Progressive encephalopathy with edema, hypsarrhythmia, and optic atrophy (PEHO Syndrome) in a Turkish child

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We report a Turkish boy with PEHO syndrome (progressive encephalopathy with edema, hypsarrhythmia, and optic atrophy). He had generalized hypotonia and abnormal eye movements during early infancy. Infantile spasms were seen in the second year of life. Arrest of psychomotor development and blindness were noticed early in childhood. Serial magnetic resonance imaging revealed progressive infratentorial atrophy with association of cortical atrophy and corpus callosum hypoplasia. This is an additional case of PEHO syndrome, to our knowledge the first such case from Turkey.

Key words: PEHO syndrome, infantile spasm, optic atrophy, brainstem atrophy.

PEHO syndrome (progressive encepalopathy with edema, hypsarrhythmia, and optic atrophy) is a newly determined autosomal recessive disorder[1]. The clinical findings are infantile spasms with hypsarrhythmia, severe hypotonia, optic atrophy and early arrest of psychomotor development. Microcephaly and progressive cerebral and cerebellar atrophy are prominent features. PEHO syndrome was first presented in Finnish families[1-5]. and then a few patients were reported from non-Finnish populations[6,7]. We present here an additional case of PEHO syndrome, to our knowledge the first such case Turkey.

Case Report

A.T., a two-year-old boy, was referred for infantile spasms. He was the first child of healthy parents of Turkish descent who were cousins. He was delivered at 40 weeks of gestational age following an uneventful pregnancy.

Birth weight was 2750 g (10^{th} percentile) and head circumference was 35 cm (50^{th} percentile). He had generalized hypotonia with abnormal eye movements at one month of age. Bilateral narrow pupils were seen at the second month of age, and pupilloplasty operations were performed in the 2^{nd} and 4^{th} months of life.

Physical findings (at two years of age): Weight, height and head circumference were 9.5 kg ($<3^{rd}$ percentile) 78 cm, ($<3^{rd}$ percentile) and 43 cm (2^{nd} percentile), respectively. There was no progress of motor skills. He was hypotonic and did not have head control. Patellar reflexes were birsk. Bilateral optic atrophy was seen in the funduscopic examination. Epicanthal folds, midfacial hypoplasia (Fig. 1), high-arched palate, gingival hypertrophy and finger tapering were noted.

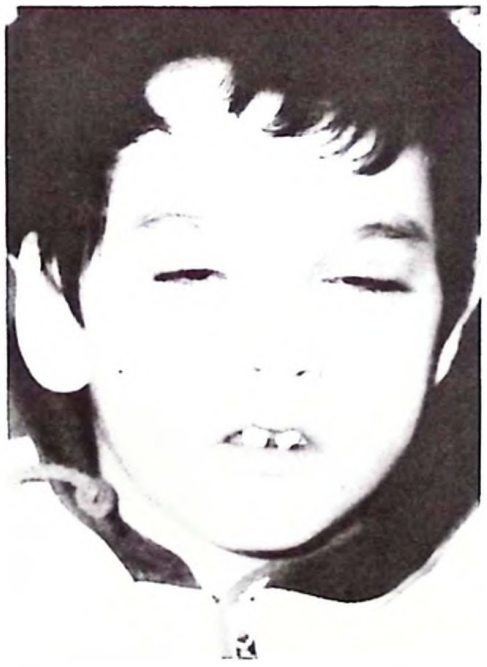


Fig. 1. Dysmorphic facial appearance (epicanthal folds, midfacial hypoplasia) of patient at five years of age.

Routine laboratory investigations of blood and cerebrospinal fluid, and extensive search for other metabolic, infectious or liver disease gave normal results (blood and urine amino acid chromatography; cerebrospinal fluid cell count, glucose and protein; urine organic acids; plasma lactate and pyruvate; ammonia levels; serum biotinidase activity; thyroid hormones; complement factors; and antibodies to cytomegalovirus and toxoplasmosis).

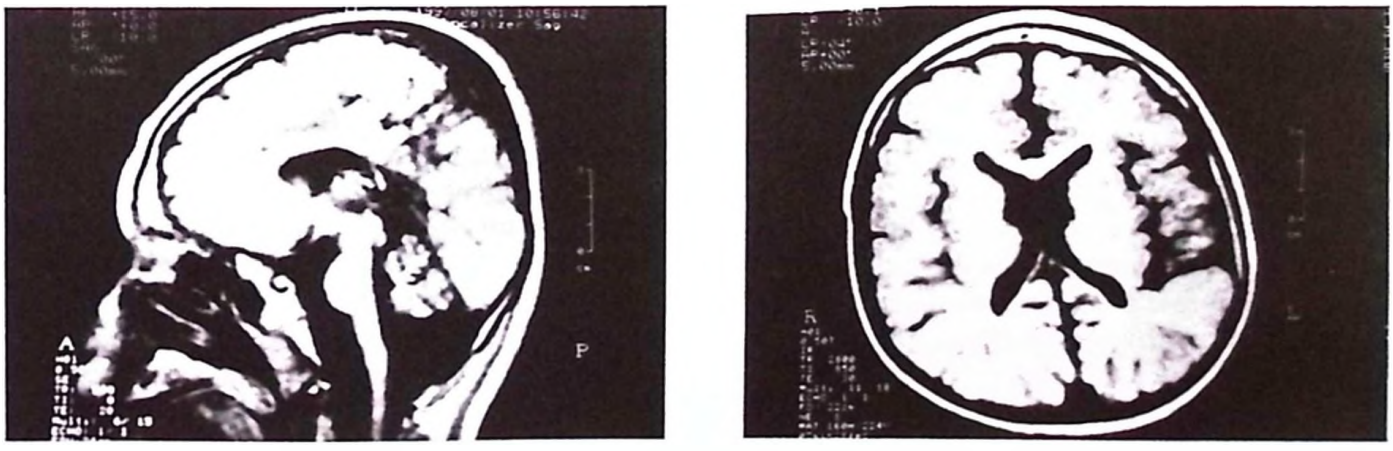
Serial EEG recordings first revealed hypsarrhythmia and then a slowing in background activity and generalized multiple slow spike-wave discharges. Cranial magnetic resonance (MR) images at two, four and six years of age revealed progressive atrophy of cerebellar vermis, slight progressive atrophy of the brainstem, diffuse corpus callosum hypoplasia, and cortical atrophy (Figs. 2a, 2b). Visual evoked potentials (VEP) were measured at five years of age with prolonged latency and abnormal wave configurations. Nerve conduction velocity (NCV) was within the normal range on the first examination done at three years of age. One year later, NICVs were compatible with polyneuropathy. Ulnar motor conduction velocity was reduced (29 m/s) and distal latency of median and ulnar nerves was prolonged. Motor conduction velocities at the lower extremities were not obtained, whereas sural nerve sensory conduction velocity was normal.

of age and ACTH treatment was repeated. After the second ACTH therapy, the patient became seizure free. At six years of age the patient had severe motor and mental retardation, hypotonia, visual failure and flexion contractures on wrists and ankles.

Discussion

In 1991, PEHO syndrome was defined by a rather nonspecific symptom complex characterized by progressive encephalopathy with edema, hypsarrhythmia, optic atrophy and dysmorphic features[1]. Neuroradiological and neuropathological studies disclosed cerebellar and brainstem atrophy as a prominent feature in PEHO syndrome[3,5].

In 1993 Somer[8] reestablished the following clinical criteria for the PEHO syndrome: 1) infantile hypotonia, 2) convulsive disorder manifesting with myoclonic jerking and infantile spasms, 3) profound psychomotor retardation with severe hypotonia, 4) absence or early loss of visual fixation with atrophy of optic disks by two years of age, and 5) progressive brain atrophy in neuroimaging studies, particularly in the cerebellum and brainstem. Supportive criteria for PEHO include: facial dysmorphic features, peripheral edema, brisk tendon reflexes in early childhood, abnormal auditory brainsten response (ABR), abnormal somatosensory evoked potential, abnormal NCV in late



(a) (b)

Fig. 2. MRI at six years of age. a) Midsagittal T1-weighted MRI demonstrates progressive atrophy of cerebellum, slight progressive atrophy of brainstem and diffuse corpus callosum hypoplasia.
b) Axial T1-weighted MRI shows cortical atrophy.

Flexor spasms were transiently controlled with adrenocorticotropic hormone (ACTH), valproate and lamotrigine between two and five years of age. Myoclonic seizures reappeared at five years

childhood and dysmyelination in MR imaging. Our patient had both the necessary criteria mentioned above and some of the supportive criteria such as facial dysmorphic features, brisk

tendon reflexes and abnormal VEP and NCVs (Table I). Progressive infratentorial atrophy, which is a prerequisite feature for PEHO syndrome, was seen in our patient. Our patient also had mild cortical atrophy. He had normal head circumference at birth but then microcephaly developed. Our patient also had narrow pupils, which has not been previously described in PEHO syndrome.

Table I. Clinical Criteria for the PEHO Syndrome

	Our patient
1. Infantile hypotonia	(+)
2. Infantile spasms	(+)
3. Profound psychomotor retardation with severe hypotonia	(+)
4. Absence or early loss of visual fixation with atrophy of optic disks by two years of age	(+)
5. Progressive brain atrophy in neuroimaging studies, particularly in the cerebellum and brainstem	(+)
6. Facial dysmorphic features (epicanthal folds, midfacial hypoplasia, gingival hypertrophy	(+)
7. Peripheral edema	(-)
8. Brisk tendon reflexes in early childhood	(+)
9. Abnormal VEP	(+)
10. Abnormal ABR	(ND)
11. Abnormal SEP	(+)
12. Abnormal NCV in late childhood	(+)

VEP : visual evoked potential.
ABR : auditory brainsten response.
SEP : somatosensory evoked potential.
NCV : nerve conduction velocity.
ND : not done.

On the basis of neuroradiological findings, Somer et al.[3] divided the patients with PEHO syndrome into two groups: 1) Group A patients (the true PEHO syndrome) mainly showed cerebellar and brainstem atrophy that appeared earlier and was more severe than supratentorial atrophy and 2) Group B patients had generalized, mainly supratentorial atrophy and abnormal gyral pattern. The patients in group B were clinically indistinguishable from group A patients, but generally showed no prominent cerebellar atrophy. Our patient had progressive infratentorial atrophy and mild cortical atrophy on his serial MR studies and was dignosed as the true PEHO syndrome.

There are some known disorders to be considered in the radiological differential diagnosis of the true PEHO syndrome. Some of the nonprogressive central nervous system malformations may resemble PEHO during the first year of life[9-10]. Dandy-Walker syndrome variants show inferior vermian aplasia and cerebellar hemispheric hypoplasia, but there is no progression like that in the PEHO syndrome[9]. In Joubert's syndrome, dysgenesis of the cerebellar vermis is typical. But these patients have a different clinical course and they show retinal dystrophy instead of optic atrophy[10].

Cerebellar hypoplasia is common in a variety of progressive disorders like pontocerebellar hypoplasia (type 1 and type 2) and carbohydrate-deficient glycoprotein (CDG)[11-13]. syndrome. Anterior spinal horn degeneration and chorea/dystonia are the hallmarks for pontocerebellar hypoplasia type 1 and type 2, respectively. These were not found in our patient.

In CDG syndromes, four types have been differentiated on the basis of the isoelectrofocusing pattern of the serum sialotransferrins[13]. In type I CDG syndrome (phosphomannomutase deficiency-PMM), abnormal slow rolling vertical or horizontal eye movements combined with slow head movements, alternating internal strabismus, and axial hypotonia with hyporeflexia are seen during the first months of life. Prominent psychomotor retardation, ataxia, deafness and retinitis pigmentosa are the late findings.

In type II CDG syndrome, the patients have stereotypic behaviors (tongue thrusting and hand-washing movements, head turning, knocking on cheeks and rocking) and facial dysmorphism (high forehead, long eyelashes, prominent base of the nose, beaked nose, upturned alae nasi, protruding upper gums, receding chin, and large dysplastic ears)[13]. Our patient did not display stereotypic movements and his facial dysmorphism was not compatible with CDG syndrome. Additionally, patients with CDG syndromes often have an extroversive and cheeful personality which was not present in our patient. On the other hand, serum levels of a number of glycoproteins (thyroid hormones, complement factors) which are expected to be low, were within normal limits.

A metabolic disorder, multiple carboxylase deficiency, is characterized by ketolactic acidosis and organic aciduria. Infantile spasms either

alone or with other neurological findings such as hypotonia, optic atrophy, developmental delay, ataxia, and hearing deficit are seen in the clinical presentation[18]. Additionally, more than 70 percent of the patients typically have cutaneous signs such as skin rash and alopecia, which were not seen in our patient. His serum biotinidase activity was also within normal limits.

Some of the neurometabolic diseases like glutaric aciduria type I and methylmalonic acidemia, and Krabbe's disease have pathognomonic radiographic features[14-16]. Besides cerebellar atrophy, white matter and/or basal ganglia involvement are prominent in those disorders. Infantile Refsum's disease may also show cerebellar atrophy[17], but cerebral changes are more severe and appear earlier in this disorder.

Aicardi's syndrome is an X-linked genetic disorder to be considered in the differential diagnosis of a female PEHO patient. The syndrome is characterized by agenesis of the corpus callosum, brain heterotopias, seizure disorder, chorioretinal lacunae, vertebral anomalies, and mental retardation[19]. Although infantile spasm with typical hypsarrhythmia may be seen in Aicardi's syndrome, it is the rule in the PEHO syndrome.

Serial neuroimaging studies indicate that the disease process of PEHO is operative during the postnatal period[3]. Therefore, a progressive metabolic disorder with unknown biochemical background is proposed in the PEHO syndrome. Further metabolic and genetic investigations are needed to explain the pathogenesis of the PEHO syndrome.

The syndrome is rare and had not previously been published from the Turkish population. For the differential diagnosis of patients with infantile spasm of unknown etiology, PEHO syndrome should be considered.

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