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NEURONAL MIGRATION DISORDERS PART I: TERMINOLOGY, CLASSIFICATION, PATHOPHYSIOLOGY, EEG AND EPILEPSY*

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SUMMARY: Turanlı G, Yalnızoğlu D, Renda Y. (Neurology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Neuronal migration disorders. Part I: terminology, classification, pathophysiology, EEG, and epilepsy. Turk J Pediatr 1998; 40: 473-480.

Intractable epilepsies and partial epilepsies, which make up a great majority of epileptic disorders, are not better recognized and their etiologies unveiled with the help of the new imaging techniques. The development of magnetic resonance imaging (MRI) permits the accurate diagnosis while the patients are alive of the neuronal migration disorders (NMD), which constitute an important group of intractable epilepsies. Previously, NMD cases were described by neuropathologists from autopsy materials, and many of these developmental disorders were not considered compatible with prolonged survival. Cerebral malformations due to neuronal migration anomalies are described in association with motor and mental retardation, learning disabilities, microcephaly, dysmorphic features and epilepsy. Neuronal migration takes place in all parts of the central nervous system (CNS) during the shaping process of the CNS; it actually includes both the central and peripheral nervous systems. However, in common usage the meaning of "neuronal migration disorders" is restricted to the neocortex. *Key words: neuronal migration, cortical dysplasia, epilepsy.*

Terminology and Classification

The terminology of neuronal migration disorders (NMDs) is rather complex, and there seems to be an urgent need for consensus on classification (Table I). The following list consists of the most commonly accepted definitions:

1. *Cortical dysplasia (focal or diffuse)* is a general term indicating all NMDs. Nodular cortical dysplasias are superficial cortical nodules, scattered over the surface of the brain with a predilection for the frontal lobe. Neurons of varying size are grouped around a radial bundle of myelinated fibers.
2. *Heterotopia* is defined as an island of gray matter surrounded by white matter, located between the ventricular wall and the cortical mantle.

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Table I: Classification of Neuronal Migration Disorders

I. Generalized
1. Agyria or lissencephaly
a) Type I (four-layered cortex)
– Isolated forms
– Miller-Dieker syndrome
– Non-classified forms
b) Type II (cortex with no distinguishable layers)
– Walker-Warburg syndrome
– Fukuyama type congenital muscular dystrophy
– Muscle-eye-brain disease
– Non-classified forms
– Neu-Laxova syndrome
– Cerebrocerebellar syndrome
2. Pachygyria (isolated mild cases)
3. Polymicrogyria
II. Localized
1. Schizencephaly
2. Porencephaly
3. Localized forms of pachygyria
– Bilateral central pachygyria
– Hemimegalencephaly
4. Nodular or laminar heterotopias

From Dobyns et al.[26] (1984), Palmini et al.[14] (1991).

3. *Agyria (lissencephaly)* is characterized by a lack of gyration or abnormally broad or simplified gyria[1]. Only Sylvian and Rolandic fissures are partially preserved. Opercularization and demarcation of insula are not seen. There are two types of lissencephaly from the clinicopathological point of view: in type I lissencephaly, agyric and pachygyric areas are seen together. It has a four-layered cortex. Cerebellar and callosal agenesis, ventricular dilation, heterotopias and other malformations may also be associated with this condition. In type II lissencephaly, there are no cortical layers but disorganized neurons, fibroglial bands and vessels penetrating dispersed neurons are characteristic findings for this entity.
4. *Pachygyria* is the presence of thick and broad gyri decreased in number. Absence of gyri is seldom seen. There are intermediate cases with agyria-pachygyria in different areas of the brain (agyria-pachygyria complex)[1].

5. *Polymicrogyria* is when there are multiple miniature malformed convolutions. Neurons reach the cortex but are not properly located at their preprogrammed position. Bilateral, symmetric location compatible with a specific arterial tracing may be observed as well as unilateral asymmetric polymicrogyria[1].
6. *Polygyria* is characterized by multiple shallow sulci and gyri with normal microscopic structure which differentiates it from polymicrogyria[1].
7. *Macrogyria* broad gyri with normal cellular architecture.
8. *Hemimegalencephaly* denotes manifest asymmetrical enlargement, particularly but not exclusively of one cerebral hemisphere. Hemimegalencephaly is histologically characterized by disturbed neuronal migration, normal architecture and glial proliferation.
9. *Diffuse subcortical laminar heterotopia (double cortex syndrome, band heterotopia).* The surface of the brain has normal appearance with a thick cortex. Underneath the normal cortex lies a second band of heterotopic gray matter separated from the normal cortex by a thin layer of white matter.
10. *Schizencephaly* is defined as bilateral holohemispheric cleft (fused or open) in the region of sylvian fissures. Neuropathological features include failure of normal sulcal and gyral development on the hemispheric surface in the region of and within the clefts, and gray matter heterotopias in the subcortical white matter beneath the cleft(s)[2,3].
11. *Perisylvian dysplasias (unilateral/bilateral opercular macrogyria/ polymicrogyria)* are located on cortical layers of sylvian fissures. They have a pachygyric appearance which cannot be properly shown on magnetic resonance imaging (MRI). There are bilateral, symmetrical thick and broad gyri and scant sulci at the insular and opercular regions. The clinical features include mental retardation, developmental pseudobulbar palsy, epilepsy and/ or arthrogryposis multiplex congenita.
12. *Minor cortical dysgenesis* consists of nests of subpial, ectopic neurons and focally disorganized cortical layering. These lesions are causative factors for partial epilepsy and mental deficiency of unknown etiology. Several neuronal dysgeneses have been reported in autism[4].

Pathophysiology

Proliferation of neuroblasts in the periventricular germinal matrix and their migration to the cortical plate begin around the sixth week and extend to midgestation period[5]. It has been shown in the developing brain that neuroblasts, proliferating in the periventricular germinal matrix, migrate to their final

preprogrammed position in the cerebral cortex via the radial glial fibers. This neuroblast-glial fiber interaction is maintained in a dynamic fashion through cell adhesion molecules[6]. When they arrive at the cortical plate, they detach from the radial glial fibers and from the cortical layers in an "inside-out" fashion. The first cells to migrate take a deeper position in the cortex; cells migrating later are laid down more superficially[5-7]. Cortical gyrus formation is determined by physical stress generated by an imbalance between the number of cells in the superficial and deeper cortical layers[8]. New findings suggest that final functional differentiation of a given neuroblast is not predetermined before migration but rather a complex function of post-migratory chemical interactions[9-11].

Cell multiplication (cytogenesis) and cell migration (histogenesis), namely, separation of the main embryonic sheets, neurulation, neuronal multiplication, neuronal migration and regional development of the cerebral vesicles take place in the first half of gestation.

In the second half of gestation, growth and differentiation of neuronal and glial cells take place: cell growth and axonal dendritic arborization, connections and synaptogenesis, myelination and gliogenesis. Main mechanisms are disturbances of "residual" histogenesis, prenatal hydrocephalus, perfusion failures/hypoxias, infections, trauma, and metabolic disturbances[4].

Neuronal production and death determine the neuronal complement of the mature brain. Programmed cell death is a normal developmental event; however, destructive processes may result in additional neuronal loss. Disturbances in cell production, in cell death or in the balance between them are the basis for numerical neuronal deficits in many microcephalies.

Most neurons destined for the human neocortex are produced before 20 weeks of gestation. Residual but important histogenetic activities continue during the last 20 weeks of pregnancy. Depending on the timing, location and the extent of the interference with the neuronal migration process, different types of neuronal migration disorders occur. Metabolic, chromosomal, hypoxic, ischemic, and infectious disorders and toxic and physical insults in the human embryo or fetus may interfere with neuronal migration, leading to severe clinical findings in extrauterine life.

Pathology ranges in severity from complete agyria (lissencephaly) to isolated areas of cortical heterotopia. Clinical spectrum varies from asymptomatic to severely symptomatic leading to death.

Electroencephalography and Epilepsy

Modern imaging techniques contributed a great deal to the etiological classification and diagnosis of epilepsies due to NMDs. In a retrospective study

of 303 patients with epilepsy, MRI was performed over a three-year period with special emphasis on neuronal migration disorders[12]. Thirteen patients with epilepsy and NMD demonstrated on MRI were identified. Four had schizencephaly, one hemimegalencephaly, two isolated heterotopias and six had localized pachy-and/or polymicrogyria. Magnetic resonance imaging can detect focal cortical dysplasia which corresponds to the epileptogenic focus on electroencephalography (EEG), single photon emission tomography (SPECT) may help to detect a functional abnormality in the same region[13].

According to Palmini et al.'s[14] series in focal cortical dysplastic lesions, patients present with complex partial seizures (67%), atonic-tonic drop attacks (27%) and status epilepticus[14]. Although EEG may reveal an epileptic zone localized in a cerebral lobe, half of all patients have diffuse epileptic foci. In this series, 28 out of 32 patients were treated surgically, while in four patients seizures were satisfactorily controlled by antiepileptic medication. In Guerrini et al.'s[15] series, patients with a focal gyral anomaly presented with intractable, sterotypic complex partial seizures. In this group generalized seizures were never seen and the EEG abnormalities remained confined to the same area. Such patients benefit from partial frontal lobectomy. Seizures were the presenting symptom in the majority of these patients; the associated neurological features such as hemiparesis were discovered after careful neurological examination. Focal seizures beginning apparently in normal children or adolescents without obvious antecedent risk factors and evolving within three years to life threatening status epilepticus should suggest occult focal cortical dysplasia[16]. Differential diagnosis should include obvious structural lesions, Rasmussen's encephalitis, and mitochondrial disease. Normal MRI studies in such patients do not exclude NMD.

A syndrome consisting of bilateral perisylvian cortical dysplasia, pseudobulbar palsy, secondary generalized epilepsy and mental retardation has been recognized[17]. Bilateral perisylvian dysplasias present with generalized convulsive and complex partial seizures and drop attacks; in some cases perioral clonic movements are observed. Electroencephalography reveals generalized epileptiform abnormality and multifocal discharges. When drop attacks cause significant disability, callosotomy is indicated. Patients with drop attacks do not benefit from resective surgery[14]. Lesions involving the perisylvian region also lead to anterior and inferomesial temporal epileptic discharges. Resection of these structures partially improves but does not cease the seizures[18]. Infantile spasms may be the presenting seizure type in some patients with the congenital bilateral perisylvian syndrome[19].

Patients with diffuse cortical dysplasias ("double cortex syndrome") experience drop attacks, partial seizures with secondary generalization and Lennox-Gastaut syndrome. Electroencephalography reveals generalized slow spike and wave

or multifocal epileptic discharges. Drop attacks leading to disability may improve after callosotomy[14].

Hemimegalencephaly and megalencephaly present with lateralized motor manifestations, secondary generalization and drop attacks. Unilateral and focal epileptogenic regions are recognized on EEG. When the motor disability is progressing to hemiparesis, a modified hemispherectomy may be performed[14-20-21]. In patients with mild motor disability, excision of the most active epileptogenic areas within the most affected hemisphere may improve seizure control[14].

In the group of nodular and laminar heterotopias, a case with temporal lobe epilepsy is reported. Patients with subcortical nodular heterotopia present with partial motor seizures secondarily generalized. Resective surgery leads to improvement in seizure frequency and severity[14].

It is not known whether EEG is clinically significant in NMD cases. However, when surgery is the therapy of choice, EEG may be an important prognostic sign. Electroencephalography findings of different types of dysplasias are reported in Quirk et al.'s[22] series. In diffuse cortical dysplasias, sharp waves with high amplitude rhythmic activity are very specific yet sensitive. This finding is more common in agyria when compared with macrogyria. In patients with macrogyria, abnormal rapid activity is observed more frequently. Localized cortical dysplasias present with focal or lateralized anomaly in 50 percent of patients; in the other 50 percent, EEG findings findings are similar to those in diffuse cortical dysplasias. Electroencephalography may be normal in all types of cortical dysplasias, especially those with subcortical anomaly.

Schizencephaly is a regional disturbance of cerebral hemispheres presenting in childhood with partial seizures, hemiparesis and variable mental retardation. Schizencephaly is reported to present with neonatal seizures as well[16].

Most of the patients with NMDs who present with intractable epilepsy have a focal unilateral dysplastic lesion. In several series with intractable epilepsy, surgical intervention is required[23]. The success of the surgery is dependent on the extent of removal of the visible abnormal area, which is more important than the electroencephalographically or corticographically defined epileptic tissue[24]. In patients with a secondary generalized epileptic process and drop attacks, callosotomy has been proven as useful palliation[25].

REFERENCES

1. Harding BN. Malformations of the nervous system. In: Adams JH, Duchen LW (eds). Greenfield's Neuropathology (5th ed). London: Edward Arnold; 1992: 521-638.
2. Yakovlev PI, Wadsworth RC. Schizencephalies: a study of congenital clefts in cerebral mantle. I. Clefts with fused lips. J Neuropathol Exp Neurol 1946; 5: 116-130.

3. Yakovlev PI, Wadsworth RC. Schizencephalies: a study of congenital clefts in cerebral mantle. II. Clefts with hydrocephalus and lips separated. J Neuropathol Exp Neurol 1946; 5: 169-206.
4. Evrard P, Miladi N, Bonnier C, et al. Normal and abnormal development of the brain. In: Rapin I, Segalowitz SJ (ed). Handbook of Neuropsychology. Child Neuropsychology Vol. 6. Amsterdam: Elseiver Science Publishers; 1992: 11-44.
5. Rakic P. Defects of neuronal migration and the pathogenesis of cortical malformations. In: Boer GJ, Feenstra MG, Mirmiran M, Swaab DF, Haaren FV (eds). Progress in Brain Research Vol. 73. Amsterdam: Elsevier Science; 1988: 15-37.
6. Edelman GM. Cell adhesion molecules. Science 1983; 219: 450-457.
7. Angevine JB, Sidman RL. Autoradiographic study of cell migration during histogenesis of cerebral cortex in mouse. Nature 1961; 192: 766-768.
8. Richman DP, Stewart RM, Hutchinson JW, et al. Mechanical model of brain convolutional development. Science 1975; 189: 18-21.
9. Walsh C, Cepko CL. Cell lineage and cell migration in the developing cerebral cortex. Experientia 1990; 46: 940-947.
10. Walsh C, Cepko CL. Widespread dispersion of neuronal clones across functional regions of the cerebral cortex. Science 1992; 255: 434-440.
11. Bayer SA, Altman J, Russo RJ, et al. Cell migration in the rat embryonic neocortex. J Comp Neurol 1991; 307: 499-516.
12. Brodtkorp E, Nilsen G, Smevik O, Rinck PA. Epilepsy and anomalies of neuronal migration: MRI and clinical aspects. Acta Neurol Scand 1992; 86: 24-32.
13. Otsubo H, Hwang PA, Jay V, et al. Focal cortical dysplasia in children with localization related epilepsy: EEG, MRI and SPECT findings. Pediatr Neurol 1993; 9: 101-107.
14. Palmini A, Andermann F, Olivier A, et al. Neuronal migration disorders: a contribution of modern neuroimaging to the etiologic diagnosis of epilepsy. Can J Neurol Sci 1991; 18: 580-587.
15. Guerrini R, Dravet C, Raybaud C, et al. Epilepsy and focal gyral anomalies detected by MRI: electroclinico-morphological correlations and follow-up. Dev Med Child Neurol 1992; 34: 706-718.
16. Chamberlain MC, Press GA, Bejar RF. Neonatal schizencephaly: comparison of brain imaging. Pediatr Neurol 1990; 6: 382-387.
17. Kuzniecky R, Andermann F, Guerrini R. Congenital bilateral perisylvian syndrome: study of 31 patients. The CBPS Multicenter Collaborative Study. Lancet 1993; 341: 608-612.
18. Andermann F, Oliver A, Melanson D, et al. Epilepsy due to focal cortical dysplasia with macrogyria and forma fruste of tuberous sclerosis: a study of 15 patients. In: Wolf P, Dam M, Jan D, Dreifuss FE (eds). Advances in Epileptology Vol. 16. New York: Raven Press; 1987: 35-38.
19. Kuzniecky R, Andermann F, Guerrini R. Infantile spasms: an early epileptic manifestation in some patients with the congenital bilateral perisylvian syndrome. J Child Neurol 1994; 9: 420-423.
20. Vigevano F, Bertini E, Boldrini R, et al. Hemimegalencephaly and intractable epilepsy: benefits of hemispherectomy. Epilepsia 1989; 30: 833-843.
21. Tinuper P, Andermann F, Villemure JG, et al. Functional hemispherectomy for treatment of epilepsy associated with hemiplegia: rationale, indications, results and comparison with callosotomy. Ann Neurol 1988; 24: 27-34.
22. Quirk JA, Kendall B, Kingley DP, et al. EEG features of cortical dysplasia in children. Neuropediatrics 1993; 24: 193-199.

23. Palmini A, Andermann F, Olivier A, et al. Focal neuronal migration disorders and intractable partial epilepsy: a study of 30 patients. Ann Neurol 1991; 30: 741-749.

24. Palmini A, Andermann F, Olivier A, et al. Focal neuronal migration disorders and intractable partial epilepsy: results of surgical treatment. Ann Neurol 1991; 30: 750-757.

25. Kuzniecky R, Andermann F, Fusco L, et al. Corpus callosotomy in the management of the congenital bilateral perisylvian syndrome. Epilepsia 1990; 31: 639.

26. Dobyns WB, Stratton RF, Greenberg F. Syndromes with lissencephaly. I: Miller-Dicker and Norman syndromes and isolated lissencephaly. Am J Med Genet 1984; 18: 509-526.

The Turkish Journal of Pediatrics 1998; 40: 481-490

NEURONAL MIGRATION DISORDERS PART II: MAGNETIC RESONANCE IMAGING*

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SUMMARY: Saatçi I, Turanlı G, Renda Y. (Department of Radiology and Neurology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Neuronal migration disorders. Part II: magnetic resonance imaging. Turk J Pediatr 1998; 40: 481-490.

With the widespread use of magnetic resonance imaging (MRI), neuronal migration disorders (NMD), including lissencephaly, pachygyria, polymicrogyria, schizencephaly, unilateral hemimegalencephaly and gray matter heterotopia, are more frequently and easily diagnosed. When NMD is a diagnostic consideration, MRI should be the imaging method of choice with the high contrast between gray and white matter it provides and its high resolution multiplanar display of anatomy. Magnetic resonance imaging displays the size, configuration and distribution of cortical gyri and cortical thickness for the evaluation of possible lissencephaly, pachygyri and polymicrogyri. It will successfully demonstrate deposits of gray matter in abnormal locations when gray matter heterotopias are present. With its multiplanar imaging capability, MRI will demonstrate the cleft extending from the pial surface to the ventricular ependyma whether the lips of the cleft are fused or separate, thus providing the diagnosis of schizencephaly. *Key words: brain abnormalities, brain MRI studies, magnetic resonance imaging, neuronal migration anomalies, schizencephaly, heterotopia, focal cortical dysplasia.*

Neuronal migration disorders (NMD) are congenital malformations caused by insults to migrating neuroblasts during the 8th-24th gestational weeks. Until the advent of magnetic resonance imaging (MRI), computerized tomography (CT) has been of assistance in the diagnosis of this group of anomalies. Magnetic resonance imaging should be the imaging method of choice when NMD is a diagnostic consideration, since it is more sensitive and more specific than CT in detecting these anomalies. Furthermore, it better delineates the abnormality with its better contrast between gray and white matter and its high resolution multiplanar display of anatomy. However, recognition of NMD on images depends on awareness of the characteristic appearance of the entities and use of the proper imaging technique.

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Lissencephaly

The term lissencephaly refers to a paucity of gyral and sulcal development on the surface of the brain. Agyria is defined as the absence of gyri on the surface of the brain and is synonymous with "complete lissencephaly" (Figs. 1a,b). The term pachygyria designates a less marked abnormality with the presence of sulci delineating broad, abnormal brain convolutions[1]. Lissencephalies can be divided into a number of subcategories based upon the morphology of the smooth brain and the associated brain anomalies[2].

Type I lissencephaly (the agyria-pachygyria complex)

Most patients in this group have areas of both agyria and pachygyria (i.e. incomplete lissencephaly). the areas of agyria are most frequently parieto-occipital in location, whereas the pachygyric areas are most common in the frontal and temporal regions[1,2].

Imaging studies of type I lissencephaly reveal a smooth brain surface with diminished white matter and shallow, vertically oriented sylvian fissures (Figs 1a,b). A thin outer cortical layer is separated from a thick deeper cortical layer by a zone of white matter (the "cell-sparse zone") that seems to myelinate normally. The gross appearance of the brain resembles that of the fetus prior to 23rd-24th gestational weeks, when sulci normally begin to form. The cerebrum has "figure eight" appearance on transverse images as a result of the shallow, vertical sylvian fissures. In cases of severe agyria, sagittal images may show callosal hypogenesis. The ventricular trigones and occipital horns are enlarged, mostly because of the underdevelopment of the calcarine sulci; hypoplasia of the callosal splenium may play a role in some patients. The brain stem often

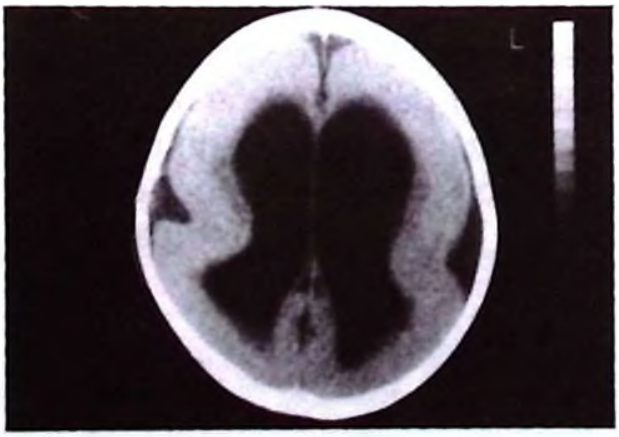

Fig. 1a

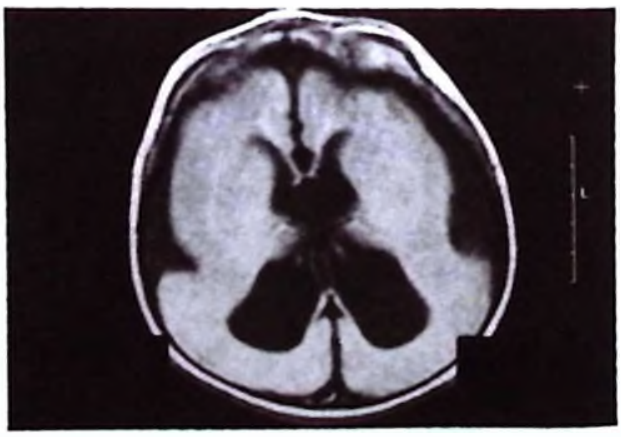

Fig. 1b

Figs. 1a,b: Type I lissencephaly
CT (a) and T1W (b) transverse MR images showing absence of cortical sulci (agyria or complete lissencephaly) with the exception of slyvian fissures, giving a "Figure eight" appearance to the brain. The lateral ventricles are enlarged, the cortex is thickened.

appears hypoplastic, probably because many of the corticospinal and corticobulbar tracts do not form[3].

Areas of pachygyria also have a thickened cortex, but broad gyri and shallow sulci are present. Pachygyria can be focal or diffuse. When focal, it can occur in any part of the brain. When diffuse, it is often associated with regions of agyria and tends to be more severe in the parieto-occipital region of the brain[4].

Type II lissencephaly (Walker-Warburg syndrome, Fukuyama's congenital muscular dystrophy, and related syndromes)

Type II lissencephaly is characterized pathologically by a thickened and severely disorganized unlayered cortex, which is disrupted by penetrating vessels and fibroglial bundles. Subcortical heterotopias are not rare. The meninges are thickened and densely adherent to the cortex, obliterating the subarachnoid space and resulting in hydrocephalus. The entirety of the cerebral hemispheres is involved[1,3].

On imaging studies, patients with type II lissencephaly have a thickened cortex with shallow sulci (which may appear intermediate between type I lissencephaly and diffuse polymicrogyria), microphthalmia and hypomyelination. More severe cases will have hydrocephalus, vermian hypogenesis, cerebellar polymicrogyria, dysgenesis of corpus callosum and, occasionally, an occipital cephalocele.

Diagnosis of microcephalia vera (type III lissencephaly) and *radial microbrain (type IV lissencephaly)* are solely based on histopathologic examination. *Microcephalia vera* is characterized by thin cortices, shallow sulci and markedly diminished callosal fibers (which originate and terminate in the outer cortical layers)[3] on pathologic examination of brain. The term *radial microbrain* has been used to describe a group of patients that were born at term with a markedly reduced brain size despite normal gyral patterns, absence of destruction or gliosis, normal cortical thickness and normal cortical lamination. The number of neocortical neurons was only 30 percent of normal. MRI scan may show microcephaly, delayed myelination and a slightly immature gyral pattern.

Diffuse polymicrogyria is sometimes referred to as *type V lissencephaly*[2]. The brain is diffusely smooth due to abnormal organization of cortical neurons, which results diffuse cortical dysplasia, or polymicrogyria. This is the type of lissencephaly seen in patients with cortical involvement from congenital cytomegalovirus infection[2].

Polymicrogyria (cortical dysplasia)

Polymicrogyria is a migration disorder in which the neurons reach the cortex but the normal six-layered lamination of the cortex is deranged. Thus, the term

cortical dysplasia may be more appropriate[2]. The results is formation of multiple small gyri. Small or large portions of the hemisphere can be involved. The most common location is around the sylvian fissure, particularly the posterior aspect of the fissure. However, any area, including the frontal, occipital and temporal lobes, can be affected.

Cortical dysplasia can have an irregularly bumpy surface or, paradoxically a smooth one, because the outer cortical layer fuses at the microsulci (Figs. 2a,b). It may have the appearance of pachygyria, with broad, thickened gyri, or it may look normal[4]. Cortical thickness in polymicrogyria is usually in the 5-7 mm range (normal 3 mm), whereas a cortical thickness of >8 mm is seen in almost all cases of pachygyria[3].

The dysplastic cortex can be flat and congruent to the arch of the normal cortex, or it may extend centripetally, appearing as if the cortex were buckled or folded inward (Figs. 3a,b and 4a,b). The character of the cortex in these regions of infolding is similar to that in superficial cortical dysplasia, with bumpy, irregular inner and outer cortical surfaces (Figs. 3a,b and 4a,b).

Typically, the dysplastic cortex is isointense to gray matter on all imaging sequences. T2 hyperintensity is present in the white matter subjacent to the dysplastic cortex in about 20 percent of patients, possibly caused by the same insult that resulted in the disorganization of the cortex (Fig. 2a). In less than five percent of the cases, calcification may be present[2]. Anomalous venous drainage is common in areas of the dysplastic cortex[5], particularly in regions where there is large infolding of the thickened cortex. In this instance, angiography is not indicated.

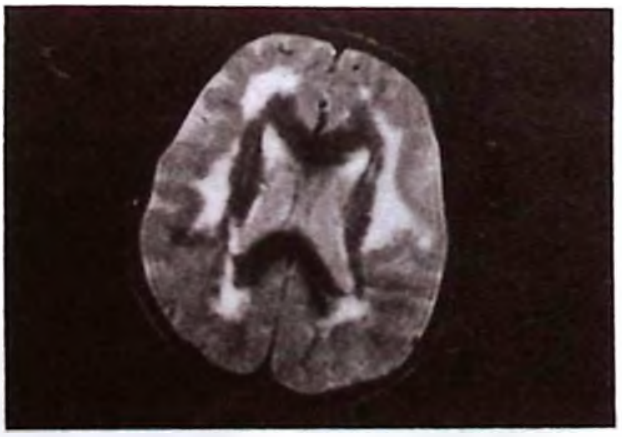

Fig. 2a

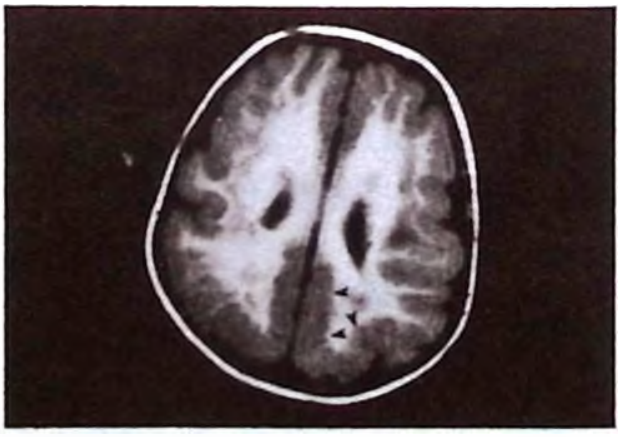

Fig. 2b

Figs. 2a,b: Polymicrogyria
T2W transverse images (a) demonstrates thickened cortex and abnormal high signal intensity in the hemispheric white matter. On T1W (b) image the microgyri can be identified (black arrowheads), particularly in the parietal region, leading to the diagnosis of polymicrogyria, in spite of the pachygyriclike appearance on T2W image.

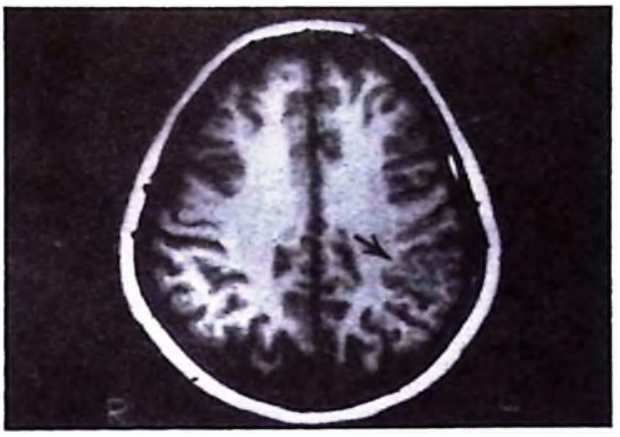

Fig. 3a

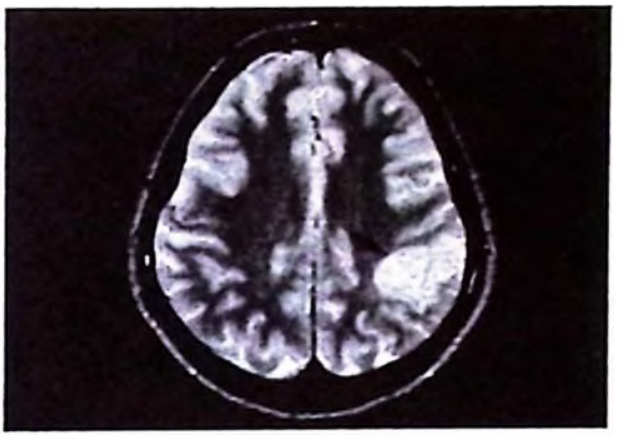

Fig. 3b

Figs. 3a,b: Focal cortical dysplasia
T1W (a) and T2W (b) transverse images showing a focal region of thickened cortex (black arrow) in the left parietal lobe with areas of trapped CSF in the infolding sulci (b).

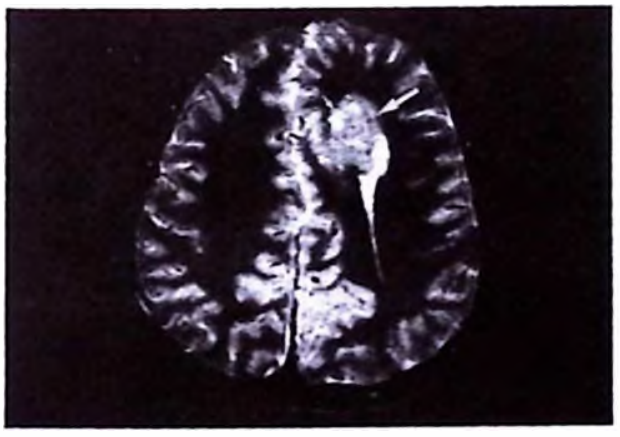

Fig. 4a

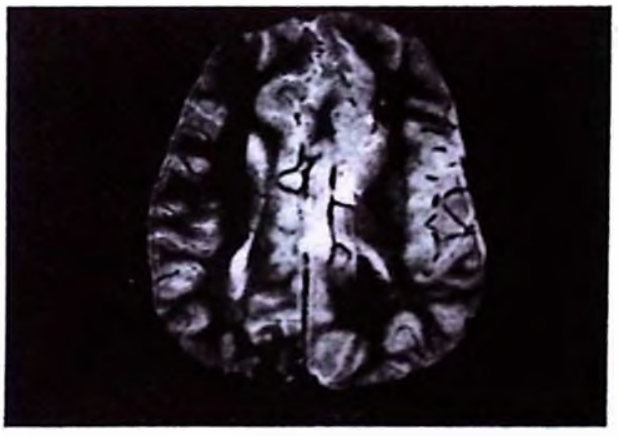

Fig. 4b

Figs. 4a,b: Gray matter heterotopia, focal cortical dysplasia
Consecutive T2W images (a,b) show the infolding of the cortex in the left frontal region, indenting on the lateral ventricle (large white arrow on figure a, black arrow on figure b). Areas of trapped CSF are seen within the heterotopic gray matter (small white arrow on figure a). Note that corpus callosum is absent, resulting in parallel configuration of the lateral ventricles and displacement of the pericallosal arteries.

A specific *syndrome of bilateral opercular cortical dysplasia (bilateral perisylvian dysplasia)* has been described, in which patients present with a syndrome of developmental pseudobulbar palsy (oropharyngeal dysfunction and dysarthria) and epilepsy[2,6]. Sectional imaging shows thick bands of gray matter in the sylvian and rolandic areas of both hemispheres; the cortical abnormality consists of polymicrogyria[7]. *Aicardi's syndrome* is another syndrome of cortical dysplasia with associated anomalies including interhemispheric cyst, gray matter

heterotopias, posterior fossa cysts, callosal anomaly, cerebellar hypoplasia, choroid plexus papillomas and microphthalmia. Myelination may be delayed[2].

Schizencephaly

Magnetic resonance imaging shows a gray matter lined cleft extending across the full thickness of the cerebral hemisphere, from the pial surface of the brain to the ventricular ependyma[8] (Figs. 5ab, 6a, 7). The cleft is commonly in the

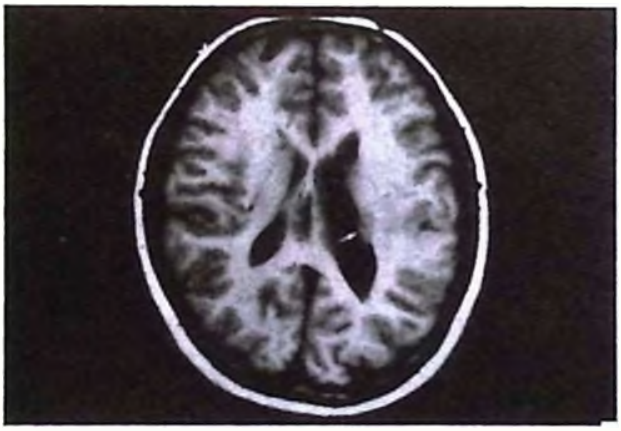

Fig. 5a

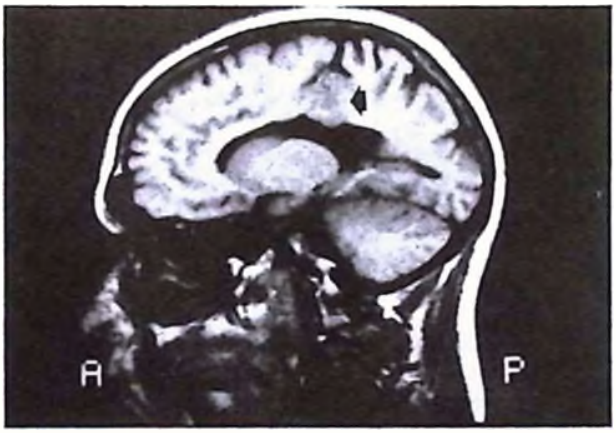

Fig. 5b

Figs. 5a,b: Unilateral closed-lip schizencephaly
a: T1W transverse image showing nodular gray matter (white arrow) at the wall of the slightly enlarged left lateral ventricle. The actual cleft of the schizencephaly could not easily be recognized on this particular image.
b: T1 weighed sagittal image demonstrating the cleft (black arrow) extending to the lateral ventricle completely fused medially with the gray matter lining. Note the dimple in the wall of the lateral ventricle indicating the continuity of the gray matter with the ventricle.

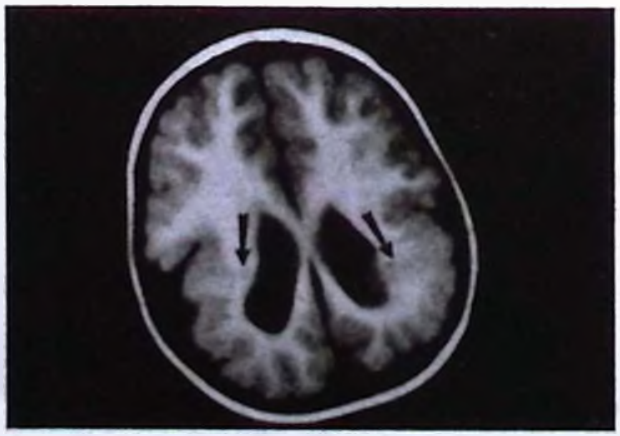

Fig. 6a

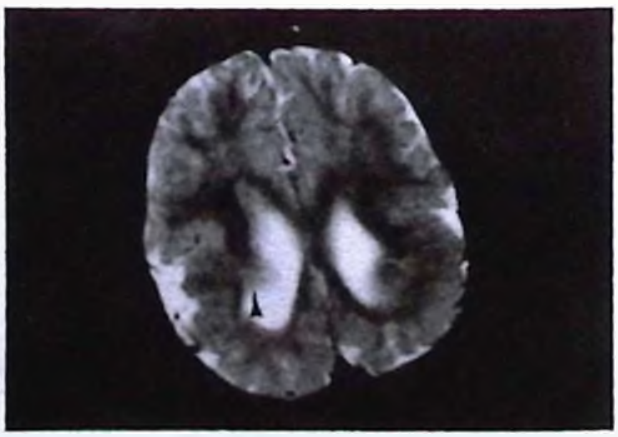

Fig. 6b

Figs. 6a,b: Bilateral open-lip schizencephaly
T1W transverse image demonstrating bilateral, symmetric, wide open clefts extending from the pial surface to the enlarged lateral ventricles. The cortex appears thickened with broad gyri and shallow sulci, giving the appearance of pachygyria.

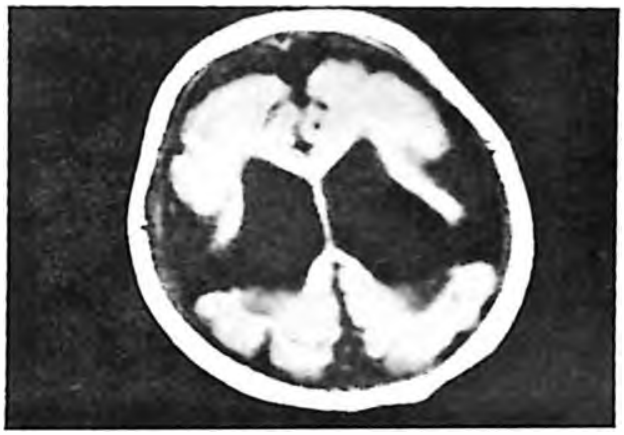

Fig. 7: Bilateral open-lip schizencephaly
T1W transverse image demonstrating bilateral, symmetric, wide open clefts extending from the pial surface to the enlarged lateral ventricles. The cortex appears thickened with broad gyri and shallow sulci, giving the appearance of pachygyria.

parietal and temporal areas of the brain, particularly involving the parasylvian region, and precentral and postcentral gyri[9,10]. Identification of the gray matter lining on the cleft is critical in differentiating schizencephaly from porencephaly. (This differentiation may be important for genetic counseling since the reported incidence of brain anomalies is five to 20 percent in subsequent siblings of children who have anomalies of cell migration)[11]. The clefts range from extremely narrow with actual fusion of the gray matter lined walls of the cleft (fused lips) (Figs. 5b, 6a) to quite large with wide separation of the walls (Fig. 7) and absence of large portions of the involved hemisphere. The gyral pattern of the cortex adjacent to the cleft is usually abnormal, demonstrating cortical dysplasia. The gray matter in the cleft may extend into the ventricle in the form of subependymal heterotopia (Fig. 5a). A dimple is usually seen in the wall of the lateral ventricle where the cleft communicates. The dimple is often a helpful sign of continuity of the cleft with the ventricle when the lips are fused[2] (Figs. 5b, 6a,b). There may be regional parenchymal volume loss and the sylvian vessels may be hypoplastic[12]. Ventricular diverticula may be present with or without lateral ventriculomegaly[12]. Cortical dysplasia may be present in the hemisphere contralateral to a unilateral schizencephaly. The septum pellucidum is absent in 80 to 90 percent of the patients with schizencephaly[2]. Approximately half of the patients with septooptic dysplasia may have accompanying schizencephaly[8,13].

Unilateral hemimegalencephaly

On CT and MRI, the involved hemisphere is moderately to markedly enlarged[2]. The cortex is typically dysplastic with broad gyri, shallow sulci and cortical

thickening. However, the gyral pattern may appear grossly normal or frankly agyric. In severely affected patients, the usually sharp border between the cortex and the subcortical white matter may blur or disappear altogether. The white matter may show areas of hypointensity on T1 and hyperintensity on T2 weighed (T1W, T2W) MR images, representing heterotopia and gliosis. The lateral ventricle on the affected side is enlarged in proportion to the affected hemisphere[7]. The frontal horn of the ipsilateral ventricle may have a characteristic configuration that is almost straight, pointing superiorly and anteriorly[2].

Gray matter heterotopia

For the purposes of clinical evaluation and prognostication, heterotopia may be divided into three groups[14]: 1-subependymal heterotopia 2-focal subcortical heterotopia 3-diffuse heterotopia. Heterotopias appear as nodular or broad regions in the subependymal, periventricular or subcortical areas that are isointense with gray matter on all imaging sequences. The most important features in distinguishing heterotopia from tumors are that heterotopias lack surrounding edema, remain isointense with gray matter on all imaging sequences (Figs, 8a,b) and with all imaging modalities, and do not enhance with contrast agents.

Subependymal heterotopias are smooth, ovoid masses that grow into the adjacent lateral ventricle, often causing the ventricle to appear compressed[14] (Figs. 8a,b). They are differentiated from the subependymal hamartomas of tuberous sclerosis by their shape (hamartomas of tuberous sclerosis are irregular and often elongated), their signal intensity (subependymal hamartomas of the tuberous sclerosis are usually iso-to hypointense compared to mature white

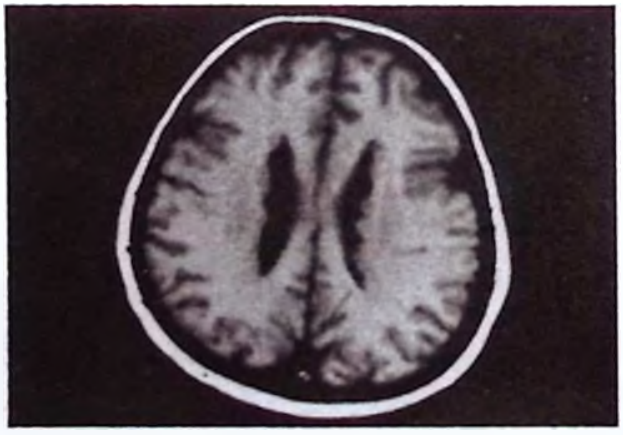

Fig. 8a

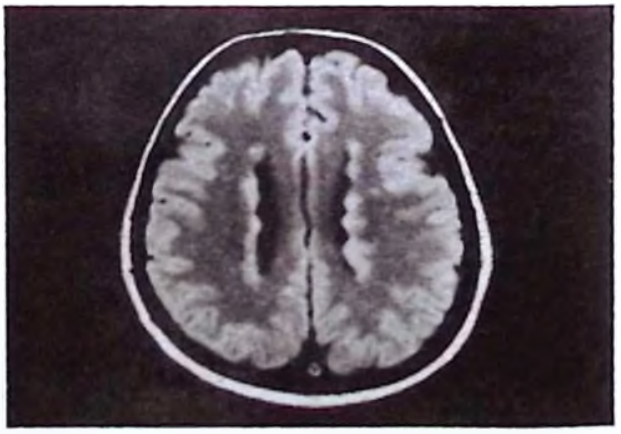

Fig. 8b

Figs. 8a,b: Subependymal heterotopia
T1W (a) and proton-density (b) transverse images showing nodules along the wall of lateral ventricles, bilaterally, isointense to gray matter on all imaging sequences. Note the indentation of the heterotopic gray matter on the ventricular wall.

matter), and the fact that they do not enhance after intravenous infusion of paramagnetic contrast[2].

Focal subcortical heterotopias will sometimes appear to contain vessels or cerebrospinal fluid, thereby mimicking tumors[14] (Fig. 4a). Closer examination will show that the vessels and cerebrospinal fluid are within infoldings of the cortex adjacent to the heterotopia. Patients with a large subcortical heterotopia may show thinning of the overlying cortex. The heterotopias may appear to exert mass effect on the adjacent ventricle or the interhemispheric fissure. The heterotopias can be differentiated from tumors, which enlarge the affected hemisphere, by the fact that the affected hemisphere is small and that the apparent mass effect is actually distortion of the hemisphere caused by the dysplasia[15].

Diffuse gray matter heterotopias include "band heterotopia" ("double cortex") and "laminar heterotopias"[14]. Laminar heterotopias are bilateral symmetrical ribbons of gray matter in the centrum semiovale[14]. Band heterotopias ("double cortex") appear as a circumferential band of gray matter that is deep in the cerebral cortex and separated from the cortex by a layer of normal appearing white matter[16] (Fig. 9). This band of gray matter has smooth inner and outer margins at its interface with adjacent white matter and the margins do not parallel the infolding of the overlying cerebral cortex[17]. The overlying cortex may appear normal, may have normal thickness with shallow sulci or may be pachygyric. The degree of cortical gyral dysplasia seems to be related to the thickness of the band heterotopia, i.e., the thicker the band of heterotopic gray matter, the more anomalous the overlying cortex[16].

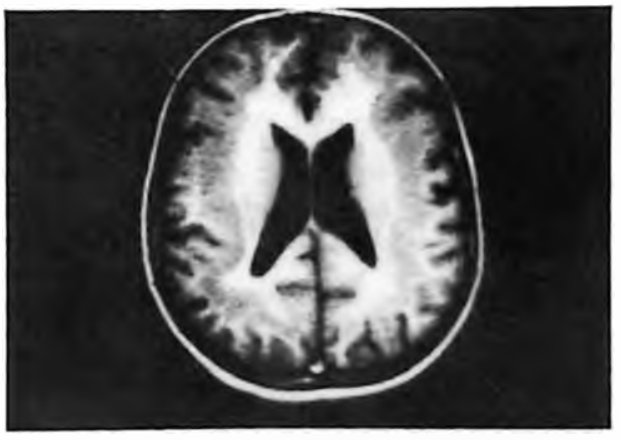

Fig. 9: "Double cortex" or band heterotopia
T1W transvers image revealing an inner layer of circumferential band of gray matter separated from the cortex by an intervening layer of white matter.

REFERENCES

1. Aicardi J. The agyria-pachygyria complex: a spectrum of cortical malformations. Brain Dev 1991; 13: 1-8.
2. Barkovich AJ. Congenital malformations of the brain and skull. In: Pediatric Neuroimaging (2nd ed). New York: Raven Press; 1995: 177-275.
3. Barkovich AJ, Gressens P, Evrard P. Formation, maturation, and disorders of brain neocortex. Am J Neuroradiol 1992; 13: 423-446.
4. Titelbaum DS, Hayward JC, Zimmerman RA. Pachygyriclike changes: topographic appearance at MR imaging and CT and correlation with neurologic status. Radiology 1989; 173: 663-667.
5. Barkovich AJ. Abnormal vascular drainage in anomalies of neuronal migration. AJNR 1988; 9: 939-942.
6. Kuzniecky R, Andermann F, Tampieri D, et al. Bilateral central macrogyria: epilepsy, pseudobulbar palsy, and mental retardation a new recognizable neuronal migration disorder. Ann Neurol 1989; 25: 547-554.
7. Palmini A, Andermann F, Olivier A, et al. Neuronal migration disorders: a contribution of modern neuro imaging to the etiologic diagnosis of epilepsy. Can J Neurol Sci 1991; 18: 580-587.
8. Barkovich AJ, Norman D. MR imaging of schizencephaly. AJR 1988; 150: 1391-1396.
9. Byrd SE, Osborn RE, Bohan TP, Naidich TP. The CT and MR evaluation of migrational disorders of the brain. Part II. Schizencephaly, heterotopia and polymicrogyria. Pediatr Radiol 1989; 19: 219-222.
10. Aniskiewicz AS, Frumkin NL, Brady DE, Moore JB, Pera A. Magnetic resonance imaging and neurobehavioral correlates in schizencephaly. Arch Neurol 1990; 47: 911-916.
11. Barkovich AJ, Sylvester HC, Norman D. MR of neuronal migration anomalies. AJR 1988; 150: 179-187.
12. Chamberlain MC, Press GA, Bejar RF. Neonatal schizencephaly: comparison of brain imaging. Pediatr Neurol 1990; 6: 382-387.
13. Barkovich AJ, Fram EK, Normal D. Septo-optic dysplasia: MR imaging. Radiology 1989; 171: 189-192.
14. Barkovich AJ, Kjos BO. Gray matter heterotopias: MR characteristics and correlation with developmental and neurologic manifestations. Radiology 1992; 182: 493-499.
15. Yasumori K, Hasuo K, Nagata S, Masuda K, Fukui M. Neuronal migration anomalies causing extensive ventricular indentation. Neurosurgery 1990; 26: 504-507.
16. Palmini A, Andermann F, Aicardi J, et al. Diffuse cortical dysplasia, or the 'double cortex' syndrome: the clinical and epileptic spectrum in 10 patients. Neurology 1991; 41: 1656-1662.
17. Barkovich AJ, Jackson DE Jr, Boyer RS. Band heterotopias: a newly recognized neuronal migration anomaly. Radiology 1989; 171: 455-458.

The Turkish Journal of Pediatrics 1998; 40: 491-501 Original

TURKISH EXPERIENCE WITH RHABDOMYOSARCOMA: AN ANALYSIS OF 255 PATIENTS FOR 20 YEARS*

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SUMMARY: Akyüz C, Sancak R, Büyükpamukçu N, Atahan L, Göğüş S, Kutluk T, Büyükpamukçu M. (Department of Pediatric Oncology, Hacettepe University Institute of Oncology, Ankara, Turkey). Turkish experience with rhabdomyosarcoma: an analysis of 255 patients for 20 years. Turk J Pediatr 1998; 40: 491-501.

Two hundred and fifty-five previously untreated patients (pts) with rhabdomyosarcoma (RMS) (age range 15 days to 17 years, median 5 years) were evaluated and treated in our institution. Head and neck primaries were seen in 125 patients (49%), abdomino-pelvic in 73 (29%), trunk and lung in 20 (5%) and extremity lesions in 37 (15%). The histology was: embryonal 137; alveolar 42; botryoid 18; pleomorphic 14. Forty-four patients could not be subclassified. The stage of the patients were as follows: 15 in stage I, 74 in stage II, 139 in stage III and 27 in stage IV, according to the IRS grouping system. Patients were treated with a combination of surgery and radiation to doses of 35-55 Gy according to the patient's age and stage. All the patients received chemotherapy according to VAC or pulse-VAC (before 1988) and modified AVAC (after 1988) protocol. Survival curves were calculated by the Kaplan-Meier method. The statistical significance of each variable was tested by the log-rank test. Overall survival was 42 percent at 10 years. Three important predictors for survival time were clinical group ($p<0.001$), age ($p<0.001$) and primary site ($p=0.005$). The best results involved clinical group I-II, age one to five years and orbital and genitourinary primary sites. An important predictor of survival time was also detected between those treated during the first ten years (1972-82) and last 10 years (1982-92), $p<0.005$. Of the 96 deaths, 37 were from progressive disease, 24 from infection, 4 during postoperative period (first 7 days), 18 from unknown causes and 13 from other causes. *Key words: rhabdomyosarcoma, childhood tumors, IRS grouping system, prognostic factors.*

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Rhabdomyosarcoma is the most common soft tissue sarcoma of childhood, representing four to eight percent of all malignant neoplasms in children under 15 years[1-3]. Rhabdomyosarcomas tend to disseminate early in the course of the disease. However, the survival rates of this tumor have increased from 30 to 70-80 percent during the last 20 years[4]. Early diagnostic methods, modern surgery, radiotherapy, multidrug chemotherapy and supportive care played an important role in this accomplishment. Nevertheless, more than half of those with newly diagnosed, unresectable (group III) or metastatic (group IV) tumors continue to die of their disease. The majority of all deaths among children with rhabdomyosarcoma occur in those who have an advanced disease at initial diagnosis. In this study, epidemiologic, clinical and histopathologic features, survival data, treatment results, and prognostic factors of childhood rhabdomyosarcoma are presented.

Material and Methods

Between January 1972 and December 1992, 255 previously untreated children under 18 years of age with rhabdomyosarcoma (RMS) were diagnosed, and followed up in our center. The cut off date for analysis in these 255 patients was December 1994. Data were obtained from patient charts and medical records. Pretreatment evaluation included history, physical examination, chest x-ray, and routine blood and biochemical tests. Further studies like bone marrow aspiration, cerebrospinal fluid examination and computerized tomography depended on the primary site. All patients were grouped according to the Intergroup Rhabdomyosarcoma Study III (IRS) grouping[5]. A biopsy/excision or debulking surgery was performed on all patients. All histopathologic specimens were reviewed by our pathologists. All patients were treated postoperatively using a Cobalt 60 teletherapy unit. The fields were determined according to the primary tumor size, surgical findings, pre-and postoperative radiological investigations. Primary tumor bed was covered with a safety margin of one-to-three cm depending on initial tumor size and applied surgery. Total dose delivered between 30-60 Gy given in 150-180 cGy increments, modified according to patient's age and site of the tumor. Attention was given to using multiple treatment fields whenever possible. Three different chemotherapeutic regimens were used depending on the year: VAC and pulse-VAC (before 1988) and modified AVAC (after 1988). The VAC and pulse-VAC consisted of sequential vincristine, actinomycin D and cyclophosphamide (orally for VAC, IV for pulse-VAC) whereas the modified AVAC protocol consisted of sequential vincristine, cyclophosphamide, adriamycin, and actinomycin D.

Prognosis was defined on the basis of survival. Survival curves were calculated by the Kaplan-Meier method[6]. Groups were compared with respect to time to

local failure and survival duration using the log-rank test[7]. Variables investigated included age, sex, race, histology, primary site, and extent of tumor at initial presentation.

Results

During the period of January 1972-December 1992, 6,505 patients with malignant tumors were seen in Hacettepe Children's Hospital. Two hundred and fifty-five (4%) of these patients had rhabdomyosarcomas. The median age was five years (range 15 days-17 years). The boy to girl ratio was 158/97 (1.6/1). Demographic features and prognostic factors were analyzed. The age and sex, primary site at presentation, histology of disease, clinical group distribution and outcome of patients are summarized in Tables I-V, respectively. A total of 146 (57%) patients were under five years of age. Table IV shows stages of the patients. Almost 65 percent of patients had primary nonresectable tumors or metastatic disease (stage III-IV) at presentation. The histological subgroups of forty-four patients were not verified. All of the unclassified rhabdomyosarcoma slides were referred from some other hospital; therefore, our pathologist could not specify the subgroups of the disease. Survival curves were calculated by the Kaplan-Meier method. The statistical significance of each variable was tested by the log-rank test. The distribution of patients by prognostic variables and 3, 5 and 10 year survival rates are shown in Table V. Survival curves according to the most important characteristics of Table V are given in Figures 1-4. The relation between the histologic subtype and sex were statistically insignificant. The clinical group was found to be the factor most strongly related to survival ($p<0.001$). The estimated survival rates at five years were 66, 49, 37, and 12 percent in Clinical Groups I to IV, respectively (Fig. 1). The second most important factor was age ($p<0.001$). The outcome of infants less than one year of age was worse than

Table I: Age and Sex Distribution of Patients with RMS

Sex (M/F)	158/97 (1.6/1)
Median age	5.4 yrs
Age range	15 days - 17 yrs
Age groups (yrs)	
< 1	14
1-5	131
6-10	71
≥ 11	39
Total	255

Table II: Primary Site at Presentation of Patients with RMS

Site	n	(%)
Head and neck	125	(49)
Nonparameningeal	50	
Parameningeal	37	
Nasopharynx	26	
Orbit	12	
Genitourinary tract	32	(13)
Bladder-prostate	19	
Vagina-uterus	6	
Paratesticular	7	
Extremities	37	(15)
Trunk	20	(7)
Other	41	(16)
Total	255	(100)

Table III: Histologic Subtypes of Patients with RMS

Histology	n	%
Embryonal	137	(53.7)
Alveolar	42	(16.4)
Botryoid	18	(7)
Pleomorphic	14	(5.4)
Undifferentiated	44	(17.2)

Table IV: Clinical Group Distribution of Patients with RMS

Clinical Group	n	%
I	15	(6)
II	74	(29)
III	139	(54)
IV	27	(11)

Table V: Survival Rate of Patients with RMS

Characteristics of Patients	n	Survival (%) 3 years	5 years	10 years	p
Age (median 5 yrs)					<0.001
<1	14	18	0	0	
1-5	131	52	48	39	
6-10	71	49	40	40	
≥ 11	39	51	40	40	
Sex					>0.05
Male	158	45	41	39	
Female	97	48	44	41	
Primary site					=0.005
Orbit	12	66	66	66	
Head and neck	125	43	36	42	
Genitourinary system	32	68	68	68	
Extremity	37	58	48	40	
Trunk	20	48	32	32	
Retroperitonium	29	38	38	30	
Histology					>0.05
Botryoid	18	56	53	53	
Embryonal	137	49	42	37	
Pleomorphic	14	51	47	47	
Alveolar	42	43	34	28	
Clinical group					<0.001
I	15	83	66	66	
II	74	61	49	49	
III	139	40	37	37	
IV	27	25	12	0	
Treatment protocols					>0.05
Classic VAC	116	42	29	22	
pulse-VAC	88	62	60	57	
modified-AVAC	37	68	64	–	

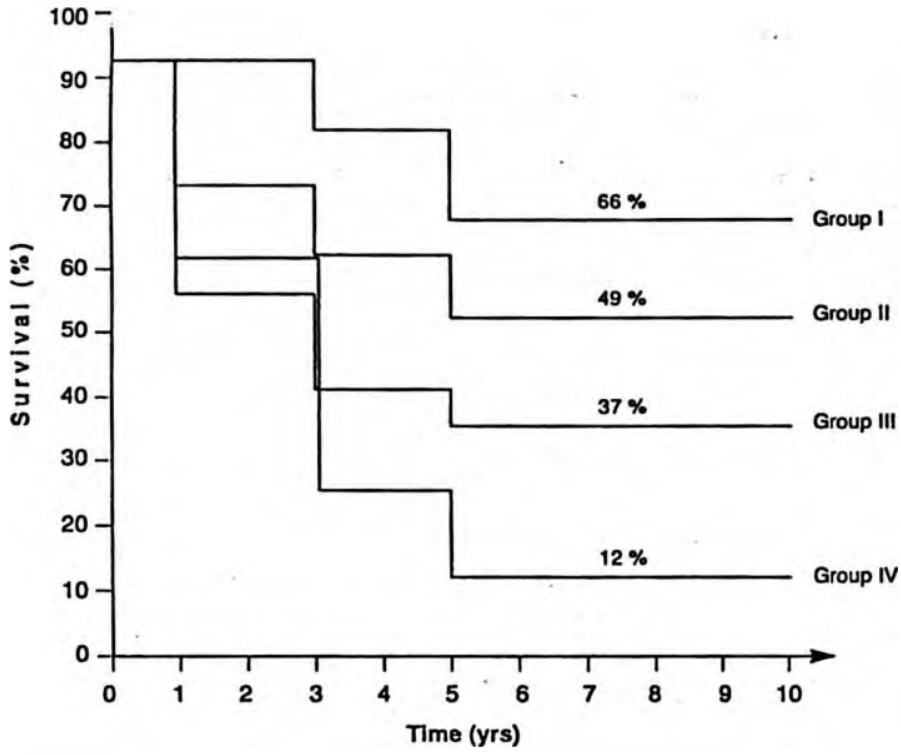

Fig. 1: Survival for RMS patients according to clinical group.

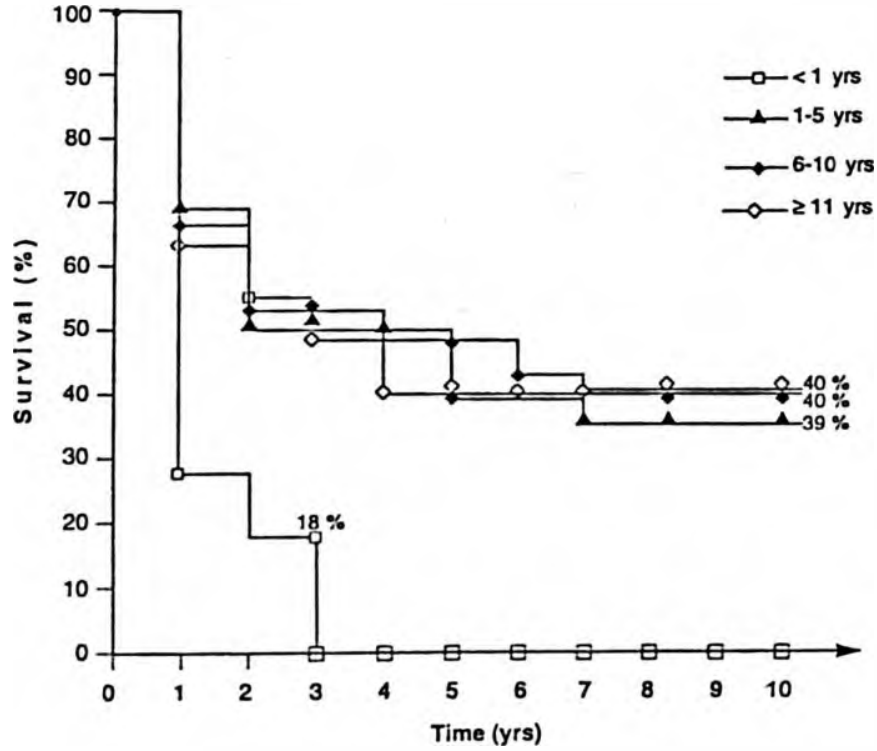

Fig. 2: Survival by age of patients with RMS.

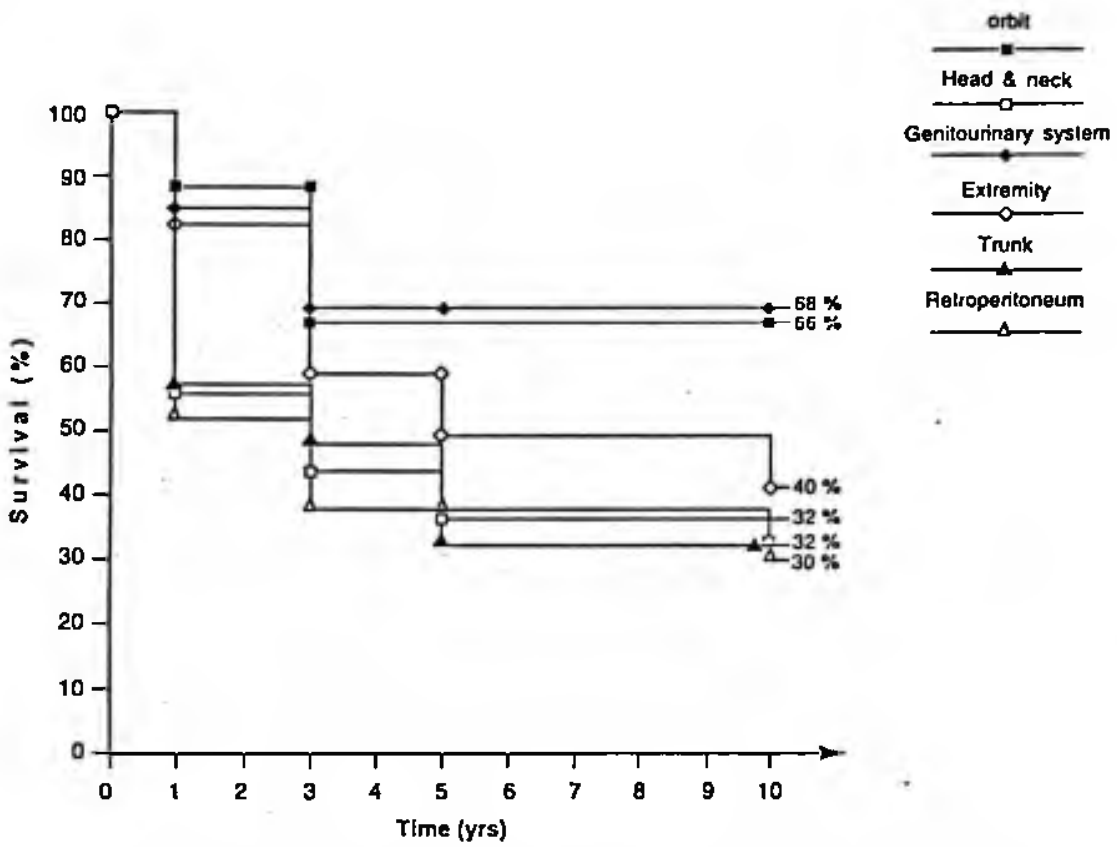

Fig. 3: Survival for RMS patients according to primary sites of tumor.

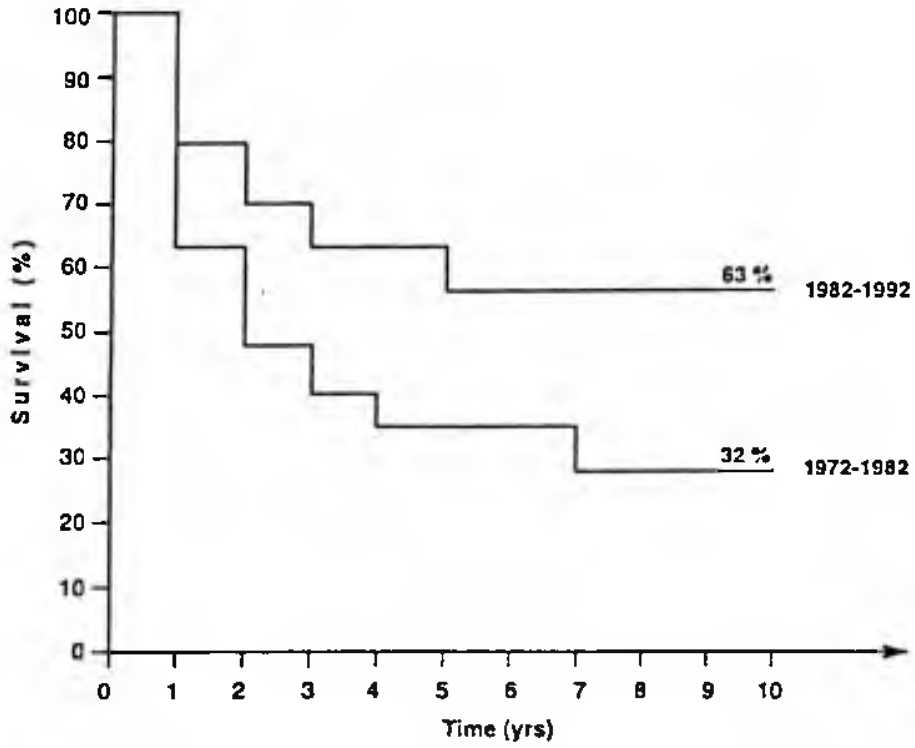

Fig. 4: Survival of children with RMS according to the years

that of older patients (Fig. 2). There was no significant relation between age and survival present except in this group. The overall survival was 27 percent in the first year. All patients in this group (n=14) died within three years after diagnosis. The third significant factor was the primary site. Figure 2 gives survival curves by primary site in all patients. The best survival was observed in patients with primary tumors of the orbit and genitourinary tract. The estimated rates of survival at five years, in decreasing order by primary site, were genitourinary tract 68 percent, orbit 66 percent, extremity 48 percent, head and neck (excluding orbit) 36 percent, and trunk 32 percent. Three different chemotherapeutic regimens were used depending on the year. There was no significant difference between the two regimens (pulse-VAC versus AVAC) in terms of survival. A significant difference with respect to survival was detected between those treated during the first ten years (1972-82) and the second ten years (1982-92), $p<0.005$ (Fig. 4).

Recurrences and/or metastatic spread: Tumor recurrence in children with localized disease at presentation occurred in the 58 patients (26%). The median time for tumor recurrence was 15.5 months. Metastases plus relapses developed in 54 patients (21%). The most common metastatic site was the lungs. The recurrence or metastases of disease occurred in 68 percent of patients within one year of diagnosis.

Ninety-six of 255 patients died during the follow-up period. Progressive disease and infection were the major causes of death (Table VI). Relapse sites and end results are shown in Table VII.

Although we did not intend to report treatment toxicities here, one patient who developed a second malignancy (osteosarcoma) at 12 years within the radiation field and died of this progressive disease deserves mentioning[8].

Discussion

In our series, the characteristics of the patients were similar to those of other series published in recent years in term of age range, sex ratio, and distribution of primary sites[6,9].

Table VI: Causes of Death in 96 Patients with RMS

Progressive disease	37
Infection	24
Postoperative (first 7 days)	4
Unknown	18
Other	13

Table VII: Relapse Patterns and Results in Patients with RMS

Local primary site	58
Pulmonary	32
Disseminated relapse (Local + Distant)	16
Other	6
Outcome of relapsed patients	
Exitus	17
Lost to follow-up	61
Alive	34

As would be expected, survival is inversely correlated with extent of disease in this retrospective analysis as well as in patients treated by combined modality therapy. The other significant prognostic factor was the primary site. The best survival was in patients having primary tumors of the orbit and genitourinary tract. In 1983 Kingston et al[10] concluded from a group of 73 patients that the major prognostic factor was the stage, but that histological type and primary site were not related to survival. The largest series is composed of 1,062 patients entered in the IRS-III and was reported in 1995 by Gehan et al[11]. The major prognostic factors were the clinical group and primary site, in contrast to histology which was not significant in this series.

It is interesting that age appeared to be an important prognostic factor in our series. The outcome of infants under one year of age was worse than that of older patients, due to life-threatening and fatal toxicities being more common in infants of that age. A similar result was reported by Ragab et al[12]. In their series, infants with rhabdomyosarcomas had a higher mortality rate than older children. Stow et al[13] and Koscielniak et al[14] had previously reported a slightly better prognosis in younger patients.

Sex and histologic type failed to be of prognostic importance in the present series; a similar result was reported in the IRS-III study[11]. Few studies have investigated the influence of histology on prognosis in childhood rhabdomyosarcoma. Patients with alveolar histology were reported to be associated with markedly decreased survival[15].

Thus, in our retrospective study, the analysis of survival of patients with RMS showed that age, stage and primary site were strongly related to prognosis. A meta-analysis was made by Rodary et al[16] on CWS-81 data, and data from the SIOP, IRS-II and Italian study (ICS). The univariate analysis showed that tumor

size, T (tumor) status, and primary site were related to prognosis in all the studies. In addition, the involvement of regional lymph nodes was found to be of prognostic importance when the data of all four studies were analyzed together. However, we could not investigate this in our series.

Improved survival rate in children with rhabdomyosarcoma has been obtained by using intensive-pulsed chemotherapy. The long-term survival rates in our series were about 42 percent with classic VAC, 62 percent pulse-VAC, and 68 percent modified AVAC protocol. Although modified AVAC regimen appears more effective than the others, the difference is not significant ($p>0.05$). German investigators[17] treated 225 patients with RMS from 1981 to 1986 using therapy similar to that in IRS-II (i.e., VAC plus adriamycin with central nervous system prophylaxis for parameningeal disease). Event-free survival rates by clinical group (I through IV) were 81, 68, 56 and 11 percent, respectively.

The overall results of this retrospective study display a significant improvement with respect to survival over time in our institution. We found survival at ten years was 32 percent before 1982 and 63 percent in the second ten years (after 1982). Despite this appreciable progress, we need more effective approaches in this tumor, especially in groups III and IV patients with rhabdomyosarcoma.

REFERENCES

1. Young JL Jr, Ries LG, Silverberg E, et al. Cancer incidence, survival, and mortality for children younger than 15 years. Cancer 1986; 58: 598-602.
2. Lanzkowsky P. Rhabdomyosarcoma and other soft tissue sarcomas. Manual of Pediatric Hematology and Oncology (2nd ed). New York: Churchill Livingstone Inc. 1995: 453-476.
3. Raney RB, Tefft M, Hays DM, Tricbe TJ. Rhabdomyosarcoma and the undifferentiated sarcoma. In: Pizzo PA, Poplac DG (eds). Principle and Practice of Pediatric Oncology (2nd ed). Philadelphia: Lippincot Com.; 1992: 769-794.
4. Mameghan H, Fisher R, Tobias V, et al. Local failure in childhood rhabdomyosarcoma and undifferentiated sarcoma: prognostic factors and implications for curative therapy. Med Pediatr Oncol 1993; 21: 88-95.
5. Lawrence W Jr, Gehan EA, Hays DM, Beltangady M, Maurer HM. Prognostic significance of staging factor of the UICC staging system in childhood rhabdomyosarcoma: a report from the Intergroup Rhabdomyosarcoma Study (IRS II). J Clin Oncol 1987; 5: 46-54.
6. Pelo R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. Br J Cancer 1977; 35: 1-39.
7. Manter N. Evaluation of survival data and two new rank order situations arising in its consideration. Cancer Chemother Rep 1966; 50: 163-170.
8. Atahan L, Akyol FH, Gürkaynak M, et al. Post-irradiation osteosarcoma of the iliac bone: a case report. Turk J Pediatr 1989; 31: 227-231.
9. William MC, Lisa G, Mohan SB, et al. The Intergroup Rhabdomyosarcoma Committee. Prognosis in Children with Rhabdomyosarcoma: a report of the intergroup rhabdomyosarcoma studies I and II. J Clin Oncol 1990; 8: 443-452.

10. Kingston JE, McElvain TJ, Malpas JS. Childhood rhabdomyosarcoma: experience of the Children's Solid Tumour Group. Br J Cancer 1983; 48: 195-207.

11. Gehan WC, Ragab AH, Dicmen PS, et al. The Third Intergroup Rhabdomyosarcoma Study. J Clin Oncol 1995; 13: 610-630.

12. Ragab AH, Heyn R, Tefft M, Hays DN, Newton WA Jr, Beltangady M. Infants younger than 1 year of age with rhabdomyosarcoma. Cancer 1986; 58: 2606-2610.

13. Stow WW, Sullivan MP, Ried HC, et al. Prognosis in childhood rhabdomyosarcoma. Cancer 1970; 25: 1384-1390.

14. Koscielniak E, Harms D, Schmidt D, et al. Soft tissue sarcomas in infants younger than 1 year of age: a report of the German Soft Tissue Sarcoma Study Group (CWS-81). Med Pediatr Oncol 1989; 17: 105-110.

15. Newton WA, Jr, Soule EH, Hamoudi AB, et al. Histopathology of childhood sarcoma, Intergroup Rhabdomyosarcoma Studies I and II: clinicopathologic correlation. J Clin Oncol 1988; 6: 67-75.

16. Rodary C, Gehan EA, Flamant F, et al. Prognostic factors in 951 nonmetastatic rhabdomyosarcoma in children: a report from the International Rhabdomyosarcoma Workshop. Med Pediatr Oncol 1991; 19: 89-95.

17. Treuner J, Kühl J, Beck J, et al. New aspect in the treatment of childhood rhabdomyosarcoma: results of the German Cooperative Soft-Tissue Sarcoma study (CWS-81). Prog Pediatr Surg 1989; 22: 162-173.

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RECOMBINANT INTERFERON-α-2A WITH OR WITHOUT STEROID PRETREATMENT IN CHILDREN WITH CHRONIC HEPATITIS B*

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SUMMARY: Özen H, Koçak N, Gürakan F, Yüce A. (Division of Gastroenterology, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Recombinant interferon-α-2A with or without steroid pretreatment in children with chronic hepatitis. Turk J Pediatr 1998; 40: 503-514.

Interferon is the most promising therapeutic agent for the treatment of chronic viral hepatitis. The results of studies suggest that corticosteroid pretreatment may improve the response rate. Twenty-nine children with chronic hepatitis B (CHB) were randomly assigned to receive recombinant interferon alpha (rIFN-α) alone (Group 1.5 million units/m² body surface, 3 times a week for 24 weeks) or to receive oral prednisone (Group 2.2 mg/kg/day for 3 weeks, discontinued by tapering the dose within 1 week) followed by rIFN-α (same dose as above). Tests for liver function and hepatitis B virus (HBV) markers including HBV-DNA were done periodically. Overall, 10 patients (34.5%) cleared hepatitis Be antigen and 13 (44.8%) HBV-DNA. Anti-HBe seroconversion was observed in nine patients (31%). Only three patients (10.3%) cleared hepatitis B surface antigen and seroconverted to anti-HBs. No response was obtained in 11 patients (37.9%). There was no statistically significant difference between the two treatment groups regarding response rate. Baseline transaminases levels and HBV-DNA concentrations were predictive parameters for HBeAg clearance. It is concluded that prednisone pretreatment does not have a beneficial effect in children with CHB. *Key words: children, chronic hepatitis B, recombinant interferon-α, prednisone.*

Clinical studies have clearly documented that both adults and children with chronic hepatitis B (CHB) and persistent hepatitis B virus (HBV) replication are at increased risk of progression to cirrhosis and hepatoma[1-4]. Disappearance of HBV replication takes place together with amelioration of liver disease. Because of its antiviral and immunomodulatory properties, interferon (IFN) is the most promising therapeutic agent for the treatment of various chronic viral infections, including chronic viral hepatitis[5]. Recently, it has been demonstrated that recombinant interferon alpha (rIFN-α) treatment of chronic hepatitis B is effective in both adults and children, with the percentage of patients responding around 30 to 40 percent[6-8].

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Initial reports of IFN treatment in children with chronic HBV infection have demonstrated a variable response rate (measured by clearance of viral DNA and hepatitis Be antigen [HBeAg], and normalization of serum alanine aminotransferase levels), between no response to 58 percent[9-13]. Complete recovery (with loss of HBsAg) is usually noted in less than 20 percent of treated individuals; similar response rates have been reported in the relatively small number of children evaluated to date[14]. Nevertheless, a significant number of patients do not respond to IFN-α therapy alone, and an alternative approach to treatment is desirable. Many drugs, including levamisole[15,16]. zidovudine[17], acyclovir[18], vidarabine[19] and interleukin-2[20], have been prescribed together with IFN to achieve a higher response rate. Corticosteroids alone have not been shown to be beneficial in treating hepatitis B virus related chronic active hepatitis. In fact, some studies have shown a deleterious effect[21,22]. However it has been shown that long or short courses of corticosteroids may result in a decline of viral replication or even successful treatment due to an immunologic rebound that follows corticosteroid withdrawal[23,24]. A severe defect in suppressor-cell activity in hepatitis B surface antigen positive chronic active hepatitis has been shown in comparison with healthy subjects[25]. The results of studies suggest that a combination therapy, in which corticosteroid is followed by antiviral drugs, is superior to corticosteroid withdrawal alone.

The aim of this study was to evaluate the possible benefit of rIFN-α administered either alone or after prednisone to children with chronic HBV infection.

Material and Methods

Patients with elevated aminotransferases concentrations (>40 IU/L) and HBeAg and HBV-DNA positivity for at least six months were included in the study. All patients had chronic hepatitis (24 chronic persistent hepatitis [CPH] and 5 chronic active hepatitis [CAH]), histologically proven by liver biopsy within one month prior to entry in the study. None of the children had decompensated liver disease or evidence of other forms of liver disease. Criteria for exclusion were antiviral therapy during the preceding 12 months, leukopenia ($<3 \times 10^9$/L), thrombocytopenia ($<100 \times 10^9$/L) or an elevated serum creatinine level, cirrhosis, and other causes of liver disease or malignancy.

Children were randomly assigned to two groups. Patients in Group 1 received five million units (MU) of human recombinant interferon alpha 2A (rIFN-α-2A) (Roferon-A, Roche) per square meter of body surface, three times a week for 24 weeks by subcutaneous injection. Patients in Group 2 received oral prednisone (2 mg/kg/day, maximum 60 mg/day) for three weeks, which was discontinued by tapering the dose within one week. After one week of rest, patients received

rIFN-α-2A as described above. Paracetamol was administered to alleviate fever and myalgia during the first weeks, if needed. If the platelet count decreased to less than $100x10^9$/L and neutrophil count to less than $1.2x10^9$/L, the next doses were withheld until the abnormality improved.

A blood sample was analyzed monthly during the treatment (24 weeks) and every three months thereafter for liver function tests, hematological parameters, and HBV markers. HBV-DNA was determined at the end of the treatment and every six months thereafter. Hepatitis B surface antigen (HBsAg), HBeAg, antibodies to HBsAg (anti-HBs), HBeAg (anti-HBe), hepatitis delta infection, hepatitis C infection, and human immunodeficiency virus were determined by commercially available radioimmunoassay kits. Liver function tests were analyzed automatically by sequential multiple autoanalysis (Hitachi 911 Automatic Analyzer), at 37 °C, with standards supplied by the manufacturer. HBV-DNA in serum was tested by dot-blot hybridization according to the method described previously[26].

A complete response was recorded if a patient had (1) cleared both HBsAg and HBeAg, (2) both anti-HBs and anti-HBe, (3) undetectable circulating levels of HBV-DNA, and (4) normal ALT and AST activity, by 12 months after initiation of therapy (6 months after the end of the treatment). A partial response was recorded when a patient had (1) cleared HBeAg with or without development of anti-HBe (2) undetectable circulating levels of HBV-DNA, and (3) normal or decreased ALT and AST activity. A minimal response was recorded when a patient had any response towards normalization of any of the efficacy parameters measured. Nonresponse was considered as persistence of HBeAg, HBsAg, detectable circulating HBV-DNA, and elevated/unchanged ALT or AST activity. In the presentation of data, responders include complete, partial and minimal responders unless otherwise noted.

All family members, whenever available, were tested for HBV markers, including HBsAg, HBeAg, anti-HBe and anti-HBc IgG. When a family member was positive for HBV (positivity for HBsAg and/or anti-HBs) the patients was considered as infected horizontally. When the patients was infected during the first year of life, the patient was considered as infected vertically if the mother was HBsAg positive.

The results were expressed as mean ± SD and a two-tailed "p" value less than 0.05 was considered as significant. Comparisons of measurable data between the two groups were done using Mann-Whitney U test. Repeated parameters in the same group were tested using Wilcoxon paired signed-ranks test or Friedman two-way ANOVA. Proportions were compared using chi-square test or Fisher's exact chi-square test when expected frequencies were less than five[27].

Results

Twenty-nine patients, aged 100.7 ± 35.5 months (range 52 to 160), were entered in this study. Sixteen of them (55.2%) were assigned to monotherapy (Group 1) and 13 of them (44.8%) to combination therapy (Group 2). Twenty-four patients (82.8%) had CPH and five CAH. All of them completed the 12 months follow-up period. The mean follow-up was 17.2 ± 3.3 months in Group 1 and 15.8 ± 3.1 months in Group 2.

The two groups were comparable with respect to age, sex, duration of HBsAg, baseline levels of ALT and of HBV-DNA and histological features (Table I). Although it was not statistically significant, the number of patients with baseline ALT values more than three times the upper limit of normal (>120 IU/L) was higher in Group 1, and baseline HBV-DNA concentrations were higher in Group 2.

Table II shows the change in serological events and laboratory parameters at the end of the treatment and 12 months after randomization. Mean concentrations of ALT decreased significantly in both groups. HBV-DNA concentrations also decreased but this decline was not statistically significant. Clearance of HBeAg

Table I: Clinical, Serological and Biochemical Characteristics of Patients in Two Treatment Groups

	Group 1 (n=16)	Group 2 (n=3)	p
Age (mos)	98.1 ± 32.8*	101.2 ± 36.1	.73
Sex (M/F)	13/3	11/2	1.0
Duration of HBsAg positivity (mos)	19.6 ± 14.0	19.2 ± 11.6	.93
HBsAg positive family member (%)	4 (25.0)	9 (69.2)	.45
Liver histology (CAH/CPH)	3/13	2/11	1.0
HBV-DNA (pg/ml)	48.5 ± 70.6	156.9 ± 212.9	.11
HBV-DNA>100 pg/ml (%)	2 (12.5)	5 (38.5)	.19
ALT (IU/L)	175.3 ± 120.9	177.6 ± 147.4	.66
ALT>3 times normal (>120 IU/L) (%)	8 (50.0)	5 (38.5)	.81
AST (IU/ml)	119.6 ± 59.9	131.8 ± 92.2	.91
Serum protein (g/dl)	7.2 ± 0.8	7.2 ± 0.5	1.0
Serum albumin (g/dl)	4.7 ± 0.4	4.7 ± 0.2	.58
Leukocyte (/mm^3)	6968 ± 1428	6746 ± 1633	.52
Hemoglobin (g/dl)	12.9 ± 0.9	12.8 ± 0.6	.96
Thrombocyte (/mm^3)	334938 ± 53971	259386 ± 74455	.32

* Plus-minus values are mean ± SD.

Tablo II: Biochemical and Serological Parameters at Baseline, Six Months and Twelve Months After Treatment

	Group 1 (n = 16)				Group 2 (n = 13)			
	Basseline#	6 months	12 months	p*	Basseline#	6 months	12 months	p*
ALT (IU/L)	175.3 ± 120.9	98.5 ± 69.6	70.1 ± 65.2	.013	177.6 ± 147.4	77.6 ± 62.7	62.1 ± 31.0	.013
AST (IU/L)	119.0 ± 59.9	80.5 ± 41.6	75.4 ± 62.5	.20	131.8 ± 92.2	81.9 ± 5.9	58.4 ± 15.8	.049
HBV-DNA (pg/ml)	48.5 ± 70.6	40.2 ± 74.3	40.3 ± 70.6	.22	156.9 ± 212.9	117.5 ± 215.2	146.8 ± 269.8	.31
Serum protein (g/dl)	7.2 ± 0.8	7.9 ± 0.6	7.8 ± 0.7	.001	7.2 ± 0.5	7.6 ± 0.4	7.5 ± 0.7	.01
Serum albumin	4.7 ± 0.4	4.9 ± 0.3	4.7 ± 0.3	.006	4.7 ± 0.2	4.7 ± 0.3	4.6 ± 0.2	.27
Leukocyte (/mm³)	6968 ± 1428	6413 ± 1718	6490 ± 973	.62	6746 ± 1633	6415 ± 692	7062 ± 2180	.37
Hemoglobin (g/dl)	12.9 ± 0.9	12.4 ± 1.1	13.4 ± 0.8	.025	12.8 ± 0.6	12.3 ± 0.9	12.7 ± 0.9	.054
Clearance of HbeAg (%)a	—	6 (37.5)	7 (43.8)		—	2 (15.4)	3 (23.1)	
Clearance of HBV-DNA (%)a	—	8 (50.0)		—	4 (30.8)	4 (30.8)		
Seroconversion to anti-HBe (%)a	—	3 (18.8)	6 (37.5)		—	1 (7.7)	3 (23.1)	
Seroconversion to anti-HBsa	—	—	3 (18.8)		—	—	—	
Responsea								
Complete response			3 (18.8)				—	
Partial response			2 (12.5)				2 (15.4)	
Minimal response			6 (37.5)				5 (38.4)	
No response			5 (31.3)				6 (46.2)	

Plus-minus values are means ± SD
* Friedman two-way ANOVA
a p>0 05 (Group 1 vs. Group 2)

and HBV-DNA occurred in most of the patients during the treatment period (80% and 92.3%, respectively), whereas the majority of anti-HBe seroconversion (5/9, 55.6%) occurred during the second six months. In one patient in Group 1, HBV-DNA clearance occurred at the 24th month. Although statistically significant differences were observed in serum protein and albumin concentrations and hemoglobin leves, no patient had abnormal levels. The mean durations of HBeAg clearance and seroconversion to anti-HBe were 4.1 ± 2.9 months and 6.8 ± 3.3 months in Group 1, and 5.5 ± 3.1 months and 6.3 ± 3.8 months in Group 2, respectively ($p>0.05$ Group 1 vs. Group 2). There was also no significant difference for HBV-DNA clearance duration between Group 1 and Group 2, 5.7 ± 2.8 and 8.6 ± 8.7 months, respectively. Seroconversion to anti-HBe occurred at 3.0 ± 2.4 months and 1.0 ± 1.7 months after HBeAg clearance in Groups 1 and 2, respectively ($p>0.05$). Seroconversion to anti-HBs occurred at 5.3 ± 3.2 months after HBeAg clearance and almost at the same time as HBsAg clearance (Table III). All patients except one in Group 1, who cleared HBeAg, seroconverted to anti-HBe.

Table III: Predictive Epidemiological, Biochemical and Serological Parameters for HBeAg Clearance

Features	Clearance of HBeAg (n=10)	No clearance of (n=19)	p
Sex			1.0
Male	8 (33.3)*	16 (66.7)	
Female	2 (40.0)	3 (60.0)	
Age (mos) (range)	95.6 ± 27.2# (56-126)	101.5 ± 37.2 (5-160)	.69
Treatment			.43
Group 1	7 (43.8)	9 (56.2)	
Group 2	3 (23.1)	10 (76.9)	
Liver histology			.31
CPH	7 (29.2)	17 (80.8)	
CAH	3 (60.0)	2 (40.0)	
HBsAg Family member positive			1.0
Present	4 (30.8)	9 (69.2)	
Absent	6 (37.5)	10 (62.5)	
Clearance of HBV-DNA			.21
Yes	7 (50.0)	7 (50.0)	
No	2 (18.2)	9 (81.8)	
Duration of HBsAg positivity (mos)	20.2 ± 14.1	19.0 ± 12.4	.94
Baseline			
ALT (IU/L)	241.3 ± 142.7	142.2 ± 113.7	0.37
AST (IU/L)	165.4 ± 85.6	103.8 ± 60.6	.037
HBV-DNA (pg/ml)	27.6 ± 85.6	133.6 ± 186.2	.028
ALT>120 IU/L	7/13	6/13	.064
HBV-DNA>100 pg/ml	0/7	7/7	0.62

* Values in parentheses are percentages
\# Plus-minus values are means ± SD

The final evaluation of efficacy 12 months after randomization revealed a complete response in three patients (18.8%) treated with IFN-α-2A alone and in none of 13 patients receiving combination therapy. Partial or minimal response was observed in eight patient (50%) in Group 1 and in seven patients (53.8%) in Groups 2. The ratio of nonresponders was 31.2 percent in Group 1 and 46.2 percent in Group 2 patients (p=0.41) (Table II). The higher response rate was observed in treated patients with low HBV-DNA concentrations (<100 pg/ml) and higher ALT levels (>3 times the upper normal value, >120 IU/L) at baseline, although statistically insignificant (p=0.062 and 0.064, respectively). All patients showed transient ALT elevation before seroconversion to anti-HBe. Age, sex, duration of hepatitis, histological conditions and baseline levels of ALT, AST and HBV-DNA were analyzed as predictive factors of a response to therapy (Table III). Only pretreatment ALT, AST and HBV-DNA concentrations were predictive factors of response rate. Neither HBV reactivation nor reappearance of previously cleared markers such as HBV-DNA or HBeAg occurred in any patient.

The source of HBV infection appeared to be horizontal in all patients except who underwent an exchange transfusion during the neonatal period because of hyperbilirubinemia. Although at least one family member was HBsAg positive in only 13 families (44.8%), seropositivity for HBV (HBsAg or anti HBs) was observed in all families. Only one child in Group 1 had a clinical history of acute hepatitis, and she had complete response. In the rest of the patients, the infection was discovered incidentally on routine screening.

All patients tolerated the treatment well without major side effects which resulted in discontinuation of therapy. There was no difference in side effects between the two groups. Fewer was seen in 20 out of 29 patients (68.9%) within two weeks. Asthenia was observed in five patients (17.2%), myalgia and abdominal pain in four (13.8%), convulsion, headache, weight loss, vomiting and anorexia in two (6.9%), and hair loss, change in mood, anxiety, leukopenia and hypothyroidism in 1 (3.4%). Two children with convulsion had a history of previous febrile convulsions and each had one episode of afebrile convulsion during the treatment. None of the side effects caused discontinuation of therapy.

Discussion

As a result of its success in several studies, alpha interferon is the only recognized therapy for chronic viral hepatitis. Clearance of HBV-DNA, HBeAg, and normalization of ALT are observed in approximately 30 to 45 percent of patients[14]. To enhance its effect, many drugs have been prescribed together with IFN to achieve a higher response rate[15-20]. Corticosteroids are one of these drugs. Although there are several reports on adult patients[28-35], reports on children are

rare. Some studies with adults showed beneficial effects[28,31,35]. whereas the majority showed no benefit[30,32-34] or even a harmful effect[29].

Reports on children also revealed controversial results. The response rate changed from 0 to 78 percent[9,36], but study designs and the dose and duration of the treatment were not similar. Children infected vertically and at an early age are less likely to have response[9]. In their first study, Utili et al.[37] reported that prednisone priming followed by rIFN-α-2A was effective in six of nine (66.7%) treated children in reducing HBV replication and disease activity. In their second study[38], similar to our study, they evaluated the efficacy of sequential treatment with prednisone and interferon on 43 children with chronic hepatitis B (34 CPH, 9 CAH). They prescribed either a one-month course of prednisone (0.6 to 0.3 mg/kg/day) followed by IFN-α-2A (3 MU/m², thrice weekly, for 12 months; 22 patients) or no treatment (21 patients). At the end of the study (20 months), clearance of HBV-DNA and HBeAg seroconversion were observed in nine (41%) of the patients treated and in two (9.5%) of the untreated controls (p=0.02). Although the IFN dose was lower than in our study, the cumulative dose was similar in the two studies. However, they did not compare the IFN regimens alone and with prednisone. Two of the treated patients (9.1%) who lost HBeAg also cleared HBsAg, and 13 (59%) patients had stable normal levels of ALT on their last examination.

The overall clearance rate of HBsAg was 10.3 percent in our study and all seroconverted patients had stable ALT levels at the end of the study. Gregorio et al.[39] conducted a multicenter-controlled trial with 95 HBV-DNA/HBeAg positive children. On follow-up between 12 and 18 months (median, 15 months) after treatment, the loss of HBeAg with anti-HBe seroconversion was more common in patients pretreated with steroids (35%) or placebo (40%) as against controls (13%). The anti-HBe seroconversion rate in our study was 37.5 percent in the combination therapy group and 23.1 percent in the IFN alone group. No statistically significant difference could be found between the two treatment groups in both studies. Giacchino et al.[40] compared lymphoblastoid interferon alone and with prednisolone, but they prescribed IFN for only 12 weeks. The influence of prednisolone priming was not statistically significant. HBeAg clearance was similar in both groups (44% after prednisolone/interferon and 53% after interferon alone, 48% overall). In one study[29], it was shown that pretreatment with prednisolone before IFN therapy might cause clinical rebound and hepatic decompensation. We did not observe hepatic decompensation or clinical rebound.

There is almost complete agreement on predictive parameters of response. A number of smaller studies have suggested that response to treatment is more likely to occur in patients with higher levels of transaminases, with recent onset,

a history of acute hepatitis and low levels of HBV-DNA. Krogsgaard et al.[41] collected data from 751 patients from 10 controlled trials on alpha interferon (lymphoblastoid or recombinant) treatment for chronic hepatitis B. When disappearance of HBeAg was considered as the major end point, the results of survival analysis showed that the HBeAg disappearance rate with or without interferon treatment was higher in patients with high aminotransferases levels, with a history of acute hepatitis and in male heterosexual patients disregarding HIV status. The relative treatment effect of alpha interferon was independent of the tested pretreatment host variables, but dependent on the total interferon dose. Although all patients seem to have the same relative benefit, the absolute benefit of alpha interferon treatment seems to be greatest in patients with high transaminases levels and with a history of acute hepatitis. Only one patient in our study had a history of acute hepatitis and she seroconverted to anti-HBs. Mean concentration of ALT was also higher in the responder than in the nonresponder in our study. Interferon dose was the same in all patients; we could not determine the effect of the cumulative IFN dose. Baseline HBV-DNA concentration was also reported as a predictor of response. All seroconverted patients had a baseline HBV-DNA level of <100 pg/ml in the study. In Utili et al.'s study[13], similar to our study, HBeAg clearance was observed in 75 percent of patients with a baseline HBV-DNA level lower than 100 pg/ml and in none with a level above 100 pg/ml. A greater degree of portal tract inflammation on pretrial biopsy is also a predictive factor[39]. However, there are studies that show the response does not correlate with the pretreatment serum transaminases levels, HBV-DNA concentrations or degree of histological activity[40].

Ethnic origin may also have an effect. In a recent study of Polish children with HBV infection treated with prednisone and IFN[36], there was a similarly high response rate (7/9, with 6 complete response) to IFN treatment in children younger than three years of age. In another study[9], HBV-infected Asian children showed no response, but the majority of the children did not have elevated ALT and were probably symptom-free carriers.

Interferon is better tolerated by children than adults[40,42]. A flu-like syndrome is the most frequent side effect and has been reported in 87 percent of children[43]. A flu-like syndrome with fever was seen in 68.9 percent of our patients. Other side effects were also similar in our study and that of Ruiz Moreno et al.[43], but we observed leukopenia in only one patient whereas they found it in 34.8 percent. In a study of 11,241 consecutive patients with chronic viral hepatitis who underwent interferon alpha treatment[42], five patients (0.04%) died during IFN therapy due to liver failure or complications arising from sepsis. Life-threatening side effects were observed in eight (0.07%) patients: two cases attempted suicide because of depression and six patients had severe bone marrow suppression.

All these symptoms completely disappeared after IFN withdrawal. All side effects also disappeared in our study after IFN withdrawal. The incidence of thyroid disease was reported as 0.6 percent and it was 3.4 percent in our study. Fatal or life-threatening side effects were not related to actual total dose or duration of IFN alpha, while the majority of patients with de novo non-hepatic morbidity received medium-to-high doses. Only 443 (4%) of the patients were younger than 20 years of age and none of them had non-hepatic morbidity.

The results show that IFN is well tolerated by children and is useful in the treatment of CHB. We conclude that it is unnecessary to add prednisone to IFN treatment as prescribed in this study because no beneficial effect could be demonstrated.

REFERENCES

1. Vajro P, Hadchouel M, Bernard O, Alagille D. Incidence of cirrhosis in children with chronic hepatitis. J Pediatr 1990; 117: 392-396.
2. Cheah PL, Looi LM, Lin HP, Yap SF. Childhood primary hepatocellular carcinoma and hepatitis B virus infection. Cancer 1990; 60: 174-176.
3. Fattovich G, Brollo L, Giustina G, et al. Natural history and prognostic factors for chronic hepatitis type B. Gut 1991; 32: 294-298.
4. Koçak N, Özsoylu Ş, Sarıalioğlu F, Göksu N. Association between hepatitis B surface antigen and hepatocellular carcinoma. Am J Dis Child 1985; 139: 858.
5. Baron S, Tyring SK, Fleischmann WR Jr, et al. The interferons. Mechanism of action and clinical appliations. JAMA 1991; 266: 1375-1383.
6. Perrillo RP, Schiff ER, Davis GL, et al. A randomized, controlled trial of interferon alfa-2b alone and after prednisone withdrawal for the treatment of chronic hepatitis B. N Engl J Med 1990; 323: 295-301.
7. Davis GL. Treatment of chronic hepatitis B. Hepatology 1991; 14: 567-569.
8. Katkov WN, Dienstag JL. Prevention and therapy of viral hepatitis. Semin Liver Dis 1991; 11: 165-174.
9. Lai CL, Lok AS, Lin HJ, Wu PC, Yeoh EK, Yeung CY. Placebo-controlled trial of recombinant alpha 2 interferon in Chinese HBsAg-carrier children. Lancet 1987; 2: 877-880.
10. Ruiz-Moreno M, Rua M, Molina J, et al. Prospective, randomized controlled trial of interferon-alpha in children with chronic hepatitis B. Hepatology 1991; 13: 1035-1039.
11. Ruiz-Moreno M, Jimenez JC, Porres JC, Bartolomé J, Moreno A, Carreño V. A controlled trial of recombinant interferon-alpha in Caucasian children with chronic hepatitis B. Digestion 1990; 45: 26-33.
12. Sokal EM, Wirth S, Goyens P, Depreterre A, Cornu C. Interferon alpha-2b therapy in children with chronic hepatitis B. Gut 1993; 34 (Suppl):S87-90.
13. Utili R, Sagnelli E, Gaeta G, et al. Treatment of chronic hepatitis B in children with prednisone followed by alpha-interferon: a controlled randomized study. J Hepatol 1994; 20: 163-167.
14. Haria M, Benfield P. Interferon-alpha-2a. A review of its pharmacological and therapeutic use in the management of viral hepatitis. Drugs 1995; 50: 873-896.

15. Fattovich G, Giustina G, Brollo L, et al. Therapy for chronic hepatitis B with lymphoblastoid interferon-alpha and levamisole. Hepatology 1992; 16: 115-119.

16. Ruiz-Moreno M, Garcia R, Rua MJ, et al. Levamisole and interferon in children with chronic hepatitis B. Hepatology 1993; 18: 264-269.

17. Janssen HL, Berk L, Heijtink RA, Kate FJ, Schalm SW. Interferon-alpha and zidovudine combination therapy for chronic hepatitis B: results of a randomized, placebo-controlled trial. Hepatology 1993; 17: 383-388.

18. Berk L, Schalm SW, de Man RA, et al. Failure of acyclovir to enhance the antiviral effect of alpha lymphoblastoid interferon on HBe-seroconversion in chronic hepatitis B. A multi-centre randomized controlled trial. J Hepatol 1992; 14: 305-309.

19. Durand M, Bost F, Maynard M, Baud M, Cohard M, Zarski JP. Vidarabine-interferon combination in patients with chronic viral hepatitis B of mutant form. Efficiency and tolerability during a pilot study. Presse Med 1996; 25: 459.

20. Bruch HR, Korn A, Klein H, et al. Treatment of chronic hepatitis B with interferon alpha-2b and interleukin-2 J Hepatol 1993; 17 (Suppl): S52-S55.

21. Lam KC, Lai CL, Trepo C, Wu PC. Deleterious effect of prednisolone in HBsAg-positive chronic active hepatitis. N Engl J Med 1981; 304: 380-386.

22. Scullard GH, Smith CI, Merigan TC, Robinson WS, Gregory PB. Effects of immunosuppressive therapy on viral markers in chronic active hepatitis B. Gastroenterology 1981; 81: 987-991.

23. Laskus T, Cianciara J, Loch T, Sluarczyk J. Short-term corticosteroid therapy for chronic active hepatitis B. Digestion 1990; 47: 115-120.

24. Nair PV, Tong MJ, Stevenson D, et al. A pilot study on the effects of prednisone withdrawal on serum hepatitis B virus DNA and HBeAg in chronic active hepatitis B. Hepatology 1986; 6: 1319-1324.

25. Nouri-Aria KT, Hegarty JE, Alexander GJ, Eddleston AL, Williams R. Effect of corticosteroids on suppressor-cell activity in "autoimmune" and viral chronic active hepatitis. N Engl J Med 1982; 307: 1301-1304.

26. Berninger M, Hammer M, Hoyer B, Gerin JL. An assay for the detection of the DNA genome of hepatitis B virus in serum. J Med Virol 1982; 9: 57-68.

27. Dawson-Saunders B, Trapp RG. Basic and Clinical Biostatistics. Norwalk, CT: Appleton and Lange; 1994.

28. Perrillo RP, Regenstein FG, Peters MG, et al. Prednison withdrawal followed by recombinant alpha interferon in the treatment of chronic type B hepatitis. A randomized, controlled trial. Ann Intern Med 1988; 109: 95-100.

29. Sheen IS, Liaw YF, Lin SM, Chu CM. Severe clinical rebound upon withdrawal of corticosteroid before interferon therapy: incidence and risk factors. J Gastroenterol Hepatol 1996; 11: 143-147.

30. Guan R, Ho KY, Yap I, et al. Treatment of hepatitis B surface antigen carriers in the early stage of the infection using recombinant alpha-interferon with steroid priming. Aliment Pharmacol Ther 1995; 9: 535-540.

31. Liaw YF, Lin SM, Chen TJ, Chien RN, Sheen IS, Chu CM. Beneficial effect of prednisolone withdrawal followed by human lymphoblastoid interferon on the treatment of chronic type B hepatitis in Asians: a randomized controlled trial. J Hepatol 1994; 20: 175-180.

32. Reichen J, Bianchi L, Frei PC, Malé PJ, Lavanchy D, Schmid M. Efficacy of steroid withdrawal and low-dose interferon treatment in chronic active hepatitis B. Results of a randomized multicenter trial. Swiss Association for the Study of the Liver. J Hepatol 1994; 20: 168-174.

33. Perez V, Findor J, Tanno H, Sorda J. A controlled trial of high dose interferon, alone and after prednisone withdrawal, in the treatment of chronic hepatitis B: long-term follow up. Gut 1993; 34 34(Suppl): S91-S94.

34. Niederau C, Heintges T, Niederau M, Stremmel W, Strohmeyer G. Prospective randomized controlled trial of sequential treatment with corticoids and alpha-interferon versus treatment with interferon alone in patients with chronic active hepatitis B. Eur J Med 1992; 1: 396-402.

35. Lok AS, Wu PC, Lai CL, et al. A controlled trial of interferon with or without prednisone priming for chronic hepatitis B. Gastroenterology 1992; 102: 2091-2097.

36. Burezynska B, Madalinski K, Pawlowska J, et al. The value of quantitative measurement of HBeAg and HBsAg before interferon-α treatment of chronic hepatitis B in children. J Hepatol 1994; 21: 1097-1102.

37. Utili R, Sagnelli E, Giusti G, et al. Effect of prednisone priming followed by alfa-interferon in treatment of children with chronic hepatitis B: an interim analysis of a controlled trial. Arch Virol Suppl 1992; 4: 277-280.

38. Utili R, Sagnelli E, Gaeta GB, et al. Treatment of chronic hepatitis B in children with prednisone followed by alpha-interferon: a controlled randomized study. J Hepatol 1994; 20: 163-167.

39. Gregorio GV, Jara P, Hierro L, et al. Lymphoblastoid interferon alpha with or without steroid pretreatment in children with chronic hepatitis B: a multicenter controlled trial. Hepatology 1996; 23: 700-707.

40. Giacchino R, Main J, Timitilli A, et al. Dual-centre, double-blind, randomised trial of lymphoblastoid interferon alpha with or without steroid pretreatment in children with chronic hepatitis B. Liver 1995; 15: 143-148.

41. Krogsgaard K, Bindslev N, Christensen E, et al. The treatment effect of alpha interferon in chronic hepatitis B is independent of pre-treatment variables. Results based on individual patient data from 10 clinical controlled trials. European Concerted Action on Viral Hepatitis. J Hepatol 1994; 21: 646-655.

42. Fattovich G, Giustina G, Favarato S, Ruol A. Investigators of the Italian Association for the Study of the Liver. A survey of adverse events in 11,241 patients with chronic viral hepatitis treated with alpha interferon. J Hepatol 1996; 24: 38-47.

43. Ruiz-Moreno M, Rua MJ, Moraleda G, Guardia L, Moreno A, Carreno V. Treatment with interferon gamma versus interferons alfa and gamma in children with chronic hepatitis B. Pediatrics 1992; 90: 254-258.

A MULTICENTER CHILD MALTREATMENT STUDY: TWENTY-EIGHT CASES FOLLOWED-UP ON A MULTIDISCIPLINARY BASIS*

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SUMMARY: Oral R, Can D, Hancı M, Miral S, Erşahin Y, Tepeli N, Bulguç AG, Tıraş B. (Dr. Behçet Uz Children's Hospital, İzmir, Turkey). A multicenter child maltreatment study: twenty-eight cases followed-up on a multidisciplinary basis. Turk J Pediatr 1998; 40: 515-523.

Twenty-eight maltreated cases were presented in this multicenter study. Hospital distribution was as follows: Dr. Behçet Uz Children's Hospital, 54 percent; Dokuz Eylül University Hospital, 21 percent; Ege University Hospital, 14 percent; Tepecik Social Security Hospital, 7 percent; Atatürk State Hospital, 4 percent. Age and sex distribution was two months to 25 years and 43 percent male, 57 percent female. The offender was the father in 71 percent, the mother in 32 percent and multiple in 25 percent of the cases. More than three child maltreatment risk factors were present in 93 percent. Nineteen patients (68%), nine of which were effectively followed-up were reported to the Social Affairs Bureau. Sixty-four percent gained acceptable health with the support of our team, 14 percent died, and 21 percent failed to comply with follow-up. A multidisciplinary group may interfere both medically and socially with these cases to interrupt the course of maltreatment. Every children's hospital needs such a team to increase diagnosis establishment necessary to initiate social support. *Key words: child abuse, child maltreatment.*

Child maltreatment (CM) is a complex issue presenting with medical, social, economic, legal, and educational problems. The nature of this syndrome necessitates the cooperation of several disciplines in order to first diagnose the cases, then to treat the acute phase health problems, follow-up and also treat the underlying pathology causing family dysfunction[1]. Several disciplines are involved in CM, including medical doctors, lawyers, prosecutors, judges, social workers, teachers, police, child development specialists, and psychologists. Each discipline has very important responsibilities in separate aspects of CM which

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cannot be replaced by another discipline. This is why cooperation among these disciplines is crucial in achieving satisfactory interference with these cases. This idea yielded the foundation of CM follow-up teams at all hospitals in developed countries accepting pediatric patients, since medical and educational professionals are the two major groups to identify CM cases[2].

We established a Child Maltreatment Follow-up Team in İzmir and have carried out since 1994 a training program through a series of lectures on CM at several hospitals and medical settings in İzmir to increase medical doctors' awareness and knowledge of the problem. From September 1996 to May 1997 we carried out monthly child maltreatment case presentation meetings during which diagnosed cases were presented from five teaching hospitals in İzmir. We would like to share our experience with our colleagues, believing it is crucial to let the pediatric community know about all the diagnosed cases until the importance of CM is recognized and appreciated throughout the country[3]. To our knowledge, this is the first case series of CM in Turkey reported predominantly from a pediatric setting.

Material and Methods

A group of physicians within the İzmir Chamber of the Turkish Medical Association gathered in 1993 to form a group to work on domestic violence.

Two subgroups were formed at first, one to deal with violence against women and one to deal with violence against children. In time, the second group was concentrating more on its task and so from the beginning of 1994, the whole group started to deal with CM.

After carrying out several projects on CM[4-6], this group initiated monthly CM case presentation meetings in İzmir in 1996. The attendants of these meetings were mainly medical doctors (pediatricians, forensic medicine physicians, child psychiatrists, general practitioners, pediatric surgeons, neurosurgeons, orthopedists, and public health and family physicians), lawyers, social workers, teachers, and psychologists. We carried out eight meetings in 1996-1997, during which 28 cases were presented from five hospitalts in İzmir. The attendants of the case presentation meetings were asked to present at the meetings any CM case they encountered or followed-up. By informing one of the authors (RO) in advance of the meeting, three to four cases could be presented at each meeting. Presenters were also asked to complete a form describing the cases so data could be collected by the authors.

Name, age, gender, and address of the patient, presenting institution, date of admission to the hospital, number of children in the family, birth order of the index case, self history and family history information, family structure, and

parental demographic information such as names, ages, occupations, diseases, educational-socioeconomic status, CM experience during childhood, substance/alcohol abuse, and marital problems were determined. The type, severity, duration and offender of CM were determined as well. A short summary of follow-up was provided by the social workers at the regional Social Affairs Bureau (SAB), who were attendants at the meetings.

Child maltreatment diagnosis was established in these cases by the recognition of any inflicted trauma directed to the child by a caretaker or someone known to the child who was at least six years older than the child and who caused psysical, sexual and/or psychological injury[1].

The types of CM were classified as physical, psychological and sexual according to medical examination and psychiatric interview findings[1]:

The severity of CM was categorized as follows by an algorithm developed by the authors. It was determined as "severe" if it was continuous and considered to be the cause of any physical or psychological handicap, "moderate" if it was continuous but caused no residual handicap, and "mild" if it was occasional with no major injury or handicap.

The outcome was determined as "physically and psychologically acceptable" if the patient complied with follow-up and there was no finding, either physically or psychologically, related to the abuse course, "death", "handicapped", and "failure to comply with follow-up".

Several features of the sexually and non-sexually maltreated children were compared by Student's t and Fisher's exact tests.

Results

We carried out eight meetings in 1996-1997 during which 28 cases were presented from five hospitals in İzmir. The attendants of these meetings were mainly medical doctors, lawyers, social workers, teachers, and psychologists.

Twenty-eight maltreated cases were presented in this multicenter study. Thirteen (46%) cases were retrospectively published case reports, the remainder (15, 54%) were diagnosed prospectively after the case presentation meetings started. Hospitals at which the cases were diagnosed were the five teaching hospitals in İzmir: Dr. Behçet Uz Children's Hospital, 15 cases (54%), 12 cases from the Department of Pediatrics and three cases from the Department of Pediatric Surgery; Dokuz Eylül University Medical School Hospital, six cases (21%), all from the Department of Child Psychiatry; Ege University Medical School Hospital, four cases (14%), all from the Department of Forensic Science; Tepecik Social Security Hospital, two cases (7%), both from the Department of Pediatrics; and

Atatürk State Hospital, one case (4%), from the Department of Obstetrics and Gynecology.

The distribution of the type of CM was psychological in 86 percent, physical in 65 percent, sexual in 46 percent, and severe neglect in four percent. Pure physical maltreatment was diagnosed in only three cases (11%) compared to 39 percent with both physical and psychological maltreatment and 32 percent both sexual and psychological maltreatment. In four cases (14%) maltreatment consisted of all physical, sexual and psychological components (Table I).

Maltreatment was severe in 22 cases (79%) compared to six moderate cases (21%). There was no case categorized as mild. All sexual maltreatment cases were evaluated as severe whereas 43 percent of non-sexually maltreated cases were moderate. However, the difference between the severity of maltreatment in the sexually versus non-sexually maltreated groups was statistically insignificant by Fisher's exact test ($p=0.08$).

The mean age was 9.6 ± 7.4 years (range between two months and 25 years). This range was between three months and 13 years in 15 children with physical and/or psychological maltreatment, with 73 percent being younger than five years of age. Among those categorized as sexual maltreatment, age distribution was between four to 25 years of age, with 77 percent being older than 13 years of age. The mean age was significantly higher in the latter subgroup (4.6 ± 4.0 vs 15.5 ± 6.0 years, $p<0.0001$).

Gender distribution was 12 male (43%) and 16 female (57%). In sexual maltreatment, however, 15 percent male compared to 85 percent female, whereas in the non-sexually maltreated group, the same distribution was 66 and 34 percent, respectively. This difference was statistically significant ($p<0.01$).

Comparisons between the sexually and non-sexually maltreated cases are shown in Table II.

Table I: Distribution of the Type and Severity of Maltreatment

Type	n	%	Severity	n	%
Psychological	24	86			
Physical	18	65	Severe	22	79
Sexual	13	46			
Neglect	1	4	Moderate	6	21
Physical/Psychological	11	39			
Sexual/Psychological	9	32	Mild	0	0
Sexual/Physical/Psychological	4	14			

Table II: Comparisons Between Sexually and Non-Sexually Maltreated Groups

Parameter		SM* n	SM* %	NSM* n	NSM* %	p
Severity of CM	Severe	13	100	9	57	NS***
	Moderate	0	0	6	43	NS
Gender	Male	2	15	10	66	<0.01
	Female	11	85	5	34	<0.0001
Age (years)		1.5 ± 6.0		4.6 ± 4.0		<0.0001

*SM: Sexually maltreated group, **NSM: Non-sexually maltreated group, ***NS: Statistically nonsignificant (p>0.05).

The offender was the father in 20 cases (71%), the mother in nine cases (32%), step-father and aunt in two cases each (7%), and stepmother, a relative and a neighbor in one case (4%) each. Multiple offenders were responsible for maltreatment in 13 cases (46%), both parents in 10, father and aunt in one, both parents and aunt in one and father and a relative in one case.

The most frequent risk factors associated with CM in this series were as follows, in decreasing order: low educational level in 21 cases (75%), parental psychological problems in 19 cases (68%), marital problems in 18 cases (64%), domestic violence in 15 cases (54%), low socioeconomic level in 15 cases (54%), divorce in 14 cases (50%), and parental alcohol dependency in 14 cases (50%). Less frequent risk factors determined were as follows: unemployment (39%), social isolation of the family (29%), parenthood before the age of 18 years (21%), parental physical illness (21%), unwanted pregnancy (18%), parental substance abuse (14%), stepparent (11%), low parental intelligence (11%), single parent (11%), immigration (7%), and parental maltreatment during childhood (4%). More than three risk factors were present in 26 cases (93%). Low educational and socioeconomic level and severe marital problems were present together in 39 percent of the patients.

Nineteen patients (68%) were reported to the regional SAB. The remainder were not reported because they were retrospective cases. Nine (47%) of the reported cases were effectively followed-up by the SAB. Ten (53%) patients could not be followed-up: seven because of false family address, two because the families lived in other cities, and one because of death while hospitalized.

On follow-up, 18 cases (64%) gained acceptable short-term physical and psychological health with the support of our team. However, long-term well-being

and freedom of continuing CM were confirmed in only 10 cases (36%) on follow-up. Twenty-two percent on follow-up showed sequelae of the maltreatment. Mortality, 14 percent in this series, was encountered in four patients. One of the cases died of nosocomial sepsis indirectly related to CM. The others died of the consequences of CM itself. Thus, true CM mortality rate in this series was 11 percent. Those three children died of drowning, incest/rape and suffocation. All were female, with an age distribution of one, four and 11 years, respectively.

Sixteen cases (57%) in this series were reported to the police department. However, information on legal actions taken is not yet available since the trials are still in process.

Discussion

Bearing in mind that approximately one percent of children referred to hospitals are diagnosed and reported as CM, according to reports coming from developed countries, one would expect at least 300,000 reported abuse cases from Turkish hospitals now that 30,000,000 of the Turkish population are under 18 years of age[1]. It is amazing, however, that only a few cases are reported in this context yearly. This is not only due to the lack of knowledge and sensitivity on the professionals' side, but also because of statistical surveillance insufficiency and the lack of a national organization program to prevent CM.

The physicians' attitudes and behaviors towards and knowledge of CM were determined in a study carried out by the İzmir Child Maltreatment Follow-up Team[4]. We learned that only 58 percent of the sampled physicians ever received any training on CM received a mostly through lectures of only one to two hours. Regarding their level of knowledge about CM, only 10% low score, and no one received high or moderate scores. This study, the results of which were somewhat anticipated, proved that there was a great lack of and dramatic need for medical training on CM.

This series is the cumulative result of the training program carried out by the İzmir Child Maltreatment Follow-up Team in İzmir. We believe that as the training program on CM becomes more organized and is regularly held, the number of diagnosed cases will increase. This assumption is already supported by the finding that the majority (54%) of cases in this series were reported from Dr. Behçet Uz Children's Hospital where the CM training program was relatively more organized in comparison to the other four teaching hospitals.

One may still wonder if CM does exist in Turkey or if it is a local problem of the population Dr. Behçet Uz Children's Hospital serves. To our knowledge there is no pediatric series reported by pediatricians in Turkey. However, there are

some series from child psychiatry or psychiatry departments as well as field studies proving that CM is as important a problem in Turkey as it is in developed countries[5,7].

Our series is the first to our knowledge in Turkey reported by a multidisciplinary team led by pediatricians. This series consists of very obvious cases as was anticipated since the recognition of more subtle cases needs a higher level of training of the medical community as a whole[2]. This is why severe cases comprised 79 percent of our series compared to the 30-40 percent of severe cases reported in literature[8].

In literature, the offender in physical abuse cases could be the father or the mother with almost equal rates[8]. This again contradicts our findings since the father was the offender in 71 percent of the cases in our series. However, this may also be explained by the high percentage of severe cases in our series since it is reported that, although fathers and mothers maltreat their children in comparable frequencies, fathers are more frequently responsible for severe and fatal cases[9,10].

The distribution of the type of CM was severe neglect (4%), sexual (46%), physical (65%), and psychological (86%), in increasing order. It was an anticipated result since some cases of sexual maltreatment were also physically maltreated. All physical and/or sexual maltreatment cases had a component of psychological maltreatment as well. We cannot yet claim this distribution represents the distribution of all CM cases in Turkey though, because of the small size of the series.

There is no significant difference in gender distribution of maltreated children in literature except for in the case of sexual maltreatment[8,11]. In our series, however, two-thirds of the physically and/or psychologically maltreated children were male. As for sexually abused children, only 15 percent were male compared to 85 percent female, which is in accordance with literature findings[11-13].

Presence of multiple risk factors in the majority of cases was an important finding in this series. Several authors have stressed this finding in order to increase the index of suspicion[1,2,8,11,12,14]. Low educational level, marital problems, parental psychological problems, domestic violence, low socioeconomic level, divorce, and parental alcohol dependency were the most frequent risk factors associated with CM in this series. We would like to stress that it should be borne in mind that a thorough social history should be taken from patients admitted to emergency units with trauma to reveal the presence of these risk factors in order to have a high index of suspicion of CM which is usually the only tool for reaching a manage diagnosis in these cases.

As for the reporting of CM cases, it is legally mandatory to report all these cases to police in Turkey, as is the case in developed countries. However, in developed countries, these cases are reported to child protective services and experts decide whether or not to take the case to court after thorough investigation of all the negatives and positives of such an action[15]. Sixteen cases in this series were reported to the police department. However, our concern about reporting these cases to police immediately is that maltreatment of these cases may continue and even become more pronounced during legal actions taken by unskilled investigators. Furthermore, some legal actions may destroy the family's unity and render the family members, including the maltreated child, in a far worse social and economic situation. This is why we, as a group, prefer to report all our cases to the regional SAB and let them decide whether it it necessary to take a legal action or not. Only in cases of sexual maltreatment and those with mortality potential do we report the cases to the police immediately. However, we believe this attitude will need further discussion in Turkey as the number of diagnosed cases increases and complications on interference ensue. Thus, we will develop in time a better medicolegal organization for reporting these cases by gaining more experience in working with maltreated children.

As for case outcome, 64 percent of cases in this series gained acceptable short-term physical and psychological health with the support of our multidisciplinary team. However long-term well-being and freedom of continuing CM were confirmed in only 36 percent of patients on follow-up. Even in developed countries, loss of patients on follow-up is frequently encountered[16,17]. In this series, though, it was encouraging to note that none experienced a severe or fatal CM episode on follow-up.

Mortality is reported to range between 0.1 and 10 percent in the literature[1,8,18]. It was high in our series (14%) compared to literature findings because more severe cases were included and also probably because one of the reporting groups was the Forensic Medicine Department staff which by definition deals only with deceased cases. Even so, the number of fatal cases was too small to compare with literature in terms of abuse type and offender.

In summary, we would like to reiterate that CM does exist in our hospitals. We need to increase medical professionals' awareness and knowledge of CM and of its risk factors so that they are more effective in recognizing such cases. Then, we should develop good reporting procedures so we can get involved in these cases and interrupt the CM course and keep these children healthy both physically and psychologically. In order to achieve all this, we believe every hospital accepting pediatric patients needs a child maltreatment follow-up team to increase diagnosis establishment.

REFERENCES

1. Leventhal JM. Child maltreatment: neglect to abuse. In: Rudolph AM, Hoffman JI, Rudolph CD (eds). Rudolph's Pediatrics (20th ed). Stanford: Appleton and Lange; 1996: 145-151.
2. Dubowitz H. Pediatrician's role in preventing child maltreatment. Pediatr Clin North Am 1990; 37: 989-1002.
3. Deschamps E. Çocuk istismarı paneli. XXI. UMEMPS Kongresi 18-24 Ekim 1993, İzmir.
4. Oral R, Can D, Vatansever K, Özenmiş M, Orhon Y. Pediatri asistanları ve pratisyen hekimlerin çocuk istismarı konusundaki tutum, davranış ve bilgi düzeyleri. 2000'e 5 kala Türkiye ve Dünyada Çocukların Durumu. XXXI. Türk Pediatri Kongresi Kitabı. 23-27 Ekim 1995, İstanbul, 187.
5. Oral R, Yavuz Ş, Can D, Kutlugün A, Genç I. Bir çocuk psikiyatri polikliniği'nde çocuk istismarı sıklığı. Çukurova Ü Tıp F Derg 1997; 22: 137-144.
6. Oral R, Miral S, Aksel Ş, et al. İzmir Çocuk Hakları Çalışma Günleri Çocuk İstismarı Grubunun Ulusal Organizasyon Planı Önerisi. Tıpta Sürekli Eğitim Derg 1997 (in press).
7. Bilir Ş, Arı M, Dönmez NB. 4-12 yaşları arasında 16.000 çocukta örselenme durumları ile ilgili bir inceleme. Çocuk Gelişimi ve Eğitimi Dergisi 1986; 1: 7-14.
8. Johnson CF. Inflicted injury versus accidental injury. Pediatr Clin North Am 1990; 37: 791-814.
9. Duhalme AC, Alario AJ, Lewander WJ, et al. Head injury in very young children: mechanisms, injury types, and ophthalmologic findings in 100 hospitalized patients younger than 2 years of age. Pediatrics 1992; 90: 179-185.
10. Garcia VF, Gotschall CS, Eichelberger MR, Bowman LM. Rib fractures in children: a marker of severe trauma. J Trauma 1990; 30: 695-700.
11. Leventhal JM. Sexual abuse of children. In: Hoekelman RA, Friedman SB, Nelson NM, Seidel HM, Weitzman ML (eds). Primary Pediatric Care (3rd ed). St. Louis: Mosby; 1997: 651-655.
12. Paradise JE. The medical evaluation of the sexually abused child. Pediatr Clin North Am 1990, 37: 839-862.
13. Green AH. Child maltreatment and its victims. A comparison of physical and sexual abuse. Psychiatr Clin North Am 1988; 11: 591-610.
14. Krugman RD. Future role of the pediatrician in child abuse and neglect. Pediatr Clin North Am 1990; 37: 1003-1011.
15. Finkelhor D, Zellman GL. Flexible reporting options for skilled child abuse professionals. Child Abuse Negl 1991, 15: 335-341.
16. Zeller B. Physical and psychological abuse: follow-up of abused and delinquent adolescents. Child Abuse Negl 1982; 6: 207-210.
17. McCord J. A forty year perspective on effects of child abuse and neglect. Child Abuse Negl 1983; 7: 265-270.
18. Krupinski E, Weikel D. The tragic problem of child abuse. In: Cronin JG (ed). Death from Child Abuse and No One Heard. Florida: Currier Davis Publishing; 1986: 97-120.

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Rh BLOOD GROUP SYSTEM IN TURKEY*

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SUMMARY: Kanra T. (Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Rh blood group system in Turkey. Turk J Pediatr 1998; 40: 525-531.

Because of the absence of original data concerning the Rh blood group system in Turkey, for the benefit of researchers interested in the human blood groups field, serological results obtained in Hacettepe University Hospitals' Blood Center between 1980 and 1996 have been evaluated for the first time in this paper. During the study, 581,606 people were evaluated for Rho (D) positivity and negativity. In addition, 5,600 people from different parts of Turkey were screened for the five major antigens (D, C, E, c, e) of the Rh blood group system and, according to the results, various gene frequencies and most likely genotypes were calculated. Results clearly show that the Rh blood group system in Turkey is completely, in line with that of the Caucasians.
Key words: Rh blood group system, gene frequencies, most likely genotypes.

The discovery of the Rh blood group by Landsteiner and Wiener[1] in 1940, which must be considered with the work of Levine and Stetson[2] in 1939, was undoubtedly the most important event in the blood group field since the discovery of the ABO system forty years before. After A and B antigens of the ABO system, Rho (D) antigen is without a doubt the most clinically important antigen of the red cell antigens.

The considerable clinical importance of the Rh blood group system arises from the fact Rh negative individuals are at risk of producing anti-Rh antibodies by entering Rh positive red cells into the circulation by either transfusion or transplacental hemorrhage. The formation of anti-Rh antibodies is potentially very serious with respect to hemolytic disease of the newborn and hemolytic transfusion reactions.

Because of the impressive complexity of the Rh blood group system, this paper concentrates on giving precise common information and commonly encountered Rh genotypes and phenotypes in Turkey, without exhaustive theoretical considerations.

Material and Methods

We tested 581,606 people, including volunteer blood donors and patients from the wards requiring blood transfusion for routine ABO and Rh (D) grouping. D positive and D negative frequencies were evaluated in this group.

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We screened 5,600 people, including randomly selected donors, individuals subjected to paternity tests; patients with natural or immune irregular antibodies in their serum; donors for newborn babies suffering from hemolytic disease due to Rh or subgroup incompatibilities, and their parents; and patients with autoimmune hemolytic anemias with warm antibodies for the five major (D, C, E, c, e) Rh antigens.

The regular tube method was employed and both saline-reactive and rapid tube test anti-sera from Dade and Organon Teknika Corp. were used for the screening of Rh_0 (D), rh'(C), rh"(E), hr'(c) and hr"(e) antigens[3].

According to the results and gene frequencies, and due to the complexity of the Rh system, only first guesses were taken under consideration to calculate the most likely genotypes. Results were expressed in accordance with both Wiener[4] and Fisher-Race[5] nomenclatures.

Since our patients and donors were from all regions of the country, we believe that these results reflect data concerning the Rh blood group system in the Turkish population.

Results

From a known gene frequencies in any blood group system, the genotype (or phenotype) frequencies can readily be calculated. As Table II shows, the most common Rh gene complexes in the Turkish population are CDe (R_1) and cde (r). Thus, the three most common Rh genotypes expected are CDe/cde (R_1 r), with a frequency of 2 x (0.4200 x 0.3850) = 0.3234 or 32 percent; CDe/CDe (R_1 R_1) with a frequency of (0.4200 x 0.4200) = 0.1764 or 17.6 percent; and cde/cde (r r) with a frequency of (0.3850 x 0.3850) = 0.1482 or 14.8 percent.

Table I: Major Rh Antigen Frequencies

Antigens	Positivity in Turks %	*Positivity in Caucasians %	**Positivity In Basques %	**Positivity in Orientals %
D	85.3	85	60-8	99-100
C	69.6	70		
E	29.7	30		
c	79.05	80		
e	95.63	98		

* Issit et al.[6]

** Mourant et al.[7]

Table II: Frequencies of Some Rh Genes in Turkey (5,600 people)

Wiener	Fisher-Race	Frequencis %
Allele	Gene Combination	
R_1	CDE	0.42
r	cde	0.385
R_2	cDE	0.16
R_0	cDe	0.0115
R^w_1	c^wDe	0.01
r'	Cde	0.0055
r"	cdE	0.0055
R_2	CDE	0.0025

Table III: Comparison of Some Gene Frequencies in Different Countries

Wiener	Fisher-Race	Turkey	England*	Sweden**	USA***			
					Whites	Blacks	Orientals	Indians
R_1	cDE	0.42	0.4076	0.40356	0.42	0.17	0.7	0.44
r	cde	0.385	0.3886	0.38205	0.37	0.26	0.03	0.11
R_2	cDE	0.16	0.1411	0.16701	0.14	0.11	0.21	0.34
R_0	cDe	0.0115	0.0257	0.01855	0.04	0.44	0.03	0.02
R^w_1	C^wDe	0.01	0.0129	0.011983	—	—	—	—
r'	Cde	0.0055	9.0098	0.00498	0.02	0.02	0.02	0.02
r"	cdE	0.0055	0.0119	0.00295	0.01	0	0	0.01
R_2	CDE	0.0025	0.0024	0.00082	0	0.01	0.01	0.06
r^w	C^wde	—	—	0.00034	—	—	—	—

* Race et al.[6]
** Heiken and Rasmuson[8]
*** Mourant et al.[7]

The similarity of frequencies seen in Turkey, England, Sweden and in the whites of the USA is quite impressive.

Because of the complexity of the Rh system and the gradual multiplicity of probable genotypes, there might be some slight differences between the expected frequencies calculated from gene frequencies and those observed in the population.

The overall frequencies of the most likely Rh genotypes and phenotypes calculated in 5,600 people are shown in Table IV.

Table IV: Frequencies of Rh Genotypes (Phenotypes) in 5,600 Turkish People

Reactions with anti-								
D	C	E	c	e	Cw	Fisher-Race	Wiener	Frequencies %
+	+	o	+	+	o	CDe/cde	R_1 r	34.48
+	+	o	o	+	o	CDe/CDe	R_1 R_1	17.7
o	o	o	+	+	o	cde/cde	r r	14.7
+	+	+	+	+	o	CDe/cDE	R_1 R_2	14.06
+	o	+	+	+	o	cDE/cde	R_2 r	11.96
+	o	+	+	o	o	cDE/cDE	R_2 R_2	3.45
+	o	o	+	+	o	cDe/cde	R_0 r	0.85
+	o	o	+	+	+	C^wDe/cde	R^w_1 r	1.17
o	+	o	+	+	o	Cde/cde	r' r	0.28
o	o	+	+	+	o	cdE/cde	r" r	0.14
+	+	+	+	o	o	CDE/cDE	R_2 R_2	0.14

As can be seen in the table, the, frequency of the most common genotype or phenotype, CDe/cde (R1 r), is 34.48 percent; frequencies of the next most common phenotypes in order are: CDe/CDe (R1 R1) 17.70 percent; cde/cde (r r) 15.22 percent (including Cde/cde and cdE/cde); CDe/cDE (R1 R2) 14.06 percent; cDE/cde (R2 r) 11.96 percent and cDE/cDE (R2 R2) 3.45 percent. These together account for approximately 96.87 percent of the total Rh phenotypes of the screened Turkish population.

Frequencies of some common Rh genotypes in Turks and some Caucasians are shown in Table V.

Discussion

The complex nature of the Rh blood group system has become even more complicated by the discovery of apparent "compound antigens", "deleted antigens" and numerous variants. These clear and detailed accounts will not be repeated here. But, it is convenient to consider the antigens 'C' and 'c', 'E' and 'e' and 'D' and 'd' as alternatives or antithetical expressions of genetic determinants which appear to reside within a single locus or genetic region of chromosome 1[12,13].

Table V: Some Common Rh Genotypes in Turks and Caucasians

Fisher-Race	Wiener	Turks (%)	English* (%)	USA Whites** (%)
CDe/cde	R_1 r	34.48	34.89	35
CDe/CDe	R_1 R_1	17.7	18.51	19
cde/cde	r r	14.7 (15.22)	15.1	15
CDe/cDE	R_1 R_2	14.06	13.34	13
cDE/cde	R_2 r	11.96	12.67	12

** Mollison, et al.[10]

** Harmening[11]

Accordance of frequencies between Turks and Caucasians is remarkable.

Five antigenic determinants (D, C, E, c, e), which are the products of genes, are situated at three distinct but closely linked loci on the chromosome. The three loci are so closely linked that crossing-over would very rarely occur. They are codominantly inherited as a unit or gene complex, and a pair of chromosomes may be heterozygous or homozygous according to the genes inherited from each parent. Both the gene and the red cell antigens are given the same symbol, and the 'd' gene is considered to be a "silent" gene or amorphous.

As seen in Table I, the frequency of the different Rh antigens varies widely in different parts of the world. For example, the frequency of Rh negatives (D negative) varies from 20-40 percent in Basques to 0-1 percent in Orientals, American Indians and Eskimos.

There are now several different theories to explain the genetic control under which Rh antigens are synthesized. Two of these theories were introduced at the time of early discoveries in the Rh system. One postulated by Wiener is that genetic control is under the influence of a single gene, producing an antigenic complex of alleles. The other, Fisher-Race's theory, suggest that Rh antigens were produced under the control of three sets of allelic genes at very closely linked loci. A third theory with numerical terminology was introduced in 1962[14]. Because of their basic differences, each employed a different terminology to describe the antigens and antibodies of the system.

The net result is that today most workers use a hybrid terminology that is based on three distinct original suggestions and on new theories of genetic control. However, since the hybrid terminology is so well established, despite the objections, it is likely to remain in use for many years.

As mentioned before, Rho (D) antigen, due to its strong antigenicity and high frequency, is the most clinically important antigen and, despite being thirty times

weaker than the D antigen, the hr' (c) is the second most clinically important antigen of the Rh system.

As for the antibodies of the Rh system, they are immune antibodies in general. Because of the antigenic potency and the population frequencies of the antigens, the anti-D antibody is of major importance with respect to hemolytic disease of the newborn and hemolytic transfusion reactions.

After anti-D, anti-c is the most important immune Rh antibody from the clinical point of view. Anti-c is often involved, especially in delayed hemolytic transfusion reactions and the hemolytic disease of the newborn.

Anti-C alone, i.e. without anti-D, is quite rare.

Anti-E is more common than anti-c, and is frequently a naturally occurring antibody. Rare examples of anti-e, like anti-c, are found only as an immune antibody[10].

In our study, due to the inadequate number of fully screened people for Rh genotypes (phenotypes), rare Rh deleted red cells, such as -D-, cD- and Rh since the D^u phenotypes, arising from either a weakly reactive antigen or suppression of a completely normal gene by the other alleles, are encountered rarely, frequency of this Rh variant has not been calculated.

Some rare Rh genotypes were also encountered during the screening. C^wDe/cde (R_1^w r) genotypes were evaluated from two cases of hemolytic disease of the newborn, due to anti-C^w.

Human blood groups could be evaluated as reliable anthropological markers. The cDE/cde (R_0, r) genotype and cDe (R_0) gene complex, which are common in Blacks as African markers, quite rare (0.85%) in the native Turkish population. But, in Eti Turks, a small group living in Southern Anatolia, besides some African blood group markers, such as Fy (a- b-), Le (a- b-), jk^a and P_1, R_0 marker was found quite high (6.89%), addition to the high frequency of Hb S[15].

The relation of autoimmune hemolytic anemias with warm autoantibody and the Rh blood group system is well documented[10]. One of the cDe/cde (R_0, r) genotypes was encountered during the studies of an autoimmune hemolytic anemia due to auto anti-D[15].

Thus, in conclusion the Rh blood group system in Turkey bears a great similarity with the Caucasian population in Europe and the USA, according to the data evaluated from 5,600 native Turkish people. No relation has been observed with the other populations, including Blacks, American Indians, Orientals and Eskimos.

We believe this original data will be a beneficial guide to researchers interested in human blood groups in Turkey.

REFERENCES

1. Landsteiner K, Wiener AS. An agglutinable factor in human blood recognized by immune sera for rhesus blood. Proc Soc Exp Biol 1940; 43: 223.
2. Levine P, Stetson RE. An unusual case of intragroup agglutination. J Am Med Assoc 1939; 113: 126-127.
3. American Association of Blood Banks. Technical Manual. Philadelphia: JB Lippincott Co; 1977: 98-108.
4. Wiener AS. Genetic theory of the Rh blood types. Proc Soc Exp Biol 1943; 54: 316.
5. Race RR. The Rh genotypes and Fisher's theory. Blood 1948; 3 (Suppl): 27-42.
6. Issit PD, Issit CH. Applied Blood Group Serology. Biological Corporation of America. Philadelphia: W.B. Saunders Co; 1981: 117-121.
7. Mourant AE, Kopec AC, Domaniewska-Sobczak K. The Distribution of the Human Blood Groups and the other Polymorphisms. London: Oxford University Press; 1976: 47-54.
8. Race RR, Mourant AE, Lawer SD, Sanger R. The chromosome frequencies in England. Blood 1948; 3: 689-695.
9. Heiken A, Rasmuson M. Genetical studies on the Rh blood group system. Hereditas Lund 1966; 55: 192-212.
10. Mollison PL, Englefriet CP, Contreras M. Blood Transfusion in Clinical Medicine. Washington: Blackwell Sc. Publ; 1987: 333.
11. Harmening D. Modern Blood Banking and Transfusion Practices. Philadelphia: FA Davis Co; 1989: 109.
12. Ruddle F. Somatic cell genetic assignment of peptidase C and the Rh linkage group to chromosome A1 in man. Science 1972; 176: 1429-1972.
13. Marsh WL. Mapping human autosome: evidence supporting assignment of rhesus to the short arm of chromosome No 1. Science 1974; 183: 966.
14. Rosenfield RE, Allen FH, Swisher SN, Kochwa SA. A review of RH serology and presentation of a new terminology. Transfusion 1962; 2: 287-312.
15. Kanra T, Özsoylu Ş, Işcan M. African blood markers in Eti Turks. Turk J Pediatr 1983; 25: 35-39.
16. Kanra T, Dündar S, Erener H, Yavuz H. A different example of autoimmune haemolytic anaemia caused by anti-D. Br J Haematol 1987; 66: 432-433.

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Fcγ RECEPTOR ALLOTYPES IN CHILDREN WITH BACTERIAL MENINGITIS*

A Preliminary Study

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SUMMARY: Tezcan İ, Berkel A.İ., Ersoy F, Sanal Ö, Kanra G. (Immunology and Infectious Diseases Units, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Fcγ receptor allotypes in children with bacterial meningitis. A preliminary study. Turk J Pediatr 1998; 40: 533-538.

IgG2 antibody is the essential subclass to protect against encapsulated bacteria FcγRIIa is the only Fcγ receptor that interacts with human IgG2. The two genetically determined allotypes of human FcγRIIa, FcγRIIa-R131 and FcγRIIa-H131 alleles have functionally different reactivities with IgG2 in vitro, and H/H-131 cells have markedly higher binding affinity for human IgG2. Homozygous FcγRIIIb-NA1/NA1 PMNLs show higher phagocytic capacity than FcγRIIIb-NA2/NA2 PMNLs. To evaluate in vivo significance of FcγRIIa and FcγRIIIb allotypes, we analyzed FcγR allotypes in children with bacterial meningitis due to Haemophilus influenzae type b, Streptococcus pneumoniae and Neisseria meningitidis. FcγRII and FcγRIIIb polymorphisms were determined by using quantitative flow cytometry. FcγRIIa were studied in 23 children with bacterial meningitis and 50 healthy Turkish controls, and FcγIIb in 18 and 43 such individuals, respectively. The distribution of FcγRIIa in the healthy Turkish control group was found to be significantly different from that in the Chinese and Japanese population ($p<0.05$), but similar to that of the white population in the USA and the Netherlands. No case (0%) had the FcγRIIa-H/H-131 FcγRIIIb-NA1/NA1 the corresponding figure in the controls was 4 (9.3%). Homozygous FcγRIIa-H/H-131 phenotype was underrepresented with borderline significance (p: 0.057) in patients below two years of age in comparison with the healthy subjects and with patients with meningitis over two years of age (p: 0.059). Although the study needs to be conducted in a large series of patients in order to draw a firm conclusion, FcγRIIa polymorphism may be a contributing factor to the increased susceptibility to meningitis with encapsulated bacteria in children below two years of age. *Key words: FcγR allotypes, bacterial meningitis.*

Encapsulated bacteria such as *Haemophilus influenzae type b, Streptococcus pneumoniae, Neisseria meningitidis* are the most common etiological agents in the bacterial meningitis of childhood[1]. Antibodies against bacterial polysaccharide capsules are of prime importance in the defense system. Opsonophagocytosis due to antipolysaccharide antibodies and an intact complement system play a role in protection against *Neisseria meningitidis.* Especially in people with a

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normal complement system, specific IgG2 antibodies are essential to protect against this microorganism[2,3]. Receptors for the Fc region of IgG, FcγR, provide an important link between cellular effector mechanisms and antibody-antigen interaction[4]. The neutrophils (PMNL) have two types of FcγRs including IIa and IIIb. FaγRIIa is the only Fc receptor with high binding affinity for human IgG2. The two genetically determined allotypes of human FcγRIIa, FcγRIIa-R131 and FcγRIIa-H131, have functionally different reactivities with IgG2. The polymorphism of FcγRIIa is attributable to one amino acid difference which is critical for IgG2 binding, a histidine (H) or an arginine (R) residue at position 131. FcγRIIa-H/H-131 cells have markedly higher binding affinity for human IgG2 than do R/R-131 cells, whereas heterozygous H/R-131 cells have intermediate affinity[5]. PMNL from homozygous FcγRIIa-R131 are less effective than FcγRIIa-H/H 131 at phagocytizing IgG2-opsonized H. influenzae type b and Staphylococcus aureus, in vitro[6].

The FcγRIIIb has an allotypic polymorphism referred to as neutrophil antigens (NA) 1 and NA2. PMNL with the NA2 allotypic form internalize Ig-opsonize particles less effectively than do PMNL with the NA1 form, in vitro[7,8].

In this study we evaluated the in vivo significance of FcγRII a and FcγRIIIb allotypes of FcγRs in children with bacterial meningitis due to *H. influenzae type b, S. pneumoniae and N. meningitidis* who did not have any primary immunodeficiency disorder.

Material and Methods

Twenty-three children who were diagnosed with bacterial meningitis by positive cerebrospinal fluid culture in Hacettepe University Children's Hospital were enrolled in the study. Of 23 children (14 male, 9 female), *S. pneumoniae* was isolated in 8, *H. influenzae type b* in 6, and *N. meningitidis* in 9. Their ages were between three months and 16 years (median age 2 years). A control group consisted of 50 healthy volunteers from different regions of Turkey.

Immunological studies including serum immunoglobulins, IgG subclasses and complement system were found to be normal.

Determination of FcγRIIa and IIIb allotypes: The FcγR allotypes were determined by quantitative flow cytometry[9]. For FcγRIIa allotyping, we used monoclonal antibody (MAb) 41H16 (provided by T. Zipft MD, Anderson Cancer Center, Tx USA), which only reacts with the FcγRIIa-R131 allotype, and MAb IV.3 (Medarex, Annandale, NJ, USA), which binds to both IIa-R131 and IIa-H131. Fluorescence was measured with a flow cytometer (FACScan, Becton Dickinson, San Jose, CA, USA).

The FcγRIIIb-NA1/NA2 allotype was also determined with immunofluorescence analysis using specific MAbs to the IIIb-NA1 (CLB/Gran 11: CLB) and IIIb-NA2 allotypes (GRM1: provided by M. Garrido, Granada, Spain).

Statistical analysis: The phenotypic distribution of FcγR allotypes between patients and controls was compared with the Fisher's exact test.

Results

FcγRIIa allotypes were determined in 23 patients and 50 healthy Turkish controls. FcγRIIIb allotypes were studied in 18 patients and 43 controls. The distribution of allotypes is given in Table I. There was no statistical difference between the patient and control groups.

We analyzed the combined phenotype frequency for FcγRIIa and FcγRIIIb. In the patient group, H/H-131 and NA1/NA1 combination (theoretically, the more resistant form in vitro) was found in none while the corresponding figure in the healthy control group was 4 (9.3%) ($p>0.05$) (data not shown).

H/H-131 phenotype was underrepresented with borderline significance (p: 0.057) in children with meningitis below two years of age in comparison with the healthy subjects and patients with meningitis over two years of age (p: 0.059, Table II).

Discussion

A number of studies have been performed from different countries on the phenotypic frequency of FcγRII and FcγRIIIb[10-13]. The distribution of FcγRIIa in a healthy Turkish group was found to be significantly different from that of Chinese

Table I: Distribution of FcγR Allotypes in Patients with Meningitis and Healthy Controls

	Patients		Controls	
	No.	%	No.	%
FcγRIIa				
H/H-131	6	(26)	18	(36)
H/R-131	8	(35	19	(38)
R/R-131	9	(39)	13	(26)
FcγRIIIb				
NA1/NA1	2	(11)	8	(19)
NA1/NA2	10	(56)	19	(44)
NA2/NA	6	(33)	16	(37)

Table II: Comparison of Controls and Patients According to Age Limit

FcgRIIa Allotypes	Patients		Controls
	<2 Years No. (%)	>2 Years No. (%)	No. (%)
H/H-131	1 (8.3)	5 (45.5)	18 (36)
Other allotypes	11 (91.7)	6 (54.5)	32 (64)

p: 0.059 p: 0.82

p: 0.057

and Japanese populations ($p<0.05$) but was similar to that of the white population of the Netherlands and the USA. No difference was found between our control group and other ethnic groups with respect to FcγRIIIb allotypes.

Although many publications mention genetic localization, molecular structure and in vitro function of FcγRs, their in vivo significance is not clear and the subject needs further clinical investigation. According to epidemiological studies performed in Japan, meningococcal disease and infections with H. influenzae are very rare; the H-131 phenotype was documented as 85 percent in the Japanese population versus 30 percent among Caucasians[10,14]. This finding suggests that FcγRIIa allotypes play a role in the resistance to infections due to encapsulated bacteria. Our study suggested that the Turkish population may have a similar susceptibility pattern to infections caused by encapsulated bacteria as observed in the white populations of the Netherlands and the USA[11,12].

Fijen et al.[13] showed a correlation between meningococcal disease and R/R 131-NA2/NA2 phenotype in adult patients with primary late complement component deficiency. Bredius et al.[15] reported that R/R-131 homozygosity was significantly higher in a group of children with fulminant meningococcal shock due to meningococcal disease in comparison with healthy controls. In our study, combined H/H-131, NA1/NA1 phenotype was not present in the patient group. This finding is rather remarkable although it was not statistically significant as a small study group.

We observed that the H/H-131 phenotype was underrepresented at a borderline significance (p: 0.057) in children with meningitis below two years of age, the age group with relatively low IgG2 levels and immature antibody response to

bacterial polysaccharides, in comparison with the healthy control subjects. The functional differences between H-131 and R-131 phenotypes may be more critical when IgG2 antibody levels are relatively low, and having the R/R-131 phenotype may be less important when IgG2 anticarbohydrate antibodies reach adult levels[16]. It is conceivable that the physiological increase of IgG2 levels may overcome the disadvantage of R/R-131 with low binding capacity for IgG2 type antibodies. Our results may support the theory that if high levels of IgG2 antibodies are used in vitro, the difference in the binding capacities between H/H/131 and R/R-131 phenotypes is decreased.

In summary, although the study needs to be conducted in a large series of patients to draw a firm conclusion, our findings suggest that FcγRIIa polymorphism may be a contributory factor in increased susceptibility to meningitis with encapsulated bacteria in children below two years of age.

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REFERENCES

1. Feigin RD. Bacterial meningitis beyond the neonatal period. In: Textbook of Pediatric Infectious Diseases. Feigin RD, Cherry JD (eds). Philadelphia: WB Saunders Company; 1981: 293-308.
2. Goldschneider I, Gotschlich EC, Artenstein MS. Human immunity to meningococcus I. The role of human antibodies. J Exp Med 1969; 129: 1307-1326.
3. Roberts RB. The relationship between group A and group C meningococci polysaccharides and serum opsonins in man. J Exp Med 1970; 131: 499-513.
4. Hulett MD, Hogarth PM. Molecular basis of Fc receptor function. Adv Immunol 1994; 57: 1-127.
5. Warmerdam PA, van de Winkel JG, Vlug A, Westerdaal NA, Capel PJ. A single amino acid in the second Ig-like domain of the human Fc gamma receptor II is critical for human IgG2 binding. J Immunol 1991; 147: 1338-1343.
6. Bredius RG, de Vries CE, Troelstra A, et al. Phagocytosis of Staphylococcus aureus and Haemophilus influenzae type B opsonized with polyclonal human IgG1 and IgG2 antibodies. Functional hFc gamma RIIq polymorphism to IgG2. J Immunol 1993; 151: 1463-1472.
7. Salmon JE, Edberg JC, Kimberly RP. Fc gamma receptor III on human neutrophils. Allelic variants have functionally distinct capacities. J Clin Invest 1990; 85: 1287-1295.
8. Salmon JE, Edberg JC, Brogle NL, Kimberly RP. Allelic polymorphisms of human Fc gamma receptor IIA and Fc gamma receptor IIIB. Independent mechanisms for differences in human phagocyte function. J Clin Invest 1992; 89: 1274-1281.
9. Gosselin EJ, Brown MF, Anderson CL, Zipf TF, Guyre PM. The monoclonal antibody 41H16 detects the Leu 4 responder form of human Fc gamma RII. J Immunol 1990; 144: 1817-1822.
10. Abo T, Tilden AB, Balch CM, Kumagai K, Troup GM, Cooper MD. Ethnic differences in the lymphocyte proliferative response induced by a murine IgG1 antibody Leu-4, to the T3 molecule. J Exp Med 1984; 160: 303-309.

11. Sanders LA, van de Winkel JG, Rijkers GT, et al. Fc gamma receptor IIa (CD32) heterogeneity in patients with recurrent bacterial respiratory tract infections. J Infect Dis 1994; 170: 854-861.

12. Osborne JM, Chacko GW, Brandt JT, Anderson CL. Ethnic variation in frequency of an allelic polymorphism of human Fc gamma RIIA determined with allele specific oligonucleotide probes. J Immunol Methods 1994; 173: 207-217.

13. Fijen CA, Bredius RG, Kuijper EJ. Polymorphism of IgG Fc receptors in meningococcal disease. Ann Intern Med 1993; 119: 636.

14. Musser JM, Kroll JS, Granoff DM, et al. Global genetic structure and molecular epidemiology of encapsulated Haemophilus influenzae. Rev Infect Dis 1990; 12: 75-111.

15. Bredius RG, Derkx BH, Fijen CA, et al. Fc gamma receptor IIa (CD32) polymorphism in fulminant meningococcal septic shock in children. J Infect Dis 1994; 170: 848-853.

16. Van de Winkel JG, Tax WJ, Groeneveld A, Tamboer WP, De Mulder PH, Capel PJ. A new radiometric assay for the quantitation of surface-bound IgG on sensitized erythrocytes. J Immunol Methods 1988; 108: 95-103.

The Turkish Journal of Pediatrics 1998; 40: 539-542 Review

ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD):*

A Practical Scale for Pediatricians

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SUMMARY: Öktem F, Semerci ZB. (Department of Child and Adolescent Psychiatry, Hacettepe University Faculty of Medicine, Ankara, Turkey). Attention deficit hyperactivity disorder (ADHD): a practical scale for pediatricians. Turk J Pediatr 1998; 40: 539-542.

Attention deficit hyperactivity disorder (ADHD) is a common disturbance causing school failure and social problems. Early diagnosis and intervention allow ADHD children to adjust and succeed at school and in daily life. To identify these patients, we designed a practical questionnaire for parents. When tested on children with ADHD (n=100), children with psychiatric problems (n=35), and on age- and sex-mached control children (n=100), this scale was found to be highly useful in distinguishing these three groups from each other, especially after the identification and elimination of items with lower specificity. The use of the Hacettepe ADHD scale is recommended for pediatricians, general practitioners and teachers to allow earlier diagnosis of this condition. *Key words: attention deficit, hyperactivity, diagnosis.*

Attention deficit hyperactivity disorder (ADHD) is among the most frequent and emphasized diagnoses in child and adolescent psychiatry clinics. Ten percent of all first applications to the Department of Child and Adolescent Psychiatry in Hacettepe University are due to ADHD[1]. It is widely accepted that ADHD starts in the preschool period and continues into adulthood. Although the symptoms may change over time, they usually impair almost all aspects of the child's educational and daily life and, if untreated, create intense psychological and social problems. Most important, this disorder can be treated successfully by a collaborative approach from the school, family and medical staff, emphasizing the need for early diagnosis and treatment[2,3].

The majority of children with ADHD are brought for medical attention because of failure to learn how to read and write, or of failure to adjust when they first start school. The first professional these children encounter is usually a pediatrician, and the first diagnosis they receive is mental retardation. However, their school achievement improves when an early diagnosis of ADHD is made and attention problems and impulsivity are appropriately treated. It is therefore extremely important for a pediatrician to recognize this entity. The diagnosis of ADHD in child and adolescent psychiatry clinics involves extensive testing using

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various scoring systems unavailable to pediatricians. In order to assist pediatricians in identifying ADHD and increase the rate of correct referral, the Department of Child and Adolescent Psychiatry in Hacettepe University developed the easy-to-score scale presented in this study.

Material and Methods

The Hacettepe Attention Deficit Hyperactivity Scale (HADHS) is a questionnaire addressed to mothers and fathers who fill it out jointly by discussing each item. All items are scored on a scale of 0 to 2, with increasing scores representing more severe symptoms and a cutt off score of 19. Scores 19 and above could suggest ADHD (Table I).

Table I: Hacettepe Attention Deficit Hyperactivity Scale (HADHS)

	No	Sometimes	Frequently
1. Has impulsive behavior (hitting friend with no reason, pushing, etc.)			
2. Moves continuously			
3. Is restless, always standing up			
4. Moves a lot, with dangerous acts, "climbing walls"			
5. Does not complete work			
6. Does not do homework			
7. Has nail biting or thumb sucking			
8. Retaliates			
9. Is stubborn, insists on demands			
10. Has problems establishing and maintaining friendships			
11. Bullies other children			
12. Is cruel towards other children			
13. Lies or tells imaginary stories			
14. Does inappropriate things as told by other children			
15. Does not comply with rules and restrictions			
16. Is quarrelsome			
17. Is gloomy and sulky			
18. Gets angry easily			
19. Cries easily			
20. Has frequent and marked mood swings			
21. Daydreams			
22. Feelings get hurt easily			
23. Is unhappy at school			
24. Bothers you more than other children			
25. Steals			
26. Has bodily complaints			
27. Gets pushed around and made fun of by other children			
28. Gets distracted easily, cannot concentrate on work			
29. Talks without thinking			

The value of this scale in describing the specific symptoms in ADHD was determined by testing three groups of children:

Group I: ADHD group consisted of children who presented to Hacettepe University Department of Child and Adolescent Psychiatry for the first time in 1995-96 and who received the diagnosis of ADHD by DSM-IV criteria (n=100, 84 boys, 16 girls), mean age 8.19 (6-12) years.

Group II: Children with psychological symptoms seen in the same department in the same period (n=35, 30 boys, 5 girls), mean age 9.06 (6-12) years.

Group III: Normal control group consisting of age- and sex-matched children, not-selected from ADHD children's classrooms (n=100, 70 boys, 30 girls), mean age 8.73 (6-12) years.

Analysis: Analysis of variance, t test and chi-square test were applied to each item separately and also to the total score.

Results

All items of the scale were developed according to the features of ADHD; however, some items proved more valuable in distinguishing children with ADHD from the other two groups (the mean scores of each item for the three groups I, II, III follow in parentheses). Most often mentioned were: "has impulsive behavior" ($\bar{X}$: 1.81, 0.82, 0.71), "moves continuously" ($\bar{X}$: 1.52, 0.76, 0.92), "retaliates" ($\bar{X}$: 1.32, 1.00, 0.75), "gets angry easily" ($\bar{X}$: 1.49, 1.10, 0.67), and "is stubborn, insists on demands" ($\bar{X}$: 1.41, 1.08, 0.75). Some other items frequently mentioned by parents included: "does not complete homework" ($\bar{X}$: 1.31, 0.76, 0.45), "is restless, always standing up" ($\bar{X}$: 1.27, 0.72, 0.37), "moves a lot, with dangerous acts", "climbing walls" ($\bar{X}$: 1.06, 0.42, 0.17), and "bothers you more than other children" ($\bar{X}$: 1.05, 0.28, 0.13). Features like "gets angry easily", "retaliates", "is stubborn, insists on demands", which are frequently thought to be typical for ADHD, were also frequently found in the other two groups, indicating low specificity.

Discussion

Attention deficit hyperactivity disorder is an etiologically heterogenous entity with several predisposing medical conditions, such as perinatal events; prematurity; genetic, autoimmune, or allergic disturbances; abnormalities in trace metal metabolism; fragile X syndrome; lead intoxication; and also family attitude and psychosocial factors[3]. The variety of associated conditions points to the importance of a detailed physical and neurological evaluation. Recognition of ADHD by pediatricians is the first step for correct evaluation and referral.

These results show that the Hacettepe Attention Deficit Hyperactivity Scale can be used reliably in screening children for ADHD, and also in the diagnosis and follow-up after treatment, especially when interpreted in conjunction with other criteria. The ease of administration and interpretation makes it useful for professional groups frequently dealing with school-age children such as pediatricians, general practitioners and teachers. Early diagnosis and appropriate treatment of children with ADHD will decrease the risk of behavioral problems and provide an economical way of preventing further complications. We therefore recommend the widespread use of this practical scale by pediatricians and all professionals taking care of children.

REFERENCES

1. Öktem F, Sonuvar B. Dikkat eksikliği tanısı alan çocukların özellikleri. Türk Psikiyatri Dergisi 1994; 4: 267-272.
2. Öktem F. Dikkat eksikliği bozukluğu. Katkı Pediatri Dergisi 1996; 5: 826-850.
3. Cantwell DP. Attention deficit disorder: a review of the past 10 years. J Am Acad Child Adolesc Psychiatr 1996; 8: 978-987.
4. Ross DM, Ross SA. Hyperactivity. New York: John Wiley & Sons; 1982: 118-157.

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THE CLINICAL PREDICTORS OF INTRAUTERINE FETAL DEATH*

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SUMMARY: Önderoğlu L, Tuncer ZS. (Department of Obstetrics and Gynecology, Hacettepe University Faculty of Medicine, Ankara, Turkey). The clinical predictors of intrauterine fetal death. Turk J Pediatr 1998; 40: 543-547.

Five hundred and thirteen (513) patients with intrauterine fetal death managed between 1983 and 1990 at Hacettepe University Hospital were analyzed retrospectively. Fetal death rate was 20.5/1,000 deliveries during the study period. The mean age of the mothers at diagnosis was 27.6 years. Of the 326 multigravida patients, 113 (34.6%) had a history of abortion and 113 had a history of previous intrauterine fetal death. The leading causes of intrauterine fetal death in this series were maternal hypertension in 167 patients (32.5%) followed by abruptio placentae in 38, Rh incompatibility in 30 and congenital anomalies in 30 patients. However, in 175 patients (34.1%), the cause of intrauterine fetal death could not be explained. Three mothers were lost: one from pulmonary embolism complicating deep venous thrombosis, one from heart failure due to rheumatic disease, and one from cerebral injury following a traffic accident. The patients with a history of fetal demise should be managed under high risk category with close antepartum surveillance, especially in the last trimester, so as to reduce intrauterine fetal deaths which are mostly attributable to preventable causes. *Key words: intrauterine fetal death.*

Intrauterine fetal death is one of the most challenging complications of pregnancy. Identification of the specific cause giving way to stillbirth is essential in order to assess the risk in future pregnancies as well as to develop preventive measures for reduction in mortality. Although autopsy studies were thought to be essential, in most of the cases clinical investigation could identify a cause for stillbirth[1,2].

The aim of the present study is to assess the clinical factors that may play a role in the etiology of intrauterine fetal death.

Material and Methods

Five hundred and thirteen (513) patients with intrauterine fetal death managed between 1983 and 1990 at Hacettepe University Hospital served as the subjects of this report. Cases with a birth weight less than 500 g were excluded from the study. The associated factors for intrauterine fetal death were classified after reviewing the antenatal records. Autopsy could be carried out in only 50 (9.6%) patients due to religious reasons. During the study period, 25,321 deliveries were performed at the institution.

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The maternal and fetal conditions which may be relevant in the etiology of intrauterine fetal death were classified as follows: 1) maternal hypertension, which was further classified as preeclampsia, chronic hypertension, superimposed preeclampsia and eclampsia, 2) abruptio placentae (without maternal hypertension), 3) maternal insulin-dependent diabetes mellitus, 4) Rh isoimmunization, 5) fetal anomaly, 6) congenital infections, 7) cord accidents or compression when two or more nuchal cords, true knots, prolapse or thrombosis of the cord were present, 8) chorioamnionitis, confirmed by histological examination of the membranes and the placenta, 9) intrauterine growth retardation, 10) unexplained death, and 11) miscellaneous reasons.

There were 491 singleton, 17 twin and one quadruplet pregnancies. There were single intrauterine fetal deaths in six of the twins and one in the quadruplet pregnancy. The study group, thus, included 513 patients with 520 stillborn infants. Only 84 (16.3%) of the patients followed regular antenatal visits from the first trimester. The weights of the stillborn infants were recorded as 500-999 g in 115 (22.1%), 1000-1499 g in 169 (32.5%), 1500-2499 g in 128 (24.6%), and 2500-4000 g in 108 (20.8%) infants.

Results

Fetal death rate was 20.5/1,000 deliveries during the study period. The mean age of the mothers at diagnosis was 27.6 years (range 17-46). The mean values of gravidity and parity were 3.06 (range 1-15) and 1.5 (range 0-12), respectively. Of the 326 multigravida patients, 113 (34.6%) had a history of abortion and 113 had a history of previous intrauterine fetal death. In 33 of them, a history of both intrauterine fetal death and spontaneous abortion were present (Table I).

The associated factors and probable causes of death in 513 cases are shown in Table II. The leading causes of intrauterine fetal death in this series were maternal hypertension in 167 patient (32.5%) followed by abruptio placentae in 38, Rh incompatibility in 30 and congenital anomalies in 30 patients (Table II). However, in 175 patients (34.1%), the cause of intrauterine fetal death could not be explained.

The congenital anomalies detected in 30 (5.7%) stillborn infants were meningocele (6), anencephaly (6), multiple fetal anomalies (5), bilateral renal agenesis (4), hydrocephalus (4), gastrochisis and bilateral hydronephrosis (2), bone and cartilage maturation defect (1), chest wall defects (1), and congenital heart disease with hydrops fetalis (1). In the intrauterine infection group there were two cases with toxoplasmosis, two with rubella and five with cytomegalovirus (CMV) infection.

Table I: Clinical Characteristics of the Patients

Characteristics	No	%
Age (yrs)		
≤19	22	4.4
20-34	460	89.6
≥35	31	6.0
Gravida		
1	187	36.5
2-4	213	41.5
>5	113	22.0
Para		
0	187	36.5
1	116	22.6
2-4	139	27.1
≥5	71	13.8
History of abortion		
Total	113	34.6
1	99	87.6
2	12	10.6
≥3	2	1.8
Previous fetal demise		
Total	113	34.6
1	61	54.0
2	29	25.6
≥3	23	20.4

Table II: Causes of Intrauterine Exitus vs Gestational Age.

	Gestational age (weeks)					
Cause	20-27	28-31	32-36	37-41	≥42	Total
Preeclampsia	19	23	29	28	–	99
Chronic hypertension	4	11	8	–	–	23
Superimposed preeclampsia	–	7	10	2	–	19
Eclampsia	7	4	12	3	–	26
Abruptio placentae	9	5	19	5	–	38
Diabetes mellitus	–	5	2	5	–	12
Rh isoimmunization	7	8	9	6	–	30
Fetal infection	2	4	2	1	–	9
Cord accidents	1	1	3	13	2	20
Amniotic infection	3	2	–	–	–	5
Placental insufficiency	–	2	2	–	–	4
Miscellaneous	5	7	7	2	2	23
Unexplained	22	40	60	50	3	175
Congenital anomalies	8	13	2	7	–	30
Total	87	132	165	122	7	513

The mode of delivery in the stillborn infants was by vaginal route in 425 cases (81.7%), primary hysterotomy in 70 cases (13.5%) and repeat hysterotomy in 25 (4.8%) cases. Of the 520 stillborn infants, 135 were macerated. Maceration was present in 102 infants with less than 37 completed weeks and in 33 full-term infants. Among the unexplained death group of 175 stillborn infants, 91 were pre-term and 85 were macerated.

Three mothers were lost due to 1) pulmonary embolism complicating deep venous thrombosis, 2) heart failure due to rheumatic disease and 3) cerebral injury following a traffic accident.

Discussion

This study draws attention to the major contributing factors and probable causes of intrauterine fetal death in a single institution. The intrauterine fetal death rate was 20.5/1,000 deliveries in this series. The corresponding rate reported from the United States is 10/1,000 births[1]. It was 3.8/1,000 in an Oxford study[3]. Recently, stillbirth was reported to range between 5-12 deliveries in 1000 births by Schauer et al.[4] and Fretts et al.[5]. The relatively higher rate observed in the present report may be attributed largely to the high number of late high-risk pregnancy referrals from other institutions as well as to insufficient peripartum care in the institution and throughout the country.

The observation of a higher mean age (27.6) and mean gravidity (3.06) is consistent with previous observations that the stillbirth rate doubles with advancing maternal age and that perinatal mortality increases with increasing parity[6-8].

When the 326 multigravida patients' obstetric histories are considered, 34.6 percent of the patients had a history of at least one intrauterine fetal death. Several studies also suggested that a previous stillbirth history is among the most significant of all historic risk factors[9-11].

The most frequent associated factors of stillbirth categories were the unexplained and the maternal hypertension groups. There was no obvious cause of the fetal death in 175 of the cases. Yudkin et al.[3] also identified unexplained deaths in a significant proportion of cases. They reported that the unexplained stillbirths made up 43 percent of all stillbirths and that risk of an impending unexplained stillbirth at 41 weeks' gestation was four times that at 33 weeks'; before 33 weeks' gestation the risk was very small. One hundred and sixty-seven of the intrauterine fetal deaths were associated with hypertensive disease and 92 of them occurred at 32 weeks or more of gestation. Two hundred and ninety-two (56.9%) of the fetal deaths occurred after the 32nd week, at a time when fetal viability is reached. Thus, a close follow-up may obviate some of the fetal deaths.

Major anomalies account for seven to 21 percent of stillborn fetuses[4]. This figure was 5.7 percent in this series. Since major anomalies are reported to occur in approximately two to three percent of all births in the general population, the contribution of congenital anomalies to this series is worth emphasizing[12-14].

In most series, it was advocated that autopsies and histological studies should be performed on all stillbirth infants and placentas to identify the cause[1,15].On the other hand, useful information could also be obtained by careful evaluation of the risk factors and by clinical examination of stillborn infants because, as seen in this study, autopsies cannot always be performed[16,17].

In conclusion, patients with a history of fetal demise should be managed under high risk category with close antepartum surveillance, especially in the last trimester, so as to reduce intrauterine fetal deaths which are mostly attributable to preventable causes.

REFERENCES

1. Rayburn W, Sander C, Barr M Jr, Rygiel R. The stillborn fetus: placental histologic examination in determining a cause. Obstet Gynecol 1985; 65: 637-641.
2. Gau G. The ultimate audit. Br Med J 1977; 1: 1580-1581.
3. Yudkin PL, Wood L, Redman CW. Risk of unexplained stillbirth at different gestational ages. Lancet 1987; 1: 1192-1194.
4. Schauer GM, Kalousek DK, Magee JF. Genetic causes of stillbirth. Semin Perinatol 1992; 16: 341-351.
5. Fretts RC, Boyd ME, Usher RH, Usher HA. The changing pattern of fetal death, 1961-1988. Obstet Gynecol 1992; 79: 35-39.
6. Hillard BM, Jeffcoate TN. Abruptio placentae. Obstet Gynecol 1966; 27: 155-167.
7. Horger EO, Smythe AR. Pregnancy in women over. Obstet Gynecol 1977; 49: 257-261.
8. Roman EA, Alberman E, Pharoah PO. Pregnancy order and reproductive loss. Br Med J 1980; 280: 715-718.
9. Hobel CJ, Youkeles L, Forsythe A. Prenatal and intrapartum high risk screening. Am J Obstet Gynecol 1979; 135: 1051-1056.
10. Morrison I, Olsen J. Perinatal mortality and antepartum risk scoring. Obstet Gynecol 1979; 53: 362-366.
11. Freeman RK, Dorchester W, Anderson G, Garite TJ. The significance of a previous stillbirth. Am J Obstet Gynecol 1985; 151: 7-13.
12. Nelson K, Holmes LB. Malformations due to presumed spontaneous mutations in newborn infants. N Engl J Med 1989; 320: 19-23.
13. Kalter H, Warkany J. Medical progress. Congenital malformations: etiologic factors and their role in prevention (first of two parts). N Engl J Med 1983; 308: 424-431.
14. Tunçbilek E, Alikaşifoğlu M, Akadlı B, Hancıoğlu A, Boduroğlu K. Türkiye'de konjenital malformasyon sıklığı, dağılımı, risk faktörleri ve yenidoğanların antropometrik değerlendirmesi. Ankara: Tübitak Matbaası 1996: 41.
15. Naeye RL. The investigation of perinatal deaths. N Engl J Med 1983; 309: 611-612.
16. Woods DL, Draper RR. A clinical assessment of stillborn infants. S Afr Med J 1980; 57: 441-443.
17. Mueller RF, Sybert VP, Johnson J, Brown ZA, Chen WJ. Evaluation of a protocol for post-mortem examination of stillbirths. N Engl J Med 1983; 309: 586-590.

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USE OF LOCALIZED PROTON NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY IN CANAVAN'S DISEASE*

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SUMMARY: Aydınlı N, Çalışkan M, Calay M, Özmen M. (Division of Pediatric Neurology, Department of Pediatrics, İstanbul University Faculty of Medicine, Çapa - İstanbul, Turkey). Use of localized proton nuclear magnetic resonance spectroscopy in Canavan's disease. Turk J Pediatr 1998; 40: 549-557.

Canavan's disease is characterized by megalencephaly, leukodystrophy and early motor and mental retardation. On computerized tomography and magnetic resonance imaging, severe changes compatible with white matter disease due to demyelination is observed. It has been demonstrated that urinary N-acetylaspartate levels are increased because of a deficiency of aspartoacylase (N-acyl-L-aspartate aminohydrolase) in these patients. In this study, with the use of proton nuclear magnetic resonance spectroscopy, we were able to demonstrate elevated levels of N-acetylaspartate compared to choline and creatine in the frontal region white matter of three patients. The in vivo measurement of N-acetylaspartate, choline and creatine in the brain by magnetic resonance spectroscopy offers an additional noninvasive diagnostic test for establishing the diagnosis of Canavan's disease. *Key words: Canavan's disease, ^{1}H nuclear magnetic resonance spectroscopy.*

Canavan's disease (CD) is a rare neurodegenerative disorder which belongs to the group of leukodystrophies. Neonatal, infantile and juvenile forms have been described. The autosomal recessive infantile form is the most common and usually presents with megalencephaly in the first months of life and progresses with a rapid deterioration of psychomotor and mental abilities, spasticity, blindness and occasionally deafness and convulsions[1,2]. On computed tomography (CT) and magnetic resonance imaging (MRI) severe white matter disease due to demyelination is observed[3-5]. Hagenfeldt et al.[6] first reported a patient with leukodystrophy and N-acetylaspartic aciduria due to aspartoacylase deficiency in 1987. In 1988, Matalon et al.[7] correlated aspartoacylase deficiency with CD by finding the characteristic spongy degeneration at brain biopsy of three children with increased N-acetylaspartate (NAA) levels in urine and plasma. N-acetylaspartate is synthesized from acetyl-

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CoA and aspartate by L-aspartate-N-acetyl transferase in the brain. It is metabolized to aspartate and acetate by aspartoacylase (aminoacylase II). In deficiency of aspartoacylase, NAA concentration in the brain is elevated and the substance is excreted in large amounts in the urine[2,8-13].

Two predominant mutations in aspartoacylase (E285A and Y231X) that lead to loss of enzymatic activity accounted for 97 percent of the mutant chromosomes among Ashkenazi Jewish patients, while in non-Jewish patients a wide spectrum of Canavan mutations has been identified[14].

Proton (^{1}H) nuclear magnetic resonance spectroscopy (MRS) may complement MRI in the diagnostic assessment of CD. In vivo qualitative measurements of cerebral metabolites, including NAA, choline (Ch), and creatine (Cr) levels, have been made using MRS. This method can noninvasively detect changes in patterns of metabolites and may allow an earlier and more specific determination of neurodegeneration without the use of ionizing radiation[15-21].

We report three non related patients with radiologically and biochemically proven CD and discuss the role of MRS in the diagnosis of this disorder.

Material and Methods

All patients were diagnosed on the basis of clinical symptoms, MRI findings and urinary NAA levels.

Patient 1. He was the first child of healthy non-consanguineous parents. At birth a macrosomia was noticed. By three months of age, developmental delay was apparent and he was noted to be hypotonic. At 23 months the child showed macrocephaly [head circumference (HC)>97th centile] with a weight at the 10th centile and length at the 25th centile. He had visual tracking difficulties but he smiled when talked to. Light reflexes and ocular fundoscopy were normal on both sides, but there was thin pendular nystagmus. He was unable to hold up his head or sit unsupported. He had spasticity of all limbs with hyperactive reflexes.

Patient 2. He was the second child of healthy unrelated parents. Developmental delay was first noted at four-and-a-half months of age at which time he had visual tracking difficulties and the onset of apathy and passivity was observed. At the age of 19 months he had relative macrocephaly with a HC between 25-50th centile, weight below 3rd centile, and length between 10-25th centile. He failed to fix or follow a visual target but responded to auditory stimuli and could recognize his mother's voice. Lack of head control and emotional responses, and spontaneous movements accompanied by limb spasticity with hyperactive reflexes were noticed. The light reflexes were normal on both sides. On fundoscopy, papillae were pale. He could be fed orally.

Patient 3. She was the first child of healthy consanguineous parents. The neonatal period was marked by hyperirritability and sucking problems. Developmental delay was apparent at seven months. at 35 months her HC was at the 50th centile, and her weight and length were below 3rd centile. She also had relative macrocephaly. She did not pay attention to visual stimuli, she had horizontal nystagmus and strabismus. Light reflexes were normal on both sides. She could recognize her mother's voice. Motor activity was decreased; she exhibited opisthotonus posture. The primitive reflexes were strongly positive, she had no head control, and there was a profound tetraspasticity and a profuse increase in deep-tendon reflexes. On fundoscopy, papillae were pale bilaterally. She could be fed orally with semi-solid food.

Investigations: In all patients, MRI demonstrated diffuse symmetrical prolongation of both the T1 and T2 relaxation times in the cerebral and cerebellar white matter, causing hypointensity of the supratentorial white matter on T1-weighted and hyperintensity on T2-weighted images. These were interpreted as demyelination or dysmyelination. There was more involvement of the cerebral white matter than of the cerebellar white matter. The internal capsule, corpus callosum and deep cerebellar white matter were unaffected.

The analysis of urine organic acids by gas chromatography mass spectrometry yielded a prominent peak of NAA not recognizable in normal age-matched children (986, 1148, 622 mmol/mol creatinine, respectively; normal <50 mmol/mol creatinine).

Magnetic resonance spectroscopy protocol: MRS examinations were performed on a 1.5-T magnetic resonance scanner (General Electric, Echospeed, Milwaukee, WI, USA) using the quadrature adult head coil. The children were sedated by means of rectal administration of diazepam (0.5 mg/kg). The method used, Probe-P, is a version of PRESS (point resolved spectroscopy), which is more sensitive to the metabolites with longer T2s, such as Cr, Ch, and N-acetylaspartate. A voxel of 2x2x2 cm in the frontal region white matter was selected using graphically defined areas of interest in the axially taken images. After global and localized shimming (in the three orthogonal planes), the water suppression was optimized and thereafter the spectra of the desired area of interest were obtained with 9 minutes 42 seconds data acquisition. For the volume selective spectroscopy, a spin echo sequence with three frequencies selective 90, 180, 180 pulses was used. The TR (repetition time) and TE (echo time) were 1500 msec and 270 msec with 256x128/8 NEX. After the scan a single phased spectrum was obtained. The examination was considered unsuccessful if the patient moved during the data acquisition; it was repeated until the spectra clearly showed the peaks of metabolites. The probe spectra covered a spectral window from 4.40 ppm - to 0.40 ppm (parts-per-million) in X-axes and the intensity in Y-

axes. The three prominent resonances were identified as NAA at 2.02 ppm, Cr at 3.0 ppm, and Ch at 3.21 ppm according to the published criteria[16,17,20,22-24]. The ratios of the intensity peaks of the metabolites were calculated.

In our patients, MRS examinations were performed at the ages of 23, 19 and 35 months, respectively. In MRS studies it is important to compare spectra from patients with those from healthy subjects of similar age[20]. We did not attempt to acquire data from healthy children for this purpose; rather, the published normal spectra were used as control data[20].

Results

The metabolite ratios obtained from the frontal region of the patients with CD are listed in Table I. When NAA peaks were compared with Cr and Ch peaks, the ratios were found to be considerably increased in favor of NAA. No significant lactate signal was observed. Table I also shows normal metabolite ratios obtained from the paraventricular region white matter of age-matched healthy children reported in the study of van der Knaap et al.[20], and from the occipital lobe white matter of a healthy 27-month-old child presented in the article of Marks et al.[25]. Representative T1-weighted image as well as localized spectra from the frontal region of patient 1 are shown in Figure 1.

Discussion

Symmetric diffuse low signal intensity on T1-weighted images and high signal intensity on T2-weighted images are characteristic MRI findings of CD. The white matter involvement is more pronounced in the subcortical region than in the periventricular area[4,26]. Symmetric hyperintensity in the dentate nuclei and involvement of the brainstem are also described[26].

Table I: Metabolite Ratios from Patients with CD and Control Subjects

Patients	NAA/Ch	Ch/Cr	NAA/Cr
1	6	0.77	4.62
2	5	0.48	2.4
3	2.92	1.33	3.88
Control subjects			
27-month-old child*		0.238	1.20
Age-matched children**	2.2 ± 0.6	2.9 ± 0.7	3.4 ± 0.6

* From the article of Marks et al. (1991).
** Values are deduced from Figure 4 of van der Knaap et al. (1990).
NAA: N-acetylaspartate, Ch: choline, Cr: creatine

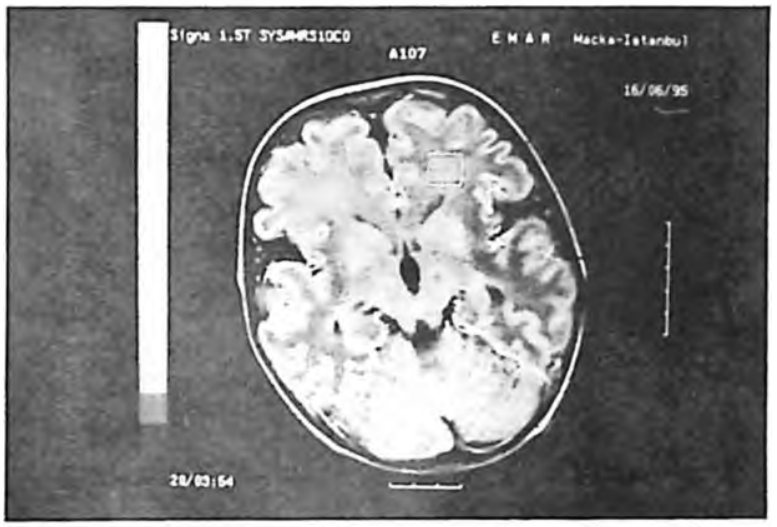

Fig. 1a

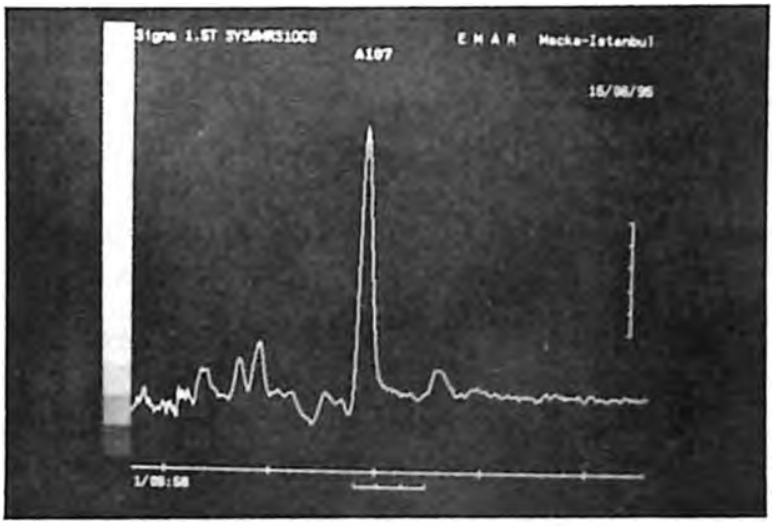

Fig. 1b

Fig. 1: T1-weighted axial image with voxel localization (a) and localized spectra from the frontal region (b) of patient. The diseased areas show signal alterations on the image. The metabolite ratios are NAA/Ch = 6, Ch/Cr = 0.77, NAA/Cr = 4.62.

The direct detection of NAA in the brain by MRS offers an additional diagnostic approach to CD. The metabolite ratios in our Probe-P studies were based on the data obtained from PRESS with a long TE sequence. Magnetic resonance spectroscopy at long echo times (135-270 msec) allows detection of four types of metabolites: Ch compounds, Cr/phosphocreatine, NAA and lactate. Because we could not correct for relaxation or saturation effects, the values of metabolite peaks reflect only relative changes and give no direct information for real metabolite concentrations. The area of interest in our study was in the frontal

region white matter, whereas in control studies the voxel was placed in different areas (paraventricular, occipital lobe white matter). It has been reported that slight differences of metabolite ratios can be seen between the regions, with the frontal regions generally showing slightly reduced values compared to those from the occipitial regions[13,17]. Different pulse sequences with long echo times (PRESS or STEAM) have been used in earlier studies[3,25]. Because only the ratios of metabolites are compared, pulse sequences seem not to be important. We agree with Rajanayagam et al.[17] that measurement of absolute concentrations rather than ratios is desirable, but to date no generally accepted method of quantification exists. As a result, a range of concentration values of the metabolites with large errors have been reported by different authors, even in the normal brain. Therefore, at present, metabolite ratios are preferable for evaluating patients.

In our study, compared to age-matched healthy children[20], NAA/Ch ratios were higher in all our patients. This finding is in accordance with results of earlier studies[23,24], in which increases in NAA and decreases in Ch resonance intensities have been reported. The high ratio of NAA to Ch may result either from an excessive amount of NAA due to a mutation of aminoacylase II resulting in a loss of function, or from the decrease in Ch which is a major component of lecithin and sphingomyelins. It has been reported that the increase of NAA in CD can be as high as several-fold over that of control[13]. One consequence of the defective catabolism of NAA is impaired myelin synthesis because NAA provides acetyl groups for de novo lipid synthesis[13]. Changes in the resonance intensity of Ch probably result mainly from increases in the steady state levels of phosphocholine and glycerol-phosphocholine. These choline-containing membrane phospholipids are released during active myelin breakdown. Thus, the resonance intensity of Ch increases in acute demyelinating lesions in humans. It is reported that chronic, slowly progressive leukodystrophies are associated with normal Ch/Cr resonance intensity ratios, presumably because the loss of myelin is so slow that significant increases of released membrane phospholipids do not accumulate[23]. In our study, Ch/Cr ratios were decreased in all cases compared to normal age-matched children. N-acetylaspartate to Cr ratio was increased in patient 1, decreased in patient 2 and within the normal range in patient 3. The increase in NAA to Cr ratio may be due either to the increase in NAA or to the decrease in Cr, which is consistent with the altered metabolic state of the brain. Tien et al.[18]. reported that a low creatine level frequently corresponded to the low-energy status of the tissue. It is also reported that total Cr concentration is relatively constant throughout the brain and tends to be relatively resistant to change[23]. Only when the total creatine pool changes as a result of a prolonged perturbation is this expected to show up as a reduction

of the MRS signal of total creatine. We suggest that the absence of a lactate signal excludes hypoxia or anaerobic glycolysis because lactate is the end product of glycolysis and accumulates when oxidative metabolism cannot meet energy requirement[23,24].

In the study of Grodd et al.[15], MRS performed in the right occipital lobe of a patient with CD revealed an increased peak from the methyl group of NAA, a reduced peak for creatine/phosphocreatine, a lack of Ch compounds, and no additional signal of lactate. In comparison with the control, the NAA signal in the child with Canavan's disease was increased by 20-25 percent. The authors explained the absence of a Ch peak with the decrease of myelin and they reported that the absence of lactate signals excluded hypoxia or anaerobic glycolysis for the reasons given above.

Grodd et al.[16] reported a seven-month-old boy with CD whose MRS revealed increased NAA content and lack of Ch-containing compounds in comparison with those values in age-matched control subject. We could not compare our results with those of the study above since the ratios of metabolites were not reported.

Marks et al.[25] demonstrated elevated levels of NAA in the occipital lobe of a 38-month-old patient with CD. In comparison with the control subject (a 27-month-old child), their patient demonstrated a 50 percent increase in NAA, a 44 percent increase in lactate, and a 51 percent decrease in Ch. The authors explained the elevation in the lactate seen in their patient as a result of greater mitochondrial dysfunction due to the increasing age of the patient. They thought that the 51 percent decrease in choline-containing compounds seen in their patient was consistent with severe demyelination. In our study, NAA/Cr and Ch/Cr ratios were found higher in all three cases compared to those of the patient reported in Marks et al.[25].

Barker et al.[3] have used MRS to quantitatively determine cerebral NAA concentrations in frontal lobe white matter of four patients with CD and in four age-matched control subjects. The most prominent features were an elevated ratio of NAA to Cr and Ch, and absolute quantification indicated that this was due to decreased Cr and Ch, as opposed to increased NAA. Cerebral NAA, measured in terms of micromoles/g weight, was not significantly different from normal despite the large increase in urinary NAA in the patients. They explained decreased Cr and Ch levels in the patients with a reduction in the number of cells per unit volume. They also noted that the reduced Ch signal could be associated with demyelination. In this study, the lactate and inositol levels were found to increase with age, indicating progressively decreasing mitochondrial oxidative activity.

Some of the discrepancies in the comparison of our results with earlier reports regarding metabolite ratios can probably be explained by differences of enzyme levels, age, and localization of the volume of interest in the cases studied. The only way to progress in the evaluation of the neurodegenerative diseases is to collect sufficient material from homogeneous populations examined with good technique and quantification of data. To do this it is necessary to have data on a sufficient number of healthy volunteers in all age classes to compare and determine normal values and confidence levels.

In conclusion, although determination of urinary NAA remains relatively simple and less expensive for establishing the diagnosis of CD, MRS provides a noninvasive method of investigating brain metabolism in infants and children. ^{1}H MRS in particular can be readily incorporated into integrated MRI-MRS examinations, and it is apparent that spectroscopy can provide new insights into the biochemical and pathophysiological basis of neurological disorders.

REFERENCES

1. Fishman MA. Disorders primarily of white matter. In: Swaiman KF (ed). Pediatric Neurology Principles and Practice (2nd ed) Vol 2. St. Louis: Mosby; 1994: 999-1017.
2. Menkes JH. Heredodegenerative diseases. In: Pine JW (ed). Textbook of Child Neurology (5th ed). Baltimore: Williams and Wilkins; 1995: 152-212.
3. Barker PB, Bryan RN, Kumar AJ, Naidu S. Proton NMR spectroscopy of Canavan's disease. Neuropediatrics 1992; 23: 263-267.
4. Barkovich AJ. Toxic and metabolic brain disorder. In: Barkovich AJ (ed). Pediatric Neuroimaging. New York: Raven Press; 1995: 55-105.
5. Chi TL, Bello JA. White matter disease. In: Lee SH, Rao KC, Zimmerman RA (eds). Cranial MRI and CT. New York: McGraw-Hill; 1992: 701-733.
6. Hagenfeldt L, Bollgren I, Venizelos N. N-acetylaspartic aciduria due to aspartoacylase deficiency-a new aetiology of childhood leukodystrophy. J Inherit Metab Dis 1987; 10: 135-141.
7. Matalon R, Michals K, Sebasta D, Deanching M, Gashkoff P, Casanova J. Aspartoacylase deficiency and N-acetylaspartic aciduria in patients with Canavan disease. Am J Med Genet 1988; 29: 463-471.
8. Moers AV, Sperner J, Michael TH, Scheffner D, Schutgens RH. Variable course of Canavan disease in two boy with early infantile aspartoacylase deficiency. Dev Med Child Neurol 1991; 33: 824-828.
9. Van der Knaap MS, Valk J. Canavan's disease. In: Van der Knaap MS, Valk J (eds). Magnetic Resonance of Myelin, and Myelin Disorders (2nd ed). Berlin: Springer Verlag; 1995: 216-219.
10. Elpeleg ON, Amir N, Barash V, et al. Canavan disease and N-acetylaspartic aciduria. Neuropediatrics 1989; 20: 238.
11. Yalaz K, Topçu M, Topaloğlu H, et al. N-acetylaspartic aciduria in Canavan disease: another proof in two infants. Neuropediatrics 1990; 21: 140-142.
12. Elpeleg ON. N-acetylaspartic aciduria in young age. Neuropediatrics 1992; 23: 112.
13. Tsai G, Coyle JT. N-acetylaspartate in neuropsychiatric disorders. Prog-Neurobiol 1995; 46: 531-540.

14. Kaul R, Gao GP, Matalon R, et al. Identification and expression of eight novel mutations among non-Jewish patients with Canavan disease. Am J Hum Genet 1996; 59: 95-102.

15. Grodd W, Krageloh-Mann I, Petersen D, Trefz FK, Harzer K. In vivo assessment of N-acetylaspartate in brain in spongy degeneration (Canavan's disease) by proton spectroscopy. Lancet 1990; 336: 437-438.

16. Grodd W, Kägeloh-Mann I, Klose U, Sauter R. Metabolic and destructive brain disorders in children: findings with localized proton MR spectroscopy. Radiology 1991; 181: 173-181.

17. Rajanayagam J, Grad J, Krivit W, et al. Proton MR spectroscopy of childhood adrenoleukodystrophy. AJNR 1996; 17: 1013-1024.

18. Tien RD, Lai PH, Smith JS, Lazeyras F. Single-voxel proton brain spectroscopy exam (PROBE/SV) in patients with primary brain tumors. AJR 1996; 167: 201-209.

19. Tzika AA, Ball WS Jr, Vigneron DB, Dunn RS, Kirks DR. Clinical proton MR spectroscopy of neurodegenerative disease in childhood Am J Neuroradiol 1993; 14: 1267-1281; discussion 1282-1284.

20. van der Knaap MS, van der Grond, van Rijen PC, Faber JA, Valk J, Willemse K. Age-dependent changes in localized proton and phosphorus MR spectroscopy of the brain. Radiology 1990; 176: 509-515.

21. Gadian DG, Cross JH, Connelly A. Paediatric applications of MRS. In: Young IR, Charles HC (eds). MR Spectroscopy. Clinical Applications and Techniques. London: Martin Dunitz Ltd; 1996: 93-104.

22. Barkovich AJ. Techniques and methods in pediatric imaging. In: Barkovich AJ (ed). Pediatric Neuroimaging. New York: Raven Press; 1995: 1-54.

23. Arnold DL, Matthews PM. Practical aspects of clinical applications of MRS in the brain. In: Young IR, Charles HC (eds). MR Spectroscopy. Clinical Applications and Techniques. London: Martin Dunitz Ltd; 1996: 139-159.

24. den Hollander JA, van der Ween JW, Luyten PR. Practical aspects of localized in vivo ^{1}H NMR spectroscopy and spectroscopy imaging of the human brain. In: Young IR, Charles HC (eds). MR Spectroscopy. Clinical Applications and Techniques. London: Martin Dunitz Ltd; 1996: 161-173.

25. Marks HG, Caro PA, Wang ZY, et al. Use of computed tomography, magnetic resonance imaging, and localized ^{1}H magnetic resonance spectroscopy in Canavan's disease: a case report. Ann Neurol 1991; 30: 106-110.

26. Topçu M, Erdem G, Saatçi I, et al. Clinical and magnetic resonance imaging features of L-2 hydroxyglutaric acidemia: report of three cases in comparison with Canavan disease. J Child Neurol 1996; 11: 373-377.

HERPES ENCEPHALITIS IN CHILDREN*

MRI Assessment

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SUMMARY: Çakmakçı H, Kovanlıkaya A, Obuz F, Kovanlıkaya İ, Pırnar T. (Department of Radiology, Dokuz Eylül University Faculty of Medicine, İzmir, Turkey). Herpes encephalitis in children: MRI assessment. Turk J Pediatr 1998; 40: 559-566.

The magnetic resonance imaging (MRI) findings in 14 patients with biopsy or polymerase chain reaction proven herpes simplex encephalitis were retrospectively reviewed to evaluate the diagnostic value of MRI in the early diagnosis of herpes simplex encephalitis in children. In addition to the early findings, follow-up MRI scans were obtained in four patients. Typical limbic system involvement was seen in 78 percent of the cases. Contrast-enhanced MRI was found to be superior to routine MRI sequences and computerized tomography (CT) in the early detection of inflammation. Follow-up MR images in four patients demonstrated the volume loss and late petechial hemorrhage in the involved regions. Magnetic resonance imaging is the method of choice in the diagnosis and follow-up of herpes simplex encephalitis. *Key words: magnetic resonance imaging, herpes simplex encephalitis, brain, computerized tomography.*

Herpes simplex encephalitis (HSE) is the most common cause of sporadic encephalitis in children[1,2]. In neonates, it tends to be part of a disseminated infection and can be due to either herpes simplex virus (HSV) type 1 or 2. Older infants, children, and adults get the disease localized to the CNS (central nervous system), which is almost exclusively HSV 1[2,3]. Herpes simplex virus encephalitis is characterized by a fulminant necrotizing encephalitis with petechial hemorrhage and early involvement of the medial temporal regions[4,5]. Mortality is high, approaching 70 percent. The success of antiviral treatment depends on early diagnosis and prompt institution of therapy[6]. This study aims to assess the role of magnetic resonance imaging (MRI) in the early diagnosis of this disease.

Material and Methods

Computerized tomography (CT) and magnetic resonance imaging (MRI) studies of 14 patients (8 females, 6 males) were retrospectively reviewed. The ages of the patients ranged from seven to 15 years with a mean age of 10.2 years. The most common clinical presentation was altered mental status. All patients had a MRI study within five to 10 hours of the initial clinical symptomatology. All 14 patients also had CT scans. All CT scans were performed with a GE 9800 HLA

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scanner in the axial plane with a 10 mm slice thickness. Both pre-and post-contrast images were obtained. Magnetic resonance imaging studies were done on a 1.0T Siemens magnet. Spin echo (SE) T2 weighted (TR msec/TEmsec: 2000/90) axial and pre-and post-gadolinium SE T1 weighted (TR/TE: 600/15) images in the axial and coronal planes were obtained. Four patients had follow-up MRI scans done 10 days after the onset of symptoms. Both MR and CT images were reviewed for the location, intensity/density, enhancement patterns of the lesions and the presence of hemorrhage.

Results

Unilateral temporal lobe involvement was detected in 10 of 14 patients. Bilateral temporal lobe involvement was seen in two patients and bilateral parietooccipital lobe involvement was present in two other patients. Temporal lobe dominance was 78 percent. One patient had isolated basal ganglia lesions. Computerized tomography was able to demonstrate the pathology in only eight of 14 patients (57%) (Fig. 1a). A Summary of CT and MRI findings is given in Table I. On MRI, lesions appeared hypointense on T1 weighted images and hyperintense on T2 weighted images (Fig. 1b). While no signal abnormalities were detected on the T2 weighted and non-contrast T1 weighted images of a patient (Case 11) (Fig. 2a), post-gadolinium T1 weighted images revealed impairment of the blood-brain barrier in the left parietooccipital region (Fig. 2b). Four of 14 patients had evidence of early hemorrhage on T1 weighted images (29%) (Fig. 1c). Contrast

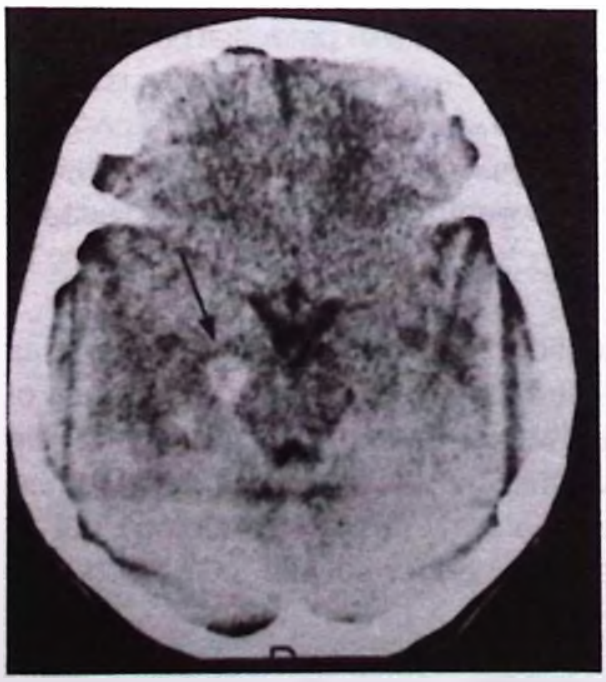

Fig. 1a

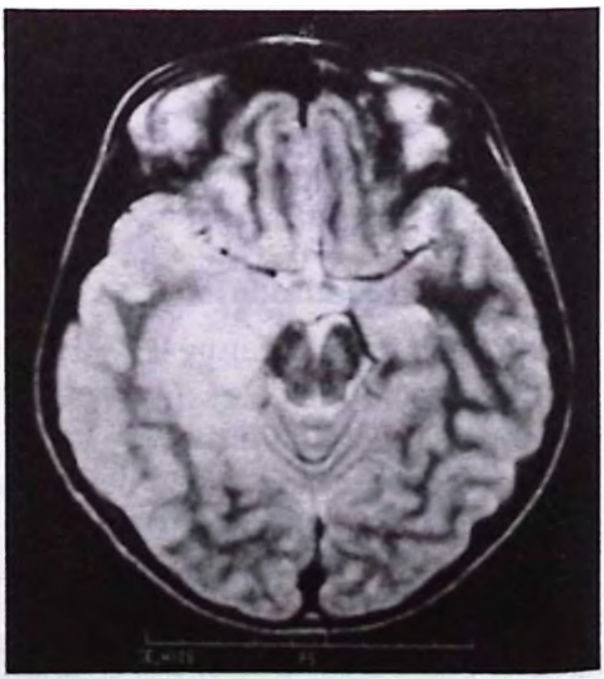

Fig. 1b

Tablo I: CT and MRI Findings of the Patient

Patient No.	Age/Sex	CT	MRI					
			Location	Intensity on T2 W1	Intensity on T1W1	Early hemorrhage	Contrast enhancement	Other
1	8/F	Normal	Right temporal	hyperintense	hypointense	–	+	
2	9/M	Pathologic	Right temporoparietal	hyperintense	hypointense	+	+	late hemorrhage
3	12/F	Normal	Left temporal	hyperintense	hypointense	–	+	
4	10/F	Pathologic	Right temporal	hyperintense	hypointense	+	+	late hemorrhage
5	7/F	Normal	Bilateral parietooccipital	hyperintense	hypointense	–	+	
6	12/M	Pathologic	Right temporal	hyperintense	hypointense	–	+	late hemorrhage
7	6/M	Pathologic	Bilateral temporal	hyperintense	hypointense	–	+	
8	15/F	Pathologic	Letf temporal	hyperintense	hypointense	+	+	
9	7/F	Normal	Left temporal	hyperintense	hypointense	+	+	late hemorrhage
10	11/F	Pathologic	Right temporal	hyperintense	hypointense	–	+	
11	10/M	Normal	Left parietooccipital	isointense	isointense	–	+	
12	13/M	Pathologic	Right temporal	hyperintense	hypointense	–	+	
13	11/M	Normal	Right basal ganglia	hyperintense	hypointense	–	+	
14	12/F	Pathologic	Right temporal	hyperintense	hypointense	–	+	

CT. computerized tomography, MRI: magnetic resonance imaging, WI: weighted image.

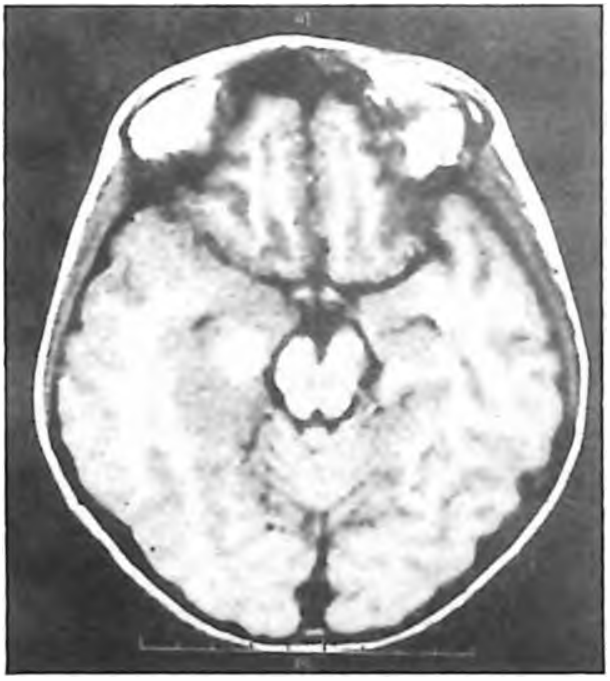

Fig. 1c

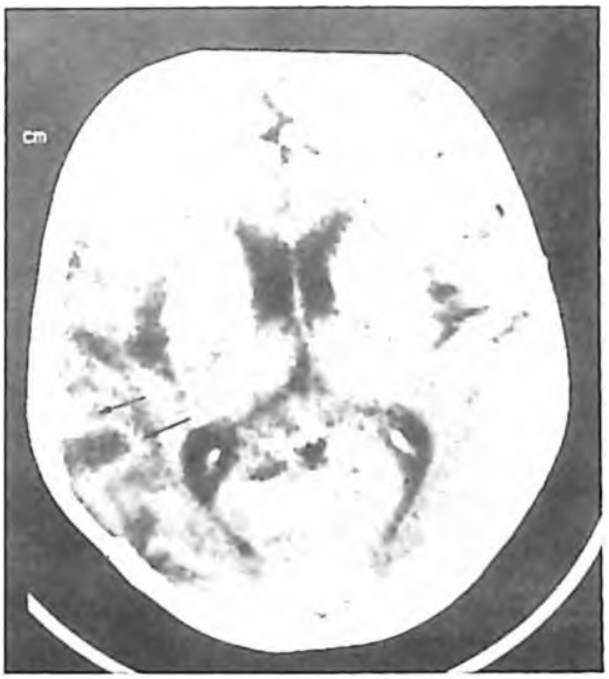

Fig. 1d

enhancement was seen in all patients. The pattern of enhancement was gyral in eight patients (Fig. 1g) and nodular in six patients. Follow-up MRI scans of the four patients demonstrated cortical atrophy and gyral hemorrhage (Figs. 1d-f). In addition to the gyral hemorrhage one patient also had hemorrhage involving the basal ganglia.

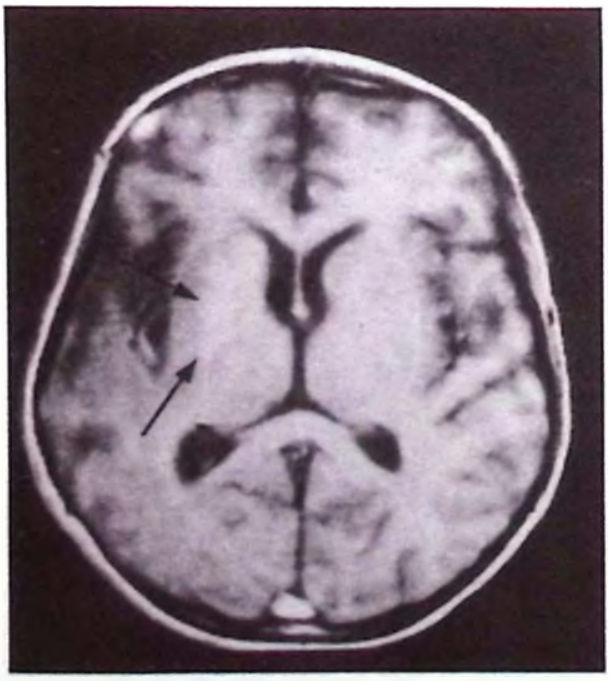

Fig. 1e

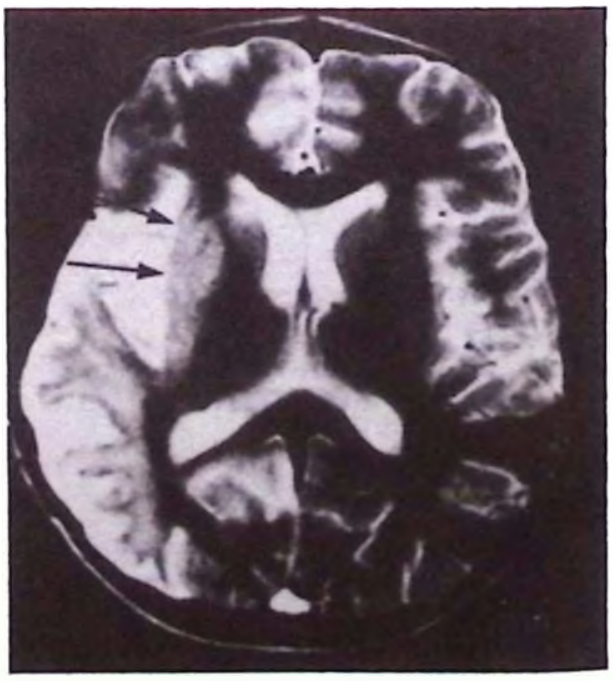

Fig. 1f

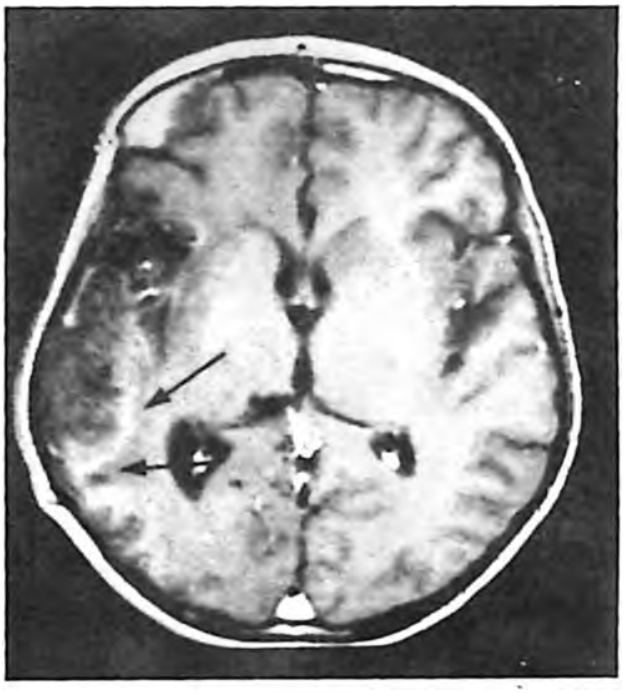

Fig. 1g

Figure 1: Case 2. Herpes virus encephalitis involving right temporoparietal lobe.
a: unenhanced axial CT scan showing early hemorrhage in the right limbic system (arrow).
b: T2 weighted axial MR image showing increased signal in the same region.
c: unenhanced T1 weighted MR image shows focal hemorrhage and sulcal effacement.
d: late follow-up unenhanced CT scan showing gyral hemorrhage in the parietal lobe (arrows).
e: late unenhanced T1 weighted MR image. f: T2 weighted MR images show basal ganglia hemorrhage (arrow) as well as postnecrotic atrophic changes within the right parietal lobe.
g: enhanced T1 weighted MR image also showing gyral enhancement (arrows).

Discussion

Diagnosis of herpes simplex encephalitis is crucial because the success of antiviral treatment depends on the early diagnosis of the disease[6]. The workup for suspected herpes encephalitis may include cerebrospinal fluid (CSF) studies, especially polymerase chain reaction (PCR) in CSF; electroencephalography (EEG); computed tomography (CT); magnetic resonance imaging (MRI); single photon emission computed tomography (SPECT); and brain biopsy[7-10]. Initial CSF profile can show increased or normal white blood cells, usually with mononuclear predominance, and elevated protein. Glucose is usually normal[1]. Blood and CSF antibody titers against HSE do not increase until the second or third week of illness. A rapid diagnostic test would offer immense advantages in care of these patients. The use of PCR to detect HSV in CSF within 25-45 hours has therefore been an exciting breakthrough in recent years. Polymerase chain reaction uses oligonucleotide primers to probe and amplify a portion of the HSV DNA polymerase gene which then can be detected by gel

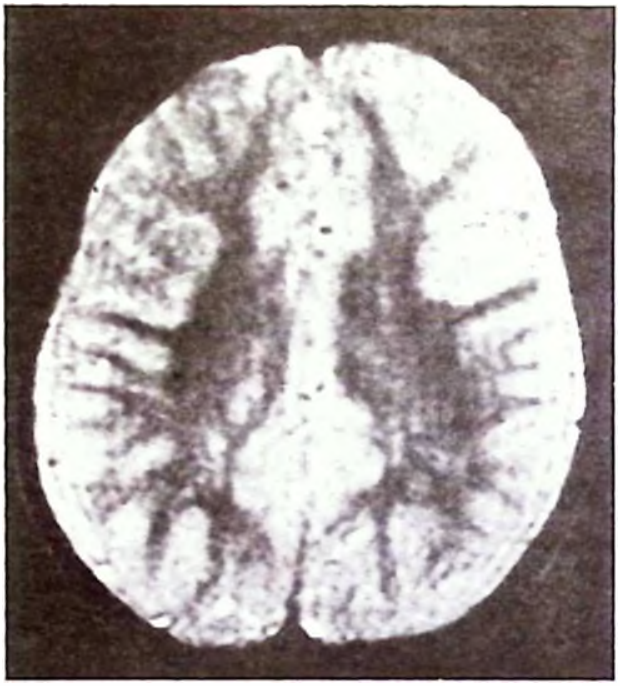

Fig. 2a

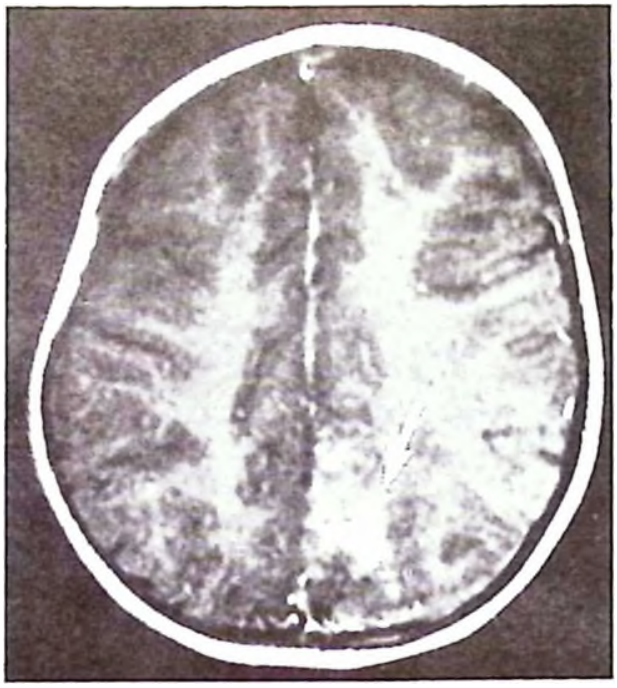

Fig. 2b

Figure 2: Case 11. Herpes virus encephalitis involving left parietooccipital lobe.
a: T2 weighted axial image showing no signal change in the affected area.
b: enhanced T1 weighted axial MR image showing disrupted blood-brain barrier due to infection in the corresponding region (arrow).

electrophoresis. The primer used in most reports will detect DNA of both HSV-1 and-2, but it does not cross-react with other herpes viruses, including Epstein-Barr virus, cytomegalovirus, Varicella, and HSV-6[7].

A characteristic temporal EEG focus and appropriate clinical signs and symptoms of acute encephalitis are indicative for HSE. However, EEG abnormalities are not consistently characteristic[1,6].

The most common CT findings in HSV infections are a poorly marginated hypodense area, mass effect and nonhomogeneous contrast enhancement. Low density usually centered in the temporal (limbic system) and frontal lobes may extend to involve cingulate gyrus, thalamus, and deep frontal and occipital lobes. Early CT scans may be inconclusive due to partial volume or beam hardening artifacts in the temporal fossa[2,5]. In this study, early CT examination demonstrated the pathology in only 57 percent of the cases.

The multiplanar capability of MRI allows a fast and accurate assessment of the temporal lobe. Subtle gyral effacements in the temporal lobe can easily be detected in the coronal plane. Because encephalitis leads to a rapid increase in water content, the involved brain parenchyma appears mildly hypointense on

T1 weighted images and markedly hyperintense on T2 weighted images. An abrupt transition to normal density at the lateral margin of the lenticular nucleus sparing the putamen has been a characteristic feature of herpes encephalitis on MRI[2-4]. Disruption of blood-brain barrier results in parenchymal and meningeal contrast enhancement on T1 weighted images[11]. In this study, with the exception of one patient, parenchymal involvement manifested as hypointensity on T1 weighted images and hyperintensity on T2 weighted images. The non-contrast T1 weighted images and the T2 weighted images were negative in a patient (Case 11) with a highly suspected clinical history of herpes encephalitis. However, the post-contrast images revealed the disruption of the blood-brain barrier in the left parietal lobe, which is a hallmark of the disease (Fig. 2). It should be noted that new sequences such as FLAIR (fluid attenuated inversion recovery) demonstrate the pathological changes much better than spin echo sequences[8,9].

Typical necrotizing HSE affects the limbic temporal lobe. Involvement of neurons through axonal transport of the virus may explain the systemic and even transhemispheric extension of the inflammation via the limbic pathways. The temporal lobe preference which was a dominant feature in this study (78%) appears to remain one of the most useful distinguishing features in addition to its bilaterality. Isolated basal ganglia and parietooccipital lobe involvement were also seen.

In the subacute phase, parenchymal petechial hemorrhage, which is consistently seen on pathological specimens, was rarely seen on CT images but may be more readily detected on MRI[2-5]. In this study, follow-up MRI demonstrated encephalomalacia and gyral and basal ganglia hemorrhages in four patients.

Recent SPECT studies suggest that an increased radionuclide uptake in the limbic temporal lobe and anterior basal ganglia in patients with acute encephalitis reflects distinct pathomorphological features in HSE rather than coincidental features[10].

The diagnosis of HSE may be delayed due to the non-specific nature of the earliest symptoms. Initially, CT findings may be equivocal, and the wait for serological results protracted. Magnetic resonance imaging is the most sensitive imaging modality in the early diagnosis of herpes encephalitis.

REFERENCES

1. Leestmo JE. Viral infections of the nervous system. In: Davis RL, Robertson DM (eds). Textbook of Neuropathology. Baltimore: Williams and Wilkins; 1991: 804-903.
2. Schroth G, Gawehn J, Thron A, Vallbracht A, Voigt K. Early diagnosis of herpes simplex encephalitis by MRI. Neurology 1987; 37: 179-183.
3. Demaerel P, Wilms G, Robberecht W, et al MRI of herpes simplex encephalitis Neuroradiology 1992; 34: 490-493.

4. Albertyn LE. Magnetic resonance imaging in herpes simplex encephalitis. Australian Radiol 1990; 34: 117-121.
5. Enzmann DR, Ranson B, Norman D, Talberth E. Computed tomography of the herpes simplex encephalitis. Radiology 1978; 129: 419-425.
6. Lester JW Jr, Carter MP, Reynolds TL. Herpes encephalitis: MR monitoring of response to acyclovir therapy. J Comput Assist Tomogr 1988; 12: 941-943.
7. Troendle-Atkins J, Demmler GJ, Buffone GJ. Rapid diagnosis of herpes simplex virus encephalitis by using the polymerase chain reaction. J Pediatr 1993; 123: 376-380.
8. Hajnal JV, Bryant DJ, Kasuboski L, et al. Use of fluid attenuated inversion recovery (FLAIR) pulse sequences in MRI of the brain. J Comput Assist Tomogr 1992; 16: 841-844.
9. White ML, Edwards-Brown MK. Fluid attenuated inversion recovery (FLAIR) MRI of herpes encephalitis. J Comput Assist Tomogr 1995; 19: 501-505.
10. Schmidbauer M, Podreka I, Wimberger D, et al. SPECT and MR imaging in herpes simplex encephalitis. J Comput Assist Tomogr 1991; 15: 811-815.
11. Sage MR, Wilson AJ. The blood-brain barrier: an important concept in neuroimaging. Am J Neuroradiol 1994; 15: 601-622.

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α-2-MACROGLOBULIN LEVELS IN EARLY RESPIRATORY DISTRESS SYNDROME*

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SUMMARY: Yurdakök M, Yiğit Ş, Gürakan B, Dündar S, Kirazlı Ş. (Neonatology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). α-2-macroglobulin levels in early respiratory distress syndrome. Turk J Pediatr 1998; 40: 567-570.

The vasoactive products of uncontrolled protease activity can play an important role in the pathogenesis of respiratory distress syndrome in newborn infants. In this study α-2-macroglobulin, which has antiproteolytic activity, was studied in the first few hours of life in preterm infants with and without respiratory distress syndrome. Mean plasma α-2-macroglobulin levels were found to be similar in both groups. These findings implicated that α-2-macroglobulin has no significant role in the pathogenesis of respiratory distress syndrome. *Key words: α-2-macroglobulin, fibrinolysis, respiratory distress syndrome, newborn infants.*

Pulmonary vascular damage is frequently encountered in newborn infants with respiratory distress syndrome (RDS)[1-4]. It has been postulated that the vasoactive products of uncontrolled protease activity can play an important role in the pathogenesis of RDS[5]. Proteinases appear in the circulation during blood clotting, fibrinolysis, and activation of the complement system. These proteinases can be inactivated by one or more of the several proteinase inhibitors in the blood. Alpha-2-macroglobulin is one of these proteinase inhibitors[5]. It has been shown that alpha-2-macroglobulin levels were significantly lower in infants with respiratory distress syndrome compared with control[6,7]. Therefore, we investigated plasma alpha-2-macroglobulin levels in preterm infants within the first few hours of life, in order to evaluate its role in the development of RDS.

Material and Methods

Thirty-five infants were included in the study. All neonates received vitamin K_1 (1 mg) intramuscularly upon delivery. Respiratory distress syndrome was

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considered to be present if all the following diagnostic criteria were fulfilled: symptoms of respiratory distress within one hour after birth and present for at least 24 hours, need for respiratory support including mechanical ventilation, and typical findings on lung x-ray and arterial blood gas analysis. None of the infants with RDS had any other disease.

Blood samples for alpha-2-macroglobulin (single radial immunodiffusion method, NOR-Partigen, Behring, Germany)[8] testing were obtained from a peripheral vein within six hours after birth, and mixed with 3.8 percent trisodium citrate in amounts according to individual hematocrit levels. The tubes were centrifuged at 3000 rpm for 10 minutes within 30 minutes of collection. The plasma was stored at –20 °C and analyzed within a month.

Results

Among 35 infants, 15 developed RDS; 20 infants with stable clinical conditions served as the control group. No significant statistical difference between the two groups was found for gestational age or birth weight. The mean plasma alpha-2-macroglobulin levels were found to be similar in both groups ($p>0.05$ by Mann-Whitney U test, Table I).

Discussion

Alpha-2-macroglobulin forms 1:1 complexes with various proteolytic enzymes, and inhibits several proteolytic enzymes in coagulation and fibrinolysis. It inhibits thrombin more slowly than antithrombin III, but acts as a rapidly acting antiplasmin[9-11]. The sites of production and biodynamics of this inhibitor are

Table I: Plasma Alpha-2-macroglobulin Levels in Preterm Infants with and without RDS

	Infants without RDS (n = 20)	Infants with RDS (n = 15)
Gestational ages (weeks)	32.1 ± 2.1 (27-35)	32.4 ± 1.7 (29-34)
Birth weight (g)	1614 ± 439 (1030-2460)	1851 ± 602 (830-2680)
alpha-2-macroglobulin (mg/dl)	116.68 ± 30.52 (44.00 – 183.30)	104.76 ± 34.37) (39.20 – 162.00)

Mean ± SD, ranges in parentheses. In all comparisons $p>0.05$ by Mann-Whitney U test.

unknown, although its production and secretion by fibroblasts, mononuclear phagocytes, platelets, and endothelial cells have been demonstrated in cell culture[12].

The concentration of alpha-2-macroglobulin in plasma ranges from 130 to 325 mg/dl[9]; however, neonatal levels are higher than those in adults[13,7]. In this study, alpha-2-macroglobulin levels in premature infants who did not develop RDS ranged between 44-183 mg/dl (116.68 ± 30.52).

A reduced fibrinolytic state has been shown in the early stages of RDS[3]. A hypercoagulable state, defective fibrinolysis, hypoproteinemia, and systemic and pulmonary edema are common features observed in RDS[5]. The characteristic pathological finding of RDS is hyaline membranes in the lung. Hyaline membranes are formed by coagulation of several proteins following parenchymal and vascular damage[14].

This study was designed to determine the role of alpha-2-macroglobulin in the pathogenesis of RDS. Low levels of protease inhibitors have been found on the first day of life in infants with respiratory distress syndrome[6,7]. These findings indicate that reduced alpha-2-macroglobulin levels may play a role in the reduction of fibrinolytic activity observed in the early stages of RDS. In contrast to these authors[6,7], our findings suggest that alpha-2-macroglobulin levels are unchanged in the early stages of RDS and that it probably has no role in the hemostatic abnormalities which arise during RDS pathogenesis.

REFERENCES

1. Stark CR, Abramson D, Erkan V. Intravascular coagulation and hyaline-membrane disease of the newborn. Lancet 1968; 1: 1180-1181.
2. Tisman G. Intravascular coagulation and hyaline-membrane disease. Lancet 1968; 2: 357.
3. Yurdakök M, Oran O, Dündar S, Tekinalp G, Kirazlı S. Reduced fibrinolytic state in early respiratory distress syndrome. Am J Hematol 1993; 42: 233-234.
4. Yurdakök M, Gürakan B, Ergin H, Kirazlı S. Increased von Willebrand factor antigen in early respiratory distress syndrome. Am J Hematol 1995; 49: 95-96.
5. Mellins RB. Pulmonary edema. In: Chernick V, Kendig EL (eds). Disorders of the Respiratory Tract in Children. Philadelphia: WB Saunders; 1990: 516-534.
6. El-Bardeesy MW, Johnson AM, Bissett LS. Serum proteinase inhibitors in infants with hyaline membrane disease. J Pediatr 1972; 81: 579-587.
7. Sveger T, Ekelund H. Variations of protease inhibitors in foetuses, newborn infants and in some neonatal disorders. Acta Paediatr Scand 1975; 64: 763-769.
8. Coan MH, Roberts RC. A redetermination of the concentration of alpha-2-macroglobulin in human plasma. Biol Chem Hoppe-Seyler 1989; 370: 673-676.
9. Van Leuven F. Human alpha-2-macroglobulin: structure and function. Trends Biochem Sci 1982; 7: 185.

10. Switzer ME, Gordon HJ, McKee PA. Proteolytic activity of alpha 2-macroglobulin-enzyme complexes toward human factor VIII/von Willebrand factor. Biochemistry 1983; 22: 1437-1444.

11. Bithell TC. Blood coagulation. In: Lee GR, Bithell TC, Foerster J, Athens JW, Lukens JN (eds). Wintrobe's Clinical Hematology (9th ed) Ch 19. Philadelphia: Lea & Febiger; 1993: 590, 594, 598.

12. Marynen P, Van der Schueren B, Van Leuven F, Cassiman JJ, Van den Berghe H. Absence of specific binding of receptor-mediated endocytosis, and of secretion of alpha-2-macroglobulin by cultured endothelial cells. Haemostasis 1982; 11: 210-214.

13. Andrew M, Paes B, Milner R, et al. Development of the human coagulation system in the full-term infant. Blood 1987; 70: 165-172.

14. Whitsett JA, Pryhuber GS, Rice WR, Warner BB, Wert SE. Acute respiratory disorders. In: Avery GB, Fletcher MA, Macdonald MG (eds). Neonatology. Philadelphia: JB Lippincott; 1994: 429-452.

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NONINVASIVE CARDIAC EVALUATION OF YOUNG PATIENT WITH CYSTIC FIBROSIS*

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SUMMARY: Küçükosmanoğlu O, Özbarlas N, Göçmen A, Özçelik U, Kiper N, Bilgiç A. (Chest Disease and Cardiology Units, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Noninvasive cardiac evaluation of young patients with cystic fibrosis. Turk J Pediatr 1998; 40: 571-578.

Cardiac involvement was evaluated by echocardiography in 26 young cystic fibrosis patients. The mean age was 48.4 months (range 3 months to 15 years). The findings were compared with 26 age-and sex-matched children without a history of cardiopulmonary complaints. All patients had normal values of left ventricular ejection fraction and fractional shortening. Interventricular septal and posterior left ventricular wall thicknesses were similar to control group but right ventricular free wall thickness was found greater than in the control group. Abnormal septal motion was documented in six patients. Right ventricular pre-ejection period to ventricular ejection time ratio was found over the upper limit of normal in two patients and there was a negative correlation with clinical Shwachman scores (r: –0,55). Left ventricular pre-ejection period to ventricular ejection time ratio was found over the upper limit of normal in five patients. For both mitral and tricuspid valves, the mean ratios of peak velocity during passive filling (E) phase of diastole to peak velocity during atrial contraction (A) phase were found significantly lower than in the control group ($p<0.05$). Early diastolic peak velocity was similar to that in the control group but late atrial peak velocity was higher in the patient group ($p<0.05$). Isovolumic relaxation time was found the same as in the control group. We conclude that cardiac changes in diastolic and systolic functions begin at very young ages in cystic fibrosis patients. *Key words: cardiac involvement, cystic fibrosis, echocardiography.*

Cystic fibrosis is the most common lethal inherited disease among Caucasians, with an incidence of 1:2500[1]. It is a multisystem disorder with lung involvement as the major cause of mortality and morbidity[2]. Cor pulmonale is a frequent terminal finding in patients with cystic fibrosis as a result of lung involvement.

Chronic cor pulmonale is defined by the World Health Organization[3] as "hypertrophy of the right ventricle resulting from diseases affecting the function and/or structure of the lung, except when these pulmonary alterations are the

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result of diseases that primarily affect the left side of the heart or of congenital heart disease*. Cor pulmonale has been demonstrated on autopsy in as many as 70 percent of children dying of cystic fibrosis[4]. Clinical recognition of cor pulmonale is often difficult because the usual signs may be a reflection of an underlying lung disease with or without cardiac failure. Neither electrocardiography nor radiography is a valuable method for diagnosis cor pulmonale in cystic fibrosis. Cardiac catheterization is an invasive procedure and cannot be done routinely. Echocardiography is a reliable, noninvasive technique that is useful in the diagnosis of cor pulmonale as well as many cardiac disorders.

The aim of the present study was to make an early determination of cor pulmonale and other cardiac dysfunction in a young group of cystic fibrosis patients and to detect a correlation between clinical status and cardiac functions.

Material and Methods

There were 29 cystic fibrosis patients (15 male, 14 female) ranging in age from three months to 15 years (mean 48.4 ± 8.6 months) in the study. Echocardiographic data were not suitable for analysis in three patients. Patients were studied during their clinically stable stage. Twenty-seven of them were outpatients; two were hospitalized, but were studied after clinical stabilization. None of the subjects were desaturated or took medications overnight. All subjects underwent count of whole blood cells, arterial pH and blood gases analysis, electrocardiography, chest x-ray radiographs and detailed echocardiographic study. All data were obtained in daytime within 24 hours. After physical examination patients were scored by Shwachman criteria[5]. Scores were determined by an investigator who was not aware of the results of the cardiac tests. In the control group, 26 age-and sex-matched children without a history of cardiopulmonary complaints underwent echocardiographic study.

Cardiac evaluation: Cardio-thoracic ratios of subjects were estimated in chest radiographs. Electrocardiographic measurements included QRS axis, amplitude of R wave and R/S ratio in V_1, and depth of S wave in V_6. Results above the upper limit of normal were accepted as evidence of right ventricular hypertrophy.

Echocardiographic studies of patients and control group were done by a blinded pediatric cardiologist using a Toshiba SSH-160A echocardiograph and 5, 3.75, 2.5 mHz transducers. Left ventricular end-diastolic and end-systolic diameters, interventricular wall thickness, posterior left ventricular wall thickness, left ventricular ejection fraction, left ventricular fractional shortening, right ventricular wall thickness, motion of interventricular septum, and left and right ventricular systolic time intervals were determined by m-mode echocardiography. Diastolic

diameters of right ventricular inflow tract, outflow tract, and right ventricular body were determined by two dimensional echocardiography[6]. Right and left ventricular diastolic filling patterns were determined by pulsed Doppler echocardiography. The examinations of mitral and tricuspid inflow were performed from the apical four chamber view, with the sample volume placed at the mitral valve and tricuspid valve annulus, respectively. Measurements included: early diastolic peak velocity (E), peak velocity during atrial contraction (A), the ratio of early-to-late time velocity (E/A) and isovolumic relaxation time.

Control group data were compared with cystic fibrosis group data by Student's t test. Cystic fibrosis group data were also compared to clinical variables by standard linear regression and correlation analysis.

Results

The Shwachman scores of patients were found excellent in seven, good in 12, moderate in six, and severe in one patient. All but one patient had hemoglobin levels more than 10 g/dl (9.7 g/dl). None of the patients had blood pH less than 7.35, paCO2 more than 45 mmHg and paO2 less than 50 mmHg.

Cardiac evaluation: Innocent murmur was heard in four patients. One patient had pansystolic murmur (ventricular septal defect was noted previously). Cyanosis was not seen in any patient. Heart rate was found significantly increased in cystic fibrosis group (mean 126 ± 5.9 vs 101 ± 2/min; $p<0.05$).

Electrocardiography showed right ventricular hypertrophy in eight patients. The evidence of right atrial dilatation (p wave greater than 2.5 mm) was not noted in any patient.

Chest radiographs showed mild cardiomegaly in two patients. Cardio-thoracic ratios were 9.57 and 0.56, respectively.

In echocardiographic examination, abnormal septal motion was documented in six patients. Five of them had flattened and one had reversed septal motion. All patients had normal values of left ventricular ejection fraction and fractional shortening (mean 65.9 ± 1.2% and 34.7 ± 0.9%, respectively), but these values were significantly less than control group values (mean 71.2 ± 1% and 39.8 ± 0.98%, respectively) ($p<0.05$). Interventricular septal wall and posterior left ventricular wall thicknesses were found similar to control group. However, thickness of right ventricular free wall was found significantly greater than in the control group (mean 5.38 ± 0.14 mm vs 4.35 ± 0.10 mm) ($p<0.05$) (Table I).

Right ventricular pre-ejection period to ventricular ejection time ratio was found over the upper limit of normal (0.30) in two patients. Left ventricular pre-ejection period to ventricular ejection time ratio was found over the upper limit of normal (0.40)[7] in five patients. Although mean values of both right and left ventricular

Table I: Results of M-Mode Echocardiographic Studies in Patients and Control Subjects

Measurement	Patient	Control	p Value
LVEF (%)	65.96 ± 1.2	71.2 ± 1.04	<0.05
LVFS (%)	34.77 ± 0.9	39.8 ± 0.98	<0.05
PLVWT (mm)	5.46 ± 0.15	5.7 ± 0.16	>0.05
IVSWT (mm)	5.42 ± 0.15	5.5 ± 0.16	>0.05
RVWT (mm)	5.38 ± 0.14	4.35 ± 0.1	<0.05
RV PEP/VET	0.23 ± 0.01	0.21 ± 0.06	>0.05
LV PEP/VET	0.33 ± 0.0014	0.31 ± 0.07	>0.05

LVEF: left ventricular ejection fraction, LVFS: left ventricular fractional shortening, PLVWT: posterior left ventricular wall thickness, IVSWT: interventricular septal wall thickness, RVWT: right ventricular wall thickness, RV PEP/VET: right ventricular pre-ejection period to ventricular ejection time ratio, LV PEP/VET: left ventricular pre-ejection to ventricular ejection time ratio.

pre-ejection period to ventricular ejection time ratios were found higher than in the control group, these differences were not significant (p>0.05) (Table I).

Diastolic measurement of right ventricular inflow tract, outflow tract and body values, which were determined by two dimensional echocardiography, were found similar to normal control group (Table II).

Right and left ventricular diastolic filling patterns were detected by pulsed Doppler echocardiography. For both mitral and tricuspid valves, the mean ratios of peak velocity filling during the passive filling phase of diastole to peak velocity during atrial contraction phase were found significantly lower than in the controls for both ventricles (p<0.05). Early diastolic peak velocity was similar to that in control group, but late atrial peak velocity was higher in cystic fibrosis patient (p<0.05).

Table II: Right Ventricular Diastolic Diameters of Patients and Control Subjects (mean ± SD)

Measurement	Patient	Control	p Value
RVIT (mm)	23.9 ± 0.1	24.2 ± 0.13	>0.05
RVOT (mm)	20.7 ± 0.9	21.2 ± 0.7	>0.05
Long Axis (mm)	37.5 ± 1.3	36.5 ± 0.9	>0.05
Short Axis (mm)	22.2 ± 1.07	22.3 ± 0.5	>0.05

RVIT: right ventricular inflow tract, RVOT: right ventricular outflow tract.

Table III: Right and Left Ventricular Diastolic Filling Parameters by Pulsed Doppler Echocardiography in Patients and Normal Control Subjects (mean ± SD)

Measurement	Patient	Control	p Value
Mitral E(m/s)	0.56 ± 0.04	0.54 ± 0.02	>0.05
Mitral A(m/s)	0.37 ± 0.03	0.32 ± 0.03	<0.05
Tricuspid E(m/s)	0.52 ± 0.05	0.50 ± 0.04	>0.05
Tricuspid A(m/s)	0.36 ± 0.04	0.30 ± 0.02	<0.05
Mitral E/A	1.51 ± 0.04	1.66 ± 0.05	<0.05
Tricuspid E/A	1.43 ± 0.04	1.67 ± 0.05	<0.05
Mitral IVRT	45.6 ± 1.07	46.2 ± 0.55	>0.05
Tricuspid IVRT	47.46 ± 1.39	46.5 ± 0.72	>0.05

E: early diastolic peak velocity; A: peak velocity during atrial contraction; IVRT: isovolumic relaxation time.

Isovolumic relaxation time was found the same as in the control group (Table III).

The right ventricular pre-ejection period to ventricular ejection time ratio significantly increased as the Shwachman score decreased (r: –0.55). The left ventricle systolic time intervals, ejection fraction and fractional shortening did not correlate with clinical scores. Our echocardiographic studies showed that 20 patients had normal hearts; one had a structural heart disease (ventricular septal defect) and five had functional cardiac abnormalities (two of them had cor pulmonale due to cystic fibrosis). This information is summarized in Table IV.

Table IV: Patients with Abnormal Cardiac Functions

Patient	Age	Gender	Score	pH	pO2	pCO2	RV PEP/VET	LV PEP/VET
1	9.5	male	40	7.38	72.9	39.0	0.450*	0.500*
2	15	female	62	7.41	85.0	37.5	0.304*	0.409*
3.	1.5	female	80	7.40	75.0	31.3	0.290	0.400*
4	3.8	male	91	7.43	84.7	34.6	0.250	0.420*
5	4.4	male	93	7.35	60.8	37.7	0.170	0.430*

* Abnormal (over upper limit of normal).

Discussion

Patients with cystic fibrosis survive longer than before because of earlier diagnosis, better nutritional management and aggressive medical intervention. However, intractability of pulmonary disease and related cor pulmonale remains the major cause of morbidity and mortality. The diagnosis of cor pulmonale in cystic fibrosis patients by physical examination is often difficult. Noninvasive evaluation of cardiac function in cystic fibrosis patients using electrocardiography, vectorcardiography, radionuclide angiocardiography and echocardiography have been reported earlier[8,9]. In the present study, we evaluated the cardiac status of a young group of cystic fibrosis patients (mean age 48.4 ± 8.6 months) by noninvasive methods. Most of the patients (73%) had good or excellent clinical scores.

Electrocardiographic findings of patients that showed right ventricular hypertrophy had no correlation with echocardiographic study and clinical scores. Siassi et al[10]. Studied 34 cystic fibrosis patients by cardiac catheterization and did not find any correlation between electrocardiographic findings and cor pulmonale.

Chronic alveolar hypoxia and recurrent pulmonary infections are responsible for the pulmonary hypertension and resultant cor pulmonale seen in cystic fibrosis. Ryland and Reid[11], in their study of the heart and lungs in patients with cystic fibrosis, observed that those with severe lung disease did not always develop right ventricular hypertrophy. When right ventricular hypertrophy was present, however, it generally reflected the degree of abnormal structural remodeling of the pulmonary vascular bed. An increase in the muscularity of small veins was also observed. As an evidence of cor pulmonale, right ventricular pre-ejection period to ventricular ejection time ratio was found abnormally elevated in two patients, and one of them also had reversed septal motion. The only parameter that was found to correlate with clinical scores was the ratio of right ventricular pre-ejection period to ventricular ejection time. Because the left ventricular pre-ejection period to ventricular ejection time ratio was found abnormally elevated in five patients, we suggested that the left ventricle was affected at the same time as the right ventricle. Left ventricular involvement may be related to right ventricular dysfunction, chronic hypoxia, hypercapnia, reduced coronary blood flow due to increased right atrial pressure and viral or bacterial infections.

Doppler echocardiographic measurements of left and right ventricular diastolic filling patterns demonstrated a significantly lower E to A peak velocity ratio and a greater atrial filling fraction than in control subjects. Johnson et al.[12] studied left ventricular diastolic filling in 25 cystic fibrosis patients with a mean age of sixteen and noted a lower E/A ratio and greater A velocity. In the present study, we showed that changes in diastolic functions begin at very young ages in cystic

fibrosis patients. We cannot say that all our patients had abnormal diastolic functions because there is no reported accurate data about diastolic functions of normal subjects. We compared the results of the cystic fibrosis group to the normal group and found that diastolic functions of the patient group were different from those of the normal group. In cystic fibrosis, pulmonary blood flow and left atrial pressure are decreased because of impaired right ventricular performance and increased pulmonary resistance. As a result, left ventricular preload also diminishes. At the same time, afterload augmentation has also been seen as a result of hypoxemia-induced vasoconstriction. These changes in preload and afterload may lead to an increase in A velocity. Right ventricular pressure and volume overload can cause flattening or reversion of interventricular septal movement and also influence diastolic filling of left ventricle. On the other hand, shortening of diastole due to increased heart rate can also be related to increased A velocity and decreased E/A ratio.

Early detection of cor pulmonale and analysis of all these parameters in young patients with cystic fibrosis may provide some useful information for management of the disease. Among the echocardiographic abnormalities detected in our cystic fibrosis patients, elevation in the right ventricular pre-ejection period to ventricular ejection time ratio seems to be the most important one clinically as it shows the presence of cor pulmonale. As these patients do not benefit from any mode of medical treatment, they are candidates for heart-lung or lung transplantation[13]. Other abnormalities detected in echocardiography (elevations in left ventricular pre-ejection period to ventricular ejection time ratio, abnormal septal motion, changes in diastolic filling patterns) show that cardiac involvement has already commenced. Further follow-up studies will be required to show whether the results of the present study have any prognostic significance.

REFERENCES

1. Koch C, Hiby N. Pathogenesis of cystic fibrosis. Lancet 1993; 341: 1065-1069.
2. Penketh AR, Wise A, Mearns MB, Hodson ME, Batten JC. Cystic fibrosis in adolescents and adults. Thorax 1987; 42: 526-532.
3. World Health Organization Expert Committee. Chronic cor pulmonale. Circulation 1963; 27: 594.
4. Royce SW. Cor pulmonale in infancy and early childhood: report on 34 patients, with special reference to occurrence of pulmonary heart disease in cystic fibrosis of the pancreas. Pediatrics 1951; 255: 255-274.
5. Shwachman H, Kulczycki LL. Long term study of one hundred-five patients with cystic fibrosis: studies made over five-to-fourteen year period. Am J Dis Child 1958, 96: 6-12.
6. Foale R, Nihoyannopoulos P, McKenna W, et al. Echocardiographic measurement of the normal adult right ventricle. Br Heart J 1986; 56: 33-44.
7. Emmanouilides GC, Hugh DA, Riemenschneider TA, Gutgesell HP. Moss and Adams Heart Disease in Infant, Children, and Adolescents- Including the Fetus and Young Adult. Vol I (5th ed). Baltimore: Williams & Wilkins; 1995 268

8. Matthay RA, Berger HJ, Loke J, et al. Right and left ventricular performance in ambulatory young adults with cystic fibrosis. Br Heart J 1980; 43: 474-480.
9. Moss AJ. The cardiovascular system in cystic fibrosis. Pediatrics 1982; 70: 728-741.
10. Siassi B, Moss AJ, Dooley RR. Clinical recognition of cor pulmonale in cystic fibrosis. J Pediatr 1971; 78: 794-801.
11. Ryland D, Reid L. The pulmonary circulation in cystic fibrosis. Thorax 1975; 30: 285-308.
12. Johnson GL, Kanga JF, Moffett CB, Noonan JA. Changes in left ventricular diastolic filling patterns by Doppler echocardiography in cystic fibrosis. Chest 1991; 99: 646-650.
13. Ramirez JC, Patterson GA, Winton TL, et al. Bilateral lung transplantation for cystic fibrosis. The Toronto Lung Transplant Group. J Thorac Cardiovasc Surg 1992; 103: 287-293; discussion 294.

EXTRAPONTINE MYELINOLYSIS IN A NINE-YEAR-OLD CHILD*

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SUMMARY: Öztürk F, Görk S, Aydın M, İncesu L, Baysal K. (Department of Pediatrics, Pediatric Surgery, and Radiology, Ondokuz Mayıs University Faculty of Medicine, Samsun, Turkey). Extrapontine myelinolysis in a nine-year-old child. Turk J Pediatr 1998; 40: 579-584.

Extrapontine myelinolysis in the pediatric age group is very rare. We report a nine-year-old girl with the classical clinical syndrome of pontine and extrapontine myelinolysis following liver trauma due to a traffic accident. She was referred to our hospital for further investigation of convulsions due to severe postoperative hyponatremia. She had no hypoxic event or other identifiable cause for the neurological symptoms. Neurological deterioration began about two days after correction of hyponatremia and followed a period of temporary improvement in hyponatremic encephalopathy. Diagnosis of extrapontine myelinolysis was confirmed with the identification of typical features on magnetic resonance imaging. The rapid correction of hyponatremia seemed the most likely cause since other biochemical tests including liver function tests were all within normal ranges. The long term clinical outcome was good. It is important to carefully monitor the rate of correction in electrolyte disturbances, and to consider the individual variation in response to therapy. *Key words: child, extrapontine myelinolysis, hyponatremia.*

Central pontine and extrapontine myelinolysis (CPM/EPM), also referred to as osmotic demyelination syndrome (ODS), is a demyelinating disease. Although occurring anywhere in the brain, it mainly involves the basis pontis[1-3]. There is controversy over its pathogenesis but recently increasing clinical and experimental evidence has shown that it is the result of a rapid or over-correction of hyponatremia[2,4,5]. It was also reported that ODS is associated with other states of hyperosmolality, such as hypernatremia, hyperglycemia or azotemia[6,7]. The majority of patients are adults, with children being affected only occasionally four cases have been published from 1987 to present. Children generally have

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an underlying disease such as adrenal insufficiency, brain tumor, liver disease or malnutrition[1]. Almost all pediatric cases reported to date had a central pontine demyelination.

We herein report a case of ODS with extrapontine involvement which developed after the treatment of severe hyponatremia and resolved afterwards.

Case Report

A nine-year-old girl was admitted to our pediatric emergency department with a complaint of seizure. As we were informed by the referring hospital and the mother of the patient who was a nurse, the patient had undergone an exploratory laparotomy following a traffic accident. A six-to-seven-cm-long laceration on the capsule of the right lobe of the liver and also a retroperitoneal hematoma were observed at surgery. She did well early after surgery but complained of headache, nausea and vomiting on the fifth postoperative day. The first generalized seizure appeared on the sixth day, lasted less than 10 minutes, and could be controlled by diazepam. Serum sodium concentration was 115 mmol/L. A replacement therapy was started, a second seizure occurred 12 hours later, and she was referred to our hospital for further investigation.

Past history was unremarkable for the patient and the family.

On examination, she was unable to cooperate but responded to verbal stimuli by opening her eyes. Temperature was 36.3 °C, respirations 24/min, pulse 80 beats/min and blood pressure 110/70 mmHg. There was a sutured incision on the forehead, and two drains were on the right side of the median incision draining the perihepatic region of the laceration and the cave of Douglas. On neurological examination, pupils were dilated and reacted normally to light both directly and consensually. The discs and fundi were normal. No lateralizing features were present. Deep tendon reflexes were symmetric and hypoactive and both plantar responses were extensor. The rest of the physical examination was unremarkable.

Urine density was 1010 and sodium in urine was 20 mmol/L. The hematocrit value was 29 percent, hemoglobin 9.9 g/dl, and WBC count 9,000/mm^3. Blood analysis revealed: serum sodium 111 mmol/L, potassium 4.6 mmol/L, ALT 45 IU, AST 50 IU and PaO_2 85 mmHg. Cranial computed tomography (CT) scan was normal. Cerebrospinal fluid analysis (CSF) disclosed no abnormalities and its culture was negative.

Treatment for hyponatremia was initiated with a fluid containing 0.9 percent sodium chloride with 5 percent glucose at a rate of 80 ml/h (1.4 m^2 body surface). Serum sodium level was 115 mmol/L after eight hours. Infusion of the same fluid was continued, and after an additional eight hours, her serum sodium was 125 mmol/L. The intravenous fluid was changed to 0.45 percent sodium chloride

with 5 percent glucose, and 27 hours after the admittance serum sodium was 142 mmol/L. By the 12th hour her general condition seemed to improve, she became cooperative and was able to talk. However, after 48 hours she became unconscious and developed persistent convulsions, affecting the left arm and the left side of the face, which were irresponsive to anticonvulsive therapy. Deep tendon reflexes were hyperactive and plantar reflexes were bilaterally extensor.

A cranial CT scan on day four revealed minimal, diffuse cerebral edema. CSF analysis on the same day was normal. Fifteen days later, magnetic resonance imaging (MRI) of the brain revealed a normal pons, but there were multiple millimetric foci of increased signal intensity in the frontoparietal periventricular white matter bilaterally on T2 weighted images (Figs. 1a, 1b).

She received intensive supportive therapy while she was comatose during five weeks. Myoclonic seizures localized to the left side of the body were partially controlled. She began to recover dramatically starting from the fifth week. When she was discharged on the 46th day of hospitalization she was able to understand verbal commands, reach her head with her hand and walk with help, although ataxic. She was making hoarse sounds (hypophonia) and suffering from a prominent dysphagia. Pharyngeal reflexes were bilaterally elicitable. Deep tendon reflexes were hyperactive on the left and normal on the right side. Plantar reflexes were bilaterally extensor.

When she was reevaluated two weeks later she was able to walk without help and her speech was dysphasic. She had less dysphagia as stated by her mother.

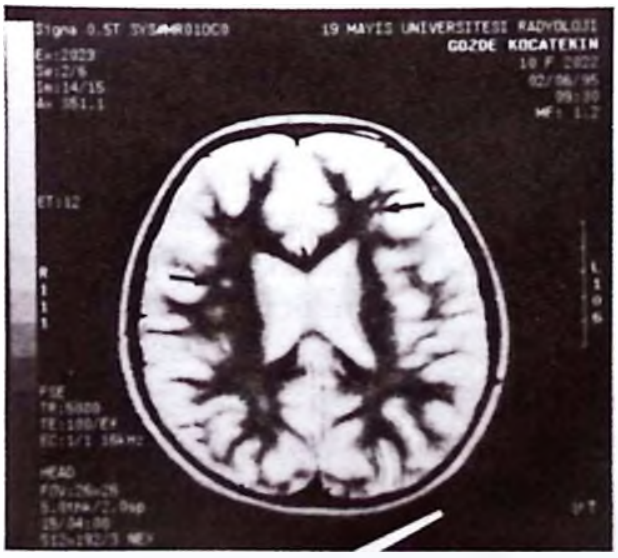

Fig 1a

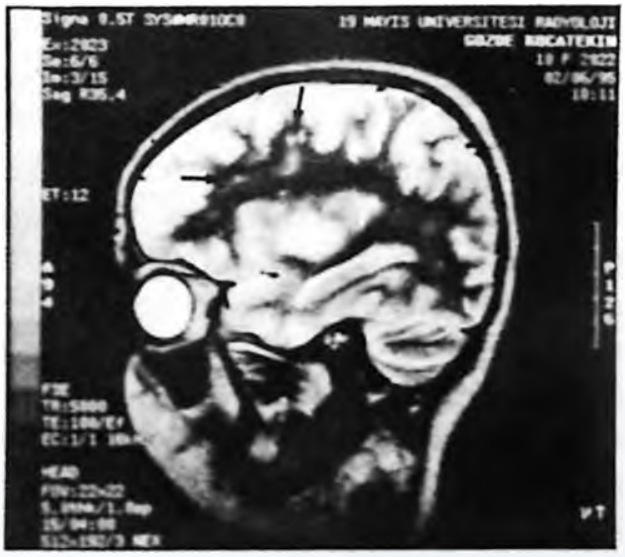

Fig 1b

Fig. 1: Axial (a) and sagittal (b) T2-weighted MR images showing high-signal intensity foci in the frontoparietal periventricular white matter areas (arrows).

Despite carbamazepine therapy she was still suffering from short duration convulsions affecting the left side of the face and the left arm two or three times a day. The convulsions and dysphasia were continuing one month after discharge.

Discussion

Hyponatremia causes a generalized metabolic encephalopathy which present as headache, nausea, vomiting, irritability, restlessness, lethargy, confusion, weakness, malaise, and seizures. These symptoms can usually be reversed with correction of the sodium deficiency[8]. However, the treatment of hyponatremia is controversial because of the risk of causing ODS. Controlled studies in animals have shown myelinolysis following rapidly corrected hyponatremia but not with uncorrected hyponatremia[9,10], although some authors have proposed that uncorrected hyponatremia can itself lead to ODS[11]. Although there is no agreement on exactly how fast an increase in serum sodium is safe, animal studies and clinical trials showed that a rise of greater tah 12 mmol/L per 24 hours and 25 mmol/L per 48 hours carries a danger of causing myelinolysis. The duration of treatment may be important, and a rate of 12 mmol/L per day may be too rapid if continued for two or three days. A general consensus is that the patient not be made hypernatremic[2,5,12].

The pathogenesis of myelinolytic lesions is obscure. It has been suggested that a rapid increase in serum sodium causes an osmotic injury to the endothelium, resulting in the release of myelinotoxic factors and/or the production of vasogenic edema[1,2]. The main pathological event is the destruction of myelin sheaths, but axons and neurons are relatively spared. The lesions are generally symmetrical and multifocal, and tend to involve the areas of white matter where there is a wide zone of conjunction between the gray and white matters[1,5]. Shortly after the correction of hyponatremia (approximately 2-6 days), as in our case, following a transient improvement which parallels the correction of the electrolyte disturbance, a progressive neurological syndrome develops reflecting the dysfunction of white matter of pontine and/or extrapontine sites including internal capsule, basal ganglia and cerebellum. Symptoms of pseudobulbar palsy such as dysphasia, changes in corticospinal reflexes, tetraparesis or tetraplegia, ophthalmoparesis, changes in pupils, convulsions, tremors, incontinence and coma may occur. It is usually fatal. If the patients survive, they may suffer from neurological deficits as severe as akinetic mutism or from less severe sequelae like dysphasia[1,2,12,13].

Although the majority of patients have been diagnosed at autopsy, antemortem diagnosis can also be achieved. Clinical suspicion is supported by radiologic studies. Especially during the early course of the disease, a CT scan may be

normal. Magnetic resonance imaging is more sensitive in diagnosis, showing prolonged T1 and T2 relaxation times in affected regions[14]. Numerous cases in the literature were diagnosed solely according to the typical clinical findings and course of the disease[3,12].

In our patient a clinical picture displaying the typical findings of ODS developed postoperatively following the correlation of hyponatremia. There were periventricular and subcortical multiple foci on MRI in accordance with ODS. On the basis of clinical findings, clinical course and MRI, a diagnosis of ODS was established. It may be proposed that the extrapontine lesions seen in the presented case could be delayed, post-hypoxic demyelination rather than EPM associated with an increase in serum sodium from hyponatremic levels. Although both conditions have superficial similarity such as a biphasic course of illness, there are distinct differences between myelinolysis and delayed, post-hypoxic demyelination. Neurological deterioration due to myelinolysis usually starts earlier and progresses more rapidly than that following hypoxia. In myelinolysis extrapontine lesions are symmetrical and multifocal, as in the presented case, not diffuse as in delayed, post-hypoxic demyelination. Our patient had no evidence of respiratory arrest or hypoxia. Respiratory difficulty during hyponatremic seizures is unlikely to lead to severe cerebral anoxia[5].

In children, there are reported cases of ODS in association with liver disease. Although there was a laceration on the capsule in our patient we could not detect any injury to the parenchyma of the liver, and the liver enzymes were normal. In view of these reasons, the most rational factor to clarify the pathogenesis of EPM in our patients seems to be the rapid correction of hyponatremia.

In our clinics, rapid correction of hyponatremia is not an accepted approach, and hypertonic saline is seldom preferred for therapy. Thus, the initial intravenous fluid for this patient was 0.9 percent sodium chloride with 5 percent glucose. After 16 hours of follow-up, when the sodium level was 125 mmol/L, the sodium was decreased to half of the initial content. Despite this reduction there was a 31 mmol/L rise in the sodium level at the 27th hour of hospitalization. Such an unintended rise can sometimes be encountered due to individual variability in patients' response to therapy.

In conclusion, a patient with hyponatremia is at risk of rapid correction of hyponatremia as well as of the danger of hyponatremia itself.

REFERENCES

1. Fishman MA. Disorders primarily of white matter. In: Swaiman KF (ed). Pediatric Neurology. Principles and Practices Vol. 2. St. Louis: CV Mosby Co; 1989: 755-775.

2. Sterns RH, Riggs JE, Schochet SS Jr. Osmotic demyelination syndrome following correction of hyponatremia. N Engl J Med 1986; 314: 1535-1542.

3. Ayus JC, Krothapalli RK, Arieff AI. Treatment of symptomatic hyponatremia and its relation to brain damage. A prospective study. N Engl J Med 1987; 317: 1190-1195.
4. Ayus JC, Krothapalli RK, Armstrong DL. Rapid correction of severe hyponatremia in the rat: histopathological changes in the brain. Am J Physiol 1985; 248: F711-F719.
5. Laureno R, Karp BI. Pontine and extrapontine myelinolysis following rapid correction of hyponatraemia. Lancet 1988; 1: 1439-1441.
6. McComb RD, Pfeiffer RF, Casey JH, Wolcott G, Till DJ. Lateral pontine and extrapontine myelinolysis associated with hypernatremia and hyperglycemia. Clin Neuropathol 1989; 8: 284-288.
7. Esforzado N, Poch E, Cases A, Cardenal C, Lopez-Pedret J, Revert L. Central pontine myelinolysis secondary to frequent and rapid shifts in plasma glucose in diabetic hemodialysis patient. Nephrol Dial Transplant 1993; 8: 644-646.
8. Mulloy AL, Caruana RJ. Hyponatremic emergencies. Med Clin North Am 1995; 79: 155-168.
9. Kleinschmidt-DeMasters BK, Norenberg MD. Rapid correction of hyponatremia causes demyelination: relation to central pontine myelinolysis. Science 1981; 211: 1068-1070.
10. Illowsky BP, Laureno R. Encephalopathy and myelinolysis after rapid corection of hyponatraemia. Brain 1987; 110: 855-867.
11. Tien R, Arieff AI, Kucharczyk W, Wasik A, Kucharczyk J. Hyponatremic encephalopathy: is central pontine myelinolysis a component? Am J Med 1992; 92: 513-522.
12. Lohr JW. Osmotic demyelination syndrome following correction of hyponatremia: association with hypokalemia. Am J Med 1994; 96: 408-413.
13. Arieff AI. Hyponatremia, convulsions, respiratory arrest, and permanent brain damage after elective surgery in health women. N Engl J Med 1986; 314: 1529-1535.
14. Morlan L, Rodriguez E, Gonzales J, Jimene-Ortiz C, Escartin P, Liano H. Central pontine myelinolysis following correction of hyponatremia: MRI diagnosis. Eur Neurol 1990; 30: 149-152.

ACUTE RHEUMATIC FEVER WITH THREE MAJOR CRITERIA: POLYARTHRITIS, CARDITIS AND CHOREA*

A Case Report

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SUMMARY: Günal N, Atakan C, Köse G, Atasay B. (Pediatric Cardiology Unit, Social Security Children's Hospital, Ankara, Turkey). Acute rheumatic fever with three major criteria: polyarthritis, carditis and chorea. A case report. Turk J Pediatr 1998; 40: 585-588.

An eight-year-old girl is presented with three major criteria of acute rheumatic fever: polyarthritis, carditis and chorea. The diagnosis was confirmed with a history of pharyngitis 15 days prior to admission and with the findings of positive acute phase reactants such as elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), elevated anti-streptolysin-O (ASO) titration, and clinical findings of polyarthritis, carditis and chorea. Patient responded well to salicylate and phenobarbital treatment. The rare association of these three major criteria in acute rheumatic fever is emphasized. *Key words: rheumatic fever, carditis, arthritis, chorea.*

Rheumatic fever, the most common cause of acquired heart disease in children and young adults, is a multisystem disease, affecting primarily the heart, the joints, the brain and cutaneous and subcutaneous tissue[1]. Particularly in developing countries, the incidence of the disease continues to be high. The diagnosis of rheumatic fever is based on the Jones criteria, in addition to evidence of group A streptococcal pharyngitis[2]. In this report, an eight-year-old girl is presented with three major criteria of acute rheumatic fever: polyarthritis, carditis and chorea.

Case Report

An eight-year-old girl was admitted to the hospital because of arthralgia and involuntary movements. She had had sore throat, fever and pruritic rash 15 days before admission. In another hospital, Group A beta hemolytic streptoccus was isolated from the throat culture and procaine penicillin was administered. She was given two injections of procaine penicillin, but it was discontinued as the symptoms subsided after the second day. Two weeks later, swelling and

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arthralgia began in the knees and ankles in a migratory manner, and the family noticed behavioral changes, involuntary movements and restlessness in the patient.

On physical examination, the patient's body temperature was 37 °C, heart rate was 120/min, and blood pressure was 90/60 mmHg. Involuntary choreic movements of the upper extremities, jerking of the head and tongue fasciculations were detected. The left knee was tender and swollen. A third-degree pansystolic murmur was heard at the apex.

The laboratory findings were as follows: hemoglobin 11 g/dl, leukocyte 10,000/mm^3, erythrocyte sedimentation rate (ESR) 78 mm/h, C-reactive protein (CRP) positive, anti-streptolysin O (ASO) titer 800 U, throat culture negative. Telecardiography showed mild cardiomegaly with a cardiothoracic ratio of 0.53, and electrocardiogram showed sinus tachycardia with a heart rate of 125 beats/min, and a PR interval of 0.16 s. Mitral valve regurgitation with a regurgitant flow velocity of 3.46 m/s and mild aortic regurgitation were detected by Doppler echocardiography. According to the above findings, our diagnosis in this patient was acute rheumatic fever with arthritis, carditis and Sydenham's chorea. Therapy was started with salicylate (100 mg/kg, in 4 doses) and phenobarbital (5 mg/kg, 3 times). At the end of the first week of therapy, clinical signs and laboratory findings had subsided. Findings of arthritis disappeared, choreic movements were diminished and the murmur of mitral valve insufficiency decreased. Erythrocyte sedimentation rate decreased to 26 mm/h, ASO to 600 U, and CRP was found to be negative. In the second week, the aspirin dosage was reduced to 75 mg/kg until the end of the third week and then was gradually reduced until it was discontinued at the end of the sixth week. All the laboratory and clinical findings were normal with the exception of a first-degree pansystolic murmur at the apex. The patient was discharged on prophylactic penicillin treatment and was scheduled for periodic control examinations.

Discussion

Rheumatic fever and its major complication, valvular heart disease, are still the most frequent cause of acquired heart diseases in children and adolescents, especially in developing countries. The incidence of rheumatic fever was found to be about 20 per 100,000 in a study from Turkey[3]. In other study from Turkey, done by İmamoğlu[4], the prevalence of rheumatic heart disease changed between 10.7 to 2.1 per 1,000, with a higher prevalence in children of low socioeconomic level. Most attacks of rheumatic fever begin with arthritis, or arthritis with carditis. Sydenham's chorea occurs much later, with a much longer latent period than

the other manifestations, usually without any evidence of acute inflammation. In our case, three major manifestations of rheumatic fever were present together with the positive acute phase reactants. To our knowledge, few cases of rheumatic fever presenting with all three major criteria at the same time[1].

Karademir et al.[5] found 100 patients with arthritis only, 59 with carditis, 40 with chorea and 24 with arthritis and carditis, out of 228 patients.

An epidemiologic study of rheumatic fever from Italy showed a progressive reduction of incidence and prevalence of the disease in the last 10 years. The percentage of carditis in the pediatric age was high (60-70%), often associated with arthritis or chorea. Relapses and residual valve disease were significantly reduced when penicillin prophylaxis was performed correctly[6].

Carapetis et al.[7] from Australia reported that Sydenham's chorea was common and associated with later development of rheumatic heart disease in 49 percent of patients, and they also showed the point prevalence of rheumatic heart disease to be 9.6 per 1,000.

Chen et al.[8] found that 20 of 89 children with rheumatic fever had chorea, and six of them also had mitral insufficiency. Prompt diagnosis and treatment of streptococcal infection and penicillin prophylaxis was stressed.

Carditis may be found without any auscultatory finding in rheumatic fever. Echocardiography can demonstrate inaudible mitral regurgitation in nearly half of the patients with arthritis or chorea[9]. In another report, carditis was found in 36.6 percent of 87 cases of acute rheumatic fever, and was associated with arthritis in 35.3 percent[10].

Carditis is the most serious cause of morbidity in acute rheumatic fever and is seen in about 50 percent of patients with the disease. Arthritis occurs in about 70 percent of patients with rheumatic fever and it is the least specific finding. Sydenham's chorea affects about 15 percent of patients with rheumatic fever[1]. The period of latency between the initial streptococcal infection and the symptoms of chorea is about three months or more, much longer than that for arthritis or carditis, which is about three weeks[11]. For this reason, all three major manifestations rarely occur together in rheumatic fever in the acute attck. Our patient had a rare combination of arthritis, carditis and chorea during the acute attack, after a short latent period of two weeks. The type of streptococcus may be related to the short latent period of the chorea. We conclude that the latent period of Sydenham's chorea may be as short as a few weeks, so this manifestation may occur with the positive laboratory findings of the acute attack, along with arthritis and carditis.

REFERENCES

1. Ayoub EM. Acute rheumatic fever. In: Emmanouilides GC, Riemenschneider TA (eds). Moss and Adams Heart Disease in Infants, Children and Adolescents (5th ed) Vol 2. Baltimore: Williams and Wilkins Co; 1995: 1400-1414.
2. Dajani AS, Ayoub EM, Bierman FZ, et al. Guideliness for the diagnosis of rheumatic fever: Jones criteria, updated 1992. JAMA 1992; 87: 302-307.
3. Saraçlar M. Frequency of rheumatic fever in Ankara. Turk J Pediatr 1977; 19: 97-100.
4. İmamoğlu A. Ankara'da ilkokul çocuklarında romatizmal kalp hastalıkları sıklığı. Ankara Üniversitesi Tıp Fakültesi Mecmuası 1975; 28: 98-100.
5. Karademir S, Demirçeken F, Atalay S, Demircin G, Sipahi T, Teziç T. Acute rheumatic fever in children in the Ankara area in 1990-1992 and comparison with a previous study in 1980-1989. Acta Paediatr 1994; 83: 862-865.
6. Pugno Vanoni MC, Sticca M, Grasso E. Rheumatic fever from 1960's to 1990's. Case records in 2 hospitals of the Lombardian area (English abstract). Pediatr Med Chir 1992; 14: 415-420.
7. Carapetis JR, Wolff DR, Currie BJ. Acute rheumatic fever and rheumatic heart disease in the top end of Australia's Northern Territory. Med J Aust 1996; 164: 146-149.
8. Chen SC, Donahoe JL, Fagan LF. Rheumatic fever in children. A follow-up study with emphasis on cardiac sequelae. Jpn Heart J 1981; 22: 167-172.
9. Veasy LG, Tani LY, Hill HR. Persistence of acute rheumatic fever in the intermountain area of the United States. J Pediatr 1994; 124: 9-16.
10. Zabsonre P, Kakou M, Deumkouma FX, Bertrand E. Echocardiography and Jones criteria in the diagnosis of rheumatic heart disease: 138 cases reviewed at the Cardiology Institute of Abidjan (English abstract). Med Trop Mars 1995; 55: 347-350.
11. Aron AM, Freeman JM, Cater S. The natural history of Sydenham's chorea. Am J Med 1965; 38: 83-95.

TOXIC METHEMOGLOBINEMIA AFTER INJECTION OF PRILOCAINE IN A NEWBORN*

A Case Report

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SUMMARY: Kara A, Yiğit Ş, Aygün C, Oran O. (Neonatology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Toxic methemoglobinemia after injection of prilocaine in a newborn: a case report. Turk J Pediatr 1998; 40: 589-592.

The acute onset of cyanosis in an infant is an alarming development. We report an infant who became cyanotic after injection of prilocaine. Prilocaine is a local anesthetic that is widely used in clinical practice, but usage in infancy easily causes methemoglobinemia. Acquired methemoglobinemia occurs in individuals exposed to an increased amount of agents that oxidize hemoglobin iron. *Key words: toxic methemoglobinemia, newborn, cyanosis, prilocaine.*

The acute onset of cyanosis in an infant is an alarming development, usually suggesting hypoxia. In an infant, cyanosis resulting from lung diseases, air leak syndrome, diaphragmatic hernia, hypoplastic lungs, cardiac diseases, persistent pulmonary hypertension, central nervous system diseases, polycythemia, choanal atresia, hypothermia, hypoglycemia, sepsis or methemoglobinemia is the chief consideration in the differential diagnosis. In the case of methemoglobinemia, the cause of cyanosis is oxidation of heme iron to the ferric state, making it less able to bind with oxygen[1]. Methemoglobinemia may be hereditary or acquired. There are reports of methemoglobinemia secondary to drug exposure[2-7]. We present a case of methemoglobinemia that occurred after the use of a local anesthetic, prilocaine.

Case Report

A full-term male infant was referred to Hacettepe University İhsan Doğramacı Children's Hospital at 25 days of life because of prenatally diagnosed right hydronephrosis. He was born to a 29-year-old woman, gravida 2, para 1, after an uneventful cesarean section, performed on request of mother. Hydronephrosis was diagnosed on routine ultrasonographic examination during prenatal period

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at sixth month. Postnatal abdominal ultrasonography showed ureteropelvic stenosis, so urinary diversion by 7F pigtail catheter was performed with ultrasonography guide on the 25th day of life. At that time, 4.5 to 5 ml (4 mg/kg) prilocaine hydrochloride (Citanest® 0.5%) was injected as local anesthesia. Within 90 minutes the infant had become dusky and by two hours he was quite blue. There were no murmurs and his pulse was normal. Blood gases done while the infant received oxygen nasally revealed normal pH, partial arterial pressure of CO_2 levels, partial pressure of O_2 155 mmHg, and arterial O_2 saturation of 99 percent. Chest radiogram and electrocardiogram were normal, hemoglobin was 12.3 g/dl and results of blood chemistry were within normal limits, including renal function test. Since the infant remained blue despite oxygen therapy and because a blood spot on filter paper took a brown color, methemoglobinemia was considered. Blood methemoglobin was determined as described in literature[8] and found to be 2.52 g/dl (20.4%) confirming a diagnosis of methemoglobinemia. Four mg (1 mg/kg) of methylene blune in 50 ml of saline was given intravenously over half an hour and a dramatic resolution of the cyanosis was seen within another half an hour. On the following day the methemoglobin level was 0.03 g/dl (5%).

Discussion

Hemoglobin is unique for its vital function of oxygen transport. Its ability to reversibly bind to oxygen depends on the heme iron being maintained in the ferrous (Fe^{2+}) state. Oxyhemoglobin, when incubated under physiologic conditions, slowly autooxidizes to methemoglobin. During the journey of red blood cells in the circulation, hemoglobin is exposed to a variety of oxidants that enhance methemoglobin formation at a rate of two to three percent per day[9]. The reduction of methemoglobin in red blood cells to ferrous form depends on electron carriers, cytochrome b_5, nicotinamide adenine dinucleotide and enzyme cytochrome b_5 reductase.

Methemoglobinemia may be hereditary (defect in the reduction of methemoglobin or in the structure of hemoglobin such as hemoglobin M) or acquired. Acquired methemoglobinemia occurs in normal individuals exposed to increased amounts of agents that oxidize hemoglobin iron. Newborns and infants appear to be unusually susceptible to the development of this form of methemoglobinemia. This increased risk is due to decreased amounts of cytochrome b_5 and cytochrome b_5 reductase in erythrocytes of newborns[1] and to easier oxidation of fetal hemoglobin to the ferric state than hemoglobin A[10]. Methemoglobinemia can be induced by a wide range of drugs and toxins. Aniline dyes, nitrates, nitrites, sulfones, acetaminophen, benzocaine, dapsone, nitroglycerin, nitroprusside, sulfanilamide and prilocaine have been described as causing

methemoglobinemia[11]. Prilocaine is a widely used local anesthetic and two of its metabolites, 4 hydroxy-2-methylaniline and O-toluidine, have been implicated in this condition[2].

Blood appears dark in color, but in contrast to deoxygenated blood, it does not change color to bright red when mixed with air in methemoglobinemia. This is the basis of a simple screening test for detection of methemoglobin[12]. A drop of blood is placed on filter paper and then allowed to dry while the filter paper is waved in the air. Blood that is not saturated with oxygen turns red, whereas methemoglobin remains brown. This test detects levels of ferrihemoglobin greater than ten percent of total hemoglobin.

Adult patients whose methemoglobin levels are above 40 percent or who appear to be symptomatic should be treated with intravenous methylene blue at a dose of one to two mg/kg as in the form of a one percent solution[1]. The level of methemoglobin should fall to normal within an hour after treatment but if not, a second dose can be administered[1,11]. In the newborn period methemoglobin levels greater than 15 to 20 percent are treated with methylene blue[10]. Ascorbic acid may be given either orally or parenterally to reduce the level of methemoglobin, but it acts much slower than methylene blue[13]. Failure to note improvements after methylene blue is administered in acquired methemoglobinemia suggests G6PD deficiency.

Acquired methemoglobinemia is a potentially harmful, even lethal process, especially in the newborn period, that may result from application of a local anesthetic, prilocaine[3-7]. It is the intent of this report to make pediatricians aware of the potential of this adverse effect of prilocaine. If methemoglobinemia is quickly diagnosed and treated, the outcome can be excellent.

REFERENCES

1. Nathan GD, Oski FA. Hematology of Infancy and Childhood (4th ed) Vol 1. Philadelphia: WB Saunders Co.; 1993: 720-726.
2. Frayling IM, Addison GM, Chattergee K, Meakin G. Methaemoglobinaemia in children treated with prilocaine-lignocaine cream. Br Med J 1990; 301: 153-154.
3. Menahem S. Neonatal cyanosis, methaemoglobinaemia and haemolytic anaemia. Acta Paediatr Scand 1988; 77: 755-756.
4. Özbek N, Sarıkayalar F. Toxic methaemoglobinaemia after circumcision. Eur J Pediatr 1993; 152: 80.
5. Marks LF, Desgrand D. Prilocaine associated methaemoglobinaemia and the pulse oximeter. Anaesthesia 1991; 46: 703.
6. Vessely MB, Zitsch RP 3rd. Topical anesthetic-induced methemoglobinemia: a case report and review of the literature. Otolaryngol Head Neck Surg 1993; 108: 763-767.
7. Kumar AR, Dunn N, Naqvi M. Methemoglobinemia associated with a prilocaine-lidocaine cream Clin Pediatr 1997; 36: 239-240.

8. Williams WJ, Beutler E, Erslev AJ, Lichtman MA. Hematology (4th ed). New York: McGraw-Hill Publishing Co.; 1990: 1732-1734.
9. Eder HA, Finch C, McKee RW. Congenital methemoglobinemia. A clinical and biochemical study of a case. J Clin Invest 1949; 28: 265-269.
10. Taeusch HW, Ballard RA, Avery MA. Diseases of the Newborn (6th e). Philadelphia: WB Saunders Company; 1991: 823-825.
11. Mansouri A, Lurie AA. Concise review: methemoglobinemia. Am J Hematol 1993; 42: 7-12.
12. Harley JD, Celermajer JM. Neonatal methemoglobinemia and red brown screening test. Lancet 1970; 2: 1223-1225.
13. Calabrese EJ, Moore GS, McCarthy MS. The effect of ascorbic acid on nitrite-induced methemoglobin formation in rats, sheep, and normal human erythrocytes. Regul Toxicol Pharmacol 1983; 3: 184-188.

A FAMILY PRESENTING GOLTZ SYNDROME (FOCAL DERMAL HYPOPLASIA) IN THREE GENERATIONS*

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SUMMARY: Seven M, Suyugül Z, Yüksel A, Geçkinli B, Hacıhanefioğlu S, Cenani A. (Genetic and Teratology Research Center, İstanbul University, İstanbul, Turkey). A family presenting Goltz syndrome (focal dermal hypoplasia) in three generations. Turk J Pediatr 1998; 40: 593-601.

In this report we present three affected females of the same family in three generations. The cases have features of focal dermal hypoplasia (Goltz syndrome). One of the three affected females is the index case and the others are her mother and her grandmother. We performed skin biopsies on them. According to histopathological examinations skin lesions were compatible with Goltz syndrome. These cases exhibited focal dermal hypoplasia (FDH) manifestations including skin, dental and skeletal abnormalities. The affected females were seen in three generations of the same family which pointed to its X-linked dominance. *Key words: focal dermal hypoplasia, Goltz syndrome, X-linked dominant.*

Focal dermal hypoplasia (FDH, Goltz syndrome) is a rare inherited dermatological disorder which is commonly associated with skeletal, dermal, ocular, oral and soft tissue abormalities.

This syndrome includes varying degrees of cutaneous lesions. These lesions show dermal hypoplasia with widespread pigmentation and depigmentation in a cribriform or linear arrangement which follows Bloschko's lines.

The syndrome is presumed to be transmitted in an X-linked dominance with lethality in males. There are a few cases of surviving affected males who may be mosaics or possibly carry a new mutation. We report three generations of females with FDH.

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Case Report

Our case, a five-year-old girl with skin abnormalities and varying mesodermal defects, is the first child of nonconsanguineous parents (Fig. 1). Physical examination revealed the areas of underdeveloped and thinned skin, localized herniations of subcutaneous fat through the attenuated dermis, areas of hypopigmentation of the skin, telangiectases and papillomas on the base of perianal area (Figs. 2 and 3). There was also regional baldness, sparse and brittle scalp hair and enamel defects (Fig. 4). Nails were poorly developed, dystrophic, spooned and hypopigmented (Fig. 5).

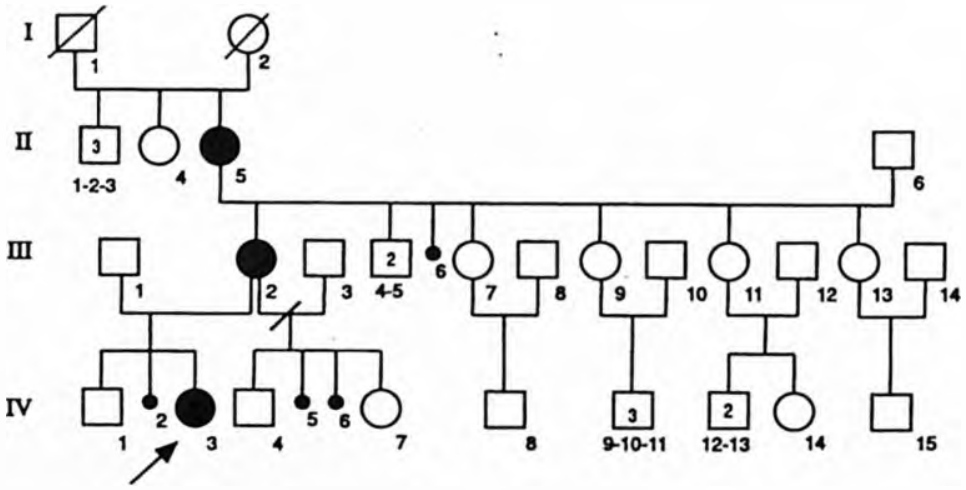


Fig. 1: Pedigree of family.

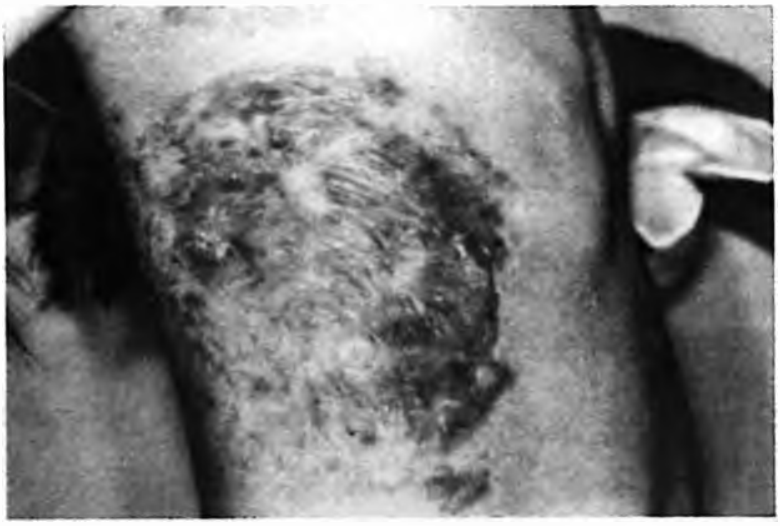


Fig. 2: Shows areas of underdeveloped and thinned skin in the patient (IV-3).

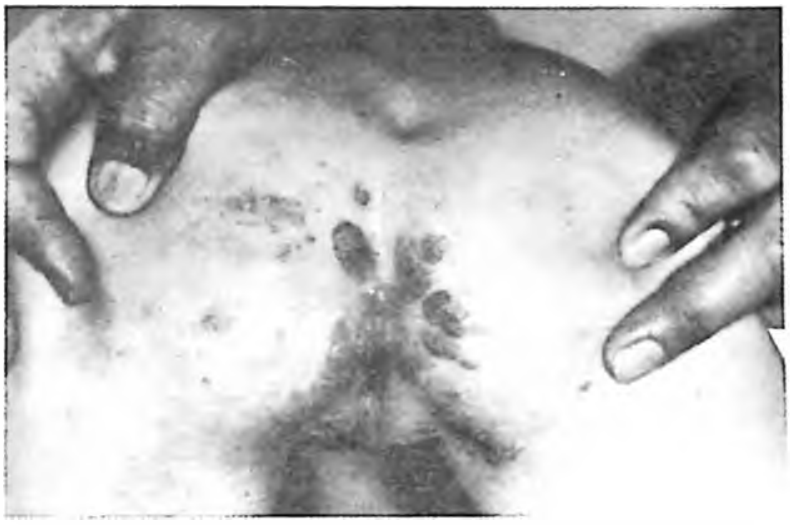


Fig. 3: Shows papillomas of patient's (IV-3) perianal area.

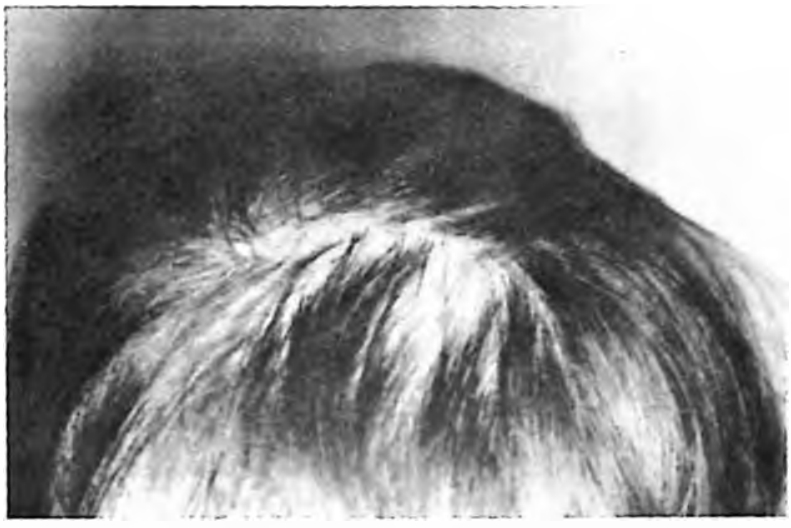


Fig. 4: Shows regional baldness, and sparse and brittle hair in the patient (IV-3).

In addition, some ocular abnormalities were discovered such as ptosis, blue sclera, irregularity of pupils, and heterochromia iridis. Skeletal abnormalities seen included scoliosis, high-arched palate and asymmetric face, trunk and extremities. An inguinal hernia was also present.

Detailed history of the case revealed the presence of cutaneous lesions, papillomas increasingly expanding in size, slight developmental delay and recurrent respiratory tract infections since birth. The papillomas were seen in the histopathologic examination of skin biopsy specimen (Fig. 6).

X-ray examination disclosed dorsal scoliosis and characteristic linear striations and cortical thinning of the long bones (Fig. 7).

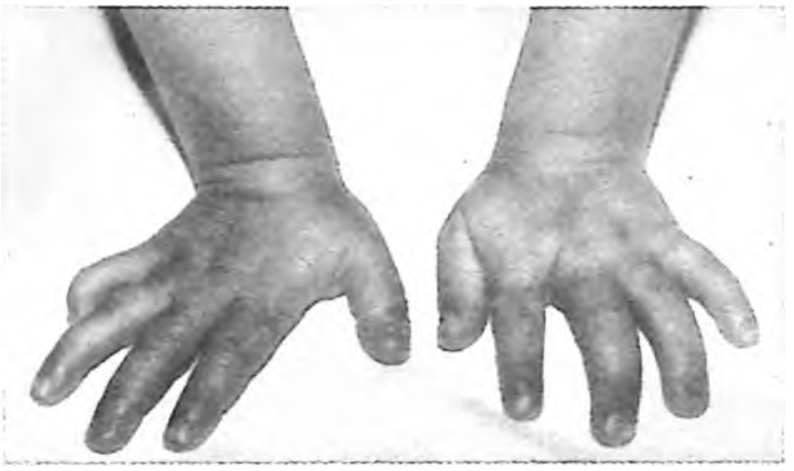


Fig. 5: Shows poorly developed, dystrophic nails and comptodactyly in the patient (IV-3).

Fig. 6: Histology of the surface showed stratified squamous epithelium with acanthosis and papillomatous hyperplasia (H.E. X40) (IV-3).

Results of complete blood cell counts, renal and liver function tests, urine analysis, total serum proteins, serum calcium and phosphorus levels were normal, but serum immunoglobulin A level was 21 mg/dl (normal range 51 ± 19 mg/dl). The other immunglobulin levels were normal.

Some of the varying anomalies of Goltz syndrome were also present in our patient's mother and grandmother. Our patient's mother had multiple papillomas in her inguinal, left scapular and axillary areas. She also had slightly erythematous, red and brown pigmented areas on her extremities and gluteal region (Fig. 8). Mild dystrophy of the toenails (Fig. 9a) and thumbnails, thinning of the hair, dental caries and scattered telangiectases were noted. Long bone x-ray and

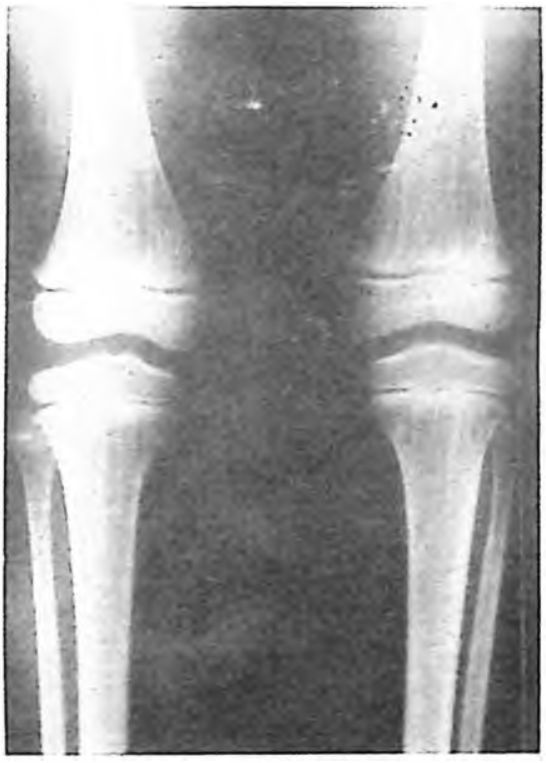


Fig. 7: Shows linear and vertical thinning and longitudinal striation of the long bones in the x-ray of the patient (IV-3).

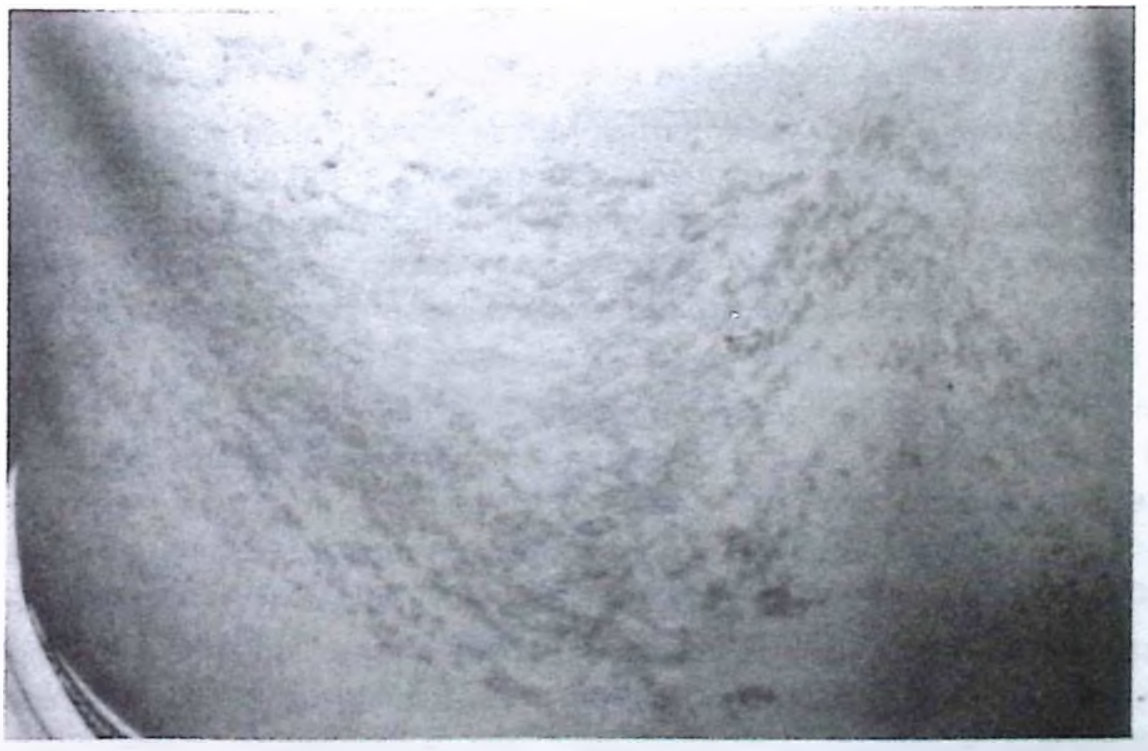
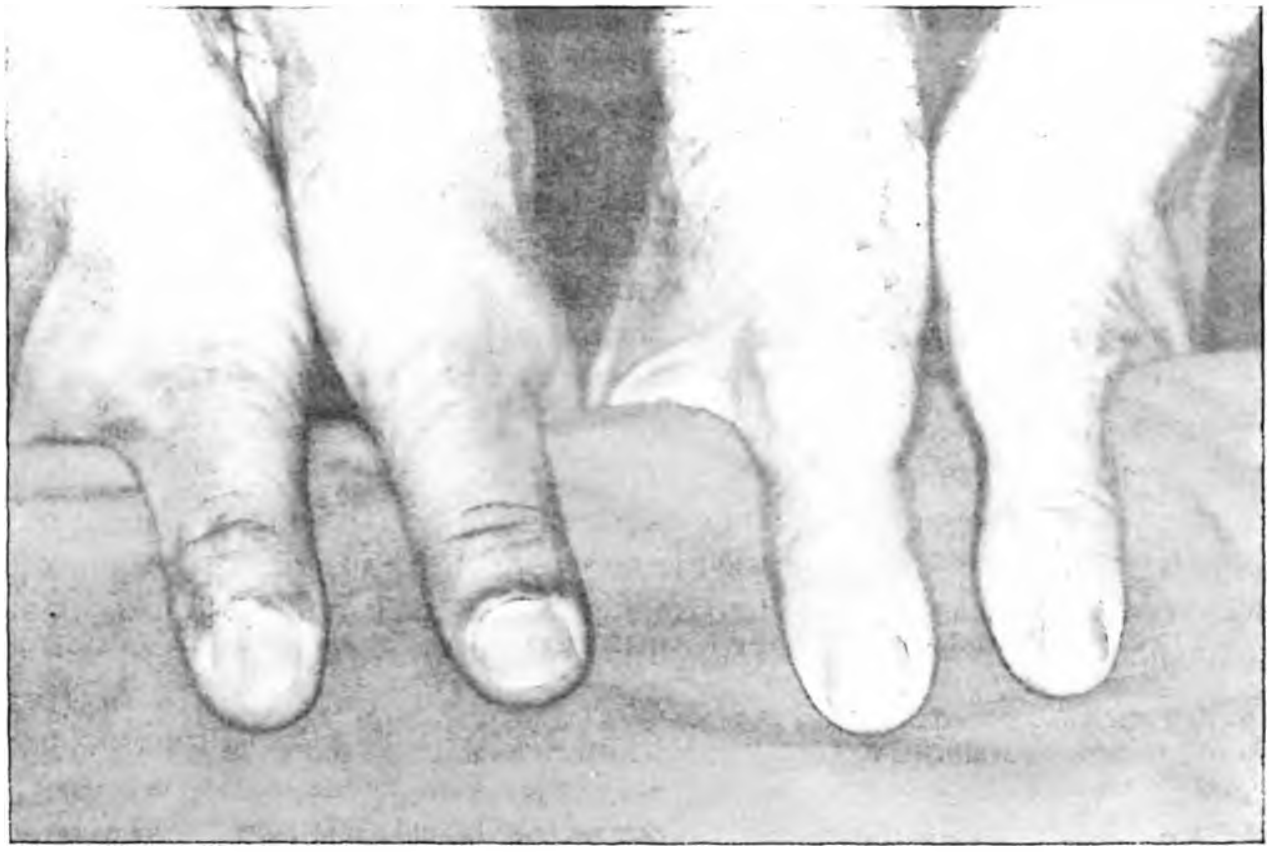


Fig. 8: Shows slightly erythematous, red and brown pigmented areas on back and abdominal area of mother (III-2)



(a) (b)

Fig. 9: Shows mild dystrophy of the nails in (a) mother (III-2) and (b) grandmother (II-5).

immunoglobulin A levels were normal. Mother's and grandmother's skin biopsy results were the same as our patient's. Our patient's grandmother had papillomas on her tongue and inguinal area since childhood (Fig. 10), and now has papillomas below her breasts. She also had red pigmented areas starting from both her axillary areas toward her arms. Also present was nail dystrophy on her left thumb (Fig. 9b).

Family history of the kindred revealed that II/4, III/7, III/9, III/11 and IV/7 cases had similiar skin lesions. We could not examine these patients because they were living in Italy.

Discussion

Focal dermal hypoplasia is a rare disorder characterized by widespread mesodermal and ectodermal dysplasia. This syndrome is an inherited dermatological disorder commonly associated with skeletal, dental, ocular and soft tissue defects. This syndrome was first described in 1962 by Goltz et al.[1] who reported four generations of female subjects in one family.

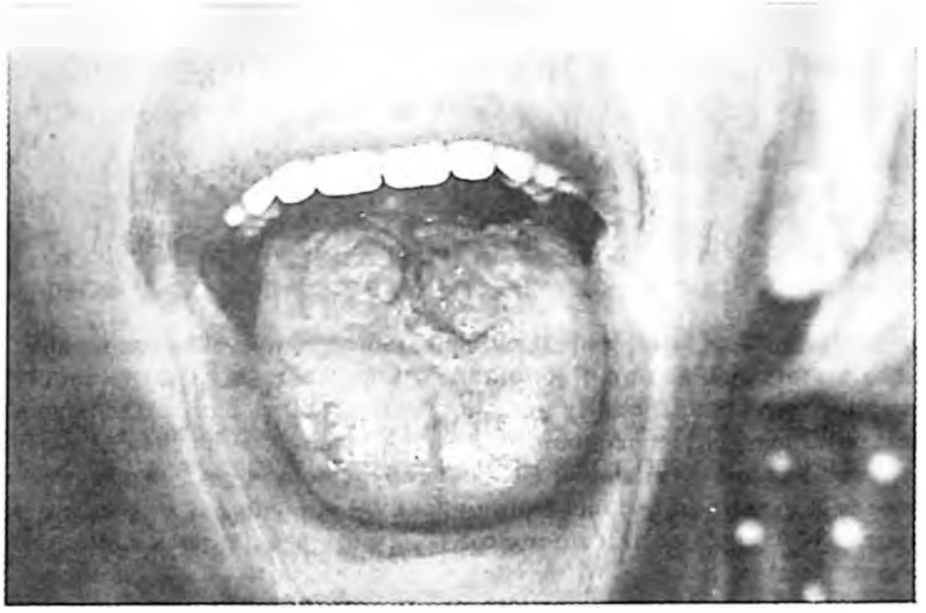


Fig 10: Shows the papilloma on grandmother's (II-5) tongue.

More than 200 cases of FDH have been reported in the literature. Most cases are seen in females and affected females have an increased incidence of spontaneous miscarriages of male fetuses. Therefore, it has been assumed that the mode of inheritance in most of the cases in an X-linked dominant trait with lethality in males. However, more than 30 affected males have also been reported[2-4]. Alternatively, an autosomal dominant mode of inheritance was based on the observations of affected males with father-to-daughter transmission[5,6]. Surviving affected males survive may be mosaics or might have Klinefelter's syndrome.

Although 95 percent of Goltz syndrome cases have been estimated as new mutations, families that were affected in four or three generations have been described in the literature[1,7]. Wechsler et al.[7] reported females with varying expressions of FDH in the same family. They have postulated that early inactivation of the X chromosome bearing the mutant gene responsible for FDH is the cause of variable expression.

In this report we describe affected females with Goltz syndrome in three generations. We also observed an excess of affected women who have spontaneous abortions. Abort material may be male fetuses. Because of this, we suspect that FDH is an X-linked dominant trait with male lethality.

The cutaneous abnormalities consist of atrophic hyperpigmented and hypopigmented macules and erythematous lesions. These lesions showed a characteristic linear or reticular distribution. Linear distribution followed Bloschko's lines. Telangiectasia was a common feature. Other cutaneous abnormalities

including lipomatous nodules and papillomatous lesions, and laryngeal and esophageal papillomas have also been described in the literature[8]. Our three cases (II-5, III-2, IV-3) had papillomas in the perianal area and on the back of the tongue. Atrophic hyperpigmented and hypopigmented lesions were also seen in their axillary areas. The skin biopsy specimens were obtained from the papillomatous lesions of the three affected cases (II-5, III-2, IV-3). The lesions showed acanthosis and papillomatous hyperplasia of the epidermis. Nail dystrophy and thinning of the hair were also noted in the three affected females. The mother (III-2) and her child (IV-3) had tooth anomalies.

Other abnormalities were skeletal anomalies including spinal anomalies such as kyphosis, scoliosis, spina bifida, anomalies of vertebrae, and rudimentary tail. Anomalies of hands and feet included hypoplasia or absence of digits, polydactyly, syndactyly, camptodactyly and clinodactyly. Radius and clavicle deformities and generalized osteoporosis were also found. The most constant radiographic sign in FDH is osteopathia striata involving longitudinal striation of long bones[9]. Index case's (IV-3) x-ray examination disclosed dorsal scoliosis and characteristic linear striations and also cortical thinning and longidutinal striation of the long bones.

Ocular abnormalities frequently found in patients with FDH include microphthalmos, anophthalmia and colobomas. Our index case (IV-3) had ptosis, blue sclera and heterochromia, but the other cases (II-5, III-2) had no ocular abnormalities.

According to the mapping studies of FDH, gene locaiton is in the region Xp22-31[10]. Naritomi et al.[10] reported two girls with terminal deletion of Xp. These patients had Aicardi's and Goltz syndrome. The two genes for Goltz and Aicardi's syndromes might be contiguous genes. Zuffardi et al.[11] demonstrated a girl having several signs of Goltz syndrome with deletion of the chromosome 9q32-qter. They concluded that in at leas some of the cases of FDH the inheritance was autosomal, although X-linked dominant inheritance cannot be ruled out in others. According to us, these results may represent a genetic heterogeneity of FDH.

In this report, the index case, her mother and her grandmother had clinical and histopathological findings compatible with Goltz syndrome. The pedigree data in this family were as follows: three affected females in three generations, with some of them having one or more abortions. Abortion material, which was not analyzed, may have been male fetuses. Thus, we suspect inheritance of this syndrome is most probably an X-linked dominant trait with lethality in males.

REFERENCES

1. Goltz RW, Peterson WC, Gorlin RJ, Ravits HG. Focal dermal hypoplasia. Arch Dermatol 1962; 86: 708-717.
2. Tora-Sola MA, Kistenmacher ML, Punnett HH, Di-George AM. Focal dermal hypoplasia in a male. Clin Genet 1975; 7: 325-327.
3. Feinberg A, Menter MA. Focal dermal hypoplasia (Goltz syndrome) in a male: a case report. S Afr Med J 1976; 50: 554-555.
4. Büchner SA, Itin P. Focal dermal hypoplasia syndrome in a male patient. Report of a case and histologic and immunohistochemical studies. Arch Dermatol 1992; 128: 1078-1082.
5. Gorski JL. Father-to-daughter transmission of focal dermal hypoplasia associated with nonrandom X-inactivation: support for X-linked inheritance and paternal X chromosome mosaicism. Am J Med Genet 1991; 40: 332-337.
6. Burgdorf WH, Dick GF, Soderberg MD, Goltz RW. Focal dermal hypoplasia in a father and daughter. J Am Acad Dermatol 1981; 4: 273-277.
7. Wechsler MA, Papa CM, Haberman F, Marion RW. Variable expression in focal dermal hypoplasia. An example of differential X-chromosome inactivation. Am J Dis Child 1988; 142: 297-300.
8. Goltz RW. Focal dermal hypoplasia syndrome. An update. Arch Dermatol 1992; 128: 1108-1111.
9. Goltz RW, Henderson RR, Hitch JM, et al. Focal dermal hypoplasia syndrome. Arch Dermatol 1970; 101: 1-11.
10. Naritomi K, Izumikawa Y, Nagataki S, et al. Combined Goltz and Aicardi syndromes in a terminal Xp delation: are they a contiguous gene syndrome? Am J Med Genet 1992; 43: 839-843.
11. Zuffardi O, Caiulo A, Maraschio P, et al. Regional assignment of the loci for adenylate kinase to 9q32 and for alpha 1-acid glycoprotein to 9q31-q32. A locus for Goltz syndrome in region 9q32-qter? Hum Genet 1989; 82: 17-19.

EARLY ASSESSMENT OF PULMONARY INVOLVEMENT IN LIMITED SCLERODERMA*

A Case Report

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SUMMARY: Ünsal E, Kılınç O, Kargı A, Çevik NT. (Departments of Pediatrics, Pulmonary Medicine and Pathology, Dokuz Eylül University Faculty of Medicine, İzmir, Turkey). Early assessment of pulmonary involvement in limited scleroderma: a case report. Turk J Pediatr 1998; 40: 603-608.

Limited scleroderma is typified by insidious progression of skin involvement. The onset of internal organ involvement is delayed until the second decade, the lungs being the most important from the prognostic point of view. Early detection of pulmonary lesions is of paramount importance. This paper presents a 16-year-old male patient with a history of Raynaud's phenomenon followed by progressive tightening of skin over the fingers, hands and face. He had early pulmonary involvement detected by high resolution computed tomography (HRCT) and proven by histopathologic examination as usual interstitial pneumonia; even the chest x-ray and pulmonary function tests were normal. A combination of prednisolone and D-penicillamine was planned for treatment because of his having both pulmonary and gastrointestinal system involvement. 99m technetium diethylenetriamine pentaacetate (99m Tc-DTPA) test is very sensitive for pulmonary lesions and it has shown a rapid clearance in the early stage. This method is also useful for following up the therapeutic trial. *Key words: limited scleroderma, high resolution computed tomography, 99m Tc-DTPA.*

Systemic sclerosis is a remarkably heterogeneous disorder with diverse initial presentations and a variable disease course, including wide differences in pace, extent and severity of any of its clinical manifestations[1]. It has an estimated annual incidence of 4.5-12 per million. Childhood onset is very uncommon and accounts for only a small proportion of patients; there are a number of case reports totalling less than 1000 patients[2]. It can be classified into several subtypes, based on the degree of skin and internal organ involvement. Limited scleroderma (CREST syndrome) is a subgroup which has a more benign course than the systemic disease. Skin thickening is less prominent and remains limited to the distal extremities, face and neck. Internal organ involvement occurs only

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after many years of the disease. The most frequent visceral manifestations are pulmonary and esophageal involvement. Esophageal dysmotility is the most common internal organ manifestation and occurs in the majority of children. Fibrosis of the lower two-thirds of the esophagus results in poor propulsive activity, and it leads to reflux[3]. Early detection of pulmonary lesions, especially at the inflammation phase, is of paramount importance, enables one to give early adequate treatment and increases the survival rate[4]. This paper presents a case of limited scleroderma with early pulmonary involvement, describes the diagnostic approach, and discusses the treatment strategy and monitoring.

Case Report

A 16-year-old male patient was referred to the Pediatric Rheumatology Department with a two-year history of his fingers turning blue, especially in winter. He had developed puffy fingers and then had progressive tightening of the skin over the fingers, hands and face in the following months. On careful questioning, it was learned that he did not have shortness of breath or mid-chest pain. On physical examination, he weighed 41 kg (under 3rd percentile), and his height was 159 cm (between 10th and 25th percentiles). The skin over the face was thickened and tightened; the natural creases of his forehead had disappeared. Oral aperture was reduced and radial furrowing was present around the lips. There was a significant change as compared to an earlier age (Fig. 1). The hands appeared shiny and taut with flexion contractions of the finger (Fig. 2). The skin was normal on the other parts of the body. Cardiovascular and

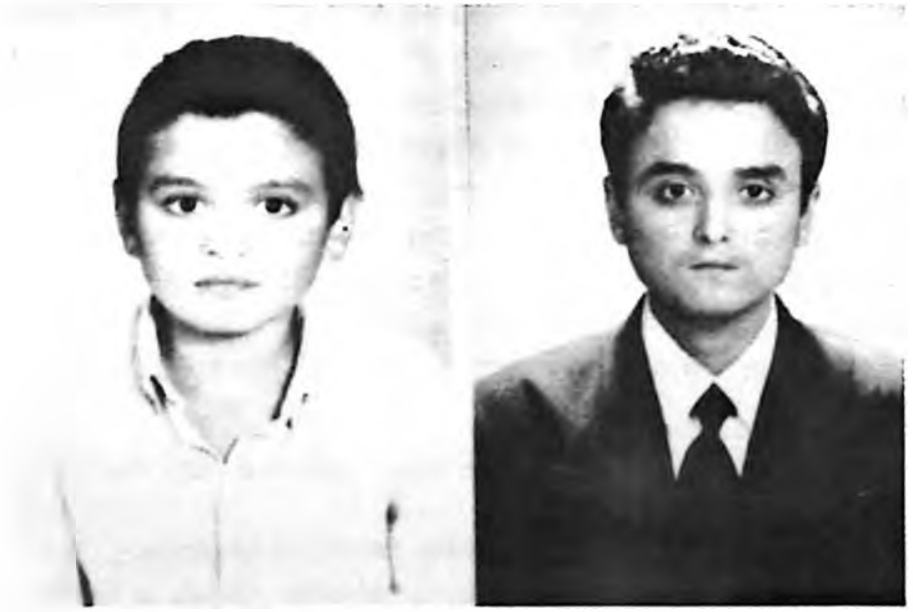

Fig 1. The patient's appearance at 12 and 16 years of age, respectively. Note especially the definite narrowing of the lips and radial furrowing.

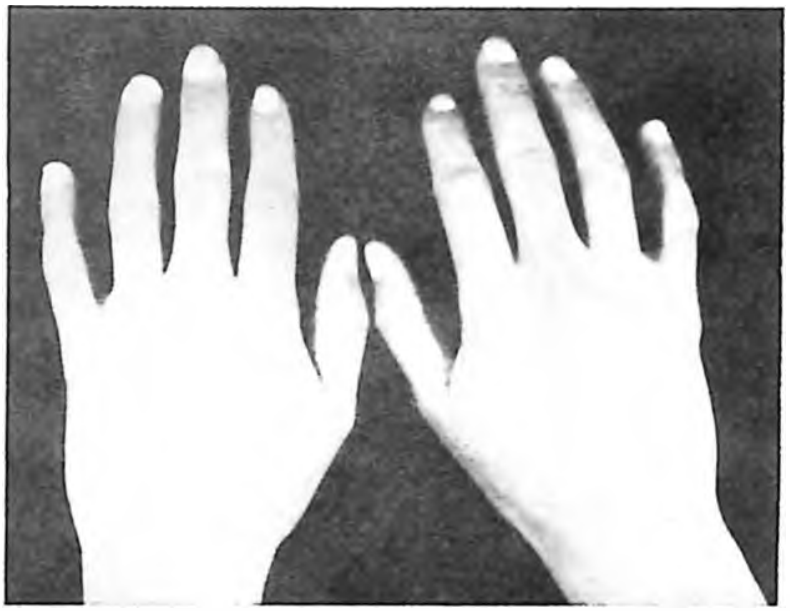

Fig. 2: Sclerodactyly and shiny appearance of the hands with flexion contractions.

respiratory system examinations revealed no pathological signs. He was diagnosed with limited scleroderma. Screenings for renal functions by routine tests and for cardiac functions, including echocardiography and thallium scintigraphy, were normal. The stool examination showed no signs of malabsorption. Gastroesophageal reflux scintigraphy was performed with the indications of pyrosis for the previous two months, and revealed reflux and delayed esophageal movements (Fig. 3). Despite a lack of signs or symptoms

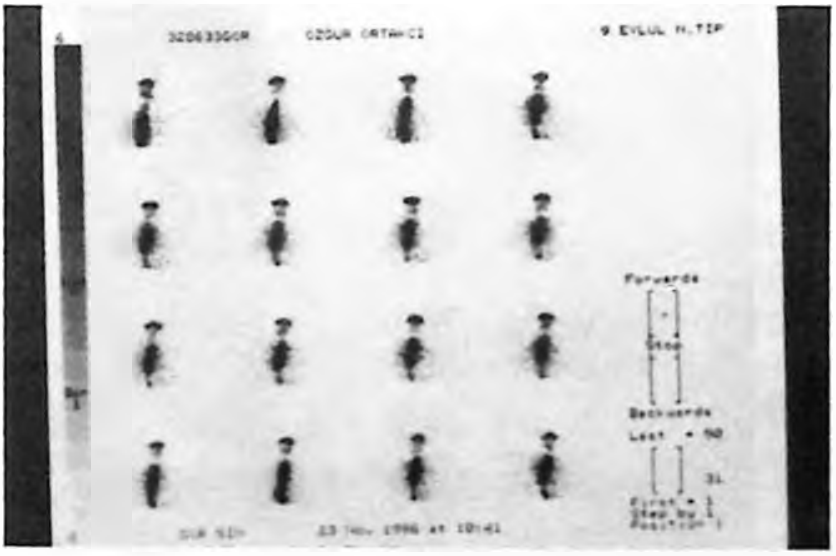

Fig. 3: There is a marked delay in esophageal movements and reflux in series taken during scintigraphy.

of lung involvement and presence of a normal chest x-ray with respiratory function tests, we wanted to evaluate the patient further considering the ominous effects of pulmonary fibrosis on morbidity and mortality. High resolution computed tomography (HRCT) of the lungs revealed small reticular patterns in the lower lobes related with fibrosis (Fig. 4). The hazy appearance of the lung parenchyma suggested an active inflammatory process. The patient underwent bronchoalveolar lavage (BAL), which was normal (90% pulmonary alveolar macrophages, 8% lymphocytes and 2% neutrophils), but histopathologic examination of the biopsy material revealed usual interstitial pneumonia (Fig. 5). 99m technetium scintigraphy was done to determine the degree of involvement as well as to make a comparison between initial findings and the progress (Fig. 6). The clearance rate was increased (t 1/2:30 min, normal value: t 1/2:80 min). Prednisolone (1 mg/kg/d) and D-penicillamine (5 mg/kg/d) therapy was planned for the early multisystemic involvement.

Discussion

Limited scleroderma is typified by insidious progression of skin involvement. Internal organ involvement, other than renal, occurs with frequencies close to that of a diffuse disease, but the onset of involvement is delayed until the second decade. Truly effective and life-extending therapy is available, especially if the diagnosis is made at the beginning of vital organ involvement[1]. The overall mortality rate in scleroderma is 50 percent at seven years, and pulmonary complications are the major cause of death[5]. In the early disease, no signs or

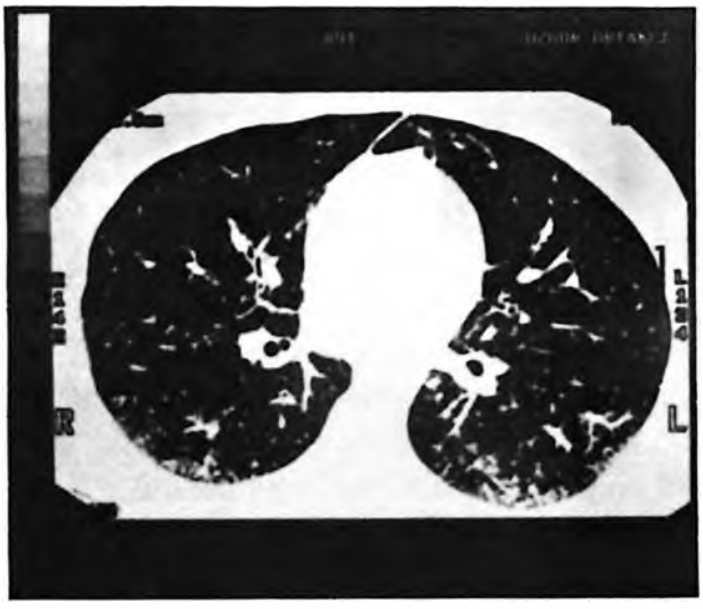

Fig. 4: HRCT findings are definitely seen as small reticular patterns in the lower lobes related with fibrosis.

Fig. 5: A mild degree of alveolar septal thickening caused predominantly by lymphocytes is seen histopathologically (X 40).

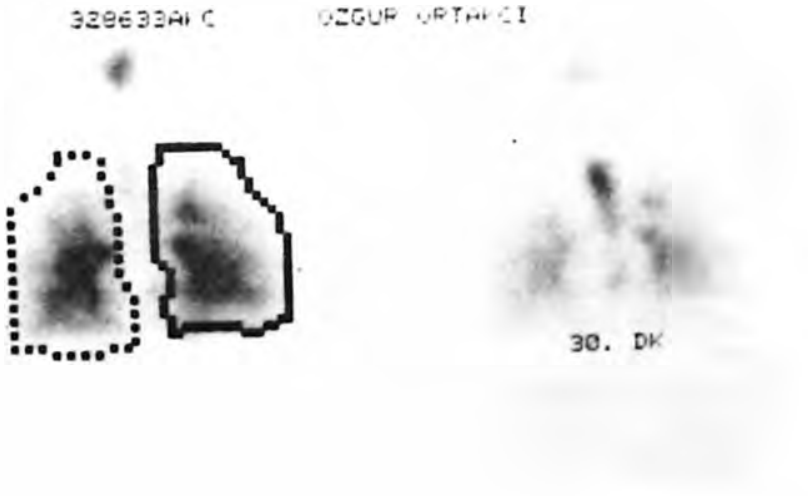

Fig. 6: 99m Tc-DTPA is markedly increased (t 1/2: 30 min).

symptoms of respiratory distress exist and chest radiography may be silent. Only HRCT is able to show early pulmonary involvement at this stage[6]. As we look for the validity of HRCT in diagnosis, we observe that it is highly sensitive in detecting pulmonary lesions (71%) when compared to x-ray films (42%), and pulmonary function tests (42%)[7]. It is also able to classify pulmonary involvement such as "small reticular" and "ground glass" patterns[8]. This patient with limited scleroderma also had normal results including respiratory function tests. Early detection of small reticular lesions in HRCT caused us to examine the lungs in detail. Despite the normal findings in bronchoalveolar lavage (BAL), interstitial pneumonia on histopathologic examination proved the lung involvement.

Regarding the involvement of skin, gastrointestinal and respiratory systems, we planned a combination therapy of prednisolone and D-penicillamine. Prednisolone was successful in treating interstitial pneumonia by delaying the fibrosis, and D-penicillamine had significantly greater effect in improving skin thickening than other disease-modifying agents[1]. Another challenge was to identify a potential marker of progression of the pulmonary disease. We preferred a scintigraphic method, 99m Tc-diethylenetriamine pentaacetate (99m Tc-DTPA). Pulmonary epithelial permeability can be studied by measuring the clearance rate of inhaled 99m Tc-DTPA. This hydrophilic molecule crosses the alveolar-capillary barrier and diffuses from the air space into the vascular space, probably passing through the tight epithelial intercellular junctions. In a recent retrospective study, abnormally rapid clearance of 99m Tc-DTPA at initial measurement was found to identify fibrosing alveolitis patients at higher risk of a decline in functional indices over the subsequent three years[9]. The authors concluded that rapid clearance was likely to reflect both interstitial inflammation and mechanical stretch of the respiratory epithelium due to the lung fibrosis. They pointed out that incomplete control of inflammation in the setting of significant lung fibrosis was an alternative explanation for fixed abnormalities in 99m Tc-DTPA clearance[10-12]. Thus, we were able to reveal both the initial degree of lung involvement, and a method to follow up the patient at regular intervals.

REFERENCES

1. Seibold JR. Systemic sclerosis. In: Klippel JH, Dieppe PA (eds). Rheumatology. St. Louis: CV Mosby Co. Yearbook Europe Ltd; 1994: 8.1-8.12.
2. Cassidy JT, Petty RE. The Sclerodermas and Related Disorders. London: Churchill Livingstone Inc.; 1995: 425-453.
3. Uziel Y, Miller ML, Laxer RM. Scleroderma in children. Pediatr Clin North Am 1995; 42: 1171-1205.
4. Holzmann H, Jacobi V, Werner RJ, Stahl E. Lung manifestation of progressive systemic scleroderma. Computerized tomographic findings. Hautarzt 1994; 45: 471-475.
5. Arroliga AC, Podell DN, Matthay RA. Pulmonary manifestations of scleroderma. J Thorac Imaging 1992; 7: 30-45.
6. Paone G, Di Michele L, Mattia P, Tonnarini R, Lucifora V, Fiorucci F. Pulmonary involvement in scleroderma. Minerva Med 1994; 85: 293-300.
7. Dellafiore L, Colombo B, Del Sante M, et al. Pulmonary involvement in scleroderma assessed with high-resolution computerized tomography and functional tests. Radiol Med 1994; 87: 608-613.
8. Dévényi K, Czirják L. High resolution computed tomography for the evaluation of lung involvement in 101 patients with scleroderma. Clin Rheumatol 1995; 14: 633-640.
9. Wells AU, Hansell DM, Harrison NK, Lawrence R, Black CM, du Bois RM. Clearance of inhaled 99m Tc-DTPA predicts the clinical course of fibrosing alveolitis. Eur Respir J 1993; 6: 770-771.
10. Wells AU, du Bois RM. Prediction of disease progression in idiopathic pulmonary fibrosis. Eur Respir J 1994; 7: 636-639.
11. Fanti S, De Fabritiis A, Aloisi D, et al. Early pulmonary involvement in systemic sclerosis assessed by technetium-99m-DTPA clearance rate. J Nucl Med 1994; 35: 1933-1936.
12. Wells AU, Hansell DM, Harrison NK, et al Clearance of inhaled 99m Tc-DTPA predicts the clinical course of fibrosing alveolitis. Eur Respir J 1993; 6: 797-802.

X-LINKED AGAMMAGLOBULINEMIA AND ISOLATED GROWTH HORMONE DEFICIENCY*

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SUMMARY: Arslan D, Patıroğlu T, Kendirci M, Kurtoğlu S. (Department of Pediatrics, Erciyes University Faculty of Medicine, Kayseri, Turkey). X-linked agammaglobulinemia and isolated growth hormone deficiency: case report. Turk J Pediatr 1998; 40: 609-612.

X-linked agammaglobulinemia and isolated growth hormone deficiency was first described in 1980 and then classified as a different primary immune deficiency. Delayed puberty in patients with X-linked agammaglobulinemia may result in delayed secretion of growth hormone (GH). To determine true isolated growth hormone deficiency, GH stimulation tests and other hypophyseal hormone evaluations must be performed. In this paper, we report a 15-year-old boy with X-linked agammaglobulinemia and isolated growth hormone deficiency, and review related literature. *Key words: agammaglobulinemia, growth hormone deficiency, delayed puberty.*

The first case of X-linked agammaglobulinemia (XLA) and growth hormone deficiency (GHD) was described in 1980 by Fleischer et al.[1]. Although sharing some clinical and laboratory features with classical XLA, this unusual association is currently classified as an independent primary immunodeficiency[2]. The molecular pathogenesis of XLA/GHD is controversial.

Since growth hormone insufficiency may result from delayed puberty, some prepubertal XLA patients were misdiagnosed as GHD. As a result, several investigators advised administering sex steroids before performing GH evaluation studies[3,4]. In this paper, we report a 15-year-old boy with agammaglobulinemia and isolated GHD without family history.

Case Report

A 15-year-old boy was admitted to hospital with diffuse bilateral bronchiectasis and marked growth retardation. He was the third child of nonconsanguineous parents. Three male siblings and a female sibling were healthy. He had recurrent respiratory tract infections from infancy. His weight was 27 kg (<3rd percentile) and height was 131 cm (<3rd percentile); SDS for height was –4.625. He had

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pectus carinatum deformity and digital clubbing, and pubertal development was consistent with Tanner 1. Laboratory studies revealed hypochromic, microcytic anemia and normal WBC count. Bone age was 11 years, sweat chloride was 8 mmol/L. The levels of serum immunoglobulins were too low, and CD19, which is a marker of B lymphocytes, was below one percent. Immunologic parameters are presented in Table I. Because of growth and pubertal retardation, the patient was evaluated endocrinologically. While serum T3, T4, TSH, basal cortisol and IGF-I levels were within normal ranges for age, basal serum levels of testosterone, FSH and LH were consistent with prepubertal stage. Basal and post-hCG stimulation testosterone levels were 7.74 and 220.06 ng/ml, respectively.

Because gonadotropin levels were consistent with stage 1, a LH-RH test was performed. After LH-RH stimulation, serum FSH and LH levels rose to 2.17 and 4.11 mIU/ml, respectively. Growth hormone stimulation tests with L-dopa and insulin hypoglycemia were performed three days after administration of 100 mg intramuscular testosterone (Sustanon®)[5]. Growth hormone levels were below the value of 7 ng/ml for two tests. Hormone evaluation studies are presented in Table II.

The patient was treated with antibiotic, chest physiotherapy and monthly intravenous immunoglobulin at a dose of 200 mg/kg of body weight. He had gained 6 cm of height during 20 months of follow-up.

Table I: Immunologic Parameters

WBC: 7,400/mm³
Absolute lymphocyte count: 2,812/mm³
Serum immunoglobulins:
IgG : 180 mg/dl (Normal ranges for age: 800-1900)
IgA : 25 mg/dl (Normal ranges for age: 85-220)
IgM : 25 mg/dl (Normal ranges for age: 75-197)
Lymphocyte subsets (flow cytometric)
CD45 : 99.9%
CD3 : 82.4%
CD4 : 25.7%
CD8 : 56.2%
CD16 : 17.8%
CD19 : 0.0%

Table I: Immunologic Parameters

T3: 152.50 (ng/dl)

T4: 11.76 (mg/dl)

TSH: 0.70 (mIU/ml)

Cortisol: 18.28 (mg/dl)

IGF-I: 224.48 ng/ml (Normal ranges for Tanner 1: 215 ± 71 ng/ml)

Testosterone (ng/ml):
Basal: 7.74 After hCG stimulation: 220.06

Gonadotropin-RH Stimulation Test

	Basal	20 min	40 min	60 min	90 min
FSH (mIU/ml)	0.63	0.84	2.17	1.83	1.61
LH (mIU/ml)	0.5	3.04	3.94	0.91	4.11

*Growth Hormone Stimulation Tests**

Time (min)	0	20	40	60	90	120
L-DOPA GH (ng/ml)	1.2			0.89	5.80	
Insulin Hypoglycemia Test						
Blood Glucose (mg/dl)	80	27	44	85	76	78
GH (ng/ml)	0.70	0.34	3.84	6.48	2.14	0.76

* After 100 mg testosterone administration.

Discussion

This boy had proportionate short stature and agammaglobulinemia without circulating B cells and normal cellular immune function. Responses to GH stimulation tests and other endocrinologic evaluation led to the diagnosis of isolated GH deficiency.

Bruton's agammaglobulinemia is characterized by an X-linked recessive mode of inheritance of a defective humoral immune system with intact cell mediated immunity[6]. Controversial results have been reported with regard to the molecular pathogenesis of XLA/GHD. Both linkage analysis and evaluation of X chromosome inactivation suggested a gene other than the classical XLA gene in the first pedigree, but were consistent with a typical XLA mutation in the second and third families[7,8].

Since this patient was a boy and had no family history consistent with XLA, he was suspected to be a sporadic XLA patient.

Some prepubertal children with decreased growth velocity have a temporary partial GH deficiency. Penny and Blizzard[9] observed very low values (<3 ng/ml) of GH after insulin or arginine stimulation tests in three prepubertal

boys with short stature. They had a significantly higher response after entering stage IV of sexual development. The delayed secretion of sexual hormones presumably would play a role in the impaired GH release in these subjects. For the diagnosis of true GH deficiency in delayed growth and puberty it seems worthwhile to repeat GH stimulation tests after a brief administration of sexual hormones[5].

This patient's basal serum testosterones, FSH and LH levels were consistent with the prepubertal stage. Follicle-stimulating hormone and LH levels were increased sufficiently after LH-RH stimulation[10]. In fact, interpretation of the LH-RH test may be difficult in GH deficient patients until the bone age has reached 12.5-13 years in males and 10.5-11 years in females[11]. Serum testosterone levels increased to 220.06 ng/dl after hCG stimulation. After priming with testosterone, GH levels, after stimulations with L-dopa and insulin hypoglycemia, were below the value of 7 ng/ml. This picture was consistent with isolated growth hormone deficiency.

As a result, we would like to suggest that in the case of hypogammaglobulinemia and short stature, GH deficiency should be kept in mind.

REFERENCES

1. Fleisher TA, White RM, Broder S, et al. X-linked hypogammaglobulinemia and isolated growth hormone deficiency. N Engl J Med 1980; 302: 1429-1434.
2. McKusick VA. Mendelian Inheritance in Man. Baltimore: Johns Hopkins University Press; 1994: 30720.
3. Gourmelen M, Pham-Huu-Trung MT, Girard F. Transient partial hGH deficiency in prepubertal children with delay of growth. Pediatr Res 1979; 13: 221-224.
4. Buzi F, Notarangelo LD, Plebani A, et al. X-linked agammaglobulinemia, growth hormone deficiency and delay of growth and puberty. Acta Paediatr 1994; 83: 99-102.
5. Hughes IA. Tests in pediatric endocrinology. In: Brook CG (ed). Clinical Pediatric Endocrinology. Oxford: Blackwell Scientific Publications; 1989: 695-705.
6. Buckley RH. Primary B-cell diseases. In: Behrman RE, Kleigman RM, Arvin AM (ed). Nelson Textbook of Pediatrics. Philadelphia: W.B. Saunders Company; 1996: 567-570.
7. Notarangelo ND, Wagner DK, Schwieterman WD, Camerino G, Fleisher TA, Nelson DL. Restriction length polymorphism analysis of patients with X-linked agammaglobulinemia and growth hormone deficiency. In: Albertini A (ed). Molecular Probes: Technology and Medical Applications. New York: Raven Press; 1989: 143-188.
8. Conley ME, Burks AW, Herrod HG, Puck JM. Molecular analysis of X-linked agammaglobulinemia with growth hormone deficiency. J Pediatr 1991; 119: 392-397.
9. Penny R, Blizzard RM. The possible influence of puberty on the release of growth hormone in three males with apparent growth hormone deficiency. J Clin Endocrinol 1972; 34: 82.
10. Hughes IA. Handbook of Endocrine Tests in Children. Bristol: John Wright and Sons Ltd; 1986: 17-18.
11. Job JC. Hypogonadism at adolescence: lack or delay of sexual development. In: Lifshitz F (ed). Pediatric Endocrinology. New York: Marcel Decker Inc, 1996: 251-266.

VARIABLE CLINICAL EXPRESSION OF HOLT-ORAM SYNDROME IN THREE GENERATIONS*

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SUMMARY: Oğur G, Gül D, Lenk MK, İmirzalıoğlu N, Alpay F, Oğur E. (Departments of Medical Genetics, Pediatrics and Radiology, Gülhane Military Medical Academy, Ankara, Turkey). Variable clinical expression of Holt-Oram syndrome in three generations. Turk J Pediatr 1998; 40: 613-618.

Holt-Oram syndrome is a distinct autosomal dominant entity presenting with upper limb defects and cardiac abnormality. No correlation between the severity of the heart and the limb defects has been established. Here we report variable clinical expression of Holt-Oram syndrome in three generations. The grandfather presented with typical upper limb defects: phocomelia of arms with three digits on each hand, congenital heart defect and narrow shoulders. His son manifested cardiac conduction disturbance with no congenital heart or skeletal defect. The granddaughter showed ventricular septal defect and moderate radial deviations of both hands with no obvious hypoplasia of the extremities. Clinical data of the presented family suggests lack of penetrance with respect to skeletal and structural cardiac abnormalities in the Holt-Oram syndrome. *Key words: Holt-Oram, syndrome variable expression, congenital heart defects, skeletal malformations.*

The Holt-Oram syndrome (HOS) is an autosomal dominant disorder characterized by upper limb abnormalities and congenital heart defects. The most frequent upper limb abnormality involves the thumbs, whereas secundum atrial septal defect is the most common cardiac malformation. A wide variability of clinical expression of the syndrome has been reported[1-10]. It is accepted that the penetrance of the gene is complete. Known gene carriers have been described without one or the other of cardiovascular or skeletal changes, but not without both. Here we report a family in which the disorder is being transmitted through an obligate carrier, the grandfather to his son and then to the granddaughter. They all presented with variable clinical expressions of HOS.

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Case Report

A pedigree depicting four generations of the index case is shown in Figure 1. The proband (Fig. 1; IV-1), a one-month-old girl born to phenotypically healthy unrelated parents, exhibited ventricular septal defect on clinical and echocardiographic examination. She manifested no severe upper limb abnormality other than bilateral radial deviation of both hands and stiffened elbow articulation (Fig. 2). Her grandfather (Fig. 1; II-3) exhibited severe upper limb defects. Bilateral phocomelia was striking. A rudimentary humerus was noted with three digits attached directly to this rudimentary arm (Fig. 3). The shoulders were narrow and sloping with a decreased range of movement. Physical examination of the heart revealed a widely split and fixed second heart sound and a moderate systolic ejection murmur at the second left intercostal margin. An atrial septal defect was suspected. No echocardiographic evaluation could be performed because of refusal to comply with further investigations. The proband and grandfather both had normal karyotypes. The proband's father (Fig. 1; III-3) had no limb abnormalities. Cardiac evaluation showed no apparent congenital heart defect; however, electrocardiographic examination revealed a first-degree heart block (Fig. 4).

Discussion

A wide variability in expression of the skeletal and cardiac features of HOS has been reported[1-10]. The expression of the skeletal malformations ranges from minor

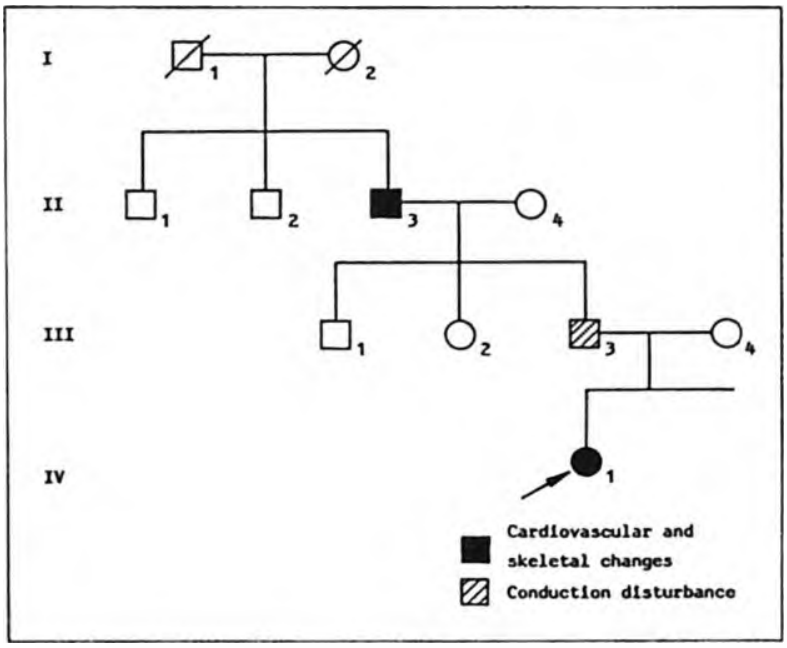

Fig. 1: Family pedigree.

Fig. 2: Proband (granddaughter) (Fig. 1; IV-I).

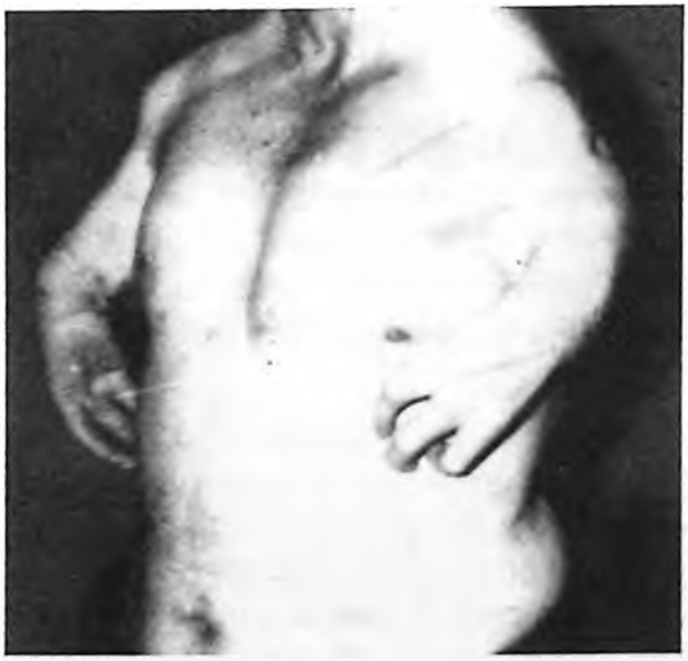

Fig. 3: Grandfather (Fig 1, II-3).

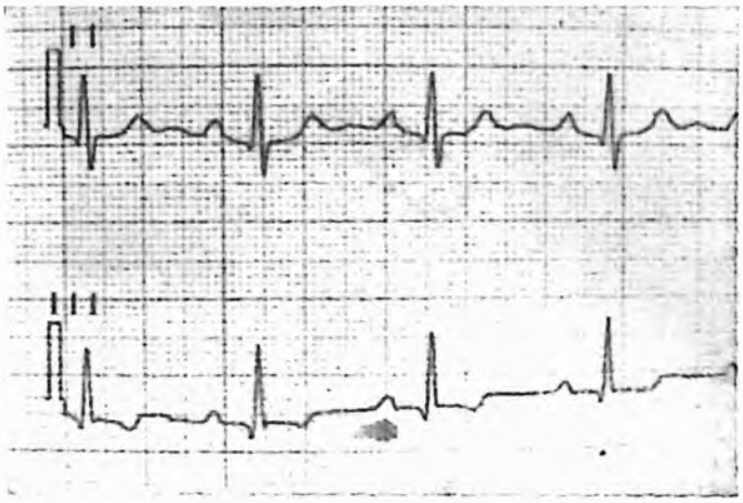

Fig. 4: First degree heart block (father of the proband).

defects, such as limitation of movement of the thumbs, to phocomelia. A range of thumb abnormalities (absent, hypoplastic, or triphalangeal thumb, or partial soft tissue syndactyly of the thumb and index finger) is commonly described. In the analysis of six cases with HOS, Tunçbilek et al.[8] reported bilaterally absent thumb, metacarps and radius. In the most severely affected patients with phocomelia, the humerus is rudimentary or absent with one or two digits attached directly to the trunk. Phocomelia is found in about 10 percent of patients. Çevik et al.[9] reported amelia, a severe skeletal malformation, in an index case and in her father, both with HOS. Other upper limb abnormalities are asymmetric length of arms, limitations of movement at the elbow, hypoplasia of the musculature and narrow and sloping shoulders. The clavicula may be short or broad[1,2,6].

Secundum atrial septal defects are the most common cardiovascular abnormalities; however, ventricular septal defects and conduction abnormalities are also frequently found[1,3,7]. Besides these common cardiac abnormalities, Günal et al.[10] reported common atrium, mitral cleft, mitral insufficiency and pulmonary hypertension in a two-year-old girl in their series of four cases with HOS.

In the presented family variable expression of HOS is well documented (Table I). The grandfather represented a severe form of skeletal abnormality with bilateral phocomelia. Heart defect, on the other hand, was not easy to detect. A careful physical examination revealed moderate systolic ejection murmur. An atrial septal defect was suspected on clinical grounds but could not be confirmed with echocardiographic examination. His son presented no skeletal or cardiac malformation yet conduction abnormality was obvious on electrocardiographic

Table I: Comparison of Clinical Features in Three Affected Members

	Grandfather	Father	Granddaughter
Skeletal changes	severe (phocomelia)	none	mild (radial hand deviation)
Cardiovascular changes	CHD	1° AV block	VSD

CHD congenital heart defect, 1° AV block. first degree atrioventricular block, VSD: ventricular septal defect.

examination. The granddaughter, on the other hand, manifested a muscular ventricular septal defect, with no gross abnormality of the thumbs but minor limitation of their movement and bilateral deviation of the hands. There was no correlation between the severity of the skeletal and cardiac malformations in either affected member.

A gene responsible for HOS (HOS1) has been mapped to chromosome 12 using linkage analysis[11]. Basson et al.[1] recently reported two large families with HOS. Genetic analyses demonstrated linkage of the disease in each family to polymorphic loci on the long arm of chromosome 12[1]. This location has been further refined through the identification of a HOS patient presenting with a complex chromosomal rearrangement involving chromosome 12[12]. Recently, Yi Li et al.[13] showed that TBX5 was mutated in affected individuals in three familial and three sporadic HOS families. The identification of TBX5 as a gene responsible for HOS points out the possibility that members of the TBX family may be responsible for some other inherited developmental disorders.

The proband's father in the presented family manifests no limb or cardiac malformations, only conduction abnormality.

To the best of our knowledge there have been no reports mentioning only conduction abnormality with no associated structural cardiac defects or skeletal abnormalities in HOS. Consequently the present clinical data suggests lack of penetrance in the syndrome with respect to both skeletal and cardiac malformations.

REFERENCES

1. Basson CT, Cowley GS, Solomon SD, et al. The clinical and genetic spectrum of the Holt-Oram syndrome (heart-hand syndrome). N Engl J Med 1994; 330: 885-891.
2. Braulke I, Herzog S, Thies U, Zoll B. Holt-Oram syndrome in four half-siblings with unaffected parents: brief clinical report. Clin Genet 1991; 39: 241-244.
3. Frontera-Izquierdo P, Cabezuelo-Huerta G. Severe Holt-Oram syndrome with pulmonary hypertension. Am Heart J 1991; 122: 250-252.

4. Gladstone I Jr, Sybert VP. Holt-Oram syndrome: penetrance of the gene and lack of maternal effect. Clin Genet 1982; 21: 98-103.
5. Glauser TA, Zackai E, Weinberg P, Clancy R. Holt-Oram syndrome associated with the hypoplastic left heart syndrome. Clin Genet 1989; 36: 69-72.
6. Hurst JA, Hall CM, Baraitser M. The Holt-Oram syndrome. J Med Genet 1991; 28: 406-410.
7. Kejariwal VK, Misra PK, Kumar A, Awasthi S. Holt-Oram syndrome with polydactyly and ostium primum defect (letter). Indian Pediatr 1989; 26: 1064-1065.
8. Tunçbilek E, Özme Ş, Besim A, Balcı S. Holt-Oram syndrome (analysis of six cases). Turk J Pediatr 1980; 22: 50-58.
9. Çevik N, Çevik N, Bilgiç A. A case of Holt-Oram syndrome severely affecting the skeleton of the upper limbs. Turk J Pediatr 1985; 27: 25-32.
10. Günal N, Özer S, Çeliker A, Özkutlu S, Balcı S. Holt-Oram sendromlu dört vakanın kardiyolojik bulguları. Çocuk Sağlığı ve Hastalıkları Dergisi 1996; 39: 171-176.
11. Terrett JA, Newbury-Ecob R, Cross GS, et al. Holt-Oram syndrome is a genetically heterogeneous disease with one locus mapping to human chromosome 12q. Nature Genet 1994; 6: 401-404.
12. Terrett JA, Newbury-Ecob R, Smith NM, et al. A translocation at 12q2 refines the interval containing the Holt-Oram syndrome 1 gene. Am J Hum Genet 1996; 59: 1337-1342.
13. Yi Li Q, Newbury-Ecob RA, Terrett JA, et al. Holt-Oram syndrome is caused by mutations in TBX5, a member of the Brachyury (T) gene family. Nature Genet 1997; 15: 21-29.

A CASE OF TRUNCUS ARTERIOSUS TYPE II*

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SUMMARY: Yurdakul Y, Yılmaz M, Demirtürk OS, Miari A, Bilgiç A. (Department of Thoracic and Cardiovascular Surgery and Cardiology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). A case of truncus arteriosus type II. Turk J Pediatr 1998; 40: 619-625.

A case of truncus arteriosus type II is reported. Truncus arterious is an uncommon congenital cardiac defect where a single great vessel exits the heart. Truncus arteriosus is usually fatal, if untreated. This defect occurs when the conus arteriosus and the truncus divide erroneously in the embryo. Palliative surgery in truncus arteriosus has been unsuccessful. Pulmonary banding has been tried and was ineffective and usually fatal. We operated on a nine-month-old (6200 g) male infant with a type II (Edwards-Collett) defect and a large ventricular septal defect. The pulmonary artery average pressure was 51 mmHg. We performed a cardiopulmonary bypass in the usual manner. Pulmonary arteries were resected from the truncal root, and primary end-to-end anastomosis of the truncal root to the ascending aorta was performed. Right ventricle to pulmonary artery continuity was provided using a valveless Gore-Tex graft. We lost our patient due to intractable pulmonary hypertension on the first postoperative day. *Key words: truncus arteriosus, cyanotic heart defects, total correction.*

Truncus arteriosus is an uncommon congenital cardiac defect in which a single great vessel stemming from the heart branches into the coronary arteries, pulmonary arteries and the ascending aorta. Truncus arteriosus is a usually fatal congenital defect which, without treatment, results in 65 percent mortality in the first three months of life due to untreatable congestive heart failure[1]. Truncus arteriosus accounts for approximately two to four percent of all congenital cardiac anomalies[2]. The single trunk in truncus arteriosus imposes an appallingly high flow and elevated pulmonary artery pressure which leads to the development of heart failure early in life. Run off from the truncal artery creates a low diastolic pressure causing a decreased coronary perfusion and a further decrease in ventricular performance. The presence of a truncal valve regurgitation further complicates the picture[2].

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This defect occurs in the embryo when the conus arteriosus and the truncus divide erroneously and the spiral septum develops deficiently. Because the spiral septum also takes a role in the closure of the ventricular septum, truncus arteriosus always occurs concomitantly with a large ventricular septal defect (VSD). Works of Garcia-Peláez and colleagues[1] concluded that the truncus arteriosus appears in the chick embryo, at 50-56 hours of incubation. They strongly believe that there is a possibility that the defect occurs in a similar way in mammals, including the human embryos[3].

In some cases of truncus arteriosus the VSD can include the tricuspid annulus and cause difficulties in closure. Unfortunately, efforts to palliate truncus arteriosus in patients with Collett and Edward's Type I or II defects by pulmonary artery banding in an attempt to decrease pulmonary blood flow yielded poor results, with most series reporting mortalities in the range of 50 to 60 percent[4]. The follow-up patients with truncus arteriosus showed a high incidence of early pulmonary vascular disease. Thus, the pioneering article of Ebert and colleagues[4] concluded that physiological correction should be performed early in life.

Case Report

We operated on a nine-month-old (6200 g) male infant who had truncus type II (Edwards-Collett) defect. The patient upon his cardiac catheterization was found to have a large VSD (Fig. 1), truncus arteriosus type I defect which, on perioperative examination, was found to be actually a type II defect. His pulmonary artery average pressure was 51 mmHg. The arcus aortae was normal

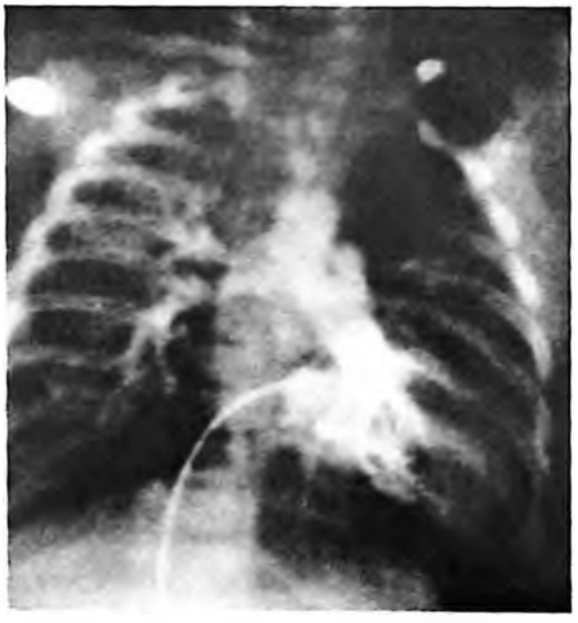

Fig. 1: Angiography showing truncus arteriosus.

and there was no patent ductus arteriosus (PDA). The patient had been operated on previously at five months of age, when a pulmonary artery banding had been performed to the left pulmonary artery.

Operational technique

After standard median sternotomy exposure, a cardiopulmonary bypass was conducted in the usual manner. We used systemic hypothermia. The ascending aorta was cannulated above the bifurcation of the truncus, and both vena cava were cannulated.

The left and right pulmonary arteries were exiting the aorta via different roots from the posterior part. We first performed a debanding of the left pulmonary artery, and then performed an aortotomy (Fig. 2). The pulmonary arteries were resected from the truncal root in continuity such that sufficient tissue surrounding the orifices of the pulmonary arteries was present for distal conduit anastomosis. Some truncal tissue had to be removed, leaving a defect at the posterior part of the future aorta. This was later repaired using a Gore-Tex (polytetrafluoroethylene) patch. Truncal valve of the ventricular outflow tract was bicuspid. There was no truncal regurgitation.

We followed guidelines of Ebert and colleagues[4], who reported that when making an initial incision in the posterior wall of the aorta, caution is necessary to avoid the suspension system of the truncal valve, and that the orifice of the left coronary artery should be identified. The commissures of the truncal valve are usually

Fig. 2: Intraoperative view of repair of truncus arteriosus. VSD is seen through right ventriculotomy, and truncus is divided.

short and the depth of the Valsalva's sinus is less than normal. Thus, it is possible that the left coronary orifice is high in the sinus and can be incised at the time of exploration of the pulmonary cuff, or that it could be incorporated into the suture at the time of closure of the aortotomy[4].

A primary end-to-end anastomosis of the truncal root to the ascending aorta was performed. Closure was carried out using a running polypropylene suture. Care was given to protect the coronary ostia. In our case we had no coronary anomalies. Afterwards, we performed a longitudinal incision to the right ventricle exposing the VSD. It was taken far enough to expose the VSD so that the ventricular opening would be adequate for the conduit. The defect was presenting as a subaortic defect, which is usual. The defect was closed in such a manner as to leave the aorta on the left side of the heart. We performed a right atriotomy such that no atrial septal defect or patent foramen ovale was present. The tricuspid valve was normal. We later used a number 14 Gore-Tex (PTFE) tubular graft to create the right ventricle outflow tract (Fig. 3). After weaning from cardiopulmonary bypass, the patient's arterial pressure was 80 mmHg. We used a full dose of dopamine (15 µg/kg/min) for support. Despite intensive therapy to prevent hypertensive crisis, we lost our patient on the first postoperative day due to the intractably high pulmonary hypertension.

Discussion

The techniques for repair of truncus arteriosus are individualized according to the specific valve morphology[5]. If there is truncal valve regurgitation, which is frequent in patients with truncus arteriosus, perioperative and late mortality are increased.

Most authors suggest that repair should be undertaken before 100 days of life when incidence of pulmonary hypertension and pulmonary hypertensive crises in the postoperative period is low[6,7]. In our case, the resistance was high with the patient at nine months of age.

Following the contributions of Ebert and colleagues[4], several reports have shown improvement in the outcome of patients undergoing operations in which complete repair and physiological correction are carried out. Survival in the first month of life is low, and thus many authors, including Sharma et al.[8], Di Donato et al.[9], and Ziemer et al.[10], continue to recommend postponing the operation until the patient is two to three months of age. According to Bove et al.[2], it is significant to mention that medical treatment is useless and further decreases the chance of the infants to gain weight, nor does it protect them from infections or pulmonary vascular disease or left ventricular dysfunction. Bove et al.[2] also point out that a valve in the pulmonary position provides a substantial hemodynamic improvement. Thus, beginning in 1986, valved conduits have been used.

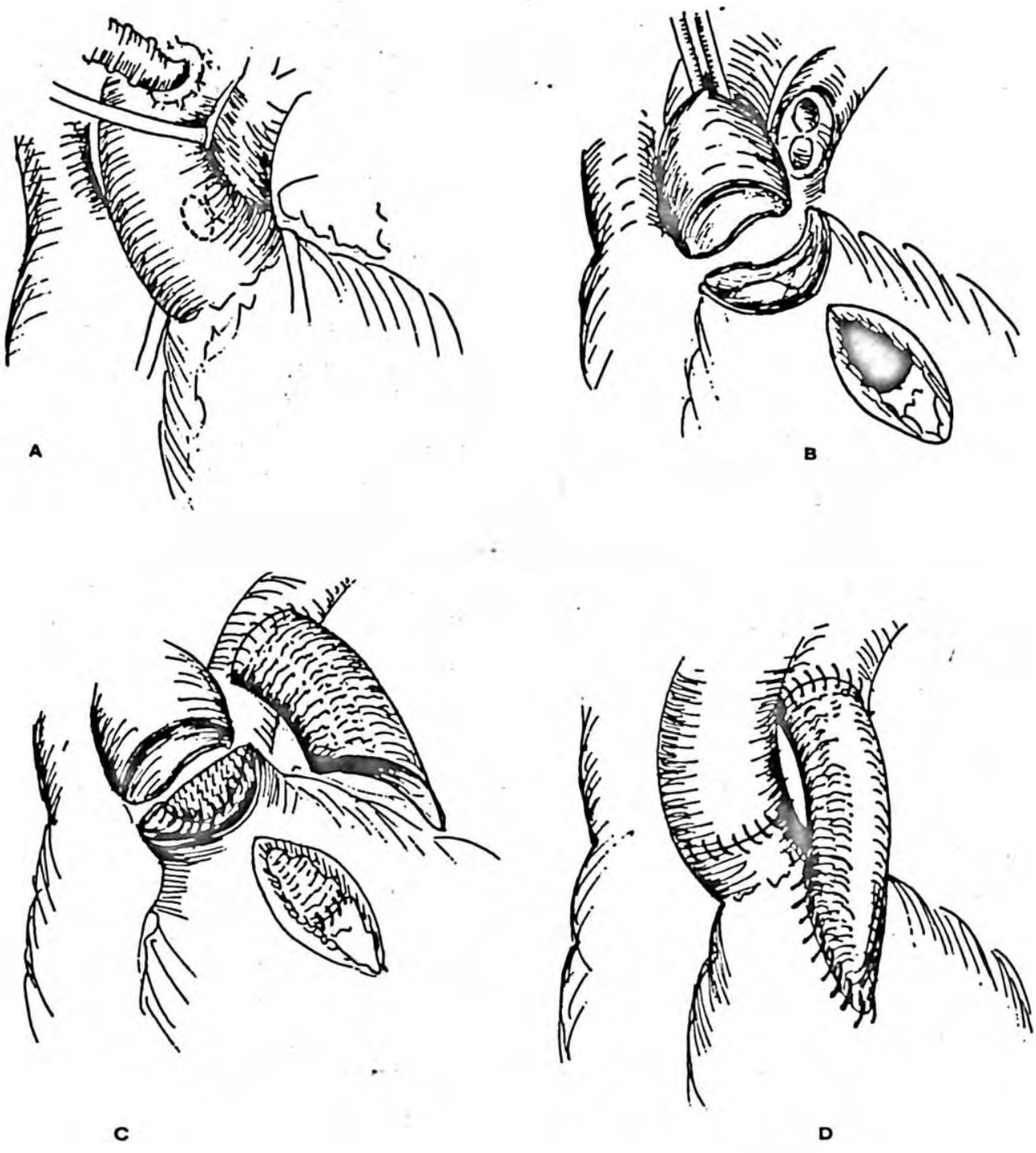

Figure 3: procedure of repairing type II truncus arteriosus.
A : preoperative schematic view of type II truncus arteriosus. Pulmonary arteries origin is seen in the posterior aspect of the truncus.
B : The VSD is seen through the right ventriculotomy. After the completely transecting of the truncus, the pulmonary arteries origin is dissected free and is separated from the aorta.
C : The VSD is closed with a patch. The distal anastomosis of the conduit to the origin of the pulmonary arteries and restoration of the posterior wall of the truncus by a patch is seen.
D : Completed repair. The aorta end - to end anastomosis is seen. The anastomosis from the right ventriculotomy to the origin of the pulmonary arteries by a conduit is seen.

Fig 3

There are four important preoperative risk factors which increase mortality in patients with truncus arteriosus[6]: 1-truncal valve regurgitation, 2-associated interrupted aortic arch, 3- coronary artery anomalies, and 4-repair undertaken after 100 days of life.

We had one (4th) of the four risk factors which many authors describe as the most vulnerable.

Repair of truncus arteriosus is most favorably undertaken within the first days of life[6], when incidence of pulmonary vascular hypertension is low. According to Ebert et al.[4], a valved conduit is preferable in the initial operation. They claim that since there are great swings in pulmonary artery pressure due to unstable resistances in the pulmonary vascular bed of an infant, a rapid increase in pulmonary artery pressure in a non-valved conduit will have an increased amount of pulmonary regurgitation and can cause sudden right ventricular failure. On the other hand, if the size of the pulmonary artery is near normal or normal for age, then a non-valved conduit seems rational[4].

Petz et al.[1] suggest that a conduit valve is not essential in the correction of truncus arteriosus even in the neonate. But they also say that a functional pulmonary valve is necessary if the pulmonary vascular resistance is high.

Repair using a valveless conduit for the right ventricular outflow tract is recommendable for infants without high pulmonary vascular resistance and who do not have right ventricular failure. Valveless conduits may cause pulmonary regurgitation, increasing the pulmonary resistance, and resulting in insufficient right ventricle output and immature pulmonary vasculature[11]. In our case a previous pulmonary banding had been performed to prevent this.

Delaying surgery to such time when a valveless conduit is suitable and the pulmonary vascular resistance is low is risky, as was seen in the case of our patient. Because this causes a hyperactive pulmonary vasculature before surgery, postoperative mortality is high. Patent foramen ovale should be retained in the neonatal reconstructions to aid right ventricular output.

Barbero-Marcial et al.[12] proposed an alternative technique for type I and II truncus cases, which should be noted. They used a corrective operative technique without use of an extracardiac conduit, and directly anastomosed the pulmonary arteries and the right ventricles, the anterior wall being constructed with a patch with a monocuspid valve.

Emphasis should be given to keeping the pulmonary vascular resistance minimized. Acute pulmonary artery hypertensive crises are difficult problems to encounter. Maintenance of high oxygen saturation and respiratory alkalosis, continuous sedation and paralysis, and avoidance of unnecessary tracheal suctioning help minimize pulmonary resistance.

REFERENCES

1. Peetz DJ Jr, Spicer RL, Crowley DC, Sloan H, Behrendt DM. Correction of truncus arteriosus in the neonate using a nonvalved conduit. J Thorac Cardiovasc Surg 1982; 83: 743-746.
2. Bove EL, Beekman RH, Snider AR, et al. Repair of truncus arteriosus in the neonate and young infant. Ann Thorac Surg 1989; 47: 499-506.
3. Garcia-Peláez I, Arteaga M. Experimental study of the development of the truncus arteriosus of the chick embryo heart. Anat Rec 1993; 237: 378-384.
4. Ebert PA, Turley K, Stanger P, et al. Surgical treatment of truncus arteriosus in the first 6 months of life. Ann Surg 1984; 200: 451-456.
5. Elami A, Laks H, Pearl JM. Truncal valve repair: initial experience with infants and children. Ann Thorac Surg 1994; 57: 397-402.
6. Hanley FL, Heinemann MK, Jonas RA, et al. Repair of truncus arteriosus in the neonate. J Thorac Cardiovasc Surg 1993; 105: 1047-1056.
7. Pearl JM, Laks H, Drinkwater DC Jr, Loo DK, George BL, Williams RG. Repair of conotruncal abnormalities with the use of the valved conduit: improved early and midterm results with the cryopreserved homograft. J Am Coll Cardiol 1992; 20: 191-196.
8. Sharma AK, Brawn WJ, Mee RB. Truncus arteriosus. Surgical approach. J Thorac Cardiovasc Surg 1985; 90: 45-49.
9. Di Donato RM, Fyfe DA, Puga PJ, et al. Fifteen-year experience with surgical repair of truncus arteriosus. J Thorac Cardiovasc Surg 1985; 89: 414-422.
10. Ziemer G, Luhmer I, Siclari P, Kallfelz HC. Truncus arteriosus type A3: complex repair with cryopreserved pulmonary homograft. Eur J Cardio-thorac Surg 1987; 1: 110-115.
11. Juaneda E, Haworth SG. Pulmonary vascular disease in children with truncus arteriosus. Am J Cardiol 1984; 54: 1314-1320.
12. Barbero-Marcial M, Riso A, Atik E, Jatene A. A technique for correction of truncus arteriosus types I and II without extracardiac conduits. J Thorac Cardiovasc Surg 1990; 99: 364-369.

Letter to the Editor

CONGENITAL TRICUSPID INSUFFICIENCY DUE TO A CLEFT IN TRICUSPID ANTERIOR LEAFLET ASSOCIATED WITH PERIMEMBRANOUS VSD*

An unusual case report

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To the Editor

Congenital tricuspid insufficiency (TI) due to a cleft in the anterior tricuspid leaflet is a rare congenital cardiac anomaly, with only 19 cases reported in the English literature[1-4]. Although most of the cases are associated with atrial septal defect or pulmonary stenosis, it can occasionally be found as an isolated anomaly. We report herein an infant who had congenital TI due to a cleft in the anterior tricuspid leaflet with perimembranous ventricular septal defect (VSD) and patent foramen ovale (PFO). We did not find any reported case with congenital TI, VSD and PFO in the literature.

A nine-month-old girl was hospitalized with the diagnosis of TI and VSD. Because of severe right heart failure and pulmonary hypertension, prompt surgical correction was necessary. On physical examination she was severely cachectic with a body weight of 5300. Minimal cyanosis was noticed; she had a systolic harsh murmur in the left 3rd space. Full blown manifestation of right heart failure was present. Echocardiographic and angiographic examination showed grade 3 TI and tricuspid annular dilatation in addition to perimembranous VSD of moderate size. Echocardiographically, TI was thought to be due to abnormal chordal attachment to the edge of the defect.

Precise diagnosis was made during the operation, In addition to a perimembranous VSD, a deep cleft in the anterior tricuspid leaflet (Fig. 1) and a small patent foramen ovale (PFO) were found. The tricuspid annulus was 35 mm in diameter. There was no abnormality in the chordal attachment. Ventricular

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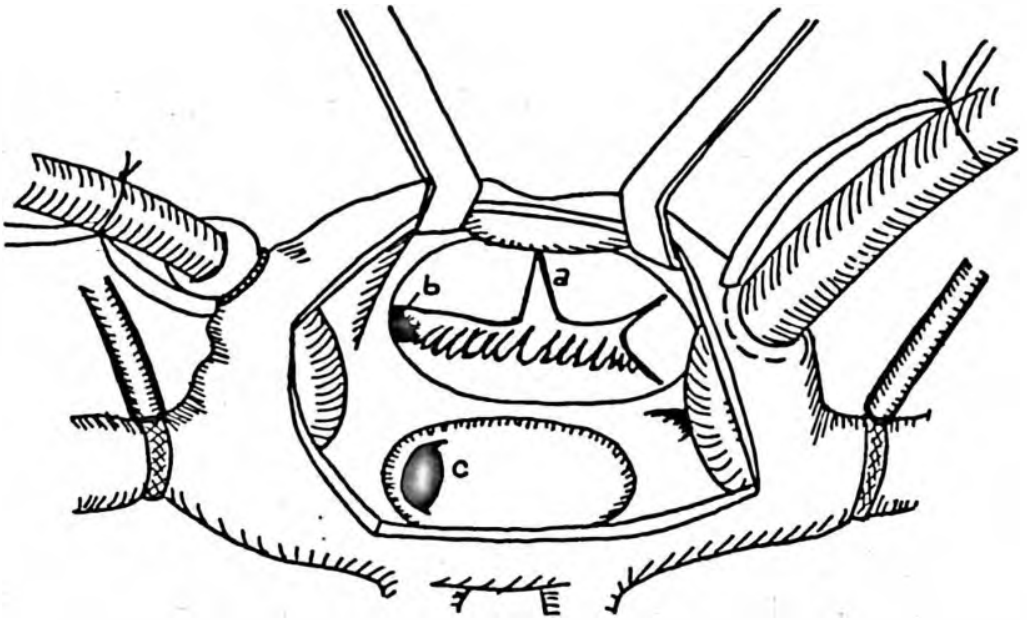

Fig. 1: Schematic drawing of the anomaly (right atrial view). a: cleft in anterior leaflet of the tricuspid valve, b: perimembranous VSD, c: small PFO.

septal defect was closed by a Dacron patch in the usual manner via right atriotomy, and the cleft was repaired by running sutures with 5/0 polypropylene. In addition, De Vega's annuloplasty was accomplished.

Postoperative course was uneventful and she was discharged on the 7th day. She had gained 4200 g and was doing well six months after the operation. On physical examination there was no right heart failure despite no diuretic therapy. Follow-up echocardiography showed a minimal insufficiency in the tricuspid valve.

There have been reports of cleft in the tricuspid valve as an isolated anomaly or in association with ASD, pulmonary stenosis, transposition of great arteries and atrioventricular connection defects. To our knowledge, this is the first reported case of congenital TI due to a cleft in the anterior leaflet of the tricuspid valve in association with perimembranous VSD and PFO.

REFERENCES

1. Eichhorn P, Ritter M, Suetsch G, von Segesser LK, Turina M, Jenni R. Congenital cleft of the anterior tricuspid leaflet with severe tricuspid regurgitation in adults. J Am Coll Cardiol 1992; 20: 1175-1179.
2. Tatabe S, Miyamura H, Watanabe H, Sugawara M, Eguchi S. Closure of isolated ventricular septal defect with detachment of the tricuspid valve. J Card Surg 1995; 10: 564-568.
3. Yokoyama S, Akimoto T, Takemura T, Haroda Y. A surgical case report of isolated congenital tricuspid insufficiency. Nippon Kyobu Geka Gakkai Zasshi 1995; 43: 1063-1068.
4. Tanji M, Iwaya F, Igari T, Ogawa T, Takahushi K, Hashimo S. A case of congenital tricuspid regurgitation associated with atrial septal defect and peripheral pulmonary stenosis. Nippon Kyobu Geka Gakkai Zasshi 1996; 44: 2146-2150.

ANNOUNCEMENTS

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KALLITHEA, HALKIDIKI, 21-25 OCTOBER 1998
VIth INTERNATIONAL CONFERENCE OF ANTICANCER RESEARCH
Inquiries to: Dr. John G. Delinassios
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HATAY, 22-24 OCTOBER 1998
XXIInd TURKISH TUBERCULOSIS AND CHEST DISEASES CONGRESS
Inquiries to: Tevfik Acar
Congress Secretariat
Verem Savaşı Derneği
Antakya
Phone : (0326) 215 23 26 or 214 35 44
Fax : (0326) 216 41 71

MERSİN, 25-28 OCTOBER 1998
IXth NATIONAL NEONATOLOGY CONGRESS
Inquiries to: Nejat Narlı, MD
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e-mail : nnarli@pamuk.cc.cu.edu.tr
web site : http://lokman.cu.edu.tr/neonatoloji

ANTALYA, 4-7 NOVEMBER 1998
VIth BALKAN PEDIATRIC CARDIOLOGY AND CARDIAC SURGERY CONGRESS
Inquiries to: Rana Olguntürk, MD
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e-mail : pedcar@behct.tip gazi.edu tr

CHA - AM, PETCHABURI 15-18 NOVEMBER 1998
III[rd] ASIA-PACIFIC REGIONAL MEETING OF THE INTERNATIONAL SOCIETY FOR NEONATAL SCREEN
NEONATAL SCREENING IN THE 21[st] CENTURY

Inquiries to: The Congress Secretariat
3[rd] APRM of the ISNS
c/o Department of Obstetrics & Gynecology
Faculty of Medicine, Ramathibodi Hospital
Rama 6 Road, Phayathai, Bangkok 10400
THAILAND
Phone : (662) 245 5828, 201 1416, 201 1412
Fax : (662) 201 1416, 246 0233

BEIRUT, 15-17 APRIL 1999
XXV[th] CONGRESS OF THE UNION OF MIDDLE EASTERN AND MEDITERRANEAN PEDIATRIC SOCIETIES AND
2[nd] CONGRESS OF THE LEBANESE PEDIATRIC SOCIETY

Inquiries to: Ghassan Issa, MD
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e-mail : GHISSA@cyberia.net.lb

İZMİR, 24-28 APRIL 1999
XIII[th] NATIONAL CANCER CONGRESS

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Fax : (0312) 467 71 78
e-mail : serena@serenatur.com.tr

İSTANBUL, 26-29 MAY 1999
JOINT MEETING OF EUROPEAN RESPIRATORY SOCIETY PEDIATRIC ASSEMBLY AND EUROPEAN SOCIETY OF PEDIATRIC ALLERGY AND CLINICAL IMMUNOLOGY

Inquiries to: Congress Bureau
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Cumhuriyet Caddesi, No: 269/2
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TURKEY
Phone : +90 212 241 65 14
Fax : +90 212 230 64 25
e-mail : ers.espaci@viptourism.com.tr
web site : http://www.viptourism.com.tr

STOCKHOLM, 13-16 JUNE 1999
IV[th] MEETING OF THE INTERNATIONAL SOCIETY FOR NEONATAL SCREENING

Inquiries to: ISNS 1999
c/o Stockholm Convention Bureau
Box 6911, S-102 39
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SWEDEN
Phone : +46 8 736 15 00
Fax : +46 8 34 84 41
e-mail : isns@stocon.se
web site : http //www.stocon.se/isns

GENOVA, 7-10 SEPTEMBER 1999
SOCIETY FOR THE STUDY OF INBORN ERRORS OF METABOLISM (SSIEM)
XXXVIIth ANNUAL SYMPOSIUM

Inquiries to: Top Congress
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Fax : +39 010 5322858
e-mail : aristea@aristea.com

ANTALYA, 14-16 OCTOBER 1999
WORLD MUSCLE SOCIETY
IVth INTERNATIONAL CONGRESS

Inquiries to: Congress Secretariat
Bakhus Travel & Tours
Tunali Hilmi Caddesi, 114/31
06700 Kavaklidere
Ankara
TURKEY
Phone : +90-(312)-466 15 00
Fax : +90-(312)-466 15 25 or 466 12 85
e-mail : bakhus@tr-net.net.tr

MANILA, 2-6 NOVEMBER, 1999
IInd WORLD CONGRESS OF PEDIATRIC INFECTIOUS DISEASES

Inquiries to: World Society of Pediatric Infectious Diseases
P.O. Box 101-53, Post code 04530
Mexico City
MEXICO
Phone and fax : (5) 606 68 56
e-mail : 74751, 1161170@Compuserve.com

TAIPEI, 26-30 MARCH 2000
Xth ASIAN CONGRESS OF PEDIATRICS

Inquiries to: Xth ACP Secretariat
6F, 400, Kee Lung Rd., Sec. 1
Taipei 110
TAIWAN
Phone : 886-2-2722-1227
Fax : 886-2-2723-4187
e-mail : pcogis@ms14.hinet.net
web site : http://www.pcogis.com.tw

STOCKHOLM, 4-8 JUNE 2000
XIIIth INTERNATIONAL CYSTIC FIBROSIS CONGRESS

Inquiries to: Congress Secretariat
Stockholm Convention Bureau
XIIIth International Cystic Fibrosis Congress
P.O. Box 6911, SE-102 39
Stockholm
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