compared with the other anthracyclines. This study has been carried out in our clinic in order to evaluate the efficiency of the acute nonlymphoblastic leukemia protocol which includes idarubicin.

Thirty-eight patients admitted to our Department between 1992-1999 and diagnosed as acute nonlymphoblastic leukemia (ANLL) were included in the study. Their median age was 7 years 6 months (range, 8 months to 14 years). Induction therapy consisted of idarubicin plus cytosine arabinoside and etoposide. Consolidation therapy consisted of two courses, followed by maintenance therapy with thioguanine, cytosine arabinoside, vincristine and cyclophoshamide.

The complete remission rate was found to be 71%. The overall survival estimate was found to be 40% for one year and 23% for three years.

We established that the protocol with idarubicin reached a higher remission ratio when compared with the other protocols with anthracycline. However, the degree of the hematologic toxicity ratios related to the therapy increased the complication ratios, which affected the long-term life analyses directly. Therefore this protocol may be revised according to socioeconomical conditions, especially in the developing countries.

Key words: acute nonlymphoblastic leukemia, idarubicin, childhood.

Acute nonlymphoblastic leukemia (ANLL) accounts for 15-20% of all childhood leukemia. Since the classical treatment methods used for ANLL have not produced the required results, experiments for new medicines are still in process[1]. The administration of intensive induction, consolidation, intensification and maintenance therapy, and performance of allogeneic or autologous bone marrow transplantation, together with appropriate supportive care, have resulted in a significant decline in the mortality rate, and the event-free survival has lengthened. However, the present treatments provide a remission of 70-80% and event-free survival of 70-80%[2-5].

Anthracycline and cytosine arabinoside are used in combination for remission induction of ANLL as the standard therapy. The most frequently used drugs in the treatment are daunorubicin, doxorubicin, epirubicin and idarubicin. Idarubicin, a synthetic daunorubicin analogue, shows an improved spectrum activity and diminishes acute or chronic toxicity better when compared with the other anthracyclines[3,6,7]. Idarubicin has a greater influence on cultured human cancer cells in cytotoxicity than the other anthracyclines[8]. It is also less cardiotoxic than daunorubicin and doxorubicin[9]. Idarubicin, which was initially used for refractory or relapse

ANLL or acute lymphoblastic leukemia, has recently begun to be used successfully as the standard therapy, especially for ANLL[7,8].

There are only a limited number of studies in the literature concerning the use of idarubicin for childhood leukemia. This study has been carried out in our clinic retrospectively in order to evaluate the efficiency of the ANLL protocol, which has included idarubicin since 1992.

Material and Methods

Thirty-eight patients (19 females and 19 males) who were admitted to the Department of Pediatric Hematology of Çukurova University Faculty of Medicine were diagnosed as de novo ANLL between March 1992 and September 1999. Their median age was 7 years 6 months (age range: 8 months to 14 years). The bone marrow smears of all the patients were evaluated morphologically according to FAB classification using Giemsa, peroxidase, Sudan Black, periodic acid-schiff and esterase stains[10]. Immunological markers were also assessed in most of those patients[11].

The therapy schedule is shown in Table I, and includes two inductions, two consolidations, and maintenance therapy or bone marrow transplantation. After completing the second consolidation therapy we began the maintenance therapy for the complete remission situations. The maintenance therapy period was one year. Bone marrow transplantation was performed in three patients.

Statistical analyses were made using SPSS v 11.0 package. Methodically, the evaluation was calculated by multivariate analyses and the life duration analyses according to Kaplan-Meier. Event-free survival and overall survival were defined for our patient group as follows: event-free survival for relapse meant the length of time to relapse as end point from the time of diagnosis; overall survival means the total follow-up time of patients from the time of diagnosis.

Results

The clinical and hematological characteristics of patients at diagnosis were as follows: hepatomegaly in 22 patients (57%), splenomegaly in 20 patients (52%), lymphadenopathy in 27 patients (71), central nervous system involvement in 7 patients (18%), and chloroma in 1 patient (2%). The mean WBC count was 39,428 mm^3 (minimum 800 mm^3-maximum 153,800 mm^3) and mean platelet count was 51,131 mm^3 (minimum 11,000 mm^3-maximum 342,000 mm^3).

The results of the protocol with idarubicin are shown in Table II. After the induction therapy, the complete remission rate was found to be 71% (27/38). The consolidation therapy was

Table I. Treatment of Acute Nonlymphoblastic Leukemia

INDUCTION PHASE (two courses every 3 weeks)	
Cytosine arabinoside	: 100 mg/m^2 every 12 hr for 30 minutes, 14 doses
Idarubicin	: 12 mg/m^2/day, 0-2 days, 3 doses
VP-16	: 100 mg/m^2/day for 60 minutes, 3-5 days, 3 doses
Cystosine arabinoside (Intrathecal)	: Day 0
CONSOLIDATION PHASE I:	
Cytosine arabinoside	: 3 gr/m^2 every 12 hr for 4 hours, 0-1 days, 4 doses
L-Asparaginase	: 6000 U/m^2 IM at 42nd hour
Methotrexate (intrathecal)	: Day 0
CONSOLIDATION PHASE II:	
Idarubicin	: 12 mg/m^2/day, 0-1 days, 2 doses
Cytosine arabinoside	: 200 mg/m^2/dose for continuous infusion, 1-5 days, 5 doses
VP-16	: 100 mg/m^2/day for 60 minutes, 1-5 days, 5 doses
Methotrexate (intrathecal)	: Day 0
If the patient has a suitably matched donor, transplantation is recommended after the consolidation therapy.	
MAINTENANCE THERAPY (to be repeated every 30 days, given for 12 cycles):	
6-Thioguanine	: 75 mg/m^2/day p.o., 0-27 days
Vincristine	: 1.5 mg/m^2 iv, day 0
Cytosine arabinoside	: 75 mg/m^2/day iv, 0-3 days
Cyclophosphamide	: 75 mg/m^2/day iv, 0-3 days

Table II. The Results of Treatment of ANLL Patients

Phase of treatment	Number of patients	Complete remission		No response and death		Relapse		Death in CR	
		n	%	n	%	n	%	n	%
Induction	38	27	71	11	29			6	15.7
CP I	21					1*	2.6	1	2.6
CP II	19					1*	2.6	3	7.8
Maintenance	15					5*	13	1	2.6
After completion of all therapy	9					1*	2.6		

CP I: Consolidation phase I.
CP II: Consolidation phase II.
CR: Complete remission.
*: These patients died in relapse.
ANLL: Acute nonlymphoblastic leukemia.

performed on 21 patients. We began maintenance therapy on 15 patients. Nine patients were taken into follow-up without medicine after the completion of therapy.

Nausea, vomiting, alopecia and mucositis developed in all patients. Hepatotoxicity was seen in eight patients (21%). Elevation in serum glutamic-oxaloacetic transaminase was seen in six patients. Hyperbilirubinemia occurred in two patients as an isolated abnormality, with normal serum glutamic-oxaloacetic transaminase. Renal toxicity and hepatotoxicity were seen in two patients and renal toxicity in one patient.

Echocardiographic examination was done on 30 patients. An initial pericardial involvement was seen in two patients. There was an atrioventricular septal defect in one patient and situs inversus totalis in one patient. Left ventricular dysfunction developed in only one patient during the treatment. This patient died due to neutropenic sepsis.

After the induction phase I therapy, 33/38 patients developed severe neutropenia (mean 10 days, minimum 2 days, maximum 30 days), and 36/38 patients developed severe thrombocytopenia (mean 12, minimum 1 day, maximum 28 days). Induction phase II therapy was performed on 25 patients. After the induction phase II therapy, in 16/25 patients severe neutropenia (mean 7 days, minimum 2 days, maximum 16 days) and in 13/25 patients severe thrombocytopenia occurred (mean 10 days, minimum 2 days, maximum 16 days). The hematologic and nonhematologic toxicities of our patient group are given in Table III.

Thirty patients were lost: 11 were lost in complete remission in the induction phase, consolidation I and II phases and in the maintenance of protocol (at the end of induction phase: 6 patients, consolidation phase I: 1 patient, consolidation phase II: 3 patients, maintenance therapy: 1 patient). The causes of death were: neutropenic sepsis (4 patients), pneumonia (2 patients), neutropenic sepsis and renal failure (1 patient), neutropenic sepsis together with renal and hepatic failure (1 patient), and complications related to bone marrow transplantation (3 patients). Eleven patients who did not go into remission died in the early period. The causes of death were: neutropenic sepsis (7 patients), neutropenic sepsis together with renal and hepatic failure (1 patient), neutropenic sepsis and renal failure (1 patient), cardiac and nervous system involvement (1 patient), and pneumothorax development during the tracheostomy due to a hemangiomatous lesion on the vocal cord accompanying the neutropenic sepsis (1 patient). Eight patients with relapse died due to ANLL progression. Eight patients are still alive.

Table III. Toxicity Rates of the ANLL Patients

	n	%
Mucositis	38	100
Alopecia	38	100
Myelotoxicitiy	36	94
Infection	35	92
Hepatotoxicity	8	21
Hepatic and renal toxicity	2	5
Bleeding	1	2.5
Renal toxicity	1	2.5
Cardiac dysfunction	1	2.5

ANLL: Acute nonlymphoblastic leukemia.

According to Kaplan-Meier life-table analyses, overall survival estimate was 40% for one year and 23% for three years (Fig. 1). When the influence on the overall survival period of patient age ($p>0.5$), gender, and WBC ($p>0.5$)

count was observed by multivariate analyses, it was found that the female gender was effective ($p<0.001$), and that the female gender was the positive factor for the prognosis (Fig. 2). Event-free survival for relapse was estimated as 32% by Cox regression analysis.

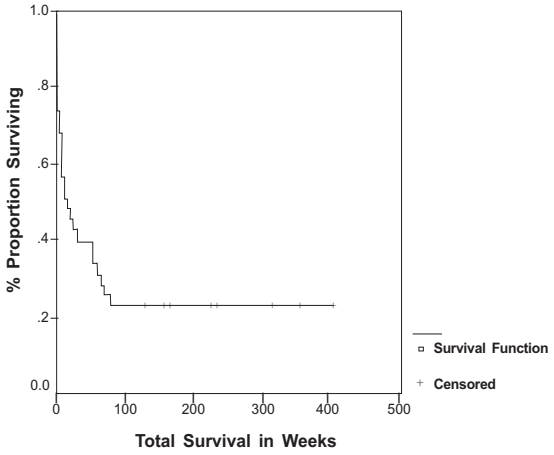

Fig. 1. Estimates of survival by Kaplan-Meier.

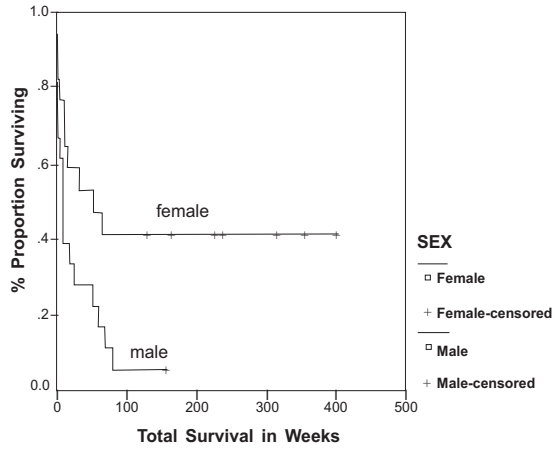

Fig. 2. Survival distribution by gender.

Discussion

Childhood ANLL chemotherapy regimen has failed to reach the required results to date. Thus, new drug treatments and new protocol developments are still being tested. Although the results (especially with bone marrow transplantation) have shown some improvements, they are still not satisfactory[4,5,12,13].

The standard treatment of ANLL is anthracycline and cytosine arabinoside in combination. Remission rate increases with the addition of mitoxantrone etoposide[13,14]. Idarubicin was used initially for adult ANLL treatment. Wiemik et al.[15] found better results for 214 adult ANLL patients who reached remission and proved long-term survival. Complete remission was found to be 70% in the idarubicin group and 59% in the daunorubicin group. Especially when etoposide was added to the therapy, remission rates could reach up to 81%[8].

In the study carried out by Mehta et al.[16], which included 52 patients, the BF 12 protocol containing idarubicin, high-dose cytosine arabinoside and etoposide was given, and the complete remission ratio was found to be 78% and overall survival ratio for three years as 49%. A recent multicenter study in Great Britain by Rassam et al.[17] used a protocol with IDA for newly diagnosed ANLL patients and relapse cases. The remission ratio for the newly diagnosed patients was found to be 57% and for the relapse cases 42%.

Heyli et al.[18] used cytosine arabinoside and idarubicin treatment on 23 ANLL adult patients and attained an 80% complete remission rate, but they could not indicate a difference in long-term survival results.

Sackmann-Muriel et al.[19] reported a 78% complete remission in the 68 ANLL childhood patients on whom they used idarubicin, cytosine arbinoside and etoposide. The four-year event-free survival estimate was 42% and overall survival estimate was 44%. Dinndorf et al.[20] reported an 80% complete remission by using the protocol with idarubicin, cytosine arabinoside and fludarabine on 10 ANLL patients with relapse and refractory. They did not observe many side effects except for hematological toxicity.

In a multicenter study carried out in our country for the first time, protocol with idarubicin was used on newly diagnosed ANLL children by Gedikoğlu et al.[21] Complete remission rate was found to be 88% and the 30-month long life duration 29%. They detected a high relapse rate and toxic effect related to the medicines.

Fludarabine, cytarabine, granulocyte colony-stimulating factor (G-CSF) and idarubicin (FLAG-IDA) protocol was used in relapsed and poor risk childhood acute leukemia by Yalman et al.[22]. In this study authors reported that FLAG-IDA protocol appeared to be myelotoxic in their patient group and was not cost effective for developing countries.

We began using idarubicin content protocol in 1992 and used the same protocol for all patients until September 1999. The remission rate, which was found to be 71% after the induction therapy, was compatible with the other studies in the literature. When evaluated according to Kaplan-Meier, overall survival estimate was 40% for one year and 23% for three years. The patients in our clinical studies could not attend controls for economic and social-cultural reasons, which affected the mortality ratio negatively.

Gastrointestinal toxic effects (vomiting, mucositis, nausea, diarrhea) and myelosuppressive effect in the ANLL patients treated with idarubicin were no different from that seen in the cases treated with other anthracyclines[7,8]. In our study group we noticed nausea, vomiting and mucositis in all our patients and treatments were given for these complications. There was also 94% myelotoxicity. 21% hepatotoxicity, 2.5% renal toxicity, and 5% renal and hepatotoxicity. This myelotoxicity comes forward as a factor prohibiting the continuation of the chemotherapy schema in a regular phase. The high ratio of myelotoxicity explains the high ratio of the patients with neutropenic sepsis.

The fact that anthracyclines cause dose-dependent cardiomyopathy, decreased left ventricular ejection fraction and congestive heart failure related to these has been proven by animal experiments, radionuclide studies and endomyocardial biopsies. However, idarubicin was tolerated in cardiotoxicity better than the other anthracyclines[7,8]. The decrease in left ventricular ejection fraction was seen less frequently in the patients treated with idarubicin. The drug dependent cardiomyopathy ratio was 5% in a study carried out on an adult patient group[9]. In Sackmann-Muriel's study cardiotoxicity ratio was found to be 1.5%[19].

In our patient group pericardial involvement was found in two patients during the analyses done premedically by echocardiography. In the heart function tests carried out after the consolidation phase II therapy, no defect was observed in these patients. Cardiotoxicity was only seen during the therapy in one patient, which was detected by echocardiography and electrocardiography. Different toxic effects mentioned above occurred in almost all of our patients. We think that the most important factors related to mortality are the long duration of neutropenia and the other toxic effects of idarubicin.

According to the results of our study, no correlation was proven between the WBC count, age and prognosis. Weinstein et al.[23] detected no relation between the WBC count and prognosis. However, sex was found to be effective. It was indicated by the Cox regression analyses that the female gender had a positive effect.

In conclusion, we have observed that the protocol with idarubicin achieves a higher remission ratio when compared with the other protocols with anthracycline. However, the magnitude of the hematological toxicity ratios related to the therapy increases the complication ratios, affecting the long-term life analyses directly. We consider that this protocol is well adjusted to the needs and socioeconomical conditions in the developing countries. This myelotoxic therapy should be taken into consideration by clinicans in view of the high mortality ratio in ANLL. In order to obtain more reliable results, we suggest that the studies should be carried out in a larger patient group and for a longer follow-up period.

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The peak oxygen uptake of healthy Turkish children with reference to age and sex: a pilot study

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SUMMARY: Gürsel Y, Sonel B, Gök H, Yalçın P. The peak oxygen uptake of healthy Turkish children with reference to age and sex: a pilot study. Turk J Pediatr 2004; 46: 38-43.

Maximal oxygen uptake (VO_2max) has an important place in the assessment of cardiopulmonary fitness. Currently there is insufficient normative data for Turkish children. With this preliminary study, we aimed to set up a normative data for our lab which may also serve as a basis for future large population based studies in Turkey. We assessed the peak oxygen consumption of 80 healthy Turkish children aged 5-13 years and examined the cardiopulmonary responses to exercise test in relation to their age, sex and body size. Dynamic lung functions were positively and significantly correlated with age. A similar correlation was observed for the peak VO_2. A significant positive correlation between peak VO_2 and body size was demonstrated only in boys for height. There were no differences in all of the test parameters with reference to sex except in the age group of 13 years. Boys who were 13 years old had higher mean values of maximal voluntary ventilation (MVV), oxygen uptake at anaerobic threshold, peak VO_2, and exercise test duration than those of girls of the same age ($p<0.05$). VO_2 plateau was detected only in 25%, and when two groups with and without VO_2 plateau were compared, there were no differences regarding the age, sex, weight, height and exercise test results. Assessment of VO_2 by graded exercise stress testing by treadmill is accepted as a safe and effective method of evaluating the physical fitness of children. Current study presents normal data for a limited subpopulation of healthy Turkish children.

Key words: maximal oxygen uptake, healthy children, treadmill exercise test.

Maximal oxygen uptake (VO_2 max) is considered to be the best index of cardiopulmonary fitness[1]. It is the highest rate of oxygen consumption by the body in a given period of time during vigorous dynamic exercise involving a large portion of muscle mass[2]. Pulmonary, cardiovascular, hematologic components of oxygen delivery and the oxidative mechanisms of the exercising muscle are the main limiting factors for VO_2 max. Regular physical activity is generally considered to be an important factor in the growth and the development of both healthy children and those affected by chronic diseases. The physiologic adaptations of normal children to exercise provide insight into the abnormalities found in children with various diseases. Exercise stress testing is an accepted mode of evaluating the peak oxygen consumption and cardiopulmonary status of children[3]. Obtaining useful and accurate laboratory measurements and interpreting test results of children with diseases depend on an understanding of normal physiological responses[3]. Currently, there is not sufficient normative data for Turkish children. Herein, we provide normal data on the peak oxygen consumption of a limited sample of healthy Turkish children aged 5-13 years and examine the cardiopulmonary responses to exercise test in relation to their age, sex and body size.

Material and Methods

Subjects

All of the children entering the study were from the same state primary school and aged between 5-13 years. Children were selected by a random number list. Twenty-five children from each age

group were invited and those whose parents gave written informed consent were accepted for the study. No attempt was made to select the children who were particularly active, and all of the subjects were attending the regular physical education class at school. Age, weight and height profiles of the study population are presented in Table I. All were healthy and taking no medications that would affect exercise performance. Children with infections were not allowed to participate in the laboratory test.

Table I. Age and Anthropometrical Data of Children by Sex (Mean±SD)

	Boys (n=43)	Girls (n=47)
Age (years)	8.84±2.88	9.70±2.64
Height (cm)	132.12±17.65	139.40±16.15
Weight (kg)	30.40±12.46	33.45±11.30

Exercise Test

All tests were conducted in the Cardiopulmonary Testing Laboratory at the University of Ankara, Department of Physical Medicine and Rehabilitation. Testing was done at various times during the day considering the school hours of each child. The children were given adequate explanation of the proposed protocol and objectives and asked to try as hard as they could. Prior to the exercise test, pulmonary function tests were performed. Flow-volume curves were obtained by forced expiratory maneuvers using Vmax29 ergospirometry (Sensormedics®, Yorbda Linda, California). Forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), FEV_1/FVC, and maximal voluntary ventilation (MVV) were measured in three consecutive trials and the best trial was accepted.

In our laboratory, most of the ergospirometric exercise tests are performed on treadmill using the Bruce walking treadmill protocol. For some patients who are known to have serious cardiopulmonary or musculoskeletal limitations, modified Bruce or Naughton protocols are preferred. We wanted to standardize the test protocol for the healthy children group as already done for the adult group. Before the study, five children of different ages were tested using several treadmill test protocols (Bruce, modified Bruce, Naughton, and Oslo) on separate days. Bruce protocol was thought to be an appropriate test to achieve a maximal test for children. However, children who were at the age of 5-6 years tolerated modified Bruce protocol better than the Bruce protocol. So we adhered to the original Bruce walking protocol for the children aged 7-13 and to the modified Bruce protocol for those who were 5-6 years old on a treadmill with 12-lead electrocardiographic monitoring (Marquette Case I: Marquette, Milwaukee, WI). Systolic and diastolic blood pressures were recorded as well. During the test, VO_2 and VCO_2 were measured continuously and analyzed with the use of a Sensormedics metabolic cart (Sensormedics®, Yorbda Linda, California). Before each test session, the gas analyzers were calibrated with certified gases of known standard concentrations. The children were permitted to hold onto the guard rails of the treadmill slightly to fell safe. They were encouraged to walk to their limit. The test was terminated when fatigue was expressed by the subject or when observed by the testing staff as sweating, hyperpnea, facial flushing and unsteady gait and considered to be consistent with an exhaustive effort.

Three criteria were used to determine whether a successful maximal test had been performed: 1. a leveling or plateauning of VO_2 (defined as an increase of VO_2 <2 ml/kg/min), 2. heart rate >195 beats/min, 3. respiratory exchange ratio >1.0[4]. Maximal heart rate attained at the end of the exercise, peak oxygen uptake or maximal oxygen uptake (VO_2 plateau) and ventilatory anaerobic threshold (VAT) were evaluated. Peak oxygen uptake was defined as the average value during the final minute of exercise. A plateau of VO_2 was defined as a less than 2 ml/kg/min increase in the average value during the final minute of the last stage, and if a plateau had been detected, the average value was accepted as maximal oxygen uptake.

Ventilatory anaerobic threshold was determined by Wasserman method[5]. Minute ventilation volume (VE)/VO_2 and VE/VCO_2 were plotted against time. The VAT occurred when there was an isolated increase in the slope for VE/VO_2 with no change in the slope for VE/VCO_2. If this point occurs then the slope for R and the slope for VE abruptly increase. The point where the VAT occurred was expressed as a percent of VO_2 maximum.

Statistical Analysis

All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS for Windows v.9.0). Values were presented as

means and standard deviations. Univariate association between age, sex, height, weight and all test parameters was assessed by Mann Whitney U test. Correlations between age and dynamic lung functions, VO_2 and body size were measured by Pearson correlation test.

Results

All of the children completed the test without any complication, and all tests were terminated upon development of fatigue in a subject. Dynamic lung functions of the children are presented in Table II in relation to age and sex groups, and in Table III, the peak cardiopulmonary responses of the children are displayed in relation to age groups and sex. Forty percent of the children tested did not meet the criteria for a successful maximal test. Dynamic lung functions were positively and significantly correlated with age: $r=0.884$, $p<0.001$ for FVC; $r=0.834$, $p<0.001$ for FEV_1; $r=0.905$, $p<0.001$ for vital capacity (VC); $r=0.714$, $p<0.01$ for MVV). A similar correlation was observed for the peak VO_2 ($r=0.337$, $p<0.001$). A significant positive correlation between peak VO_2 and body size was demonstrated only in boys for height ($r=0.422$, $p<0.05$) (Table IV). There were no significant differences in all of the test parameters with reference to sex expect the age of 13 years. Boys who were 13 years old had significantly higher mean values of MVV, oxygen uptake at anaerobic threshold, peak VO_2, and exercise test duration than those of girls of the same age.

A plateau of VO_2 was detected in 23 children. NO significant difference was found between the two groups who displayed a plateau of VO_2 and those who did not in relation to age, sex, height and weight. Various properties of the two groups are presented in Table V. Ventilatory anaerobic threshold was not detected in five children (one was 9 years old, one was 13 and the rest were 5).

Table II. Dynamic Lung Function Test Results by Age Groups and Sex (Mean±SD)

Age (years)	Sex	FVC[a] (L/min)	FEV1[b] (L/min)	FEV1/FVC[c]	VC[d] (L/min)	MVV[e] (L/min)	Z	P
	Boys	35.2±7.82	19.65±5.17	169.38±3.07	12.17±3.85	8.80±2.46	-0.507[a]	0.650
5-6							-0.781[b]	0.475
	Girls	36.68±8.65	21.92±4.01	178.86±17.04	11.21±1.34	7.93±1.57	-1.767[c]	0.088
							-0.213[d]	0.837
							-1.173[e]	0.250
	Boys	38.06±7.41	20.58±6.39	190.13±6.78	9.79±3.94	8.50±1.77	-1.540[a]	0.139
7-8							-0.742[b]	0.470
	Girls	37.37±7.23	20.46±5.67	188.89±19.61	10.67±3.52	10.31±1.77	-0.958[c]	0.351
							-1.541[d]	0.139
							-1.540[e]	0.139
	Boys	43.82±9.48	26.82±8.76	178.83±22.84	10.67±2.10	12.90±2.25	-0.271[a]	0.792
9-10							-0.613b	0.594
	Girls	38.96±6.45	24.07±7.71	186.18±10.35	10.23±2.46	11.54±1.87	-0.866[a]	0.440
							-0.118[d]	0.995
							-0.108[e]	0.958
	Boys	46.29±6.41	27.71±5.97	181.00±10.76	12.55±1.67	14.73±2.06	-1.446[a]	0.152
11-12							-0.775[b]	0.468
	Girls	41.41±8.18	27.01±6.46	192.09±15.75	12.55±1.67	14.73±2.06	-0.953[c]	0.349
							-1.066[d]	0.295
							-1.409[e]	0.173
	Boys	47.95±5.66	30.14±3.33	198.67±6.38	14.09±1.53	16.56±1.81	-0.471[a]	0.689
13							-1.414[b]	0.181
	Girls	40.47±5.99	22.96±4.59	189.33±13.21	10.99±1.66	13.08±1.71	-1.419[c]	0.181
							-0.510[d]	0.683
							-3.064[e]	0.001

FVC: forced vital capacity; FEV1: forced expiratory volume in 1 second; VC: vital capacity; MVV: maximal voluntary ventilation.

Table III. Peak Cardiopulmonary Responses to Treadmill Exercise by Age Groups and Sex (Mean±SD)

Age (years)	Sex	VO_2[a] Peak (ml/kg/min)	VO_2[b] at Vat (ml/kg/min)	Peak[c] heart rate (beat/min)	Systolic[d] BP (mmHg)	Diastolic[e] BP (mmHg)	Exercise[f] test time (min:sec)	Z	P
								-0.307[a]	0.765
	Boys	35.23±7.82	19.65±5.17	169.38±13.07	118.08±14.94	70.00±11.55	12.17±3.85	-1.171[b]	0.270
5-6								-1.071[c]	0.311
		36.68±8.65	21.92±4.01	178.86±17.04	138.57±16.76	81.43±12.15	11.21±1.34	-2.368[d]	0.019
	Girls							-1.852[c]	0.097
								-0.119[f]	0.938
								-1.637[a]	0.114
	Boys	38.06±7.41	20.58±6.39	190.13±16.78	125.00±10.69	78.75±3.54	9.79±3.94	-1.540[b]	0.139
7-8								-0.337[c]	0.743
								-0.247[d]	0.815
	Girls	37.37±7.23	20.46±5.67	188.89±19.61	130.56±23.24	80.00±8.66	10.67±3.52	0.000[e]	1.000
								-0.481[f]	0.673
								-0.251[a]	0.808
	Boys	43.82±9.48	26.82±8b76	178.83±22.84	123.33±13.66	80.00±6.32	10.67±2.10	-0.977[b]	0.368
9-10								-0.352[c]	0.733
								-0.052[d]	0.961
	Girls	38.96±6.45	24.07±7.71	186.18±10.35	124.55±12.93	78.18±8.74	10.23±2.46	-0.800[e]	0.525
								-0.704[f]	0.525
								-1.338[a]	0.197
	Boys	46.29±6.41	27.71±5.97	181.00±10.76	136.00±13.50	83.00±9.40	12.55±1.67	-0.247[b]	0.809
11-12								-1.766[c]	0.085
	Girls	41.41±8.18	27.01±6.46	192.09±15.75	128.18±13.28	76.36±11.20	12.55±1.67	-1.292[d]	0.223
								-1.462[e]	0.173
								-0.916[f]	0.387
								-2.123a	0.036
	Boys	47.95±5.66	30.14±3.33	198.67±6.38	144.17±19.60	80.00±6.32	14.09±1.53	-2.670[b]	0.004
13								-1.183[c]	0.272
	Girls	40.47±5.99	22.96±4.59	189.33±13.21	128.89±10.54	75.00±10.00	10.99±1.66	-1.901[d]	0.066
								-1.268[e]	0.272
								-2.946[f]	0.002

VO_2: oxygen uptake; VAT: ventilatory anaerobic threshold.

Table IV. Correlation Between Dynamic Lung Functions, Peak VO_2, Age and Body Size

		FVC (L/min)	FEV1 (L/min)	MVV (L/min)	VC (L/min)	VO_2 Peak (ml/kg/min)	Exercise test time (min:sec)
Age (years)	All	0.884 (0.000)	0.834 (0.000)	0.714 (0.000)	0.905 (0.000)	0.337 (0.000)	0.126 (0.235)
	Boys	0.902 (0.000)	0.901 (0.000)	0.798 (0.000)	0.910 (0.000)	0.554 (0.000)	0.203 (0.191)
	Girls	0.850 (0.000)	0.768 (0.000)	0.562 (0.000)	0.895 (0.000)	0.253 (0.089)	0.076 (0.610)
Height (cm)	All	0.887 (0.000)	0.845 (0.000)	0.751 (0.000)	0.926 (0.000)	0.233 (0.028)	0.119 (0.265)
	Boys	0.884 (0.000)	0.902 (0.000)	0.812 (0.000)	0.902 (0.000)	0.422 (0.005)	0.258 (0.095)
	Girls	0.892 (0.000)	0.791 (0.000)	0.631 (0.000)	0.950 (0.000)	0.218 (0.145)	0.033 (0.826)
Weight (kg)	All	0.908 (0.000)	0.879 (0.000)	0.786 (0.000)	0.923 (0.000)	0.209 (0.049)	0.121 (0.258)
	Boys	0.924 (0.000)	0.948 (0.000)	0.846 (0.000)	0.932 (0.000)	0.285 (0.064)	0.218 (0.160)
	Girls	0.886 (0.000)	0.823 (0.000)	0.709 (0.000)	0.920 (0.000)	0.249 (0.095)	0.075 (0.616)

Values show correlation coefficients, and p values are presented in parenthesis.

FVC: forced vital capacity; FEV1: forced expiratory volume in 1 second; MVV: maximal voluntary ventilation; VC: vital capacity; VO_2: oxygen uptake.

Table V. Comparison of Physical and Test Parameters Between Children with and without VO_2 Plateau (Mean±SD)

	Children with VO_2 plateau (n=23)	Children without VO_2 plateau (n=67)	Z	P
Age (years)	8.61±2.84	9.52±2.73	-1.417	0.157
Height (cm)	131.04±17.48	137.31±17.24	-1.620	0.105
Weight (kg)	30.30±12.30	33.42±11.81	-1.329	0.184
Peak oxygen uptake (ml/kg/min)	40.02±8.27	40.61±8.17	-0.143	0.887
Exercise test time (min:sec)	12.16±1.86	11.10±3.01	-1.739	0.082

VO_2: oxygen uptake.

Discussion

Exercise can be useful as a physiologic stress to elicit findings and abnormalities that are not evident at rest. So exercise testing is often used as a stress test. Breath-by-breath analysis for measuring respiratory gas exchange during exercise has been shown to be valid and reproducible to an acceptable degree also for children[6]. In many studies, normative data for healthy children of different ethnic groups have been obtained, and different methods were used for exercise stress testing[4,7-10]. It is advisable, however, that each laboratory evaluate its own method, since the characteristics of those commercially available may differ, and normative data may differ due to the ethnical differences[10]. In a former study[11], cardiovascular responses to Bruce treadmill test of healthy Turkish children were reported, but our study is the first reporting the respiratory gas analysis during exercise test in Turkish children. The former study assessed the mean endurance time, heart rate and blood pressure responses to exercise in children aged 4-15 years. However, they did not measure the maximal oxygen uptake, and since the age range of all children and grouping range were different from that of our subjects, it is inappropriate to compare the results.

The results show that peak VO_2 values of Turkish children 7-8 years of age were lower than those of North American children[8], but the values were similar for the children 9-13 years old. Children of 11-13 years of age of both sexes have better peak VO_2 values than those of British children[7], who were tested by cycle ergometer. Since the testing methods were not similar, it is difficult to compare the results.

In a Norwegian study in which peak VO_2 of healthy children and children with congenital heart diseases was compared, a different treadmill testing protocol (Oslo protocol) was used[9]. Norwegian healthy children have higher peak VO_2 than Turkish children, but anthropometrical measures also differed. Their mean height and weight were more than those of Turkish children. These differing results also indicate the necessity of normative data for each ethnic, age and sex group.

The peak VO_2 of both sexes increased with age and this is in accord with reports from other laboratories[7-9,12,13]. In this population group the correlation of peak VO_2 was stronger with height than weight in boys, but when corrected for age the correlation became insignificant. Exercise time was also strongly correlated with increasing age.

There were no significant differences in the test results between boys and girls, as was expected on the basis of previous results. However, beyond the age of 12 years, boys' peak VO_2 was higher than girls' peak VO_2, Similarly, Lenk et al.[11] found longer endurance times in boys than girls in older ages (10-15 years). The difference between boys and girls has been attributed to differences in hemoglobin concentration and body size[7]. Another explanation is based upon the girls' greater accumulation of subcutaneous body fat during the circumpubertal years. In this study, neither hemoglobin concentrations nor pubertal evaluation were assessed, so it is hard to make any further comment on this difference in light of the existing data.

The appearance of a VO_2 plateau indicates that the subject has provided a sufficient exercise effort to identify a true VO_2. Secondly, the presence of a VO_2 plateau has served as a cornerstone for the argument that oxygen delivery and/or utilization is the limiting factor in progressive endurance exercise tests. Studies in children, however, have consistently indicated that a VO_2 plateau is not typical

during "maximal" exercise tests, appearing as infrequently as 30-50% in some reports[3,8,14-16]. In this study population, VO_2 plateau was detected only in 25%, and when two groups with and without VO_2 plateau were compared, there were no significant differences as to age, sex, weight, height and exercise test results. There seemed to be on predictive factors for the appearance of VO_2 plateau, and both groups had similar peak VO_2.

Graded exercise stress testing by treadmill is a safe and effective method of evaluating the physical fitness of children. The current study presents normal data only for a limited subpopulation of healthy Turkish children, hence one should be careful before applying these preliminary results to the entire population. However, the data obtained may serve as laboratory reference values in the evaluation of children with various heath problems affecting physical fitness.

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Alcohol drinking behaviors among Turkish high school students

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SUMMARY: Alikaşifoğlu M, Erginöz E, Ercan O, Uysal Ö, Albayrak-Kaymak D, İlter Ö. Alcohol drinking behaviors among Turkish high school students. Turk J Pediatr 2004; 46: 44-53.

The aim of this study was to evaluate the prevalence, behavioral patterns and correlates of regular alcohol drinking in high school students.

This cross-sectional study involved the completion of a modified version of "Health Behavior in School Age Children" (HBSC 1997/1998) questionnaire by 4,153 grade 9-11 students from 26 randomly selected high schools in İstanbul. Chi-square test, Spearman correlation test and forward stepwise multiple logistic regression model were used for statistical analyses as appropriate.

Overall, 61% of students were experimental drinkers, and 46% of the students were current drinkers. There was a significant difference between female and male students with respect to reporting current alcohol drinking at grade 9 and 11 ($p>0.05$ for each comparison). Regular drinking was reported by 6% of students. Male students were more likely than female students to report regular drinking at each grade ($p<0.01$ for each comparison). Nineteen percent of the students reported that they had been really drunk at least once during their lifetime. Male students were more likely than female students to report an occasion of drunkenness at each grade ($p<0.05$ for each comparison). All types of drinking behavior rates tended to increase across grades for both genders ($p<0.05$ for each comparison).

In logistic regression analysis the following were all independently associated with regular drinking: being in grade 11, smoking cigarettes currently, lifetime drug use, bullying others, being sexually active, playing computer games ≥4h/week, exercising ≤1h/week, spending ≥four evenings with friends, at ease in talking to same gender friends, tiredness in the morning, perceived as good-looking/beautiful, higher educational level of the mother and perceived poor academic achievement.

The results of this study showed that alcohol consumption is prevalent among high school students. There is therefore a need for school-based alcohol prevention programs which also deal with family and peer influences on drinking.

Key words: adolescence, substance use, risk behaviors.

In recent years there has been growing concern about teenagers' alcohol problems. This concern has been stimulated by evidence of increasing alcohol use by teenagers and by the presence of an association between alcohol drinking in teenage years and alcohol abuse and dependency in adulthood[1].

In Turkey, although purchase of alcohol is forbidden by individuals younger than 18, alcohol remains the most widely used psychoactive substance among adolescents[2,3]. Examining the prevalence of alcohol drinking patterns among adolescents and the factors that correlate with adolescent alcohol use is the first step towards establishing an appropriate prevention program. The existing literature proposes a number of factors related to causes and associations of drinking among adolescents, especially among those in whom alcohol use shows an abusive pattern, including weak bond with family, alcohol attitudes and behaviors of family and peers, academic difficulties, and other health risk behaviors such as fighting, unplanned sexual activity, suicide, homicide and motor vehicle accidents[4-12].

The aims of this study were a) to provide data about the prevalence of alcohol drinking patterns in high school students, b) to compare the prevalence of alcohol drinking behaviors by gender and grades, and c) to determine the factors correlated with regular alcohol use.

Material and Methods

This study was part of a cross-sectional study that was conducted to determine the health status and health behaviors, and the factors that influence them, of high school students in the metropolitan area of İstanbul. İstanbul is the largest city in Turkey, with a population of approximately 10 million. The population selected for sampling in this study were high school students. Ethical permission for this study was obtained from the University of İstanbul and the Department of Education of İstanbul.

Population

The study sample included 4,153 randomly selected 9th through 11th grade students attending 26 randomly selected high schools. The schools were general or vocational, and public or private.

Students were sampled using a stratified cluster procedure. Schools were the primary sampling unit. The sample was stratified on the basis of location of the district (metropolitan core, small city, suburban or rural) and school types. The schools were chosen from a list provided by the Department of Education[13]. High schools (n=28) were selected randomly within each of the 19 districts. The students' classrooms were also selected randomly within schools, and all students in the class who were present on the day the survey was administered were included.

The sample size for each of the three grades was 1,500 students (1,290 students from public schools, 210 students from private schools). Students were selected in order to represent both the public or private general and vocational schools in appropriate proportions. This represents 154,959 (86% of the total students) students from 208 public high schools and 24,666 (14% of total students) students from 140 private high schools in the city. This calculation assumed a 95% confidence level, 80% of power, ± 3% error and an effect size=1.44.

Procedures

Selected schools were informed about the survey by a letter to the school principal. Two weeks later a phone call was made to schedule the survey. All school principals agreed to participate in the study except those in two private schools. Completion of the survey took one 45 to 60 minute class period. Data were collected during the second semester between March and April 2000.

A self-report survey questionnaire was administered in the classroom in the presence of one of the researchers, a trained surveyor and the class/home room teacher. Researchers followed a standardized protocol in giving instructions to students and answering questions about individual items. Student participation was voluntary; however, no student refused to cooperate in the research. Verbal and written instructions reminded students of the importance of giving honest answers, not writing their names on the questionnaire to maintain confidentiality, and not talking during questionnaire completion.

Instrument

The international version of "Health Behavior in School Age Children" (HBSC) 1997/1998 survey was the main instrument used in this study[14]. HBSC 97/98 was used with the permission of the representative of the WHO regional office for Europe during the 1997/1998 survey. This questionnaire consisted of two sections: core and foci. The core questions gathered information on selected demographic characteristics; health related behaviors; general perceptions of personal health, psychosocial adjustment, peer relationships and support; and perception of the school and its influence. The focus questions of the survey included those about school experiences, relationship with parents, socioeconomic status and body image. We also selected several items from the optional package of HBSC 97/98 survey. These included: 1) items on violence to complete a core picture of youth violence in the city; and 2) items on injury to provide information regarding the epidemiology of medically treated non-fatal injuries among high school children in the city. Researchers also added several items to the survey to assess illicit drug use (1 item) (non-prescribed sedative and antidepressant, anabolic steroid, inhalant, cannabis, marijuana, LSD, cocaine, heroin and amphetamine use), physical and sexual abuse (6 items) and sexual behaviors (2 items).

The final questionnaire used in this study consisted of 84 items. The questionnaire form was first translated into Turkish and then was

translated back into English. It was piloted on 120 students (grades 9, 10, and 11) who were selected from a public high school that was not included in the main sample. Minor wording changes were made to clarify the meaning of certain questions.

Measurement

Three self-reported items assessed alcohol use. To determine experimentation with alcohol, students were asked "Have you ever tasted an alcoholic drink?". Respondents were categorized as "abstinent" for "no" response, as "ever used" for "yes" response, or as "not applicable" for "don't know" response. To determine the frequency of current alcohol use, students were asked "At present, how often do you drink anything alcoholic (beer, wine, raki, gin, liquor, vodka and/or others) on a 5-point scale for each ranging from 1 to 5 [every day (1), every week (2), every month (3), rarely (4) to never (5)]. Students who reported drinking some kind of alcoholic beverage every month (1) to rarely (4) were categorized as "occasional drinkers". Students who claimed that they had drunk something alcoholic once a week or more were categorized as "regular drinkers". The final variable assessed in this study was "perceived drunkenness", which was assessed through the question "Have you ever had so much alcohol that you were really drunk?" on a 5-point scale ranging from "No, never" (1) to "Yes, more than 10 times" (5).

The independent variables included socio-demographic characteristics (school grade, gender), family factors (educational level of both parents, ease in talking to parents, self-appraisal of the family economic status), peer factors (time spent with friends both directly after school and at night, ease in talking to both same and opposite gender friends, the number of close friends, ease in making new friends), school factors (perception of teachers' opinion about the student's performance, truancy, concept that school is boring, feelings about school, feeling pressured by school work, tiredness in the morning), individual perception (self-reported health, happiness and loneliness, perceived attractiveness and fatness) and other health behaviors (current cigarette use, drug use, bullying of others, physical fighting, carrying a weapon, being sexually active, exercising, watching television and playing computer games for a long period). The independent variables and how they were dichotomized for the logistic regression analyses are listed in appendix 1.

Data Analysis

In univariate analysis, chi-square test was used to determine how alcohol drinking behaviors changed between genders in the same grade. Spearman correlation test was used to determine how alcohol drinking behaviors changed by gender across grades. Forward stepwise multiple logistic regression model (likelihood ratio) was used to determine the independent variables influencing regular alcohol drinking behavior. All variables were included in the logistic model, because all factors could be a correlate of regular alcohol consumption.

Consistency Determination

Students who responded inconsistently to two or more pairs of related items were excluded from the study. The inconsistencies were noted on questions about substance use or/and on sexual victimization. Students who were under 15 years old and over 20 years old were also completely omitted from all analyses.

Results

The total number of adolescents in this study was set at 4,500. However, owing to refusal by two private schools principals (n=120), the exclusion of unreliable questionnaires (n=47), the exclusion of respondents younger than 15 years old or older than 20 years old (n=94) and the absence of students in the classroom (n=86), the total obtained sample was 4,153 adolescents.

Forty seven percent of the sample (n=1955) were females. The age range in the sample was 15 to 20 years, with a mean age of 16.4 (SD=±1.10) years. Approximately equal numbers of subjects were recruited from grades 9 (n=1324), 10 (n=1511) and 11 (n=1318).

The total number of students who provided answers for the question "Have you ever tasted an alcoholic drink?" was 4,069 (98.5% of the total students: 1928 female, 2141 male). Sixty one percent of students (female: n=1181, 61%, male: n=1286, 60%) reported that they had tasted an alcoholic drink. There was no significant difference between female and male students with respect to reporting having tasted

an alcoholic drink at each grade (Table I). There was a remarkable increase in this behavior across grades for both genders (female: r=0.13, p=0.0001; male: r=0.12, p=0.0001).

Forty six percent of the students (females: n=840, 43.5%; males: n=1016, 47.4%) reported alcohol consumption at least rarely (current user). There was a significant difference between female and male students with respect to reporting current alcohol consumption at grades 9 and 11 ($p<0.05$ for each comparison) (Table I). Current drinking rate tended to increase across grades for both genders (female: r=0.17, p=0.0001; male: r=0.15, p=0.0001).

Forty percent of students (females: n=776, 40%; male: n=839, 39%) reported alcohol consumption occasionally.

Six percent of the students (female: n=64, 3.3%; male: n=177, 8.4%) reported regular drinking. Male students were more likely than female students to report regular drinking at each grade ($p<0.01$ for each comparison) (Table I). Frequency of regular drinking also tended to increase across grades for both genders (female: r=0.11, p=0.001; male: r=0.14, p=0.0001).

Nineteen percent (female: n=313, 16%, male: n=485, 22%) of the students reported that they had been really drunk at least once during their lifetime (Table I). Eleven percent of male students and 6% of female students reported that they had been really drunk twice or more. Male students were more likely than female students to report an occasion of drunkenness at each grade (Table I) ($p<0.05$ for each comparison). There was a remarkable increase in drunkenness rate across grades for both genders (female: r=0.15, p=0.0001; male: r=0.16, p=0.0001).

In logistic regression analysis, being in grade 11, smoking cigarettes currently, lifetime drug use, bullying others, being sexually active, playing computer games ≥4h/week, exercising ≤1h/week, spending ≥four evenings with friends, ease in talking to same gender friends, tiredness in the morning, perceived as good-looking/beautiful, higher educational level of the mother and perceived poor academic achievement were all independently associated with regular drinking (Table II).

Higher educational level of the father, having difficultly in talking to father and mother, perceived higher economic status of the family,

Table I. Alcohol Drinking Behaviors: Gender Differences in the Same Grade (chi square test results)

	Grade 9			Grade 10			Grade 11		
Variables	Total N=1290 n %	Female N=592 n %	Male N=698 n %	Total N=1482 n %	Female N=716 n %	Male N=766 n %	Total N=1297 n %	Female N=620 n %	Male N=667 n %
Ever tasted alcohol	657 (51)	301 (51)	356 (51)	941 (63)	458 (64)	483 (63)	869 (67)	422 (68)	447 (66)
Current alcohol use	459 (36)	187 (32)	272 (39)*	699 (47)	328 (46)	371 (48)	698 (54)	325 (52)	373 (55)*
Occasional alcohol use	417 (32)	177 (30)	240 (34)	626 (42)	308 (43)	318 (41)	572 (44)	291 (47)	281 (42)
Regular alcohol use	42 (3)	10 (2)	32 (5)§	73 (5)	20 (3)	53 (7)§	126 (10)	34 (5)	92 (14)§
Ever been drunk	147 (11)	47 (8)	100 (14)§	300 (20)	125 (17)	175 (22)§	351 (27)	141 (22)	210 (31)§
Drunkenness once	87 (7)	30 (5)	57 (8)	172 (12)	82 (12)	90 (12)	185 (14)	85 (14)	100 (15)
Drunkenness 2-3 times	47 (4)	13 (2)	34 (5)	96 (6)	39 (6)	57 (7)	108 (8)	45 (7)	63 (9)
Drunkenness 4-10 times	4 (0.3)	2 (0.2)	2 (0.3)	19 (1)	4 (0.6)	15 (2)	29 (2)	5 (0.8)	24 (4)
Drunkenness >10 times	9 (0.6)	2 (0.2)	7 (1)	13 (0.8)		13 (2)	299 (2)	6 (1)	23 (3)

* p=0.05, § p=0.01.

Table II. Predictors of Regular Drinking: Forward Stepwise Logistic Regression (likelihood ratio)

Variables	β	Sig	Exp (β)	95% C.I.	
Being in 11th grade	1.41	0.0001	4.1	2.08	8.04
Poor academic achievement	0.7	0.003	2.01	1.26	3.20
Current cigarette use	0.8	0.001	2.22	1.36	3.60
Drug use	1.17	0.0001	3.21	1.85	5.59
Feeling tired in the morning	0.57	0.01	1.77	1.13	2.78
Playing computer games ≥4h/w	0.566	0.01	1.76	1.10	2.81
Ease in talking to same gender friends	1.41	0.0001	4.09	1.90	8.79
Spending ≥ four evenings with friends	0.72	0.003	2.05	1.26	3.32
Bullying others last school term	0.58	0.01	1.78	1.11	2.87
Being sexually active	0.98	0.0001	2.68	1.66	4.32
Exercising ≤1 h/week	0.83	0.001	2.29	1.42	3.70
Higher educational level of mother	0.90	0.0001	2.46	1.55	3.91
Being good looking/beautiful	0.51	0.02	1.67	1.06	2.63

physical fighting, carrying a weapon, ease in making new friends, having more close friends, ease in talking to opposite gender friends, dislike of school, concept that school is boring, increased absence from school, feeling pressured by school work, feeling less healthy and happy, feeling lonely more often, perceived fatness, spending more time with friends after school and watching TV ≥4h/day were not independently associated with regular drinking after adjustment for gender and grades.

Discussion

The purpose of our study was to determine the profile of alcohol drinking behavior of İstanbul high school students. Approximately equal percentages of male (60%) and female students (61%) reported that they had tried some kind of alcoholic beverage. These figures are similar to those found in 1995 in İstanbul High School students[2]. Female alcohol experimentation rate in our study was similar to that found in the country with the lowest rate in the HBSC 98 study (Slovakia, 62%), while male experimentation rate was lower than that found in all countries[14]. These figures are also different from those found in the United States[15].

In this study, 47% of male students and 43.5% of female students reported that they drank alcohol at least rarely. Eight percent of male students and 3% of female students reported that they were regular drinkers. If one considers that having used alcohol at least 3-5 times during the previous month is equivalent to being a regular drinker, in our study the regular drinking rate was lower than that found in 1995 and 1998 in İstanbul High School students[2,3]. Female regular drinking rate in this study was similar to that found in the country with the lowest rate in the HBSC 98 study (Hungary, 3%) while male regular alcohol drinking rate was lower than that a found in all countries[14]. These figures also differ from those found in populations of 16-year-old adolescents in some European countries[2].

Drunkenness at least once during lifetime was reported by 19% of students (22% male, 16% female). The percentage of drunkenness in this study was also lower than that reported in 1995 and 1998[2,3]. The differences between our results and those of the studies performed in 1995 and 1998 may be attributed to the differences between study methodologies. In our study, the percentages of male (11%) and female (6%) students who reported drunkenness twice or more were also lower than those found in all countries in the HBSC 98 study[14]. The differences between the results of our study and those of European countries may be attributed to cultural and religious norms in Turkey.

Although our students' alcohol drinking patterns significantly differ from those of the European countries, the results of two other national studies and our results still indicate that adolescent alcohol use is a reality in our community. Our results also indicate that all drinking behaviors increased significantly in students through grades 9 and 11. This is an important finding which might help us in determining the timing of prevention programs. Our results and those found in other surveys indicate that prevention programs should be established before the high school years.

This study also provides evidence about significant correlates of adolescent regular alcohol consumption. Male gender was a significant correlate of regular drinking as in other surveys[2,14,16]. Higher educational level of the mother was the only parental correlate of regular drinking. Similarly, a previous study has shown that higher educational level of the mother is an important determinant of alcohol use[17]. Among factors related to peers, ease in talking to same gender friends and spending more time with friends in the evening correlated with regular drinking. These results showed that students who engage in drinking alcohol tend to socialize more with their peers than those who do not drink alcohol. In this study, among school factors, poor academic achievement and tiredness in the morning were factors correlated with frequent drinking. Low level of school connectedness and poor academic achievement were also previously reported to have influence on adolescent drinking behaviors[7,18-20]. The only individual variable which correlated with regular drinking was perceiving one self as attractive. However, in the HBSC study, this factor was not found to be related to alcohol consumption among 15-year-old students[14]. Our results also suggest that other health risk and problem behaviors such as current cigarette use, illicit drug use, bullying others, and being sexually active correlated with regular drinking. These data again reveal the strength of the associations between health risk and problem behaviors[3,14,21-23]. In our study, playing computer games ≥4 h/week

and exercising ≤1h/week were also found to be correlated with regular drinking. This may indicate a relationship between leisure time activities and alcohol drinking behaviors. This co-occurrence may also reflect the effect of socio-cultural factors.

The similarity between our results and those of previous studies from western countries showed that correlates of regular drinking do not change from culture to culture[2,3,7,8,14,16-23].

The limitations of the study should be acknowledged. Although this study suggests factors which would be expected to correlate with adolescent regular alcohol use among İstanbul high school students, it is not possible to draw conclusions about causality because the data were cross-sectional. Further longitudinal researches are needed to determine the cause-effect relationship between regular drinking and its correlates. Social desirability effect is another limitation of this study. This is a cross-sectional survey and the prevalence of alcohol drinking behaviors is based on self report of alcohol drinking experiences with no corroboration from other sources. There may be significantly under-reporting or over-reporting of the information, depending on whether the behavior is thought to be desirable. In this study, to reduce such biases, efforts were taken to ensure confidentiality and anonymity of responses.

We did not ask any questions about other problematic behaviors such as delinquency, suicidal ideation, being a member of a gang or driving while drunk which would help us in identifying problematic alcohol users. Thus, we do not know whether problematic alcohol use is a concern among our high school students. Further studies need to be performed to distinguish this subgroup clearly from those who drink alcohol causally.

The analyses presented in this paper constitute a baseline data set which can be used for comparisons in future surveys targeting 15-20-year-old adolescents' drinking behavior. This study also provided a description of some of the characteristics of regular drinkers. This is important for developing drinking prevention and intervention programs in Turkey. Our results indicate that parent as well as peer influences should be addressed in these programs. Students and their parents should be aware of the many and varied social influences on drinking behavior and the consequences of adolescent drinking. Students should also learn about effective alcohol refusal skills. Finally, drinking prevention programs should also target other health risk behaviors. Health care providers should screen adolescents, especially those found to be at risk of drinking routinely, for drinking behaviors, and they should also realize that adolescents who drink regularly could be engaged in other health-risk and problematic behaviors.

Appendix 1: Independent Variables

1. How often do you smoke cigarettes at present?
a) Every day
b) At least once a week but not every day
c) Less than once a week
d) I do not smoke
a versus b+c+d

2. Have you ever used substances such as inhalant, cannabis, cocaine, heroin/morphine, marijuana, nonprescription sedative/antidepressant, LSD, amphetamine or anabolic steroid to fell high or to have more energy?

	40 or more times (1)	20-39 times (2)	10-19 times (3)	3-9 times (4)	1-2 times (5)	No (6)
a) Inhalant	☐	☐	☐	☐	☐	☐
b) Cannabis	☐	☐	☐	☐	☐	☐
c) Cocaine	☐	☐	☐	☐	☐	☐
d) Heroin/morphine	☐	☐	☐	☐	☐	☐
e) Marijuana	☐	☐	☐	☐	☐	☐
f) Sedative/Antidepressant	☐	☐	☐	☐	☐	☐
g) LSD	☐	☐	☐	☐	☐	☐
h) Amphetamine	☐	☐	☐	☐	☐	☐
i) Anabolic steroid	☐	☐	☐	☐	☐	☐

1+2+3+4+5 versus 6

3. Outside school hours: How many hours per week do you usually exercise in your free time to the extent that you get out of breath or sweat ?
a) None
b) About half an hour
c) About 1 hour
d) About 2 to 3 hours
e) About 4 to 6 hours
f) 7 hours or more
a+b+c versus d+e+f

4. now many hours per day do you usually watch TV?
a) Not at all
b) Less than half an hour a day
c) Half an hour to 1 hour
d) 2 to 3 hours
e) 4 hours
f) More than 4 hours
a+b+c+d versus e+f

5. How many hours per week do you usually play computer games?
a) Not at all
b) Less than 1 hour a week
c) 1 to 3 hours
d) 4 to 6 hours
e) 7 to 9 hours
f) 10 hours or more
a+b+c versus d+e+f

6. How many evening per week do you usually spend out with your friends?

0 1 2 3 4 5 6 7 evenings

0+1+2+3 versus 4+5+6+7

7. How easy is it for you to talk to the following persons about things that really bother you?

	Very Easy (a)	Easy (b)	Difficult (c)	Very Difficult (d)	Don't have or see this person (e)
1. Father	☐	☐	☐	☐	☐
2. Mother	☐	☐	☐	☐	☐
3. Friends of the same sex	☐	☐	☐	☐	☐
4. Friends of the opposite sex	☐	☐	☐	☐	☐

a+b versus c+d+e

8. Do you think you are:
a) Very good looking
b) Quite good looking
c) About average
d) Not very good looking
e) Not at all good looking
f) I don't think about my looks
a+b+ versus c+d+e

9. Is it easy or difficult for you to make new friends?
a) Very easy
b) Easy
c) Difficult
d) Very difficult
a+b versus c+d

10. How many close friends do you have?
a) None
b) One
c) Two
d) Three or more
a+b+c versus d

11. How healthy do you think you are?
a) Very healthy
b) Quite healthy
c) Not very healthy
a+b versus c

12. In general, how do you feel about your life at present?
a) I feel very happy
b) I feel quite happy
c) I do not feel very happy
d) I'm not happy at all
a+b versus c+d

13. Do you ever feel lonely?
a) Yes, very often
b) Yes, rather often
c) Yes, sometimes
d) No
a+b versus c+d

14. How often do you feel tired when you go to school in the morning?
a) Rarely or never
b) Occasionally
c) 1-3 times a week
d) 4 or more times a week
a+b versus c+d

15. In your opinion: What do your class teachers think about your school performance compared to your classmates?
a) Very good
b) Good
c) Average
d) Below average
a+b versus c+d

16. How do you feel about school at present?
a) I like it a lot
b) I like it a bit
c) I do not like it very much
d) I do not like it at all
a+b versus c+d

17. How pressured do you feel by the school work you have to do?
a) Not at all
b) A little
c) Some
d) A lot
a+b versus c+d

18. How well off do you think your family is?
a) Very well off
b) Quite well off
c) Average
d) Not very well off
e) Not at all well off
a+b versus c+d+e

19. During the past 12 months, how many times were you in a physical fight?
a) I have not been in a physical fight
b) 1 time
c) 2 times
d) 3 times
e) 4 or more times
a versus b+c+d+e

20. Do you think your body is
a) Much too thin
b) A bit too thin
c) About the right size
d) A bit too fat
e) Much too fat
f) I do not think about it
a+b+c versus d+e

21. How often have you taken part in bullying other students in school this term?
a) I haven't bullied others in school this trem
b) Once or twice
c) Sometimes
d) About once a week
e) Several times a week
a versus b+c+d+e

22. During this term, how many times did you carry a weapon, such as a knife, club or gun on school grounds?
a) I did not carry a weapon during this term on school grounds
b) 1 time
c) 2-3 times
d) 4-5 times
e) 6 or more times
a versus b+c+d+e

23. Have you ever had sexual intercourse?
a) Yes
b) No

24. How often do you spend time with friends right after school?
a) 4-5 days a week
b) 2-3 days a week
c) once a week or less
d) Have no friends right now
a+b versus c+d

25. How often do you think that going to school is boring?
a) Very often
b) Often
c) Sometimes
d) Rarely
e) Never
a+b versus c+d+e

26. How many days did you skip classes or school this term? (use appropriate word to indicate truancy)
a) 0 days
b) 1 day
c) 2 days
d) 3 days
e) 4 or more days
a+b+c versus d+e

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A peer education example on HIV/AIDS at a high school in Ankara

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Adolescence is a transition period between childhood and adulthood in which physical, sexual and psychosocial changes occur. Sexually Transmitted Infections (STI) are the most common reproductive health problems adolescents face. Peer education is a very useful method in adolescents' education, especially on risk factors and risk taking behaviors. This peer education intervention study, including two base line studies (one before and one after the intervention), was conducted in four classes of an Anatolian high school in Ankara in 2000. The aim of the study was to evaluate the success of the peer education model. There was a significant difference in the general scores of the students before (29.52; SD=4.38) and after (31.89; SD=4.96) education by peer educators (p=0.000). This study might have assisted the study population in establishing safe sex practices for a healthy sexual future.

Key words: HIV/AIDS, peer education, adolescent, Turkey.

Adolescence is a transition period between childhood and adulthood in which physical, sexual and psychosocial changes occur. Generally in developing countries, adolescents' knowledge about sexuality and methods of preventing sexually transmitted infections (STIs) is not sufficient. Therefore, young people are at high risk of STIs in the event of unsafe sex[1-3].

Sexually transmitted infections are the most common reproductive health problems adolescents face. One in every 20 teens has one STI every year, most of which remain undiagnosed, causing chronic and serious complications, whereas HIV/AIDS can have life-threatening results[4].

In Turkey, age of sexual initiation tended to be earlier, similar to in that seen other countries of the world. According to some of the studies carried out in Turkey, the age of sexual initiation was found to be around 18-20 years, and only the half of these teens was reported as using a contraceptive method[5,6]. The source of sexual information has been shown to be newspapers, magazines, books, family and friends, although the content and quality of this information was not clarified[7,8]. There has not been a purposeful, sufficient and systematic sexual education program for adolescents, who comprise one fourth of the population.

Peer education is a very useful method in adolescent education, especially on risk factors and risk taking behaviors. The previous studies which aimed to determine the knowledge of high school students on HIV/AIDS and to evaluate the success of the peer education program, nevertheless contained limited information on HIV/AIDS[9-15].

Material and Methods

The study was conducted at an Anatolian high school with 1,910 students in 24 classes in 2000. The study population consisted of eight classes and 369 second year students.

The base line study, which aimed to evaluate the knowledge of the students about HIV/AIDS, especially means of infection and of prevention, was conducted in December 2000. The questionnaire also aimed to asses students' responses by using a HIV/AIDS case. Two students, one male and one female, were selected as peer educators from each class.

An education program was scheduled every week and included the following discussion subjects: male and female anatomy-physiology of the reproductive system; types of STIs; etiopathology, progress and treatment of HIV/AIDS; preventive precautions against sexually

transmitted diseases and HIV/AIDS; family planning methods; and communication skills. The researchers gave the prepared texts to the peer educators one week before the discussion.

One male and one female researcher trained peer educators through lectures and by moderating discussions together. After a basic training of 10 weeks, the peer educators discussed and organized their activities. They prepared several posters about the situation of HIV/AIDS in the world, the symptoms of AIDS, means of infection and of prevention of the disease, and the feelings of the patients with AIDS, etc. These posters were placed on billboards in the school corridors.

Every peer educator voluntarily prepared at least one poster on HIV/AIDS and they changed the posters every week. The peer educators gave some short presentations on HIV/AIDS in the classrooms and they had small group discussions on HIV/AIDS with their classmates.

After the peer educators' activities, the second base line study was carried out. The questionnaire used in this study was the same as the one used in the previous study. Four of the eight classes were chosen as samples. The same students participated both in the first and the second base line studies. The maximum knowledge score that a student could receive was 35. The statistical test for paired groups was used in analysis.

There were 148 students interviewed in the first and second base line studies (total 296).

The distribution of the students by class, sex and age is shown in Table I. Of the 148 students, 54.1% were female and 45.9% male. The median age was 16 years (83.8% were 16 years old).

Table I. Students by Age, Sex and Class (June, 2001)

	Number	%
Classes		
Science A	27	18.2
Science E	43	29.1
Math B	41	27.7
Math C	37	25.0
Sex		
Female	80	54.1
Male	68	45.9
Age		
15	17	11.5
16	124	83.8
17	7	4.7
Total	148	100.0

The mean score of the students on HIV/AIDS (31.89±4.96) in the second base line study was higher than their mean score in the first base line study (29.52±4.38), and there was a statistical difference between the two studies. A statistical difference was found both between sexes and between classes (Table II).

Table II. Students' Scores on HIV/AIDS Before and After Peer Education (December 2000-June 2001)

Parameters	Scores of knowledge		P*
	First base line study	Second base line study	
Total score	29.52 (SD=4.38)	31.89 (SD=4.96)	0.000
Sex			
Female	29.78 (SD=4.30)	31.72 (SD=4.99)	0.002
Male	29.21 (SD=4.47)	32.07 (SD=4.96)	0.000
Classes			
Science A	29.88 (SD=4.55)	32.34 (SD=4.51)	0.020
Science E	29.73 (SD=4.37)	31.53 (SD=4.59)	0.020
Math B	30.41 (SD=3.73)	32.91 (SD=4.31)	0.000
Math C	28.18 (SD=4.73)	30.97 (SD=6.10)	0.000
Poster			
Read	29.48 (SD=4.48)	31.88 (SD=5.84)	0.000
Did not read	29.96 (SD=4.03)	32.15 (SD=4.10)	0.000
Short class presentation			
Yes	29.66 (SD=4.46)	31.84 (SD=5.62)	0.000
No	29.66 (SD=4.11)	32.06 (SD=4.46)	0.000
Small group discussion			
Yes	30.02 (SD=4.01)	32.20 (SD=5.38)	0.000
No	28.75 (SD=4.58)	31.34 (SD=4.32	0.000
Self assessment of the students about their knowledge on AIDS			
Good	30.34 (SD=3.37)	33.72 (SD=3.52)	0.000
Mediocre	30.29 (SD=3.79)	32.64 (SD=4.18)	0.000
Inefficient	26.71 (SD=5.42)	27.92 (SD=6.12)	0.300

* The statistical test for paired groups was used for analysis (n=140).

The peer educators actively conveyed their knowledge about various issues regarding HIV/AIDS such as characteristics, route of transmission and preventive methods of the diseases by presenting posters on the billboard in the school, giving lectures in their classrooms, and through discussions among their peer group. Table III summarizes the means by which students received information. Only 37.8% of the students stated that they had read the posters prepared by the peer educators whereas the others said that they had never seen any poster at the school. More than half of the students (58.1%) participated in small group discussion.

Table III. Means by Which Information on HIV/AIDS was Conveyed According to the Students (June, 2001)

	Number (n=148)	%
Read the posters	56	37.8
Contributed to the small group discussion	86	58.1
Listened to the short class presentations	40	27.0

The topics of the billboards and small group discussions as recalled by the students are given in Table IV. Among the students who read the posters, 75.0% mentioned that they had read the characteristics of AIDS and 87.5% recalled reading about the means of transmission. Students participating in small group discussions on HIV/AIDS with the peer educators accounted for 58.1% of the study group. The topics found more interesting were means of (80.3%) and prevention methods (62.8%). Twenty-seven percent of the students mentioned that they had listened to the short class presentations given by peer educators. 80.3% of them indicated that the topic was on means of transmission, and 62.8% of the students underlined prevention methods; 24.0% expressed means of transmission as the most interesting topic.

It is noteworthy that the percentage of family members, friends and magazines mentioned as a source of information on HIV/AIDS declined after the intervention, while the frequency of teacher and school sessions increased (Table V). In addition, 41.1% of the participants mentioned the AIDS club, 20.3% mentioned the girl peer educator and 21.9% mentioned the boy peer educator in their class.

Table IV. Topics of the Billboards and Small Group Discussions as Recalled by the Students (June, 2001)

Billboards	(n=56)
Characteristics of HIV	57.1
Characteristics of AIDS	75.0
Means of transmission of AIDS	87.5
Preventive measures against AIDS	87.5
Behavior and attitudes against AIDS patients	53.6
Small Group Discussions	**(n=86)**
Characteristics of HIV	19.7
Characteristics of AIDS	52.3
Means of transmission of AIDS	80.3
Preventive measures against AIDS	62.8
Behavior and attitudes against AIDS patients	37.2

Table V. Sources of Information on HIV/AIDS (December 2000-June, 2001)

Source of information	First Base Line study (n=140)* %	Second Base Line study (n=148) %
Mother-Father	37.1	39.1
Sister	5.0	5.7
Brother	5.1	5.7
Radio, TV	88.5	70.3
Newspaper-magazine	86.4	80.7
Book	41.4	38.0
Computer-Internet	31.5	31.4
School classes	25.0	45.3
Teacher	8.2	27.6
Health personnel	17.1	27.6
Girlfriend	18.5	21.4
Boyfriend	18.3	21.4
The AIDS club of the school	—	41.1
Girl peer educator in the class	—	20.3
Boy peer educator in the class	—	21.9

* Some students did not answer this question.

Discussion

Today, there are nearly 35 million HIV/AIDS cases in the world. By now 18.8 million people around the world have died of AIDS and 3.8 million of these were children. In 1999, alone, 5.4 million people were infected with HIV. It is estimated that there are 420,000 AIDS cases in Eastern Europe and Middle Asia, and 220,000 cases in the Middle East and North Africa[16]. Worldwide, the HIV epidemic is spreading at a rate of over 6,000 new infections per day. Data show a steady rise in HIV rates among those 13 to 19 years of age. Approximately three

million teenagers contract a sexually transmitted disease (STD) each year, and teens account for one quarter of the 12 million STD cases estimated annually. Roughly 25% of sexually active adolescents become infected with an STD every year[17].

In Turkey, there have been 1,325 cases reported to the Ministry of Health since the first case in 1985. The numbers of HIV/AIDS cases have been continuously increasing, and the epidemiology of HIV/AIDS changing. The percentage of young people with HIV has increased in the last 10 years[18]. Also, there is some evidence from recent studies that the age at first sexual intercourse is decreasing. According to the local studies, the age of sexual initiation is around 18-20 years, and only half of the teens in Turkey reported that they had used a contraceptive method[5,7,19]. According to the Turkish Demographic and Health Survey, almost one-third of husbands aged 25-29 had begun to have intercourse by the age of 18. It is obvious that there is an increase in the frequency of sexually active people among youth compared to their older cohorts[20].

In most of the previous studies, it was emphasized that high school and university students have limited knowledge about HIV/AIDS and STDs[21-26]. The source of sexual information has been mentioned as newspapers, magazines, books, family and friends, although the content and quality of this information was not clarified[7,8]. In Turkey, there has not been a purposeful, sufficient and systematic sexual education program for adolescents, who comprise one fourth of the population. Therefore, improvement in their correct knowledge and development of safe sex practices against STDs and AIDS through intervention studies are required.

The peer education model is not a new approach. It has been applied toward various topics for years. Recently, it has been used for protecting adolescents from STIs, especially HIV/AIDS. Furthermore, it has been used to inform high school and university students on some important health topics, including sexual health, by NGOs in Turkey[27].

In this study, peer group education was used to improve the knowledge of high school students about HIV/AIDS. The results were successful and encouraging. Most of the students who thought that their level of knowledge was insufficient received higher scores after the peer education intervention.

Peer education has been used widely and very effectively in the developed countries; the results of the studies show that the peer education model is successful, and peers enjoy learning from each other in school-based studies[9-15]. Also, the peer educators were found to be more successful than adult trainers in some studies.

All peer educators prepared billboards; some organized short class presentations and some had conversations with their friends about HIV/AIDS. They stated that their friends were eager to learn about HIV/AIDS. The most interesting topic was mentioned as means of prevention. Although family planning methods were not included in the curriculum of the intervention program, the students expected to hear more about "safe sex". In the routine curriculum of high school students in the first grade, there is only one session regarding health topics so important during their lives. This session should be expanded to cover the areas where the students have insufficient information.

The scores of the students who read the billboards about HIV/AIDS versus those who did not were found significantly different. Similar findings were valid for the groups who participated in the other activities compared to the ones who did not. The number of the students who did not participate in any type of activity was 25. There was also a statistically significant difference between the scores of these students in the two base line studies. There might have been an information bias where in students did not give correct information about their activities. It can be assumed that there were discussions on these subjects between the students. Mere physical presence at school was sufficient for a student to obtain information on HIV/AIDS.

Although students declared television, radio and magazines as the sources of information in both of the studies, AIDS club, teachers and discussion sessions were more emphasized as the source in the second study. Nevertheless, as there was no official lecture about HIV/AIDS in the second year high school program, this intervention most likely raised students and teachers' attention to HIV/AIDS. In the education system the teachers are not only

lecturers on specific topics but they may be also a guide or a counselor for the students on various issues. This study demonstrated that teachers could play a role as a resource for students in establishing healthy life styles, such as prevention from acquiring STI/HIV.

Lack of a control group is a limitation for this study. We had no control group for ethical reasons. The intervention in this study was planned to improve adolescent students' sexual health status. During the intervention period, there was no other special program on this issue except the peer education program. It was not ethical to not inform a subject of the students on HIV/AIDS, as the information might protect them from the disease. The results seem to confirm that the peer education program caused the statistical difference between the scores of the students in first and second base line studies.

Another and probably more important limitation of the study was the absence of information about the sexual practice of the participants. However, high school students in metropolitan areas may have sexual intercourse before 17 years, as mentioned in some local studies. The most important objective of the peer education is to encourage and establish correct behavior, using condoms during sexual intercourse. It is very important to support safe sex practices among young people to have a healthy generation in the future. The results of numerous peer education studies have stated that peer education was also successful in changing teens' behaviors safely[28-30].

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Tumors of the maxillofacial region in children: retrospective analysis and long-term follow-up outcomes of 90 patients

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SUMMARY: Tanrıkulu R, Erol B, Haspolat K. Tumors of the maxillofacial region in children: retrospective analysis and long-term follow-up outcomes of 90 patients. Turk J Pediatr 2004; 46: 60-66.

The aim of this study was to carry out a retrospective analysis of maxillofacial tumors in children and to present the lnog-term follow-up results.

Our study was performed with a retrospective analysis of 90 patients under the age of 15 years with maxillofacial tumor treated in our clinic between 1985-2002. In addition, treatment modalities and long-term follow-up results of these patients were evaluated.

According to our results, it was established that maxillofacial tumors were mostly observed in the 11-15 age group (39 cases, 43.3%) and on the mandible (48 cases, 53.3%). There were 21 (23.3%) odontogenic, 63 (70%) benign non-odontogenic and 6 (6.7%) malignant non-odontogenic. Mixed tumors were the most common type of the odontogenic tumors, and mesenchymal tumors were the most common non-odontogenic tumors.

Surgical excision, curettage or en bloc resection were adequate for treatment of these tumors.

Key words: tumor, maxillofacial, child.

A tumor is defined, in brief, as abnormal growth of tissue, and tumoral formations are classified under two main headings, benign and malignant.

A number of retrospective studies have been done on tumors of the maxillofacial region[1-5]. While pediatric tumors are far from uncommon, few studies on these have included retrospective analysis, demographic distribution, histopathologic spectrum, and treatment and follow-up outcomes[6-8].

The aim of the present study was to investigate the distribution of pediatric odontogenic and non-odontogenic tumors of the maxillofacial region according to age, sex, biological behavior, histopathologic spectrum, and location, as well as to evaluate treatment modalities and long-term follow-up outcomes.

Material and Methods

The present study was carried out on 90 patients who attended our clinic between 1985 and 2002 who were 15 years old or younger at the first visit, had healthy medical files, were radiographically and clinically diagnosed with odontogenic or non-odontogenic tumors, and were given appropriate treatment.

Seventy-five cases of pyogenic and peripheral giant-cell granuloma determined in our survey of medical records were excluded since they fell under the classification of reactive hyperplasia; only neoplastic formations were evaluated.

Tumoral formations were grouped under three main headings: odontogenic, benign non-odontogenic, and malignant non-odontogenic. Distributions according to age and sex, as well as histopathologic spectrum and location, were determined. In addition, distribution according to location was investigated for the subgroups of odontogenic and non-odontogenic tumors (epithelial, mesenchymal and mixed, fibrous lesions, vascular neoplasms, and neurological tumors).

Finally, the treatment modalities and long-term follow-up outcomes were assessed.

Results

Ninety children attending our clinic between 1985 and 2002 at ages ranging from 0 to 15 years with tumoral masses located in the maxillofacial region were included.

Age distribution was as follows: 15.6% (14 patients) were 0-5 years old, 41.1% (37 patients) were 6-10, and 43.3% (39 patients) were 11-15 (Table I). There was no noteworthy discrepancy in sex distribution, with the numbers of female and male patients being similar (43 girls, 47 boys) (Table I).

Of the 90 tumoral masses, 21 (23.3%) were odontogenic, 63 (70%) were benign non-odontogenic, and 6 (6.7%) were malignant non-odontogenic (Table I).

With regard to distribution according to tumoral mass location, the mandible was most frequently affected (48 patients, 53.3%), followed by the maxilla (27 patients, 30%) (Table II).

The location and frequency of the 21 odontogenic tumors indicated that the most frequent tumor type was mixed (12 patients, 13.3%) (Table III).

Our assessment of non-odontogenic tumors based on biological behavior, histopathologic spectrum, and location showed that slightly more than half of the tumors in this group (49 patients, 54.4%) were of mesenchymal origin, and that the majority of these were giant-cell neoplasms (36 patients) (Table IV).

Table I. Distribution of Tumors According to Age, Sex, Biologic Behavior and Tissue Origin

Age	Female	Male	Total	%	Tumor	Number	%
0-5	6	8	14	15.6	Odontogenic	21	23.3
6-10	17	20	37	41.1	Benign non-odontogenic	63	70
11-15	20	19	39	43.3	Malignant non-odontogenic	6	6.7
Total	43	47	90	100	Total	90	100

Table II. Distribution of Tumors According to Location

Location	Number	%
Mandible	48	53.3
Maxilla	27	30
Oral Mucosa	7	7.8
Tongue	2	2.2
Submandibular Area	2	2.2
Mandible+Maxilla	4	4.4
Total	90	99.9

Table III. Distribution of Odontogenic Tumors According to Location

			Location		
		Tumor	Mandibula	Maxilla	Total
Epithelial	2 2.2%	Ameloblastoma	–	2	2
Mesenchymal	7 7.8%	Odontogenic Fibroma	1	2	3
		Cementifying fibroma	3	1	4
Mixed	12 13.3%	Odontoma	5	3	8
		Ameloblastic Fibroma	4	–	4
	23.3	Total	13	8	21

Table IV. Distribution of Non-Odontogenic Tumors According to Biological Behavior and Location

		Tumor	Location						
		Benign	Mandible	Maxilla	Oral Mucosa	Tongue	Sub-mandibular	Disseminated	Total
Epithelial	5 5.6%	Verruca vulgaris	–	–	4	1	–	–	5
Mesenchymal	49 54.44%	Fibromatosis	–	1	–	–	2	–	3
		Fibroma	4	1	1	–	–	–	6
		CGCG	21	8	–	–	–	–	29
		GCT	2	5	–	–	–	–	7
		Osteoma	2	–	–	–	–	–	2
		Congenital epulis	1	1	–	–	–	–	2
Fibrous Osseous	4 4.4%	Ossifying fibroma	1	–	–	–	–	–	1
		Fibrous dysplasia	1	1	–	–	–	–	2
		Cherubism	–	–	–	–	–	1	1
Vascular	3 3.3%	Hemangioma	1	–	1	–	–	–	1
		Lymphangioma	–	–	–	1	–	–	1
Neurological	1.1%	NT	–	1	–	–	–	–	1
	Malignant								
R.E.S.	3 3.3%	Burkitt's lymphoma	1	–	–	–	–	2	3
Mesenchymal	3 3.3%	ERMS	–	–	–	–	–	1	1
		Round-cell sarcoma	–	2	–	–	–	–	2
	76.6%	Total	34	20	6	2	2	4	69

CGCG : Central giant-cell granuloma.
GCT : Giant-cell tumor.
NT : Neuroectodermal tumor.
ERMS : Embryonal rhabdomyosarcoma.
R.E.S. : Reticuloendothelial system.

The malignant non-odontogenic tumors in this study were determined to be Burkitt's lymphoma (3 patients), round-cell sarcoma (2 patients), and embryonal rhabdomyosarcoma (Table IV).

Treatment Modalities and Follow-up Outcomes

The majority of the 90 children with tumoral masses were treated with surgical excision, en bloc resection, and curettage. Some patients, however, received treatment specific to criteria such as the clinical behavior and extent of the lesion.

In one of the 36 patients with giant-cell lesions, involvement of the entire left mandible was observed, and, after hemimandibulectomy, the mandible was reconstructed with iliac bone graft, costochondral graft, and reconstruction plate; there was no recurrence on two-year follow-up (Figs. 1a-1b, 2). In five patients, giant-cell lesions (in the mandible in 2 and the maxilla in 3) exhibited aggressive behavior, causing destruction to the cortical bone, and were large enough to cause facial deformities; these patients were treated with surgical curettage and en block resection (Figs. 3a-3b, 4). Follow-up periods ranged from three months to 16 years. No recurrence was observed in any of the patients with giant-cell lesions, including the 16-year-old. The other giant-cell lesions were small and, after curettage under local anesthesia, follow-up was recommended, but none of these patients' follow-up periods exceeded one year.

One of the two patients with fibrous dysplasia, classified as a fibrous lesion, refused treatment, while the other, a 12-year-old girl, underwent staged surgery in three different periods: excision, en bloc resection, and osteoplastic contouring. She suffered no recurrence during 12-year follow-up. One patient (age 7) with cherubism, a fibrous lesion characterized by extensive involvement of the jaw and facial bones, has been under our supervision for approximately five years, and remission is expected during puberty.

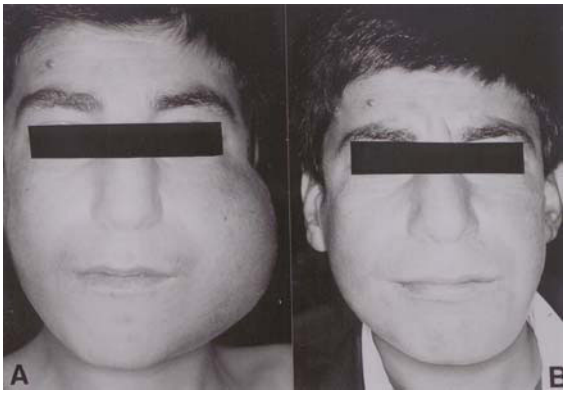

Fig. 1a-b. The patient with aggressive giant-cell lesion, preoperative and postoperative view.

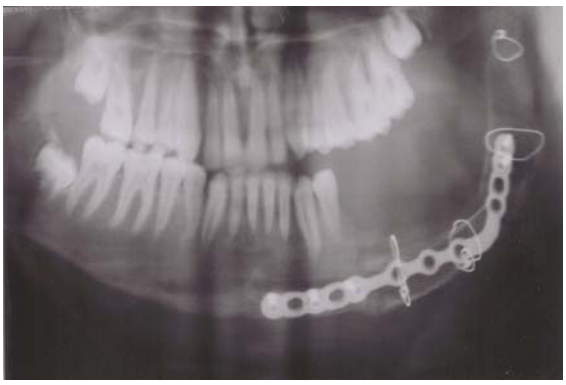

Fig. 2. Postoperative panoramic view of the same patient.

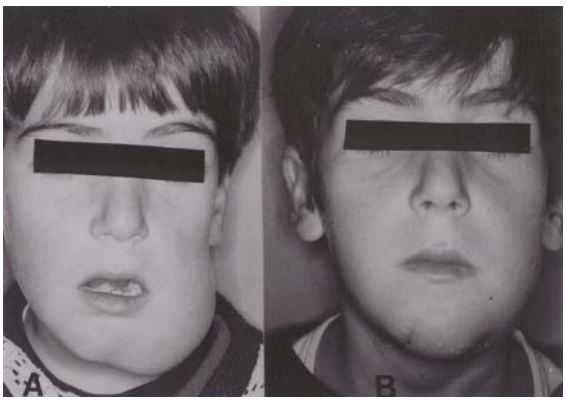

Fig. 3a-b. The aggressive giant-cell lesion on a seven-year-old girl. Preoperative and postoperative view.

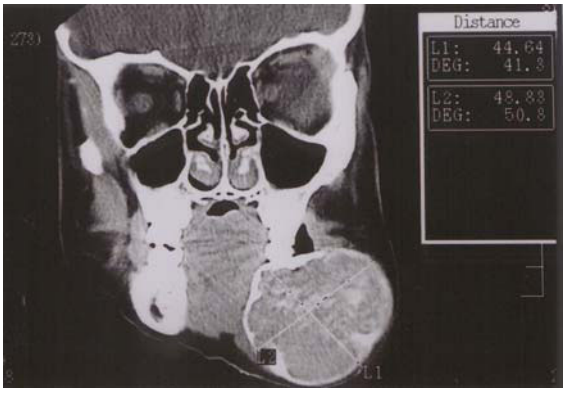

Fig. 4. Preoperative computerized tomography (CT) view.

Despite being categorized as benign tumors, ameloblastomas have a high rate of recurrence, and there is a risk of malignant transformation. One of the two patients with ameloblastoma underwent surgery approximately seven years ago, and thus far has not experienced recurrence. The other patient did not attend postoperative follow-up and examinations. Ameloblastic fibroma, a tumor of odontogenic origin, was determined in four patients (Table III). Two of these lesions were observed to have caused widespread destruction, affecting almost the entire hemi-mandible, and local exicision and curettage were performed. There was no recurrence during a mean follow-up period of seven years, and, with new bone formation in the region, the mandibular bone was reshaped in both patients.

The six-month-old patient with a neuroectodermal tumor underwent tumor excision, and recidivation was not observed during four years of follow-up. This patient's follow-up and supervision are still in progress.

Appropriate chemotherapy or radiotherapy were recommended in the oncology centers for three patients with Burkitt's lymphoma, a malignant non-odontogenic tumor, for one patient with embryonal rhabdomyosarcoma, and for one patient with round-cell sarcoma. While remission after chemotherapy was observed in one patient with Burkitt's lymphoma, the other four of the six malignant cases were not followed up. Another patient with round-cell sarcoma underwent surgery in our clinic approximately seven years ago, and is currently in good health.

Discussion

The majority of tumors of the mouth and jaw in children are benign[7,9]. Tanaka et al.[7] reported that only 3% of their cases were malignant in nature. In another study, benign tumors composed 93% of cases[9]. The present study, in parallel with the above-mentioned studies, showed a significant proportion (93.3%) of cases to be benign, with only six out of 90 (6.7%) being malignant. The reason for this ratio being less may be related to the smaller number of malignant tumors cases who applied to our clinic.

In contrast, studies performed in Nigeria have yielded malignancy rates of 40% or more[8,10]. Of Arotiba et al.'s malignant tumors[8] 22.4% were Burkitt's lymphoma, as were 44.8% of Asamoa's[10]. A high-grade non-Hodgkin's lymphoma, this tumor was first described in 1958 by Dennis Burkitt[11]. It is a prevalent neoplasm in children, and is endemic in Africa, although there is also a non-endemic form (North American Burkitt's lymphoma)[11]. The high incidence of malignant tumors in these studies may be accounted for by the endemism in Africa.

Tanaka et al.[7] reported that pediatric tumors occur most frequently in the 6-11-year age group (43.8%), followed by the 12-15-year group (31.4%). In a 102-patient series, they reported that 28 of 33 odontogenic tumors were in the 6-11 group, attributing this to the fact that crown formation of the permanent teeth is usually completed at 4-5 years of age[7].

A number of other researchers have reported higher incidences of tumor in the 11-15 age group[8,12]. The incidences for girls and for boys are reported to be approximately equal[7,8]. In the present study, in agreement with the literature, maxillofacial tumors occurred most frequently at 11-15 years of age (43.3%), while the rates for girls and for boys were similar.

In various studies on tumors, the mandible is reported to be the most frequently affected area[7,8]. In the present study, 53.3% of cases had mandibular involvement.

The great majority of pediatric jaw tumors are non-odontogenic[6,8,13,14]. Choung and Kaban[6] reported one ameloblastoma and odontomas of small diameter, as opposed to 47 non-odontogenic tumors. In a 46-patient series assessing benign jaw tumors, Dehner[13] found only four odontogenic tumors. In our series, non-odontogenic tumors accounted for 76.7% of tumoral formations, a considerable proportion.

Of all odontogenic tumors, ameloblastomas are the most controversial in terms of treatment[11,15]. Treatments range from surgical curettage to bloc excision or resection[11]. In planning treatment for pediatric tumors, authors stress the importance of the growth development of the jaw, and of esthetics and functional concerns in later periods of life[16,17]. In line with this view, with a single exception, we avoided radical resection in the treatment of all tumors, whether they were ameloblastomas or other benign odontogenic or non-odontogenic tumors. In addition, it has been reported that pediatric ameloblastomas are generally unicystic and do not extend beyond the cystic wall of the tumor cell[16]. In the present study,

there was no recurrence in the case of the cystic ameloblastoma that was located in the maxilla and exhibited growth into the sinus, which we were able to follow-up in the long-term.

Of benign non-odontogenic tumors in our series, tumors of mesenchymal origin were the most common (49 cases). This is in agreement with the literature data[6,8].

Of tumors mesenchymal in origin, giant-cell lesions had the highest incidence (36 cases). Choung and Kaban[6] reported that, a in their series, giant-cell lesions were the most common tumors of mesenchymal origin. Clear histopathologic distinction is not possible between central giant-cell granuloma and giant-cell bone tumor, both giant-cell lesions[6]. The histopathologic criteria to be considered in the diagnosis of real giant-cell tumors have been described, but the distinction between these two lesions cannot be made by histopathologic findings alone[6]. Therefore, in the diagnosis of cases we reported as giant-cell bone tumor and central giant-cell granuloma, in addition to histopathologic evaluation, intraoperative evaluation and he tumors's macroscopic appearance were important diagnostic criteria. The fact that the preliminary diagnoses we made based on our surgical experience were confirmed histopathologically suggests to us that, in giant-cell tumors, a specimen's microscopic appearance is more hemorrhagic, fragile, and liver-tissue-like in appearance than in central giant-cell granulomas, and that in central giant-cell granulomas, a tumoral tissue of solid, fibrous structure is dominant in the periphery of the surgical specimen; hence the curettage and enucleation of central giant-cell granulomas are easier. As a result of this observation, the following factors were determined to be criteria that must be considered in intraoperative evaluation and in the tumor's macroscopic appearance: the fragility, color, and consistency of the tumor tissue; whether or not it is hemorrhagic; and the ease of curettage and enucleation. Furthermore, the literature indicates that giant-cell lesions of the jaw may exhibit a variety of behaviors, and that central giant-cell granulomas may have as much changeability as aggressive lesions or malignant giant-cell tumors[6,18]. In giant-cell bone tumors in particular, recurrence is more expected due to aggressive clinical characteristics, and treatment consists of a range of surgical methods, from surgical curettage to hemimandibulectomy and reconstruction with bone graft[6]. There was no recurrence in any of our seven patients with giant-cell bone tumors. There was also no recurrence requiring a second operation in the six patients with giant-cell granuloma, which exhibited aggressive behavior and caused widespread bone resorptions and cortical perforations in places. One of these patients was treated with hemimandibulectomy, and the others with enucleation and curettage. Erol and Özer[19] reported that a central giant-cell granuloma in a six-year-old patient had caused widespread bone destruction in the corpus and ramus and that, after surgical curettage, there was no recurrence during long-term follow-up.

Another pathology that is histopathologically indistinguishable from giant-cell lesions is cherubism[6,11], a hereditary disease exhibiting autosomal dominant transfer[11]. It generally begins before the age of two, and spontaneous regression is expected after puberty. Choung and Kaban[6] followed up two cherubism patients, ages two and four, for 38 and 41 months, respectively, and determined minimal change. Our patient who attended our clinic at age seven and was diagnosed with cherubism has been followed up for approximately five years, and regression in puberty is expected.

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Effect of topiramate on enlargement of head in Canavan disease: a new option for treatment of megalencephaly

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Canavan disease (CD) is a rare autosomal recessive genetic disorder characterized by early onset progressive spongy degeneration of the brain involving the axon's myelin sheath. Patients with CD have leukoencephalopathy and megalencephaly; clinically they show a variable course ranging from slow neurodegenerative course to no neurological development or rapid regression. Current treatment is symptomatic including management of seizures and spasticity. Topiramate (TPM) is a novel antiepileptic drug for treatment of a broad spectrum of seizure types in adults and children. We used TPM in two of our patients diagnosed with CD at six months of age. At seven months and 15 months' follow-up, respectively, each patient showed a decrease in head growth velocity. We suggest that TPM can be used in patients with CD and possibly in other childhood neurodegenerative diseases with leukoencephalopathy and megalencephaly. Further studies are required to reveal the underlying mechanisms that lead to decreased head growth velocity, and to conclude whether this ameliorates the clinical course of CD.

Key words: Canavan disease topiramate, megalencephaly, leukoencephalopathy.

Canavan disease (CD) is a rare autosomal recessive genetic disorder characterized by early onset progressive degeneration of the brain[1]. Mutations in aspartoacylase gene located on short arm of chromosome 17, resulting in loss of enzyme activity, lead to an excess of N-acetylaspartate (NAA)[2,3]. The diagnosis can be confirmed by elevated NAA in the urine, blood and spinal fluid, and in the brain by using magnetic resonance spectroscopy, in a child presenting with megalencephaly, developmental delay and neurodevelopmental deterioration[3,4]. Prenatal diagnosis and genetic counseling are possible by molecular analysis when the mutations are known, and by analysis of amniotic fluid for NAA using stable isotope dilution technique[5].

The management currently is symptomatic, such as treatment of seizures and spasticity. Gene therapy protocols are under development[4-6]. A number of drugs and other substances have been reported to be able to reversibly modify the NAA content of the vertebrate brain in vitro. Ethanol and alcohol dehydrogenase inhibitors have been shown to reduce NAA levels of brain in mice in vivo[7]; however, the role of these agents in the treatment of CD is not established.

Topiramate (TPM) is a new antiepileptic drug effective for treatment of a broad spectrum of seizure types in adults and children. In vivo and in vitro preclinical studies indicate that TPM has multiple mechanisms of action and suggest a broad spectrum of anticonvulsant activity[8]. Results of placebo-controlled trials using TPM as adjunctive therapy in children 16 years of age or younger indicate that the most commonly reported adverse events were somnolence, anorexia, fatigue, and nervousness. During the double-blind portion of the placebo-controlled studies involving children, the use of TPM did not result in any discontinuations due to an adverse event[8].

We used TPM for the treatment of seizures in two of our patients with Canavan disease, taking into consideration its broad antiepileptic

spectrum, safety profile in children, and neuroprotective effect, to see whether TPM would have an effect on enlargement of the head, control of seizures, and the clinical course of the disease.

Case Reports

Case 1

This 13-month-old girl was first evaluated in our clinic at the age of six months with the complaints of enlargement of the head, developmental delay, and decreased alertness. Parents were first cousins. The family had two healthy children, a 12-year-old boy and a 10-year-old girl. Two male sibs with similar complaints died at eight months and nine months of age. Parents refused further evaluation at that time. Physical examination of our patient at the age of six months revealed a head circumference of 48 cm (>95p). She was unresponsive to the environment, had no head control and was unable to follow objects. She had spasticity and brisk deep tendon reflexes; plantar responses were extensor bilaterally. Clinical diagnosis of CD was confirmed by laboratory evaluation including urinary organic acid profile with an excretion of NAA, 1680 mmol/mol creatinine (Normal: 0-15 mmol/mol creatinine), and cranial magnetic resonance imaging (MRI) demonstrating diffuse involvement of cerebral and cerebellar white matter with brainstem involvement. She started to experience subtle seizures around six months of age and was placed on TPM 2 mg/kg. Her head circumference was 48 cm (>95p) at the age of seven months and 48.7 cm (>95p) at the age of 13 months. Her head-growth curve is shown in Figure 1. After initiation of TPM, her head growth velocity decreased, and she had no clinical seizures. Follow-up visits revealed optic atrophy, and persistence of spasticity. Developmentally she showed no gains compared to initial evaluation. The amount of NAA excretion in urine remained high at 1840 mmol/mol creatinine.

Case 2

This was a 21-month-old boy who presented to our clinic at the age of six months with the complaints of global developmental delays, no head control and megalencephaly. He had myoclonic jerks during sleep and episodes of cyanosis lasting for a few seconds. Pregnancy and delivery were uneventful. He was the first child, and his parents were relatives; family history was otherwise negative. Physical examination revealed a head circumference of

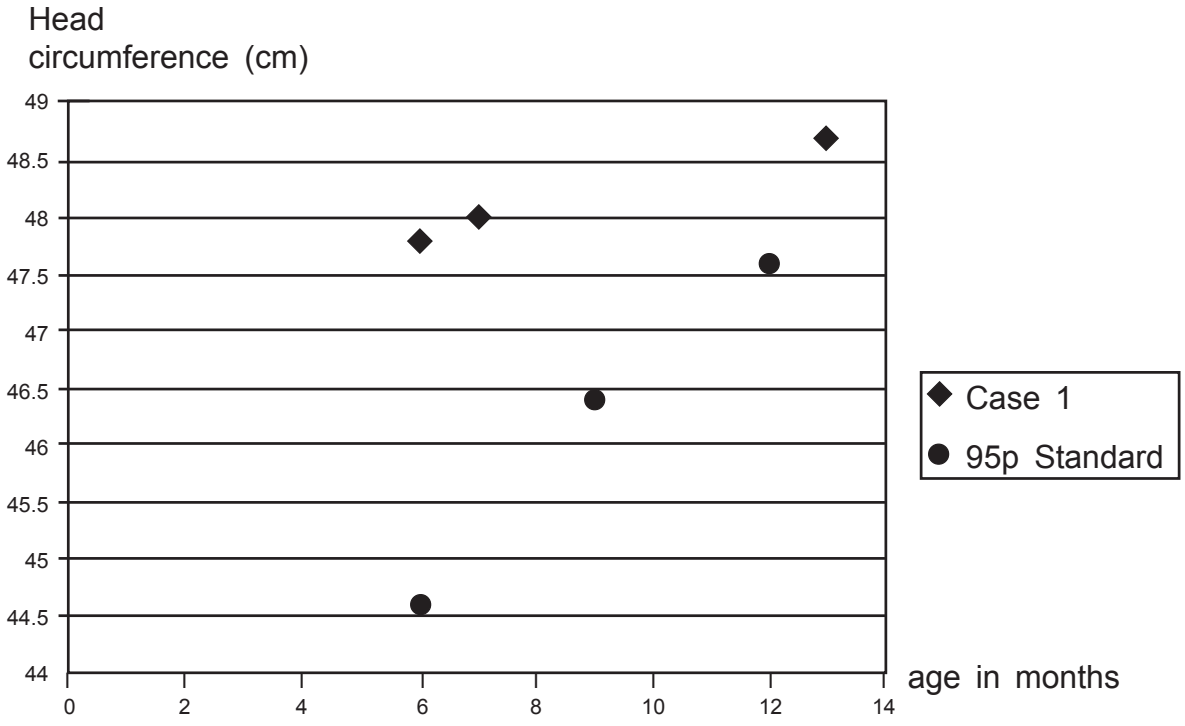

Fig. 1. Head circumference of case 1 compared to 95 p of standard.

47.5 cm (>95p), spasticity with increased deep tendon reflexes, and no head control. His urinary organic acid profile was consistent with CD. He was started on TPM 2 mg/kg at six months of age. Follow-up at 12 months and 21 months showed head circumference to be 50 cm (>95p), and 50.5 cm (>95p), respectively. His head-growth curve is shown in Figure 2. He began to recognize his mother at the age of 16 months; however, showed no further developmental gains. The amount of NAA excretion in urine was 2170 mmol/mol creatinine (N: 0-15). MRI of the head at the time of the diagnosis is shown in Figure 3.

Discussion

The pathogenesis of CD is characterized by degeneration of the axons' medullary sheaths, while the axons themselves remain intact. Further, there is elevated cerebrospinal fluid pressure, intramyelinic edema and a spongioform degeneration associated with swelling of astrocytes. These indicate a profound fluid inbalance in the brain. Deficiency of aspartoacylase, a lysosomal enzyme, results in accumulation of NAA, leading to NAA acidemia and NAA aciduria[9]. Currently there is no known function for NAA, and the treatment for CD is symptomatic including

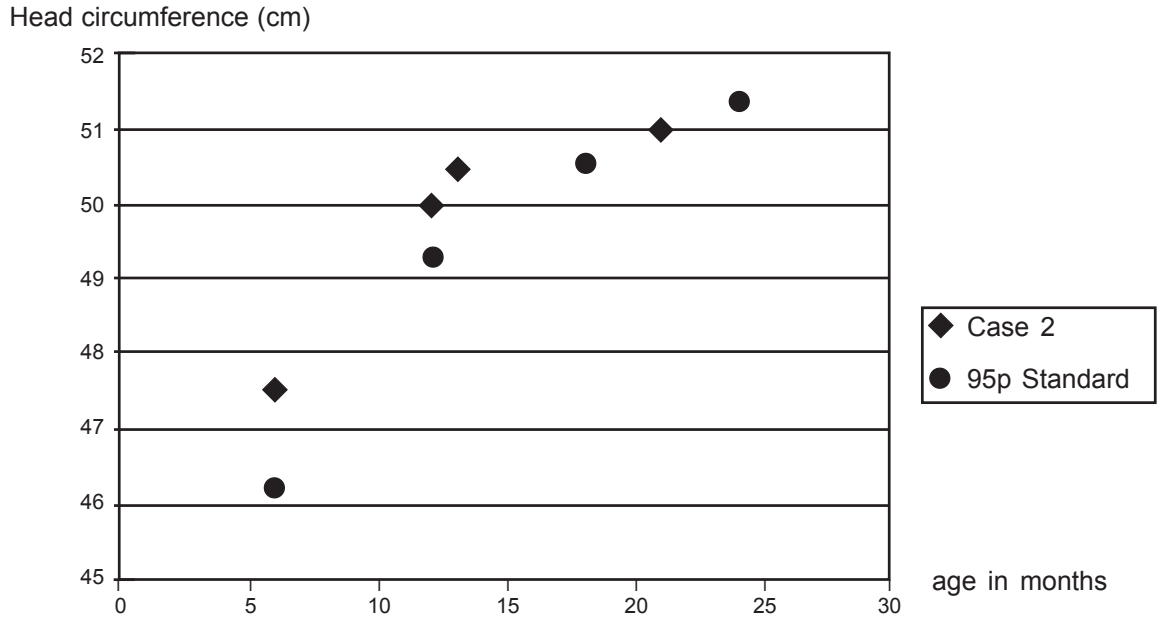

Fig. 2. Head circumference of case 2 compared to 95 p of standard.

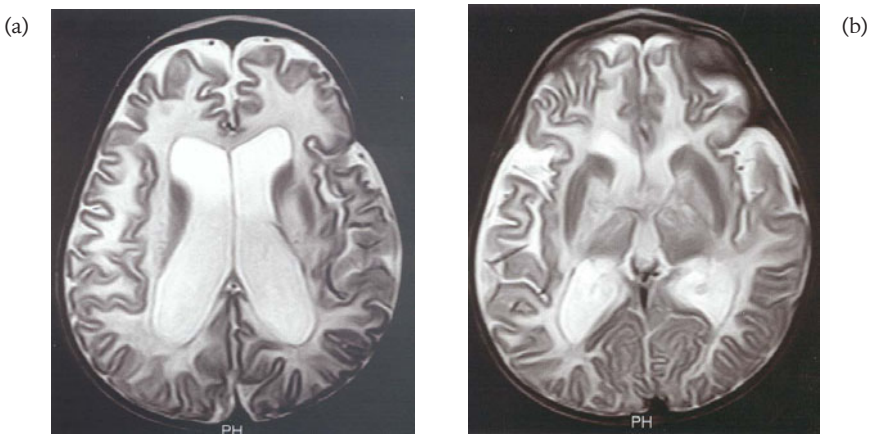

Fig. 3a-b. T2 weighted transverse images show enlargement of ventricles, involvement of cerebral white matter including u-fibers and globus pallidi. The thalami are also involved bilaterally.

management of seizures and spasticity. Baslow[10] attempted to explain the underlying pathophysiological mechanisms in CD and emphasized molecular water pumps. Baslow[10] proposed that in normal individuals the NAA-water that is liberated from the axon via an NAA-water co-transporter into the periaxonal water space between the axolemma and the surrounding oligodendrocyte or at the nodes is rapidly hydrolyzed by aspartoacylase on the myelin-containing membrane of the oligodendrocyte. After hydrolysis the aspartate and acetate can be actively taken up by astroglial processes that are present at the axon internodes and synapses, which may via additional astroglial processes also be connected to the blood system or the ventricular walls. In CD the observed absence of myelin-associated aspartoacylase on the juxtaposed glial-myelin membrane would result in the build-up of NAA-water in the space between the axon and the oligodendrocyte and increased hydrostatic pressure in that space. As NAA is not actively taken up by brain cells, the only pathway for NAA-water out of the axon-glial water space in CD is extracellular, between the axon-wrapped layers of the glial-myelin repeating lamellar membranes. It is proposed that in CD the continuous production and liberation of NAA-water from the axon would result in the intramyelinic edema that has been observed in this disease, the subsequent demyelination and loss of glial cells in the characteristic spaces, and in the spongy appearance of the white matter of the brain that is associated with advanced stages of CD.

In CD, macrocephaly is evident by six months, and at one year the head circumference is in the 90th percentile or above[11]. We observed that under treatment with TPM our patients showed a relative decline in head growth velocity, which we think could be due to decreased accumulation of water in the brain. Since our patients had persistent NAA acidemia while the head growth velocity decreased, we believe enlargement of the head ameliorated through a route that was not affected by the accumulation of NAA in the brain.

Preclinical studies indicate that TPM has at least four mechanisms of action that may contribute to its anticonvulsant activity[8]. These include the following: blockade of voltage-dependent NA+ channels, GABA potentiation through a novel or nonbenzodiazepine modulatory site, antagonism of a kainate subtype of the glutamate receptor, and inhibition of carbonic anhydrase. We believe the arrest of head growth velocity in our patients could have been due to TPM's effect on water transport in the brain. A trial with acetazolamide to reduce white matter concentration and NAA was tried for a period of five months. Acetazolamide was helpful in reducing the intracranial pressure, but did not reduce water concentration or NAA levels[12]. Therefore we think that the effect of TPM on water accumulation and head growth velocity may not be solely due to inhibition of carbonic anhydrase. We plan to obtain cerebral MRI and MR spectroscopy under treatment with TPM, to see if there are visible changes.

Long-term follow-up of patients is necessary to conclude whether arrested head growth will ameloriate the clinical course of the disease. NAA itself was shown to be neurotoxic[13], therefore one might conclude that preventing or decreasing water accumulation in the brain per se may not ameloriate all consequences of the disease. We suggest that studies on histological specimens and animal models of CD on the effect of TPM may be helpful not only for new treatment options for CD but also for other types of degenerative neurological disorders with leukoencephalopathy and megalencephaly.

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A newborn infant with generalized glutathione synthetase deficiency

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SUMMARY: Yapıcıoğlu H, Satar M, Tutak E, Narlı N, Topaloğlu AK. A newborn infant with generalized glutathione synthetase deficiency. Turk J Pediatr 2004; 46: 72-75.

Pyroglutamic aciduria (5-oxoprolinuria) is a rare autosomal recessive disorder caused by either glutathione synthetase deficiency (GSSD) or 5-oxoprolinase deficiency. The severe form of the disease, generalized GSSD, is characterized by acute metabolic acidosis, usually present in the neonatal period with hemolytic anemia and progressive encephalopathy.

We report a female infant who had a severe metabolic acidosis with high anion gap, hemolytic anemia, and hyperbilirubinemia. High level of 5-oxoproline was detected in her urine and a diagnosis of generalized GSSD was made. She died of severe metabolic acidosis and sepsis at the age of six weeks.

Key words: glutathione synthetase deficiency, newborn.

Pyroglutamic aciduria (5-oxoprolinuria) is a rare autosomal recessive disorder caused by either glutathione synthetase deficiency (GSSD) or 5-oxoprolinase deficiency. 5-oxoprolinase deficient patients have normal acid-base status and do not have hemolytic anemia[1].

Glutathione synthetase deficiency has two clinical forms: generalized and erythrocyte GSSD. The former is severe with clinical features of severe metabolic acidosis, hemolytic anemia, hyperbilirubinemia, neurologic disabilities and sepsis[1,2]. It has been described in 40 patients from 35 families[2]. Here we report a newborn infant with generalized GSSD.

Case Report

The baby was admitted to our newborn intensive care unit for evaluating metabolic disease when she was four days old. She was born after a term pregnancy to a healthy mother, G3P1. Her parents were second-degree cousins. They had one healthy son; the second child had died at 17 days due to sepsis and metabolic acidosis.

Our case was normal at birth and was fed mother's milk. On the 3rd day of life she became tachypneic. A severe metabolic acidosis was detected and she was referred to our hospital. On admission her weight was 2720 g (10-25 p), length 49 cm (50 p), and head circumference 35 cm (75-90 p). Vital signs were as follows: temperature: 36.4°C, heart rate: 137/min, respiratory rate: 68/min and blood pressure: 80/36 mm Hg. She was lethargic and tachypneic. The remainder of the physical examination was unremarkable. She had a severe metabolic acidosis (pH: 6.9, base excess –25 mmol/L, anionic gap 32) without lactic acidosis (lactic acid: 27 mg/dl) or ketoacidosis. Urine and blood metabolic screening, plasma amino acid chromatography, renal function tests and eye examination were normal. She had a hemolytic anemia with progressive direct hyperbilirubinemia (17.8/8.2 g/dl). She required several packed blood transfusions. Glucose-6-phosphate dehydrogenase (G6PD) activity was within normal limits. The urine gas chromatography/mass spectrometry showed massive excretion of pyroglutamic acid. The laboratory findings of the patient are given in Table I. She was treated with intravenous sodium bicarbonate solution to overcome her metabolic acidosis. Nevertheless, she maintained a variable degree of metabolic acidosis. During the second week of hospitalization she developed sepsis and died when she was 41 days old. Parents did not give permission for autopsy.

Table I. Laboratory Findings of the Patient with Generalized Glutathione Synthetase Deficiency

Blood gases	pH: 6.9, PCO_2: 43 mmHg, PO_2: 78 mmHg, base excess -25 mmol/L, HCO_3: 3 mmol/L
Complete blood count	Hb: 5.3 g/dl, Htc: 18%, WBC: 14,000/mm^3, platelets: 207,000/mm^3 peripheral smear: significant anisopoikilocytosis
Anionic gap	32
Total/direct bilirubin	17.8/8.2 g/dl
Plasma amino acid chromatography	Normal
Urine metabolic screening	Normal
Blood metabolic screening	Normal
Pyroglutamic acid excretion in urine	3 times excretion of pyroglutamic acid of normal (normal internal standard: 130 mmol/molcre)
G6PD activity	Normal
Lactic acid	27 mg/dl

G6PD: glucose-6-phosphate dhydrogenase.

Discussion

Glutathione is a tripeptide containing glutamic acid, cysteine and glycine. The cysteinyl moiety of glutathione provides the reactive thiol group that is responsible for detoxification of reactive electrophiles and peroxides[3]. Glutathione normally regulates its own biosynthesis by inhibiting γ-glutamylcysteine synthetase, the enzyme catalyzing the first step in the γ-glutamyl cycle. When glutathione concentration is reduced, γ-glutamylcysteine formation increases and this dipeptide is converted to 5-oxoproline in the plasma; some of the 5-oxoproline is excreted in urine. As it is a highly acidic compound it causes metabolic acidosis[1,2].

Clinically there are two different forms of GSSD. The severe form of the disease, generalized GSSD, is characterized by decreased cellular levels of glutathione, severe metabolic acidosis, massive urinary excretion of 5-oxoproline, elevated levels of 5-oxoproline in blood and cerebrospinal fluid (CSF), increased rate of hemolysis, central nervous system symptoms and granulocyte dysfunction. The milder form is associated with low levels of erythrocyte glutathione and compensated hemolytic disease and does not lead to 5-oxoprolinuria[1,2,4,5]. GSSD is inherited as autosomal recessive trait.

Clinical signs usually first appear during the neonatal period. After the neonatal period, the condition is usually stabilized but may deteriorate during an infection due to severe acidosis or electrolyte imbalance. Five of 40 patients reported in the literature died in the neonatal period due to severe acidosis and infection[1,2]. Patients have progressive central nervous system damage including mental retardation, ataxia, spasticity and seizures. As it has a variable phenotype, it is difficult to predict the outcome in patients. Increased susceptibility to bacterial infections due to defective granulocyte function was reported in two patients with GSSD[6].

The present case had a severe metabolic acidosis with a high anionic gap, hemolytic anemia, hyperbilirubinemia, and high levels of 5-oxoprolinuria. Thus she was diagnosed with generalized GSSD. She was the product of a cousin marriage and a sister had most likely died of the same metabolic disease.

The generalized form is postulated to be due to mutations affecting the catalytic properties of the enzyme whereas the erythrocyte form of

glutathione synthetase (GSS) deficiency is postulated to be due to a mutation primarily affecting the stability of the enzyme[2]. GSS gene exists in chromosome 20q11.2[7]. Eighteen different mutations have been identified in 17 patients[1]. We could not perform a mutation analysis in this patient.

Pyroglutamic aciduria may also be due to secondary causes such as acetaminophen, antibiotic therapy or vigabatrin use[1,8-11]. Sepsis appears to be associated with hepatic glutathione pool reduction and may cause pyroglutamic aciduria[12].

Diagnosis is usually made clinically and there is massive excretion of L-5-oxoproline (up to 1 g/kg/day) in urine. Decreased activity of GSS can be demonstrated in erythrocytes, leukocytes and cultured fibroblasts. Parents show intermediate levels of GSS. Prenatal diagnosis of GSSD is possible by analyzing 5-oxoproline in amniotic fluid, or by enzyme analysis in cultured amniocytes or chorionic villi samples[2].

Treatment involves correction of metabolic acidosis initially by parenteral compounds followed by oral maintenance, antibiotic treatment if there is an infection, and supportive care. In the neonatal period it is important especially to prevent hyperbilirubinemia in order to protect the brain from kernicterus. Anemia often needs to be treated with blood transfusion. As there is increased sensitivity to oxidative stress, such anti-oxidative agents as vitamin E, C, and N-acetylcysteine have been used[13-15]. Drugs avoided in G6PD deficiency should also be restricted in GSSD. Oral administration of glutathione analogues have been shown to increase glutathione concentration in leukocytes and plasma with no effect on 5-oxoproline excretion in urine[13-14]. High doses of α-tocopherol may improve erythrocyte survival in GSS deficient patients[15]. Predicting the prognosis is difficult. It depends on the type of mutation, severity of acidosis, associated bacterial infections and the quality of supportive therapy.

In conclusion, pyroglutamic aciduria (5-oxoprolinuria) should be considered in a newborn with severe metabolic acidosis, hemolytic anemia, hyperbilirubinemia and neurologic deterioration. Excessive urinary 5-oxoproline excretion must be investigated to confirm the clinical diagnosis. Prenatal diagnosis is available and should be offered to parents.

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Symptomatic kidney involvement in a child with tuberous sclerosis

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SUMMARY: Hergüner MÖ, Karabay-Bayazıt A, Noyan A, Altunbaşak Ş, Anarat A. Symptomatic kidney involvement in a child with tuberous sclerosis. Turk J Pediatr 2004; 46: 76-78.

Tuberous sclerosis complex is an autosomal dominant disorder of cellular proliferation and differentiation with variable penetrance and a high spontaneous mutation rate that affects multiple organs, including the kidney. Kidney involvement is commonly asymptomatic and bilateral, and rare in childhood, especially under 10 years. Herein, we report a case of unilateral renal angiomyolipoma in a nine-year-old girl with tuberous sclerosis who had symptoms of pain and macroscopic hematuria.

Key words: tuberous sclerosis, renal angiomyolipoma.

Tuberous sclerosis (TS) is a disease characterized pathologically by the presence of hamartomas in multiple organ systems such as brain, skin, retina, bone, heart, lung and kidney. Its main clinical manifestations include epilepsy with intractable seizures, mental retardation, behavioral problems, and skin lesions[1,2].

The renal lesions in TS are angiomyolipomas and renal cysts, but renal carcinoma can also occur. Angiomyolipomas are found in an estimated 50 to 80% of the patients, but the real incidence of renal cysts is unknown[3,4].

Renal lesions can cause clinical problems secondary to hemorrhage or compression, which rarely cause end-stage renal failure[2].

Here we describe a patient with TS with unilateral renal angiomyolipomas who had pain and macroscopic hematuria. This case is worthy of attention because the symptoms occurred at an earlier age than expected.

Case Report

A nine-year-old girl with TS was admitted to our hospital with lumbar pain and macroscopic hematuria. She was born to non-consanguineous parents after a non-complicated pregnancy. The clinical onset of her condition was reported at around age 18 months with seizures. Her father and brother were also similarly affected and a paternal aunt had mental retardation. Her father was also diagnosed with renal carcinoma in another hospital. She irregularly took antiepileptic drugs until nine years, and had never undergone renal imaging as a part of routine evaluation and follow up. Her history revealed that she had paroxysmal flank pain and macroscopic hematuria since the age of six years. On examination, moderate mental retardation; large adenoma sebaceum on her nose, cheeks and chin; shagreen patch over the lumbosacral region; multiple hypopigmented spots over the trunk and limbs; several small angiofibromas, especially over the scalp; and brisk tendon reflexes were found. Other systemic and neurological findings were normal. Physical examination of the affected brother was identical to our index case.

The results of routine biochemical tests were normal. On her routine analysis, only microscopic hematuria was detected. Urine culture was sterile. Renal ultrasonography (USG) and computerized tomography (CT) revealed hyperechoic lesions with the same density as renal sinus fat tissue within the right kidney parenchyma, localized to the lower pole, which were defined as angiomyolipomas. Left kidney findings were normal (Fig. 1).

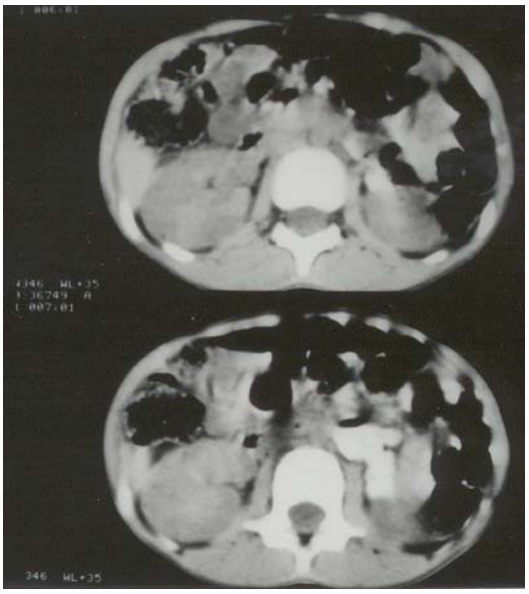

Fig. 1. Abdominal CT showing changes in the left kidney.

Discussion

The most common renal lesion in patients with TS is angiomyolipoma, found in an estimated 50 to 80% of the patients[4-6]. The tumor is composed of tissues normally present in the kidney, but these are of abnormal quantity, arrangement, or degree of maturation. Microscopic examination reveals fatty tissue consisting of mature cells, rich vascular tissue with many tortuous vessels, and smooth muscle[7].

Characteristically, the renal lesions of TS are usually relatively indolent and innocuous, but can become symptomatic because of renal enlargement and related complications[7]. The reported complications of renal angiomyolipoma include partial obstruction of the collecting system, sometimes urinary system infections or nephrolithiasis, and spontaneous hemorrhage, which can lead to hemorrhagic shock in 20% of the cases with angiomyolipomas[5,7]. Our patient had pain and macroscopic hematuria. Her urine culture was sterile and on her DMSA, no findings of pyelonephritis were detected. The tumor is usually benign, but there is a possibility that a renal carcinoma could develop. Our patient's father with TS was also diagnosed as renal cell carcinoma in another hospital.

The second lesion found in TS is the renal cyst. Its real incidence is unknown, but is less than that of angiomyolipoma. The cysts frequently occur in children with TS, and may be the first clinical manifestation of the disease. The incidence of angiomyolipomas increases with age, but the incidence of renal cysts does not appear to be age related[6,7].

The age at which renal lesions occur in patients with TS is highly variable. But in published series, most patients with angiomyolipoma were older than 10 years. In one study, the renal lesions in patients occurred when they were two months to 54 years old[5]. Most of them had angiomyolipoma. In another study, one newborn patient had solitary renal cyst and she had an asymptomatic father[6].

These two abnormalities in TS can occur separately or together and are usually multiple and bilateral. In several series, the incidence of renal lesions in patients with TS was found between 54 and 100%; the specific incidence is 47 to 73% for angiomyolipoma, 18 to 53% for renal cysts, and 12 to 27% for both lesions[5]. Although up to 12% of all persons may harbor small lipomas and angiomyolipomas, TS should be strongly suspected in patients with multiple or bilateral renal angiomyolipomas. Multiplicity and bilateral localization were important differences between the TS cases and the isolated angiomyolipomas. But our patient had unilateral angiomyolipoma. This could be related with her age.

Before the widespread availability of ultrasonography, CT and magnetic resonance imaging (MRI), angiomyolipomas were essentially indistinguishable from renal cell carcinomas. The ability to differentiate these tumors has a significant impact on treatment and prognosis[3,5]. The radiographic findings with intravenous pyelography (IVP) and angiography are similar. Ultarosongraphy may give a clue to the diagnosis, because it will show hyperechogenicity of the fat. Fat tissue produces typical images on CT, being more easily visualized by CT than MRI. In 95% of the case, a CT scan can differentiate angiomyolipoma from renal cell carcinoma. A radiolucent area within the mass indicates fat and is pathognomonic for angiomyolipoma[6-9]. If the margin of the tumor and kidney are indistinct or there is calcification within the mass, renal cell carcinoma should be suspected. Biopsy is not needed for the diagnosis and should be avoided because of risk of bleeding, which can lead to deterioration of renal function, sometimes necessitating nephrectomy.

In conclusion, periodic renal surveillance is indicated in children with TS complex to identify those with growing lesions who can be treated with embolization or partial nephrectomy before hemorrhage, which may result in loss of the kidney[3]. Renal ultrasonography must be performed every two to three years before puberty and yearly thereafter.

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A case of tuberous sclerosis presenting with dysrhythmia in the first day of life

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SUMMARY: Akalın F, Baysoy G, Öztürk B, Yalçın Y, Ekici G, Yılmaz Y. A case of tuberous sclerosis presenting with dysrhythmia in the first day of life. Turk J Pediatr 2004; 46: 79-81.

Cardiac rhabdomyoma (CR) is the most common primary cardiac tumor in childhood. Although CRs are asymptomatic in many cases, they may cause arrhythmia, heart failure and fetal hydrops. Babies with arrhythmia in the neonatal period must be investigated for structural heart disease including CR. Cardiac rhabdomyoma may either present as an isolated tumor or may be related with tuberous sclerosis. Arrhythmia due to CR may be the initial sign of tuberous sclerosis. We report a case of tuberous sclerosis presenting with ventricular premature beats and second-degree atrioventricular block in the first day of life who was found to have multiple CR during echocardiographic examination.

Key words: arrhythmia in neonates, cardiac tumor, rhabdomyoma, tuberous sclerosis.

Cardiac rhythm abnormalities are not rare in neonates and may be detected in healthy neonates; however, the infants with dysrhythmia must be evaluated for structural heart disease, fetal distress or infection[1]. Cardiac tumors are another cause of arrhythmia, and cardiac detected by echocardiography, and about 50% of CR are related with tuberous sclerosis[2,3]. The cranial tubers found in cranial imaging studies may be helpful in diagnosis of tuberous sclerosis in such cases[4]. We report a neonate presenting with dysrhythmia in the first day of life and found to have CR due to tuberous sclerosis.

Case Report

ED, a one-day-old male infant, was born following an uneventful pregnancy. He was the first child of a healthy 25-year-old mother. Family history was negative for cardiac or genetic disorders. His birth was 3,200 g. Cardiology consultation was needed because of irregular rhythm found during routine examination in the first day of life. The physical examination was completely normal except for the irregular heart sounds. No murmurs were present on cardiac auscultation. The size and configuration of the heart was normal on the chest X-ray. Electrocardiogram showed frequent atrial and ventricular premature beats (Fig. 1) and low-grade second-degree atrioventricular (AV) block. The echocardiographic examination showed multiple hyperechogenic masses, 1-2 mm in diameter, within the left ventricular myocardium, and involving the lateral wall, interventricular septum and left ventricular outflow tract; they were presumed to be rhabdomyoma (Fig. 2). Propranolol 2 mg/kg/day was started for

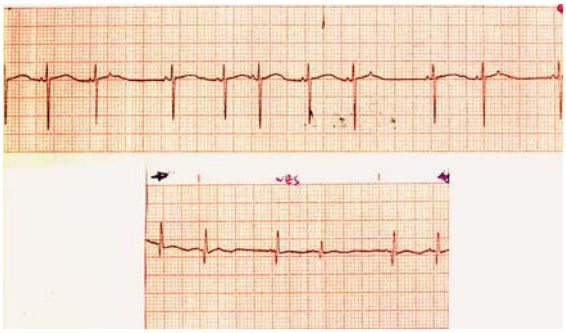

Fig. 1. The electrocardiogram showing the non-conducted atrial premature beats and ventricular premature beats.

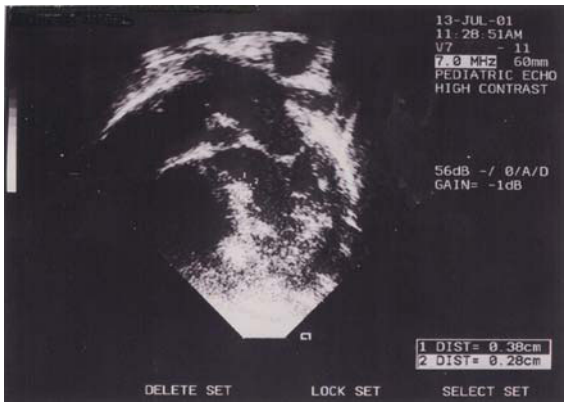

Fig. 2. The multiple rahbdomyomas within the interventricular septum demonstrated by two-dimensional echocardiography.

treatment of arrhythmia. The 24-hour Holter monitorization performed both before and under propranolol treatment revealed frequent atrial and ventricular premature beats and low-grade second-degree AV block. The cranial computerized tomography (CT) and magnetic resonance imaging (MRI) studies revealed multiple calcified tubers located on the subependymal region of both lateral ventricles and bilateral parietal subcortical white matter (Figs. 3a, 3b). Electroencephalography showed multiple epileptic foci, and vigabatrin was started. Tuberous sclerosis was diagnosed with these findings. Two hypopigmented patchy lesions on the left ankle located dorsally and on the back of the patient were found during the follow-up

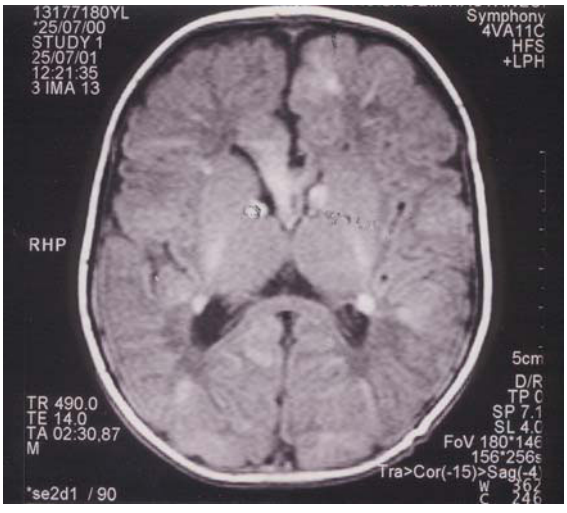

Fig. 3a. Subependymal and subcortical multiple tubers demonstrated by T1 weighted axial cranial magnetic resonance imaging.

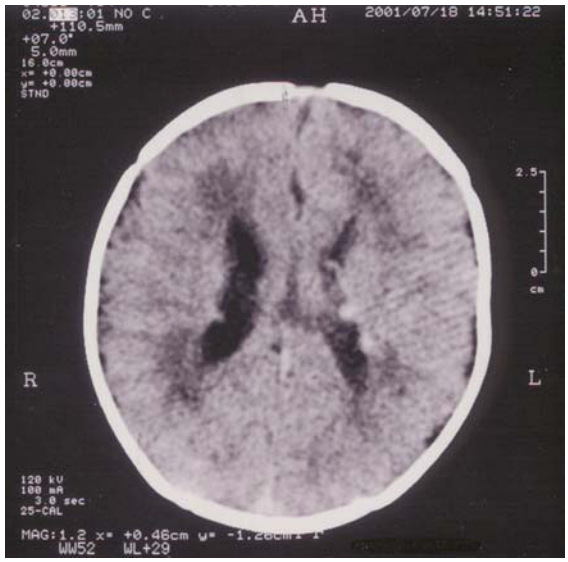

Fig. 3b. Subependymal calcified tubers on the left lateral ventricle demonstrated by cranial computerized tomography.

examination of the baby in the first month; they were not present during initial examination. At the age of nine months, he had attained normal weight and height but neurologic development was retarded. No seizures were observed during the follow-up period; however, the ventricular extra-systole existed on the electrocardiogram.

Discussion

Tuberous sclerosis (TS) is an autosomal dominant multisystem disease and its incidence is 1: 6,000-30,000 in the normal population. Genetic heterogeneity is present and gene locus is found on the 9th and 16th chromosomes, which are both tumor suppressing genes[2,4]. TS is characterized by hamartomas involving primarily the brain, retina, skin, kidneys, heart and lungs. The specific findings are cortical dysplasia (tubers), subependymal nodules, giant cell astrocytoma, retinal astrocytic hamartoma, and fascial angiofibroma, less specific findings are cardiac rhabdomyoma, renal angioepithelioma and angiomyolipoma of lungs, liver, gonads or adrenal glands[5]. Mental retardation and epilepsia are common. Our patient did not show clinical evidence of seizures but epileptic foci were found on EEG. Neuromotor development of the patient was found to be retarded during his follow-up examination, and he still had head lag at six months.

Primary cardiac tumors are rare in childhood. CR are the most common primary cardiac tumors in children[3]. The number of diagnosed cases with CR is increasing due to the development of non-invasive diagnostic methods. CR are the earliest recognizable hamartomas in TS; they can be detected even during fetal life. CR are found in 50% of patients with TS[3]; on the other hand, 40-80% of the patients with CR have TS[6,7]. Early diagnosis of TS was possible by echocardiographic diagnosis of CR in our patient.

Cardiac rhabdomyoma may present with a murmur, arrhythmia, heart failure or exercise intolerance[7]. Heart failure due to left ventricular outflow tract obstruction and severe arrhythmia may cause fetal hydrops. The reported types of dysrhythmia are Wolff-Parkinson-White syndrome, supraventricular tachycardia, atrioventricular block and ventricular tachycardia[6]. CR are composed of embryonal Purkinje cells, are postulated to act as microscopic or macroscopic accessory conduction pathways and may predispose ventricular preexcitation[2]. Serious arrhythmia is rare in neonates but may be found during intra-uterine life. The other causes of dysrhythmia may be congenital cardiac abnormalities, electrolyte disturbances, neonatal asphyxia, and neonatal lupus[1]. Echocardiographic evaluation is needed for diagnosis of structural abnormalities in neonates presenting with dysrhythmia.

Conservative approach is recommended in patients with CR since spontaneous regression of the tumor occurs in about 60-100% of cases[7]. Medical or surgical intervention is considered according to the severity of clinical findings. Surgical resection is needed in patients with significant left ventricular outflow obstruction. Radiofrequency ablation is another option in patients with intractable arrhythmia who are responding to medical treatment[8,9]. Our patient did not develop life-threatening arrhythmia during follow-up, and we preferred medical treatment with propranolol in order to prevent ventricular tachycardia.

In conclusion, in rhythm problems in neonates, cardiac rhabdomyoma and tuberous sclerosis must be suggested and echocardiographic examination must be performed. Cranial imaging is usually helpful in definitive diagnosis of tuberous sclerosis in such patients.

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Ectomesenchymoma: case report and review of the literature

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Ectomesenchymoma (EMCH) is a rare tumor that may arise in the brain or soft tissue. This tumor type is defined as a form including ectodermal components represented by neuroblasts or ganglion cells and differentiated mesenchymal structures of various types. The mesenchymal component is most often a rhabdomyosarcoma, but liposarcoma, malignant fibrous histiocytoma, leiomyosarcoma, chondrosarcoma, malignant schwannoma, and osseous elements have also been recorded. We report a case of an abdominal malignant ectomesenchymoma, containing three components, schwannoma, embryonal rhabdomyosarcoma, and ganglion cells, in a four-month-old infant. We also review 43 previously reported cases.

Key words: ectomesenchymoma, rhabdomyosarcoma, ganglion cells, malignant schwannoma.

Ectomesenchyme refers to the mesenchymal cells that are derived from the neural crest. Ectomesenchymomas (EMCH) are malignant tumors believed to arise from this tissue. They are characterized by both neuroectodermal and mesenchymal components[1]. These tumors are traditionally composed of well-differentiated neuroblastic cells (neuroblastoma, ganglio-neuroblastoma, ganglioneuroma), peripheral primitive neuroectodermal tumors (PNET) and one or more malignant mesenchymal elements, usually rhabdomyosarcoma. It stands as a distinct clinicopathologic entity[2]. This rare tumor has been described in the central nervous system and in various soft-tissue sties. In this report we describe a four-month-old infant who had an intra-abdominal ectomesenchymoma, and we review the literature.

Case Report

A four-month-old boy was admitted to our hospital because of a one-week history of progressive distention of the abdomen. There was no history of vomiting. On physical examination, the child appeared moderately ill and anemic. He had a rectal temperature of 36.6°C, and a heart rate of 152 per min. His weight and length were 6 kg and 64 cm, respectively. He had a moderately distended abdomen with active bowel sounds, and a large, nontender, smooth, palpable mass extending from the umbilicus to the inguinal region in the right lower quadrant. Prerectal mass was detected by rectal examination.

Laboratory examination revealed a blood hemoglobin of 7.0 g/dl, hematocrit 19.8% white cell count (13,800) per cubic millimeter, and a platelet count of 556,000 per cubic millimeter. CA-125 and 15-3 levels were higher than normal values (72.8, 22.9 respectively). Other biochemical and urinary analysis results were unremarkable and other tumor markers not detectable.

Abdominal radiography revealed a few dilated loops of small intestine, with gas and stool in the rectum. A computed tomographic (CT) scan of the abdomen, obtained after oral administration of contrast material, showed a solid mass, 8.7x5.5 cm, that displaced the bladder anteriorly and superiorly.

The tumor was surgically removed. The tumoral specimen from the intraabdominal surgery measured 9x8.5x6 cm and weighed 250 g. This mass appeared to be well circumscribed but non-encapsulated. Cut surface of the lesion showed fibrillar appearance of a firm mass, predominantly gray-white in color. Areas of necrosis and hemorrhage were present.

Microscopically, the tumor was densely cellular and composed predominantly of small, round and spindle-shaped cells with high nuclear-to-

cytoplasmic ratio and a high mitotic rate. The tumor had three components, schwannoma, embryonal rhabdomyosarcoma, and ganglion cells. The rhabdomyosarcomatous component had poorly differentiated areas composed of small, polygonal cells having round, hyperchromatic nuclei, and scant cytoplasm. This component displayed some recognizable round, oval, or spindle rhabdomyoblasts. Some rhabdomyoblasts were idendtified by variably abundant eosinophilic cytoplasm that was commonly granular or fibrillar (Fig. 1). The schwannomatous component had typical spindle-shaped nerve sheath cells with hyperchromatic nuclei and a considerable number of cells with mitosis (Fig. 2). Ganglion cells displaying various degrees of maturity were mixed with spindle-shaped cells (Fig. 3).

Immunohistochemical stains were performed for desmin, myoglobin, neuron-specific enolase (NSE), and S-100 on formalin-fixed tissue. The rhabdomyosarcomatous component displayed strong cytoplasmic staining for desmin and myoglobin. The schwannomatous component was negative for desmin and myoglobin, and positive for S-100. The ganglion cells were positive for NSE.

With the characteristic properties described above, the tumor was diagnosed as an ectomesenchymoma.

Postoperative follow-up was uneventful. He was discharged on the 5th postoperative day, and referred to the pediatric oncology clinic for chemotherapy.

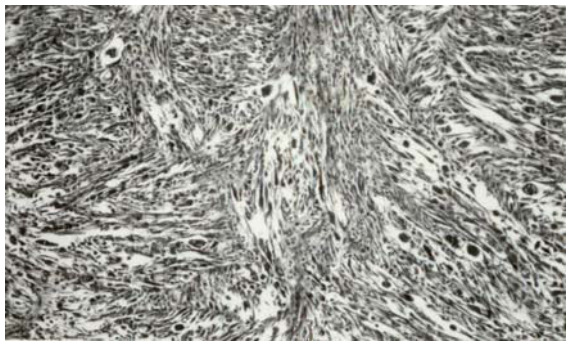

Fig. 1. Rhabdomyoblastic differentiation in the tumor mass. Some rhabdomyoblasts are identifying with abundant eosinophilic cytoplasms (H-E X 125).

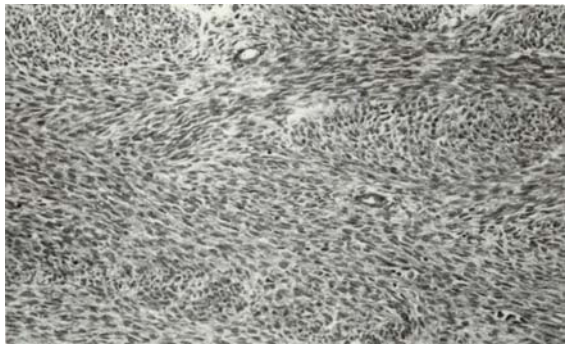

Fig. 2. The schwannomatous component composed of typical spindle-shaped nerve sheath cells with hyperchromatic nuclei and considerable mitotic figures (H-E X 125).

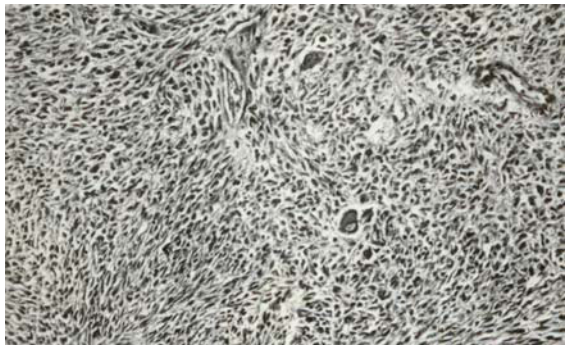

Fig. 3. The ganglion cells mixed with spindle-shaped cells (H-E X 125).

Discussion

Malignant ectomesenchymomas are rare tumors composed of neuroblast and/or ganglion cells and malignant mesenchymal tissue(s) of various types, usually rhabdomyosarcoma[3,4].

The most widely accepted theory suggests that this tumor arises from the remnants of migratory neural crest cells and thus from the mesenchyme[2-10].

In the late nineteenth century, Platt[11] discovered that the dorsal ectoderm of the head contributed to the mesenchymal cells forming the cartilage of the visceral arches and dentine. She coined the term "mesectoderm", but the term ectomesenchyme is now popularly used to designate mesenchymal cells of neural crest origin. Holimon and Rosenblum[4] proposed the

term "gangliorhabdomyosarcoma" for a tumor in the cerebellopontine angle containing ganglioneuroma and rhabdomyosarcomatous elements. Later, Naka et al.[8] proposed the term EMCH after finding a variety of malignant mesenchymal elements in a retroperitoneal tumor mixed with ganglioneuroblastoma.

The clinical, histological, and cytochemical data for all 44 reviewed cases of ectomesenchymoma (including the case we report) are summarized in Table I. This tumor affects predominantly young children: 81.6% (39.5% infants and 42.1% 1-13 years old) were children under 13 years old and 18.4% are adults. The male-to-female ratio

Table I. Review of Cases in the Literature

No.	Reference	No. of cases	Age	Presentation	Gross appearance	Histology	Treatment	Follow-up
1	Ingraham (7)	1	10 yrs	Cerebellar	NA	Atypical GC, RMS	Incomplete res	Died 12 mo.
2	Holimon (4)	1	2.5 yrs	Ear and nasopharynx	Polypoid, firm, gray-white, necrotic mass	GN, RMS	CT, RT	Died 6 mo., met.
3	Naka et al. (8)	1	2 yrs	Abdominal	Fragile, gray, necrotic zones	NB, GN, RMS, UM, LS, chondroid areas	P. Res, RT, CT	Died 6 mo., met.
4	Karcıoğlu et al. (9)	1	6 mo.	Facial	Gray-white, lobulated, friable mass	GN, RMS, Sch, melanocytes	P. Res, CT, RT	No. Rec. 7 mo.
5	Shuangshoti (16)	1	20 yrs	Neck	Encapsulated firm, gray-white, cystic and necrotic areas	GN, RMS, malignant Sch., meningioma, osseous component	Res., local rec. 3 mo., RT	NA
6	Schmidt et al. (22)	1	New-born	Cheek	Circumscribed, Lobulated tan-gray	NB, RMS	CT, res. At 6 mo, rec., res. and CT	Adriamycin Toxicity; died 18 mo.
7	Cozzutto et al. (6)	1	3 yrs	5 Cord	Encapsulated	GC, RMS, MFH,LM	Res. and CT	No. rec. after 3 yrs
8	Cozzutto et al. (6)	1	NA	NA	NA	GC, IE	NA	NA
9	Shuangshoti et al. (14)	1	49 yrs	Thigh	Firm, lobulated, chondroid, necrotic areas	NB, glial tumors, chondrosarcoma	Res, RT, CT	Died 11 mo., met.
10	Sirikulchayannota (17)	1	25 yrs	Wrist	Circumscribed, Yellow-white mass	NB, malignant Sch.	Mulitple excision and amputations	Lost to follow-up After amputation
11	Kodet et al. (18)	1	7 mo.	Paratesticular	NA	GN, RMS	Res., RT CT	No rec 12 yrs
12	Kodet et al. (18)	1	8 mo.	Perineal	NA	GN,RMS	RT, CT	Died at age 4 yrs
13	Kodet et al. (18)	1	4 mo.	Pelvic	NA	GN, RMS	CT, res.	No rec. 9 mo
14	Kawamoto et al. (3)	1	10 mo.	Retroperiton	Encapsulated, fibrous myxoid, necrotic tissue	GN, RMS	Rs. and CT	No rec. 3 yrs
15	Kawamoto et al. (3)	1	4 mo.	Abdomen	Encapsulated, soft, lobulated	NB, RMS	Res. and CT	No rec. 16 mo.
16	Kasantikul et al. (19)	1	5.5 yrs	NA	NA	Neuroglia, SM, CD	NA	Rec. 2 mo.
17	Kasantikul et al. (19)	1	1 yr	Retroperiton	NA	GN, RMS	NA	Died 1 mo., met.
18	Kasantikul et al. (19)	1	20 yrs	Scrotum	NA	GN, RMS	NA	NA
19	Kasantikul et al. (19)	1	36 yrs	Parapharynx	NA	Neuroglia, MFH	Excision, RT	No rec. 6 mo.
20	Strother et al. (10)	1	NA	NA	NA	NA	NA	NA
21	Paulus et al. (20)	1	1.5 yrs	Meningeal	NA	NA	NA	NA
22	Fellinger et al. (21-22)	1	NA	NA	NA	NA	NA	NA
23	Dias et al. (23)	1	NA	NA	NA	NA	NA	NA
24	Matsko et al. (15)	1	5.5 yrs	Orbita	NA	NE, RMS	P. Res, CT, RT	No rec. 18 mo.
25	McCune et al. (24)	3	4-20 yrs	Thigh, arm and abdominal cavity	NA	Case 1: PNET, RMS Case 2: PNET, RMS Case 3: NB, RMS	NA	NA
26								
27								
28	Pellin et al. (25)	1	NA	NA	NA	PSTS, SM, NE	NA	NA
29	Kogner et al. (26)	2	4 yrs	NA	NA	NA	NA	NA
30			6 yrs					

Table I. Review of Cases in the Literature (Continue)

No.	Reference	No. of cases	Age	Presentation	Gross appearance	Histology	Treatment	Follow-up
31	Kilpatrick et al. (27)	1	9.5 mo	Scrotal	NA	Mature GC, RMS	NA	Alive 9.5 yrs
32	Apostolides et al. (28)	1	35 yrs	VIIth nerve	NA	GC, AT, Sch, SM	Total res	NA
33	Mouton et al. (29)	1	7 mo.	Scrotum	Well-C.	GC, RMS, LDCCP	Surgery CT	No rec. 7 mo.
34	Mouton et al. (29)	1	8 mo.	Pelvic	Well-C., yellow-graft	GC, RMS	CT, res. of tumor	No rec.
35	Mouton et al. (29)	1	6 mo.	Inguinal	Firm, white nodular	GC, RMS, LDCCP	Res., CT	No rec. 18 mo.
36	Mouton et al. (29)	1	4.4 yrs	Forearm	NA	NE, RMS, LDCCP	Surgery, CT, res.	No rec. 14 mo.
37	Mouton et al. (29)	1	2 mo.	Scrotal	Circumscribed	NE, LDCCP	Biopsy, CT, res.	No rec. 32 mo.
38	Hajivassilou et al. (13)	1	5 mo.	Pelvic	NA	GN, RMS	CT, total res.	No. rec. 18 mo.
39	Goldsby et al. (30)	1	16 mo.	Abdominal	NA	GC, SC, CD	Res., RT, CT	NA
40	Freitas et al. (31)	1	3.8 yrs	Intracranial	Irregular boundaries, Whitish and rubbery	GC, RMS	Res, rc. 4 mo. Later, RT, CT	Died 14 mo. after res.
41	Govender et al. (1)	1	5 mo.	Prostate	Lobulated tumor with a Rubbery consistency	GN, RMS	Biopsy, surgery, CT, res., CT	Died 8 mo. after res.
42	Tse et al. (32)	1	13 yrs	Retroperiton	Well-C, firm	Mature GC, RMS	NA	NA
43	Papos et al. (33)	1	10 yrs	Cerebral	NA	NA	NA	NA
44	Current case	1	4 mo.	Intraabdominal	Well-C., firm and gray-White cut section	RMS, malignant Sch., GC	Res., CT	No more follow-up

AT : Adipose tissue, CD: Cartilaginous differentiation, CT: Chemotherapy, GC: Ganglion cells, GN: Ganglioneuroma, IE: Indefinite elements, LDCCP: Less differentiated cells and cellular processes, LM: Leiomyoma, LS: Liposarcoma, met: Metastases, MFH: Malignant fibrous histiocytoma, mo: Monts, NA: Data not available, NB: Neuroblastoma, NE: Neural elements, PNET: Peripheral primitive neuroectodermal tumors, P. Res: Partial resection, PSTS: Primitive soft tissue sarcoma, Rec: Recurrence, Retroperiton: retroperitoneal, RMS: Rhabdomyosarcoma, Res: Resection, RT: Radiotherapy, Sch: Schwannoma, SM: Smooth muscle, SC: Spindle cells, S cord: Spermatic cord, UM: Undifferentiated mesenchyme, Well-C: Well-circumscribed.

was 20: 14 (58.8% and 41.2%) and anatomical sites were reported in 36 of these 44 cases as follows: the head and neck (11 cases 30.5%). (6 cases 16.7%), the scrotum (6 cases 16.7%), the abdomen (5 cases 13.9%), the retroperitonael space (4 cases 11.1%), the pelvis (2 cases 5.6%), the perineum (1 case 2.8%), and the prostate (1 case 2.8%)[1,3,4,6-10,12-33]. In the present case the patient was four months old and male. The tumor had intraabdominal location.

Clinically significant symptoms are uncommon and have usually been related to local pressure from the tumor. Laboratory examinations generally cannot help except in cases where

neuroblastomatous components are present, with laboratory data showing elevated vanillylmandelic acid in urine[31]. In our case, laboratory results were nonspecific.

On examination by the naked eye, these cases are well circumscribed gray or tan, and composed of firm tissue. Some cases were described as being lobulated and having focal necrotic areas (Table I).

Histological data were available for 37 tumors: ganglioneuroma was found in 12 tumors (32%), ganglion cells in 11 (30%), and neuroblastoma in 6 tumors (16%), and other neural elements were described in 8 (22%) of these lesions. Rhabdomyosarcoma was present in 31 (84%), and other mesenchymal elements were found in 9 (24%) cases.

In our case, the tumor was well circumscribed but not encapsulated. It was a firm mass and predominantly white in color. Cut surface of the tumor was fibrillar in appearance. Areas of necrosis and hemorrhage were present.

Microscopically, the tumor was composed of ganglion cells, schwannoma and embryonal rhabdomyosarcoma areas.

Ectomesenchymomas are frequently confused with rhabdomyosarcomas due to the fact that their neural components are easily overlooked. However, high concentration of the plasma neuropeptide-Y-like immunoreactivity (P-NPY-LI) in ectomesenchymoma can distinguish this tumor from rhabdomyosarcoma, which presents normal concentrations of the P-NPY-LI[26].

The differential diagnosis of ectomesenchymoma includes mainly teratoma, Wilms' tumor, benign and malignant triton tumors, and other collision tumors[2,6,9,13,17].

The therapeutic management data were mentioned in 27 of 44 cases, including the current case (Table I). Resection together with pre- or post-surgery chemotherapy was the treatment that presented the best results, with only two deaths in 13.

Due to the fact that we could not follow-up this patient, we have no information about the prognosis of the case.

We believe that in the differential diagnosis of tumors in childhood and infancy, the ecto-mesenchymoma should always be remembered.

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Absent pulmonary valve syndrome diagnosed by fetal echocardiography

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Prenatal echocardiographic diagnosis of heart defects is important because it permits counseling of the parents with regard to prognosis and treatment options and prepares the medical team for the treatment postnatally. A male infant with absent pulmonary valve syndrome diagnosed prenatally at 22 weeks' gestation is reported. This congenital anomaly is characterized by absent or rudimentary pulmonary valve cusps, conoventricular septal defect, and massive dilatation of the pulmonary arteries. Soon after delivery the infant developed cyanosis and respiratory distress. The infant was placed in prone position for the relief of bronchial compression and nasal continuous positive airway pressure was (CPAP) started. Although the clinical status of the infant improved after supportive treatment, he deteriorated acutely and died at the age of five days. Fetal diagnosis remains an integral part of successful management of children with heart disease. Despite the potential benefits of prenatal diagnosis, it is hard to show significant improvement in mortality, especially in severely affected cases.

Key words: fetal echocardiography, prenatal diagnosis, absent pulmonary valve syndrome.

Congenital heart disease (CHD) is the most common form of severe congenital abnormality, with an incidence of 8 per 1,000 live births, and accounts for >20% of perinatal deaths resulting from congenital malformations[1-3]. Prenatal diagnosis of CHD is important for proper perinatal and neonatal management. Today fetal echocardiography is indicated in high risk pregnancies, but a significant proportion of CHD occurs in fetuses with no definable risk factors. The reported sensitivity of fetal echocardiography has ranged between 70-85% in some series[1,4]. Conotruncal anomalies, including double outlet right ventricle, tetralogy of Fallot, transposition of the great arteries, absent pulmonary valve syndrome and truncus arteriosus, can be diagnosed by prenatal echocardiography with a high degree of accuracy[4]. Although routine fetal screening by fetal echocardiography in low-risk obstetric populations is not currently the standard of care, standard four chamber view of the fetal heart is recommended as screening tool[5].

Absent pulmonary valve syndrome (APVS) is characterized by absent or rudimentary pulmonary valve cusps, conoventricular septal defect, and massive dilatation of the pulmonary arteries[6-7]. Some infants with the severe form of this syndrome die early in the newborn period owing to severe respiratory distress due to compression of the tracheobronchial tree by massively dilated pulmonary arteries. Early diagnosis and supportive case in the newborn period are important for the survival of these severely affected infants.

Case Report

A 21-year-old primigravida pregnant woman was referred to our hospital because of cardiomegaly detected during routine prenatal obstetric ultrasonography performed at 18 weeks' gestation. No risk factors indicating high risk, including diabetes and hypertension, were present. On admission at 22 weeks' gestation, fetal echocardiogram demonstrated cardiac apex on the left side, atrioventricular

and ventirculoarterial concordance with situs solitus, and right ventricular dilatation with left and right ventricular diastolic diameters of 9.8 mm and 13.4 mm, respectively. Inlet ventricular septal defect, agenesis of the pulmonary valve cusps and massive dilatation of pulmonary arteries (13-18 mm) consistent with APVS were detected (Fig. 1). Color and continuous Doppler examination demonstrated acceleration of pulmonary blood flow velocity of 2.5 m/sec and massive pulmonary valve insufficiency (Fig. 2). Fetal heart rate was 127/minute. On prenatal ultrasonography no associated malformation was detected. On follow-up at 28 weeks' gestation, minimal pericardial effusion and grade 1-2 tricuspid insufficiency were detected. Ventricular systolic function was at the lower limit. At 37 weeks' gestation left and right ventricular diameters were found dilated with enlarged left and right pulmonary arteries (Fig. 3). After each routine follow-up visit the pediatric cardiologist, neonatologist, and obstetrician discussed the clinical status, delivery time and delivery mode of the fetus. The prognosis of the disease and termination of pregnancy were discussed with the parents but they did not accept termination of pregnancy.

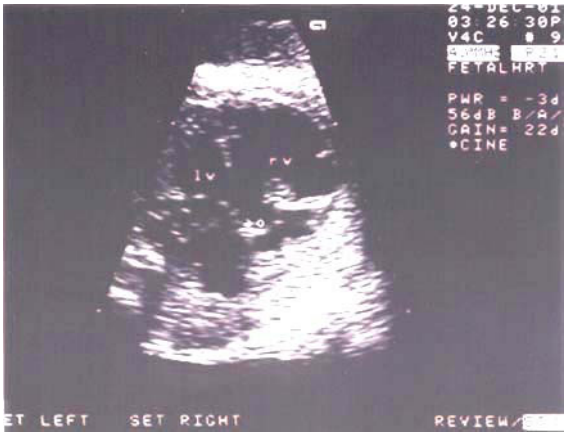

Fig. 1. Modified five chamber view of fetal heart at 22 weeks' gestation demonstrating enlarged right ventricle (rv), inlet ventricular septal defect and overriding of aorta to the interventricular septum.

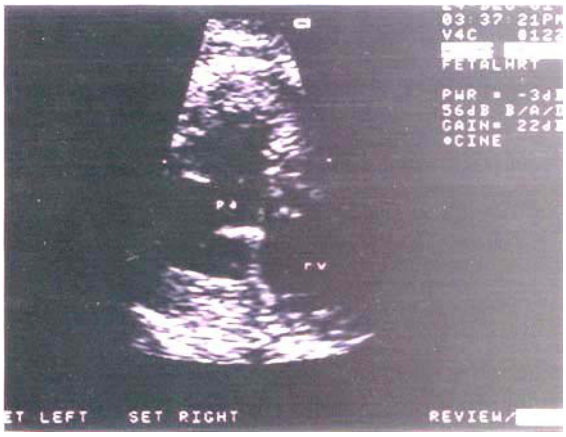

Fig. 3. Aneurysmal dilatation of the pulmonary artery with markedly enlarged main pulmonary artery (pa) bifurcating into left and right pulmonary arteries and dilated right ventricle (rv). The pulmonary valve annulus is stenotic, and no discrete pulmonary valve is detected.

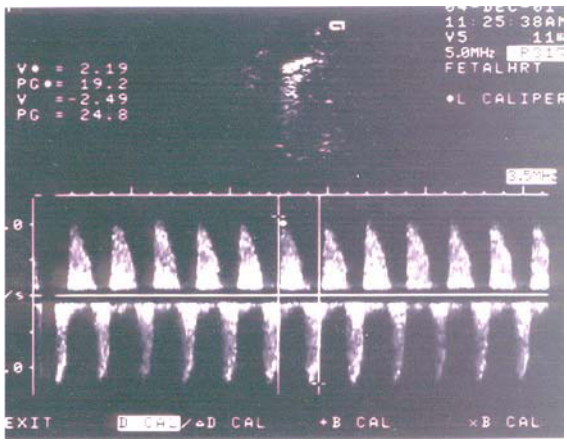

Fig. 2. The continuous wave Doppler signal in the axis of main pulmonary artery showing systolic and diastolic regurgitant jets of approximately 2.19-2.49 m/sec bidirectionally.

A male infant weighing 3,880 g was born at a gestational age of 40 weeks via spontaneous vaginal delivery. A neonatologist and a pediatric cardiologist were ready in the delivery room. Soon after delivery the infant developed cyanosis and respiratory distress. His heart rate and blood pressure on admission were 128/minute and 84/45 mm Hg, respectively. Peripheral circulation was poor, pulses were palpable and grade 4/6 to-and-fro murmur was audible at the left sternal border. The liver was palpable 3 cm below the right costal margin. No morphological anomaly was detected on clinical examination. The chest X-ray showed cardiomegaly with a cardiothoracic ratio of 65%, and marked prominence of the upper left cardiac border due to enlarged pulmonary infundibulum. Right hilus was prominent due

to dilated right pulmonary artery; peripheral pulmonary vascular markings were normal. Arterial blood gases revealed a moderate respiratory acidosis. Serum electrolytes were normal and calcium level was 8.9 mg/dl. Karyotype analysis was normal.

Postnatal echocardiography revealed extensive dilatation of right ventricle and right atrium, inlet ventricular septal defect of 11 mm diameter, and overriding aorta. Pulmonary valve cusps were absent with huge dilatation of the pulmonary arteries. The diameters of right and left pulmonary arteries were 24 mm and 22 mm, respectively. Grade 2-3 pulmonary insufficiency was detected. Left ventricular function was normal.

The infant was immediately taken to the NICU, placed in prone position for the relief of bronchial compression and nasal continuous positive airway pressure (CPAP) was started. After starting CPAP and positioning, the clinical status and arterial blood gases of the infant improved. On day 3 enteral feeding was started and tolerated. However, the patient deteriorated acutely and died at the age of five days. During hospitalization the heart rate and SPO_2 values of the infant varied between 104-158/min and 68-84%, respectively. The latest blood gases revealed normal CO_2 and low O_2 tension.

Discussion

Accurate echocardiographic diagnosis in utero is important because it permits counseling of the parents with regard to prognosis and treatment options and prepares the medical team for the treatment postnatally[3,8,9]. A detailed cardiac scan can usually be performed in specialized centers with expertise in the diagnosis of CHD. It is important to detect high risk pregnancies and refer them to specialized centers. However, it is known that a significant proportion of CHD occurs in fetuses with no definable risk factors. Perhaps the most important indication for a fetal echocardiography is the suspicion of an abnormal heart on a screening obstetric sonogram. If cardiac screening is confined to the four chamber view, approximately 70% of the cardiac anomalies can be detected[10]. If the great arteries are also examined, 90% of major heart disease cases would be detectable prenatally[9]. Ideally, a complete fetal echocardiography is performed at 16 to 20 weeks' gestation because adequate identification of cardiac structures is generally not possible before that time[3]. The major benefit of the fetal echocardiography is to be able to provide the family with information regarding the prognosis of the specific defect, so that further management can be planned and coordinated with the multidisciplinary team consisting of a pediatric cardiologist, neonatologist, obstetrician and cardiovascular surgeon.

Absent pulmonary valve syndrome (APVS) is characterized by dysgenesis of the pulmonary valve, severe pulmonary insufficiency, and massive enlargement of pulmonary arteries, and occurs in approximately 3% of cases of tetralogy of Fallot[6]. Tracheobronchomalacia is present due to compression from the massive branch pulmonary arteries. Patients are divided clinically into two groups: neonates with severe respiratory distress, and older children who survived the neonatal period. The patient reported here is in the former group. Neonates in this group typically present soon after birth with severe respiratory distress, cyanosis, and hyperinflation due to tracheobronchial compression[6,11]. Mechanical ventilation with high positive end-expiratory pressure may help to stent open airways and improve gas exchange. In this patient we did not intubate the infant but rather preferred nasal CPAP, avoiding the risks of intubation and ventilator-related injury. The patient's clinical status improved after supportive treatment. However, despite vigorous, conservative medical treatment the patient deteriorated acutely and died at the age of five days.

Despite the potential benefits of prenatal diagnosis, it is hard to show significant improvement in mortality, partly because fetal echocardiography preferentially detects more severe forms of CHD which have a high mortality rate.

In conclusion, fetal diagnosis remains an integral part of the successful management of children with heart disease. It is clear that early fetal echocardiography is feasible and that complex CHD such as APVS can be detected in early pregnancy. Postnatal management of the severely affected infants with APVS is difficult. Despite prompt and optimal supportive care severely affected infants die early during the newborn period owing to severe respiratory distress, feeding difficulties and cardiovascular compromise.

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Adult type anomalous origin of the left coronary artery from the pulmonary artery

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Anomalous origin of the left coronary artery from the pulmonary artery (ALCAPA) is a clinical entity characterized by myocardial necrosis which becomes symptomatic shortly after birth; survival beyond infancy is uncommon because of severe left heart failure.

To our knowledge, it is rare for an ALCAPA patient to survive to adulthood. Here we present a case of a 17-year-old girl with ALCAPA who was referred to our hospital because of palpitation and dyspnea.

Key words: anomalous origin of the left coronary artery from the pulmonary artery, adult type, coronary anomalies.

Anomalous origin of the left coronary artery from the pulmonary artery (ALCAPA) is a rare congenital anomaly occurring in approximately 1 in 300,000 live births[1]. This syndrome can cause severe myocardial ischemia or infarction leading to left ventricular dysfunction, mitral insufficiency, congestive heart failure, and death. Without surgical intervention, about 90% of patients with ALCAPA die within the first year of life[2]. We present a 17-year-old girl with adult type ALCAPA syndrome who survived to her present age without any symptoms except for a six-month history of palpitation and dyspnea.

Case Report

A 17-year-old girl was admitted to our hospital for attacks of palpitation and dyspnea. Physical examination revealed a grade II-III/VI systolic murmur in the fourth left intercostals space. Her chest radiograph was normal except for pulmonary congestion. Baseline electrocardiogram (ECG) showed inverted T waves and ST depression in leads V4-V6. Holter electrocardiographic recordings revealed sinus tachycardia. Echocardiography revealed a dilated left atrium and left ventricle with hypokinetic anterior septum. Left ventricular function was in normal limits (end-diastolic diameter: 54 mm, end-systolic diameter: 35 mm, ejection fraction: 65%, shortening fraction: 35%). Color flow mapping and pulsed Doppler investigation demonstrated moderate mitral regurgitation and abnormal flow pattern in the pulmonary artery (Fig. 1). Coronary angiography revealed a tortuous widely dilated right coronary artery communicating through extensive collaterals with the left coronary artery which was filling the pulmonary artery (Fig. 2).

The left main coronary artery was reimplanted in the aorta and she has been free of subjective symptoms for nine months.

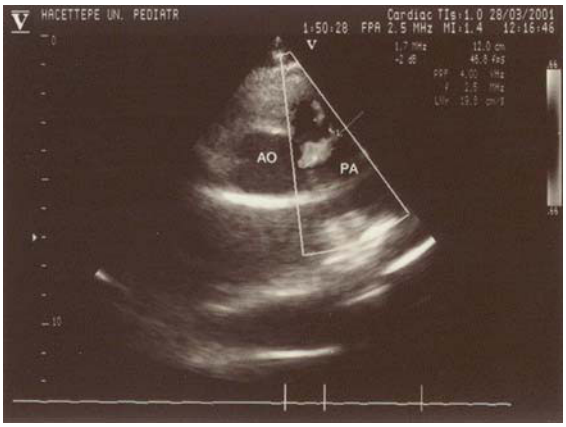

Fig. 1. Doppler color imaging reveals abnormal flow pattern in the pulmonary artery on transthoracic echocardiographic short axis view. (PA: pulmonary artery, Ao: Aorta).

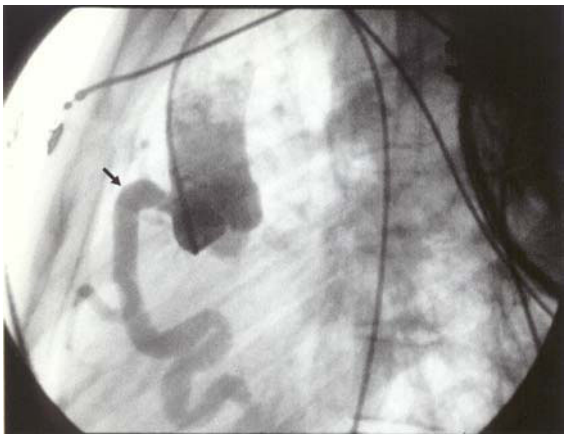

Fig. 2a. Coronary angiography, left anterior oblique view. Catheter is in the aorta. Early phase of angiography reveals a tortuous widely dilated right coronary artery.

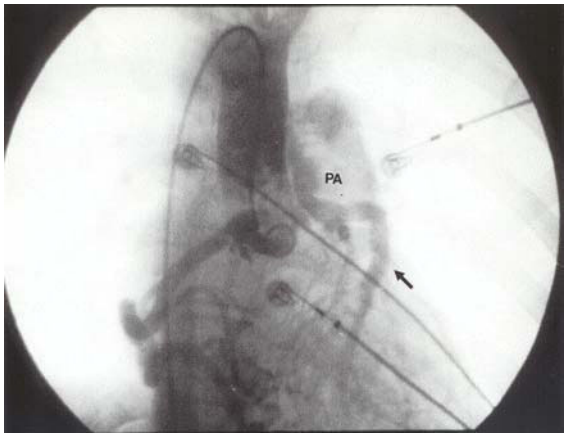

Fig. 2b. Late phase of same angiography reveals extensive collaterals and left coronary artery filling the pulmonary artery. (PA: Pulmonary artery).

Discussion

Usually, patients with ALCAPA reveal no symptoms in the neonatal period because of physiologic hypertension and the still open ductus arteriosus. A few weeks to months after birth, most infants with this disorder become symptomatic. The balance between speed of closure of the ductus, regulation of the pulmonary hypertension and the speed of development of preexisting collateral between the right and left coronary arteries will determine the extent of myocardial necrosis[3].

Anomalous origin of the left coronary artery from the pulmonary artery was classified into two groups as an infantile type and an adult type according to clinical presentation. In general, ALCAPA is often associated with an acutely ill-appearing infant and high mortality, which is classified as infantile type. However, in rare cases, some patients reach adulthood[4-6], as seen in our case. Our patient survived to this age because of extensive collateralization from the right coronary artery to the left coronary artery as revealed by coronary angiography.

The diagnosis of coronary artery anomalies requires a high index of suspicion during the history and physical examination. Not in infants but in children and adolescents, nonspecific symptoms include shortness of breath, atypical chest pain, fatigue on exertion, and palpitations, as seen in our patient who was admitted for attacks of dyspnea and palpitations. However, sudden death may be the first and only sign of this syndrome. Clues to diagnosis of ALCAPA include a continuous murmur, a murmur of mitral insufficiency, or signs of left ventricular dysfunction. Although not fully satisfactory, echocardiogram may be used for confirmation of this syndrome. In selected cases transesophageal echocardiography may be useful in the diagnosis[7]. Although other techniques may adequately identify the origin of the coronary artery in an anomalous presentation, only coronary arteriography reliably documents the course of the coronary artery[8]. As shown in our case, coronary artery venous fistula was suspected before angiography and the exact anomaly was later confirmed by coronary arteriography.

An aggressive approach to early repair in all children with ALCAPA is warranted, regardless of the degree of the left ventricular dysfunction. By histologic studies it has been shown that, in patients with ALCAPA syndrome, biopsy specimens taken from the region perfused by the anomalous artery showed a variable degree of fibrosis[3]. Corrective coronary artery surgery appears to be the most reasonable choice for patients with ALCAPA. Although the patients with adult type are more asymptomatic, surgical correction should be undertaken as soon as the diagnosis is established.

The severity of preoperative cardiac dysfunction and ventricular dilation is not predictive of outcome, whereas the degree of preoperative mitral regurgitation is[9]. Even some patients who have severe mitral regurgitation may require mitral valve replacement[10]. In this case, although

a moderate degree of mitral regurgitation was demonstrated, this was not considered to be a poor prognostic factor.

After surgical repair to establish blood flow to the left coronary artery from the aorta dramatic improvement in left ventricular function occurs and normalizes within two to three years[2,3,11,12]. However, the extent of recovery of myocardial blood flow reserve and its potential physiologic significance in long-term survivors of surgical repair of ALCAPA are not known[12].

In conclusion, whenever an adult patient is admitted for dyspnea and palpitation, adult type ALCAPA syndrome should be suspected. Because of marked improvement in morbidity and mortality with surgical correction, it is important to recognize this rare disorder[2,10].

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Pediatric cerebellar cystic oligodendroglioma: case report and literature review

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SUMMARY: Baysefer A, Düz B, Erdoğan E, Deveci MS. Pediatric cerebellar cystic oligodendroglioma: case report and literature review. Turk J Pediatr 2004; 46: 95-97.

Oligodendrogliomas rarely occur in the posterior fossa of childhood and constitute approximately 1% of pediatric brain tumors. Only six pediatric posterior fossa oligodendroglioma cases have been reported to date and none of them were cystic. The authors present a seven-year-old girl with cystic, cerebellar midline localized tumor. A standard suboccipital craniectomy was performed and the tumor was histologically confirmed as oligodendroglioma. After operation the patient underwent radiation therapy and at one the-year follow-up, no recurrence of the tumor was observed.

Key words: pediatric oligodendroglioma, cyst, astrocytoma.

Oligodendrogliomas constitute approximately 1% of pediatric brain tumors[1,2]. The most common localizations of oligodendrogliomas in the pediatric population are supratentorial, with the majority of them in the frontal lobe. Involvement of the frontal and parietal lobes was reported by Razack et al.[3] as 42.1% and 36.6%, respectively. Infratentorial oligodendrogliomas have been reported in six pediatric cases in the literature to date.

The authors report the first cystic oligodendroglioma localized in the posterior fossa in the midline in a seven-year-old girl.

Case Report

A seven-year-old girl admitted to our department with a one-month history of vomiting and the slight loss of tandem gait. Brain magnetic resonance imaging (MRI) revealed a cystic lesion in the cerebellum localized in the posterior fossa in the midline. Contrast enhancements were seen in the T1-weighted images. There was hydrocephalus. The brain stem and the cerebral aqueduct were minimally compressed by the tumor. MRI findings resembled cerebellar cystic astrocytoma (Figs. 1, 2). We preoperatively examined the creberospinal fluid (CSF) for malignant cells but the result was negative.

The patient underwent surgery. A standard suboccipital craniectomy was performed. The cyst of the lesion was first aspirated, and then the capsule of the tumor was totally excised under operation microscope. There was mural nodule other than the tumor capsule. The fourth ventricle was not opened in the operation. There was no complication after the surgery. Pathological examination revealed oligodendroglioma (Fig. 3). The tumor was histologically determined and then the patient underwent radiation therapy. One year later follow-up MRI showed no recurrence of the tumor.

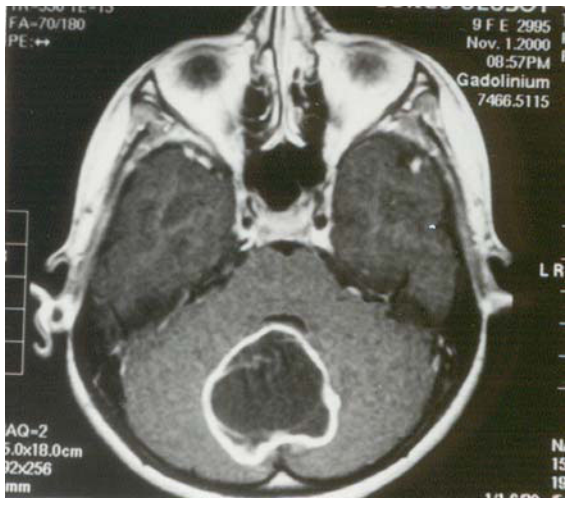

Fig. 1. The T1-weighted, axial magnetic resonance image after gadolinium enhancement. The fourth ventricle is compressed.

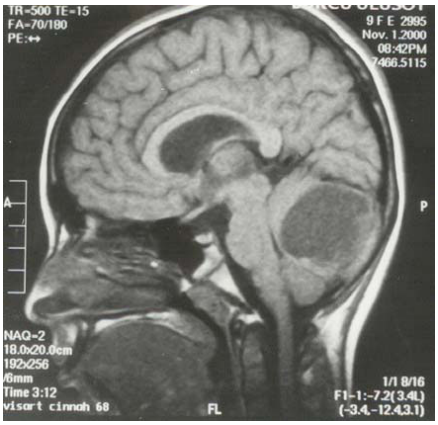

Fig. 2. The T1-weighted, sagittal magnetic resonance image.

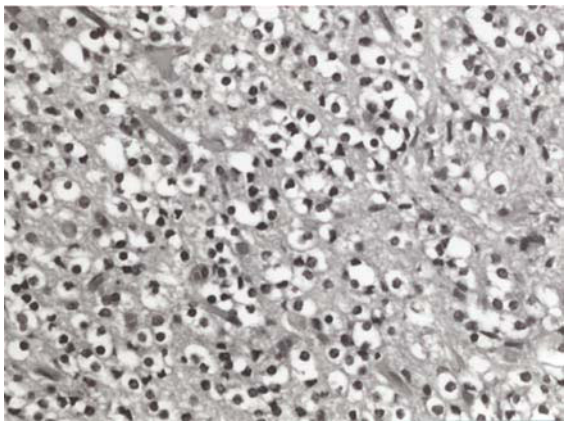

Fig. 3. Fibrillary and vascularized background of oligodendroglioma: many calcium spherites were seen among oligodendrocytes (H&E, x200).

Discussion

Oligodendrogliomas of the cerebrum account for 1% of pediatric brain tumors[1,2]. Posterior fossa localized oligodendrogliomas have been reported randomly in the literature. There are only six cases in the literature reported to date and none was cystic. The first case of cerebellar oligodendroglioma in the literature was reported by Holliday et al.[4] in 1980. Packer et al.[5] reported four cases of oligodendroglioma of the posterior fossa in childhood. According to Packer et al, posterior fossa origin is relatively more common in childhood. Bhatoe[6] from India reported the "childhood cerebellar vermian oligodendroglioma" in 1999 (Table I).

The differential diagnosis among pilocytic astrocytoma and other astrocytomas is important, because the pilocytic astrocytoma has a better prognosis than diffuse astrocytoma counterparts, especially when it occurs in the cerebellum[7]. Rosenthal fibers assist in distinguishing the pilocytic astrocytoma from other variants. These fibers, typical structures for pilocytic astrocytomas, are highly eosinophilic, hyaline structures. They are round, oval, or beaded, with slightly irregular margins[8]. In addition, eosinophilic droplets of protein are sometimes found intracellularly in association with Rosenthal fibers. Their bright pink color, similar to Rosenthal fibers, distinguishes them from mucoid degeneration in oligodendrogliomas. Neither Rosenthal fibers nor eosinophilic droplets were present in this cerebellar tumor.

Table I. Cases of Cerebellar Oligodendrogliomas in Childhood

Authors and year	Patients	Mean age	Pathology
Holliday et al.[4], 1980	1	--	Oligodendroglioma
Packer et al.[12], 1985	4	7.5	Malignant oligodendroglioma[3] Oligodendroglioma[1]
Bhatoe et al.[6], 1999	1	--	Oligodendroglioma

--: not available.

The diagnosis of oligodendrogliomas or ependymomas is suggested preoperatively when intratumoral or peritumoral calcification is noted on neuroimaging studies. In this case neither MRI nor cranial computed tomography revealed any calcification. The tumor was cystic and contrast enhancement was seen in the T1-weighted images. Preoperative diagnostic studies indicated cerebellar cystic astrocytoma. The diagnosis is achieved histologically by pathological examination.

The cellular features of ependymomas vary between fibrillar and epithelial, posing special problems of differentiation, not only from other gliomas. Presence of rosettes would confirm suspicion of an ependymoma, but some samples of ependymoma also lack rosettes. Clear cell ependymomas, uncommon gliomas, resemble mixtures of oligodendroglioma and ependymoma.

They usually include perivascular rosettes and cilia, which are absent in oligodendrogliomas. A pure oligodendroglioma is less fibrillar than clear cell ependymoma[9]. The pure oligodendroglioma differs from other gliomas, except for a few ependymomas, in having an epithelioid rather than a fibrillar appearance. This appearance is most evident within the central portion of the neoplasm, which is mostly crowded with neoplastic cells. Well-differentiated oligodendrogliomas usually have sheets of monotonous cells with uniform central nuclei, surrounded by a perinuclear clear halo of cytoplasm, therefore resembling fried eggs[10]. Perinuclear halos were also an important feature of the biopsy specimens of our case. There is a delicate network of capillaries, and it contains numerous foci of calcification. However, microcalcospherites are also commonly seen in other glial tumors such as ependymomas and pilocytic astrocytomas.

Dysembryoplastic neuroepithelial tumor (DNT) has been described in the posterior fossa[11], and may show an oligodendroglioma-like hypercellularity. The nodules of DNT are composed of cells more uniform in size with nuclear chromasia than those of oligodendroglioma. Unlike the nodules occasionally seen, nodules of DNT are more discrete and patterned. In DNT, particularly paranodular and internodular cortices include mucin accumulation and isolation of neurons within mucous pools ("floating neurons") rather than satellitosis. Intra nodular cells are often arranged in clusters or intricate patterns, unlike the cells of oligodendroglioma.

Subarachnoid metastatic disease (SAMD) secondary to a dissemination of childhood primary central nervous system neoplasms is well documented[12,13]. SAMD is frequently a thin coating on the cord, nerve roots, or meningeal surface[14,15]. Sensitive evaluation for SAMD requires cytopathologic evaluation of the cerebrospinal fluid[13], but several series have documented that even multiple samples of CSF may not yield an accurate diagnosis[16]. In our case, preoperative examination of CSF was not positive for malignant cells. On the basis of their experience, Packer et al.[5] suggested local and presymptomatic craniospinal radiation for all children with oligodendroglioma of the posterior fossa. But because of the rarity of posterior fossa localized oligodendrogliomas, there is no evidence that radiation therapy prolongs survival in these cases. Only local radiation was performed in this case.

Finally, although cerebellar oligodendrogliomas are very are lesions, they should be kept in mind in pediatric patients.

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Monocular temporal hemianopia in a young patient

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SUMMARY: Acaroğlu G, Güven A, İleri D, Zilelioğlu O. Monocular temporal hemianopia in a young patient. Turk J Pediatr 2004; 46: 98-100.

A 12-year-old girl presented with a history of sudden visual hemi-field loss in the left eye. The visual field defect was a clear-cut temporal hemianopia in the left eye; eye was normal. Complete eye examination and neuro-imaging of brain and opto-chiasmal region revealed normal structural findings. The visual field defect was suspected to be non-organic. This assumption was proven to be the diagnosis when simultaneous binocular fields showed the same pattern, although the contralateral eye's nasal hemi-field was intact. This symptom was alleviated by reassurance and placebo treatment.

Key words: functional visual loss, monocular temporal hemianopia, non-organic visual field defects, opto-chiasmal junction.

A clear-cut monocular temporal hemianopia requires an intracranial lesion localized in a very specific para-chiasmal area to affect only the crossing nasal retinal fibers from the ipsilateral eye. A case presenting with such a visual field defect is reported to discuss the etiologic possibilities and to demonstrate the usefulness of simultaneous binocular static perimetry in the differential diagnosis.

Case Report

A 12-year-old girl realized, after staring at the sun for a while, that she could not see in the left hemi-field of her left eye. She was taken to a nearby university hospital where the interpretation of the findings was left homonymous hemianopia. Magnetic resonance imaging of the brain was obtained which was reported as normal.

She was referred two days later when her visual field defect (VFD) remained the same in repeated testing, for an opinion regarding her visual fields.

Her visual acuities were 20/20 in both eyes and color vision was normal. She had equal pupils that were normally reactive to light and near stimuli. The optic nerves and retinal periphery appeared normal on dilated fundus examination. She was complaining about a frontal headache and left-sided eye pain. There were no other neurological symptoms. Her past medical history was insignificant. The results of her visual field testing with static perimetry are shown in Figures 1a and 1b.

A pediatric neurologist was consulted, who ruled out hemi-spatial visual inattention and decided her complete neurological exam was normal. An EEG was scheduled in order to eliminate any central nervous system pathology without a corresponding structural lesion on neuro-imaging. Although her brain magnetic resonance imaging (MRI) was normal, it was repeated with special attention to the chiasm and left opto-chiasmal junction. The next day the patient returned with the new, (again normal) MRI. At this time, we strongly suspected a functional VFD and requested she do another testing, this time with both eyes open. The result of her binocular visual field test, which is shown in Figure 2, left us confident that we were dealing with a functional monocular temporal hemianopia.

Further consultation with her parents revealed that she was a bright student, and that she had received much attention from her teacher at the time her symptom appeared. Her parents were informed about the possible situation. It was explained to the patient that if there was no alleviation of the symptom with medicine, we would "unfortunately" have to request an EEG. We prescribed vitamin supplements and non-steroidal anti-inflammatory eye drops to be administered "hourly".

She came in the next day stating that she was much better and ready to have a new visual field test. Her left visual field is shown in Figure 3. The "blind" field was sliding towards the temporal periphery. She and her parents were shown the

progression to normal in her visual field, and were sent home with reassurance and with an appointment two weeks later, at which time she demonstrated excellent visual field on testing.

Discussion

A patient with a monocular temporal hemianopia is likely to have a lesion in the ipsilateral optic nerve, close enough to the chiasm to selectively impair conduction in crossing nasal retinal fibers from the ipsilateral eye, but too anterior to affect crossing nasal retinal fibers from the contralateral eye. The combination of a relative afferent papillary defect (RAPD), with or without optic disc pallor on the side of the monocular temporal field loss implicates compression of the optic nerve at its junction with the chiasm[1]. Hershenfeld et al.[2]

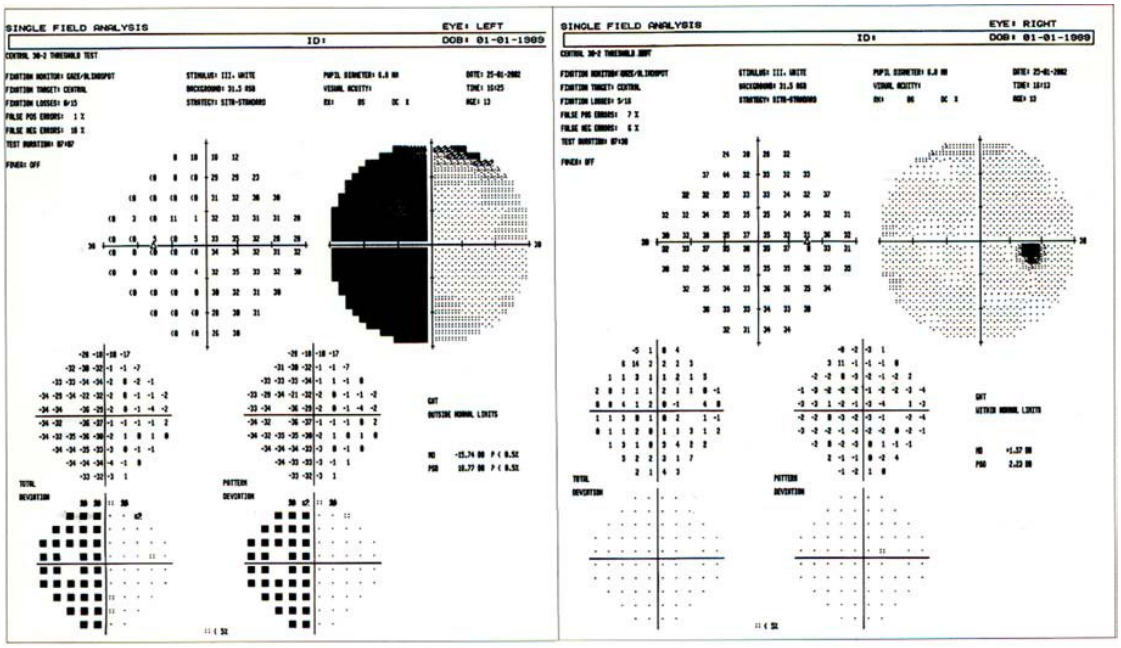

Fig. 1. Initial left (a) and right (b) visual fields of the patient.

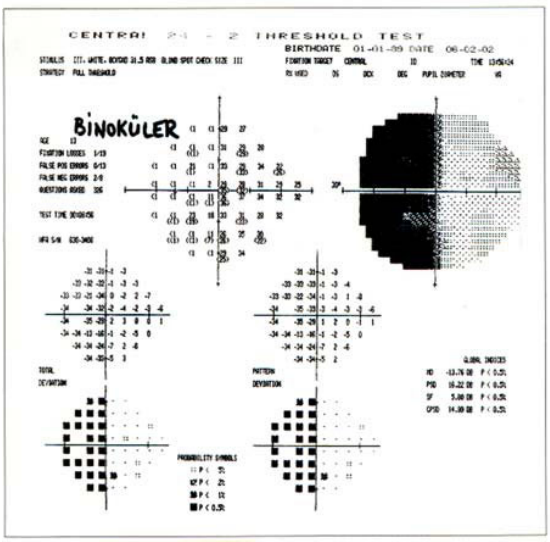

Fig. 2. Binocular simultaneous visual field of the patient.

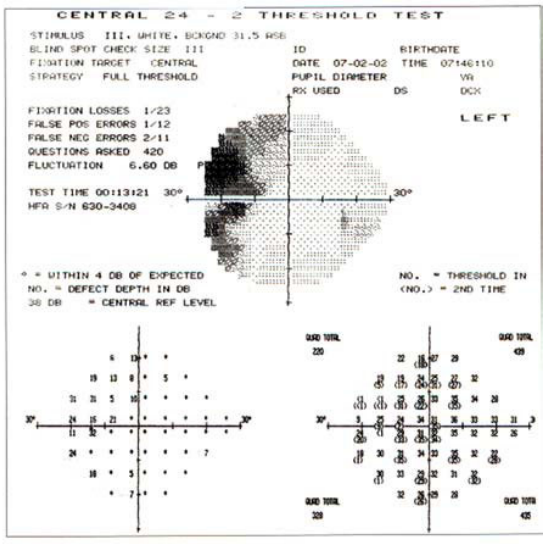

Fig. 3. Left visual field of the patient, performed one day after the diagnosis.

reported 24 cases of monocular temporal hemianopia, 19 of which were caused by juxta-sellar lesions, primarily pituitary adenomas. Most of the cases had RAPDs. Only two cases were regarded as functional VFDs.

Absence of an RAPD and normal neuro-imaging of the para-sellar region implied that there was no structural evidence for our patient's symptom. Therefore, in order to definitely diagnose the functional nature of the finding, we performed binocular simultaneous visual field testing. This method is specifically recommended for such monocular VFDs[3,4]. A "real" temporal hemi-field defect is expected to be smaller and more peripheral when viewed binocularly, with the help of the contralateral eye's normal nasal hemi-field.

Gittinger et al.[5] reported four adults whose initial symptoms were complete monocular temporal hemianopia, headache and eye pain. The functional nature of the VFDs was verified with binocular simultaneous testing. Assi et al.[6] reported two such cases and demonstrated spontaneous improvement towards normal.

Non-organic ocular disorders in children are mostly encountered in girls around age 10. The condition is usually bilateral and the commonest complaints are blurred vision, distorted or small images, and, only occasionally, VFDs. Tunnel vision is the most frequent VFD. Hemianopias, especially monocular hemianopia, are rare[7].

It should also be mentioned that automated static perimetry, as currently practiced, cannot differentiate functional from organic visual field loss[8]. The patients can produce reproducible non-organic VFDs and do not show fixation losses or increased number of false positive/negative errors[3], as was the case in our 12-year-old patient.

In a study of functional visual complaints, psychosocial problems relating to parental divorce, poor school performance and attention-getting behavior were common in the young patients[9]. Catalano et al.[10] stated that associated signs and symptoms such as headaches, diplopia, micropsia etc. were common in these children. Their experience also suggested that regardless of severity, reassurance and follow-up were the most effective therapy and psychiatric referral was only rarely necessary.

It is useful to demonstrate the non-organic nature of the situation to the parent and reassure them about the excellent prognosis. The child should also be informed that s(he) has a problem, which s(he) is absolutely capable of overcoming. The patient should only be referred to the psychiatrist if a minimal follow-up period does not eliminate the symptoms[7,10]. We spoke to the patient and her parents separately using appropriate terms and requested the parents not to confront the child, but rather support and encourage her. We also added a short-term placebo treatment to our reassurance, which was effective in 24 hours. The patient's symptom showed marked resolution overnight, and complete resolution followed in less than two weeks. The interesting example emphasizes the capability of a child to produce such a specific functional VFD and demonstrates what proper management should have been. Monocular temporal hemianopia without RAPD and with normal neuroimaging should have prompted us, at the first visit, to perform a binocular simultaneous test before going into consultations and more specific investigations.

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Isolated hypoglossal nerve palsy in a child

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SUMMARY: Aynacı FM, Şen Y, Boz C, Orhan F. Isolated hypoglossal nerve palsy in a child. Turk J Pediatr 2004; 46: 101-103.

We report an 11-year-old boy who had isolated hypoglossal nerve palsy one week after symptoms and signs of urticarial lesions. Neuroradiological examinations and other investigations for etiology of hypoglossal nerve palsy and urticaria were normal. We suggest that all patients with hypoglossal palsy must be carefully evaluated for atypical findings and etiologies.

Key words: hypoglossal nerve palsy, urticaria.

Except for paresis of the facial nerve, mononeuropathies in childhood are very rare. Isolated hypoglossal nerve palsy is a rare condition and may be due to vaccination, aneurysms, trauma, dislocation of vertebrae, intracranial tumor or infectious processes such as infectious mononucleosis. In the literature, there are a few reports about isolated, unilateral hypoglossal nerve palsy[1-9].

In this report, we present a patient with isolated hypoglossal nerve palsy following urticarial lesions which might have been due to preceding viral infections.

Case Report

An 11-year-old male patient was well until four weeks before admission, when he experienced symptoms and signs of urticaria on his body and in his oral cavity. Corticosteroid and antihistaminic therapy was given orally in a local hospital. One week following the onset of urticaria, the patient noticed his tongue was atrophic and deviated to the right side on protrusion. There was no history of trauma, vaccination, viral infection, stroke or surgery. Physical examination revealed blood pressure of 110/80 mmHg; skin was normal in appearance. He did not have lymphadenopathy or organomegaly. He was alert and cooperative, and his neurological examination was completely normal except for findings in the tongue. The right side of the tongue was atrophic and deviated to the right side on protrusion (Fig. 1), and fasciculations were noted.

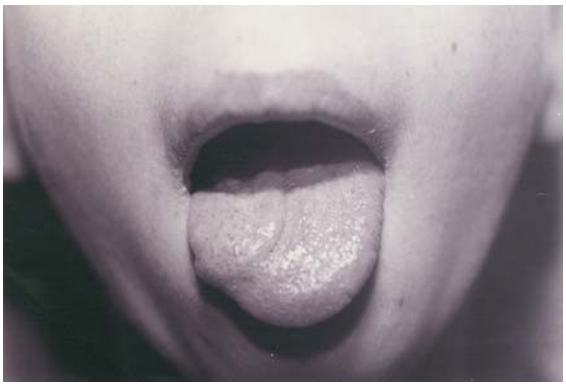

Fig. 1. The right side of the patient's tongue is atrophic and deviates to the right side on protrusion.

On laboratory investigations: the routine complete blood cell count, peripheral blood smear, urinalysis findings, biochemical investigations, slide test for infectious mononucleosis (monospot), herpes simplex virus IgM and G, anti cytomegalovirus (CMV) IgM and G, and Epstein-Barr virus (EBV) VCA IgM were negative. Epstein-Barr virus VCA IgG was positive in titers: 3.1 (N:<1.0). VDRL, ANA, anti dsDNA, ASO, CRP, Latex, Hbs Ag and other hepatitis markers, blood immunoglobulin levels, virus panels including respiratory syncytial virus, adenovirus, influenza A and B, and parainfluenza were normal. Throat swab culture for streptococcal pharyngitis and skin prick tests for common allergens were negative. C1q esterase level was normal. No parasite was detected on stool investigation.

Electrophysiologic evaluation was performed three weeks after the onset of symptoms using Nihon Kohden Neuropach 2 EMG equipment. Compound muscle action potentials (CMAPs) were recorded from lingual muscles with surface clip electrodes. Active recording electrode was placed over ventral surface of tongue (middle of tongue surface, 1 mm from midline) and reference electrode 3 cm proximal. The stimulus was supramaximal, 0.2 ms in duration, and cathode proximal. Nerve conduction studies of left hypoglossal nerve were normal, but right side showed markedly low CMAPs amplitudes with prolonged distal latency. Concentric needle electromyography (EMG) of the right side revealed 2+ fibrillation and positive sharp waves with no recruited motor units. Electrodiagnostic studies repeated five months later showed that right hypoglossal CMAPs amplitudes were midly increased. On needle EMG rare recruited motor units action potentials appeared with 1+ fibrillation.

The chest roentgenography, X-ray of the skull and sinus roentgenography were normal. Cranial and cervical magnetic resonance imaging (MRI) did not reveal any brain tumor or ischemic lesion. On the MRI, hypoglossal nerve and hypoglossal foramen were normal. He was treated with multivitamins, and examined periodically every other week. Now, at the 20th week of therapy, minimal recovery was recorded clinically and on EMG.

Discussion

Hypoglossal nerve motor composition is highly complex and not fully understood, with the nucleus consisting of four topographically distinct subnuclear columns[4]. Peripheral lesions of the hypoglossal nerve are generally classified into four categories: extramedullary intracervical lesions, hypoglossal foramen lesions, extracranial lesions of the XIIth nerve at the base of the skull, and cervical hypoglossal nerve lesions[7]. In our patient, investigations of the cervical base of the skull showed no abnormal findings.

Isolated, unilateral hypoglossal nerve palsy is rare and usually results from vaccination, carotid and vertebral artery aneurysms, trauma, dislocation of the first cervical vertebra, intracranial neurilemoma or from infectious mononucleosis[1-3,5,6,8,9]. Keane[4] described the causes and characteristics of hypoglossal nerve palsy in a review of 26 years of personal experience. In this patients, the most common cause was tumors and the second most common gunshot wounds. Other causes included stroke, hysteria, multiple sclerosis, surgery, Guillain-Barré neuropathy and infection. Keane could not describe any specific cause in 3% of his patients.

Urticaria affects up to 20% of the population at some time. Acute urticaria may be produced by a number of factors such as infectious agents, foods, insect bites, inhalants, drugs, physical factors, collagen vascular diseases, genetic disorders, neoplasms and hyperthyroidism[10]. The most common infectious causes of the urticaria are streptococcal pharyngitis, sinusitis, hepatitis, mononucleosis, viral infections and parasites. In our patient, we could not establish the cause for urticaria except for EBV IgG positivity. Investigations for collagen vascular diseases were normal. There was no history of drugs, insect bites, inhalants, physical agents, nor any notable family history. In our patient, we thought that the urticaria might have been due to preceding viral infections.

In cases of infectious mononucleosis, the incidence of dermatitis is 3% to 19%. It appears during the first few days of illness. Sometimes urticarial or scarlatiniform eruptions are seen[11]. Neurologic symptoms may occur following acute EBV infection in the absence of symptomatic infectious mononucleosis[12]. Neurologic complications of EBV infection include lymphocytic meningitis, encephalomyelitis, polyneuritis and mononeuritis[6]. While any of the cranial nerves may be affected during EBV infection, palsies of cranial nerve VII are most common. Other forms of cranial nerve involvement include anosmia, bilateral sensorineural hearing loss, hypoglossal nerve palsy, and extraocular muscle palsies. In younger children, EBV infections may not have characteristic symptoms and heterophil antibody titers may be negative. The acute illness may be diagnosed if VCA-specific IgM is present in serum. VCA IgM responses disappear after several months, whereas VCA+IgG levels persist for life[11]. In our patient, VCA IgG level was increased but VCA IgM level was normal. For that reason we cannot say that the urticaria and hypoglossal palsy were due to EBV infection.

Only 15% of the patients with hypoglossal paralysis recovered completely or nearly completely. A rapid onset of hypoglossal nerve

palsy resolves in a minority of patients without specific diagnosis or treatment[1,7]. In our patient, we noted minimal recovery at the 12th week. On the EMG reevaluation there was recovery at needle EMG findings but there was no change at nerve parameters.

As a result, we believe that all patients with hypoglossal nerve palsy must be carefully evaluated for systemic disorders and infectious agents such as EBV others.

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