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PEHO Syndrome (Progressive Encephalopathy with Edema, Hypsarrhythmia, and Optic Atrophy): Neuroradiologic Findings

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PURPOSE: To investigate the radiologic characteristics of the clinical progressive encephalopathy with edema, hypsarrhythmia, and optic atrophy (PEHO) symptom complex. This complex is nonspecific, but within this syndrome, a subgroup with a defined neuropathologic phenotype and apparently autosomal recessive inheritance exists. METHODS: Brain CT or MR studies were performed on 21 patients with the clinical PEHO syndrome. Their previous neuroradiologic studies were re-evaluated. RESULTS: Twelve patients (group A) showed uniform changes with early progressive brain atrophy accentuated infratentorially, and abnormal myelination. The gyral pattern was normal. Brain atrophy of nine patients (group B) differed by being less progressive, supratentorial, and often combined with abnormal gyral formation. CONCLUSIONS: Postmortem studies permitted correlation of radiographic and morphologic findings in three cases. Two autopsied group A patients were compatible with the true PEHO syndrome, while one group B patient was incompatible. Group A seems to correspond to the core group of the PEHO syndrome. During a patient's life, a suggestive diagnosis of the true PEHO syndrome is thus feasible, although neuropathologic studies are needed for a conclusive diagnosis.

Index terms: Brain, diseases; Degenerative brain disease; Brain, magnetic resonance; Brain, computed tomography; Pediatric neuroradiology

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The progressive encephalopathy with edema, hypsarrhythmia, and optic atrophy (PEHO) syndrome (1) is a clinically defined progressive encephalopathy, characterized by infantile spasms with hypsarrhythmia, profound psychomotor retardation, severe muscular hypotonia with brisk tendon reflexes, subtle dysmorphic facial features, subcutaneous nonpitting edema, and visual failure with optic atrophy. At birth, most patients are healthy or only slightly hypotonic, but all develop progressive neurologic symptoms necessitating a medical examination by 6 months of age. The occurrence of affected siblings of both sexes suggests an autosomal recessive inheritance, but no clue to the pathogenesis has been found in extensive laboratory investigations (1). We made a longitudinal study of the neuroradiologic findings of patients whose diagnoses were based on medical history and physical characteristics.

Patients and Methods

Seven of the original PEHO patients (1) were re-investigated. Eleven new patients were collected by informing neuropediatricians about the PEHO syndrome, and by actively searching for new patients in institutions for the mentally retarded. The inclusion criteria were based on the information received from the original PEHO cases (Table 1). The ages of these patients varied from 1.6 to 12.9 years.

During the study, three new patients presented with infantile spasms, extreme floppiness, and visual failure. These cases were also investigated. Their ages varied from 0.4 to 0.8 years at the time of the initial study. Two had a neuroradiologic follow-up study at the age of 2 years.

There were 21 patients, six boys and 15 girls. Three patients had siblings who had died of a similar disease.
before this study. The patients were thoroughly investigated in order to exclude other metabolic diseases.

In the present study, nine patients had a brain magnetic resonance (MR) study and 12 patients a brain computed tomography (CT) scan. The degree of brain atrophy was assessed visually. In seven patients, MR imaging was performed unenhanced on a 1.0 T imager. In these examinations, myelination could be assessed by using marker sites (2). Spin-echo (SE) T2-weighted images, 2500/22-90/1 (TR/TE/excitation) were obtained in every case, and T1-weighted axial or sagittal images, SE 500-600/15/2, in most cases. Slice thickness was 4 or 5 mm. In two patients, a 0.02 T MR imager was used, with a slice thickness of 10 mm. In the axial SE T2-weighted study, 2000/250/4 was supplemented with either sagittal T1-weighted SE 500/40/16 or T2-weighted SE 2000/250/4 images.

Brain CT scanning was performed using a slice thickness of 4 to 5 mm infratentorially and of 8 to 10 mm supratentorially. The matrix size was 256 × 256. No contrast enhancement was used.

All previous neuroradiologic studies of the patients were obtained from local hospitals and re-evaluated. In one case, only a written report of a previous study was available. The initial CT scan of three patients dated from the first month of life, but in most cases, the first study had been made at age 3 to 6 months. Two patients had been studied by a pneumoencephalography in infancy. There was at least one previous neuroimaging study of all patients except one. Five patients had two, and two patients had three previous neuroimaging studies.

Results

On the basis of neuroradiologic findings, the patients could be divided into two groups: group A (12 patients) and group B (nine patients). Each of the three patients who had a similarly affected sibling belonged to group A.

Group A: Generalized, Mainly Infratentorial Atrophy

The initial CT scan or pneumoencephalography study was normal in four patients (ages 3 days and 0.4, 0.5, and 0.6 years). Eight patients (age 0.1–1.2 years) had mild or moderate cerebellar or brain stem atrophy in the first study, and an axial CT scan showed a connection between the fourth ventricle and an enlarged cisterna magna. Cerebellar atrophy appeared to originate in the inferior vermis. It was present in all studied patients by the end of the first year,

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**TABLE 1: Inclusion criteria of the patients**

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<th>Feature</th>
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<td>A. Features present in all patients except marked:</td>
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<tr>
<td>Seizure onset at 2–52 weeks of life*</td>
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<tr>
<td>Infantile spasms and/or hypsarrhythmia*</td>
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<td>Early arrest of mental development</td>
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<td>Profound hypotonia with no head support or ability to sit unsupported</td>
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<td>Poor/absent visual fixation from the first months of life</td>
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<td>B. Additional features, present in most patients</td>
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<td>Subcutaneous peripheral and facial edema</td>
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<tr>
<td>Microcephaly developing by 12 months of age</td>
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<tr>
<td>Dysmorphic features (epicanthi, midfacial hypoplasia, protruding lower parts of auricles, receding chin, tapering fingers)</td>
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<tr>
<td>Pale optic discs</td>
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*Case 21 had generalized seizures from birth.

**Hypsarrhythmia** is the characteristic electroencephalogram finding seen in the majority of cases with infantile spasms.
and it became moderate to severe by the age of 3 years. Supratentorial changes were milder, and emerged later than those infratentorial. There were no structural abnormalities, only a hypoplastic corpus callosum in one patient, and the gyral pattern appeared normal. No cortical heterotopias, mesial temporal sclerosis, porencephalic cysts, or calcifications were seen, and the basal ganglia appeared normal.

As the children grew older, there was a pro-
progression of both infra- and supratentorial atrophy (Figs. 1-4). The cerebellar hemispheres and the vermis became extremely atrophic and the brain stem appeared narrow (Figs. 3C, 3D, and 4C). Supratentorially, the cortical atrophy was accentuated in the frontal and temporal areas, and the interhemispheric fissures were wide (Fig. 4D). The lateral ventricles, especially the occipital horns, became enlarged, but there were no signs of increased intracranial pressure. MR imaging in four patients (age 0.8–7.6 years) showed abnormal high signal intensity of the white matter dorsal and superior to the ventricular trigones, around the anterior horns and in centrum semiovale (Fig. 5).

**Group B: Generalized, Mainly Supratentorial Atrophy**

Cerebral atrophy associated with a less severe cerebellar atrophy with a later onset and less progressive course was characteristic of patients in group B. Even the supratentorial atrophy tended to be milder than in group A. The myelination appeared normal in each of the three cases that could be evaluated for that feature, whereas
the gyral pattern was abnormally coarse in five patients (Fig. 6). One of these cases showed remarkably enlarged ventricles with very little brain parenchyma already in infancy, and the finding was essentially the same at 12 years of age. Another patient demonstrated atrophy of the right hemisphere (Fig. 6C), first registered at one month of age, and probably due to an intrauterine insult. On the other hand, the neuroimaging studies of four patients were either normal or showed only mild supratentorial atrophy.

Discussion

The PEHO syndrome is defined by a rather nonspecific symptom complex, seen in several disorders with very different pathologic manifestations. However, within this clinically defined syndrome, there is a subgroup of patients with an apparent autosomal recessive etiology and characteristic neuropathologic features. In this study, the group A patients showed cerebellar and brain stem atrophy that appeared earlier and
Fig. 5. Abnormal high signal intensity of white matter in two group A patients of different ages, suggesting demyelination or dysmyelination. Axial T2-weighted MR images (SE 2500/90).
A, Age 3.9 years. Abnormal high signal intensity for this age is seen in centrum semiovale.
B, Age 7.6 years. Abnormal confluent high signal intensity areas are seen in white matter around anterior and posterior horns.

Fig. 6. Radiologic abnormalities of three patients from group B, not considered to have the true PEHO syndrome.
A, Age 19 months. Axial CT scan shows the presence of only a few flat gyri and grossly enlarged lateral ventricles.
B, Age 2.7 years. Axial T1-weighted MR image (SE 600/15) shows coarse gyral formation in the frontal and temporal lobes, and cortical and central atrophy.
C, Age 11.9 years. Axial CT scan shows abnormal gyral formation of the right hemisphere and reduced white matter especially around the right occipital horn. The right lateral ventricle is enlarged and the right frontal lobe shows cortical atrophy.

was more severe than supratentorial atrophy. The patients in group B were clinically indistinguishable from group A patients, but generally showed no cerebellar atrophy; if infratentorial atrophy existed, the supratentorial changes were always more severe. The range of severity and character of the radiographic abnormalities in group B was wide. In several cases, they were virtually non-