THE CHILD
A JOURNAL OF PEDIATRICS
OPEN ACCESS
Vol 1 - No. 1 - february 2013 Bi-monthly Journal of Pediatrics - ISSN 2240-791X

Progressive encephalopathy, with oedema, hypsarrhythmia, and optic atrophy (PEHO syndrome): report of the first italian cases

Salpietro V[1], Gitto E[1], Romeo AC[2], Manti S[1], Granata F[3], Cilona S[3], De Vivo D[1], Valenti S[1], Fede C[1], Polizzi A[4], Briuglia S[1], Mankad K[5], Ruggieri M[6]

[1] Department of Pediatrics, University of Messina
[2] Department of Surgical Specialities, Ophthalmology Clinic, University of Messina
[3]Department of Radiology, University of Messina [4]Institute of Neurological Sciences, National Research Council, Catania
[5]Great Ormond Street Children's Hospital, London [6]Department of Educational Sciences, University of Catania

Abstract

PEHO syndrome is a rare progressive infantile encephalopathy with onset within the first few months of life.

Few patients fulfilling the diagnostic criteria for PEHO syndrome have been reported outside Finland. Affected infants have facial dysmorphism and suffer from severe hypotonia, profound mental retardation, convulsions (often with a hypsarrhythmic EEG pattern), transient or persistent peripheral oedema and optic atrophy. Cerebellar and brainstem atrophy are usually present on neuroimaging. Pathogenesis is unclear.

Although an autosomal recessive inheritance is suspected, no chromosomal abnormalities, candidate causative genes or biochemical abnormalities have yet been identified. In the present report we describe the clinical, ophthalmological and radiological features of two italian siblings (1 boy and 1 decesead girl), diagnosed as PEHO syndrome.

Our cases could be regarded as the first description of this rare neurodegenerative disorder in Italy.

Further molecular investigations of this family (exome sequencing) are in process and could lead in a near future to identify the causative gene of this devastating syndrome.

Backgrund

In 1991, Salonen [1] described this syndrome in 14 Finnish patients. In the 1990s, Somer collected 53 patients with suspected PEHO syndrome from Finland but discarded half because they did not fulfill the uniform characteristics for the syndrome. It was she who determined the strict criteria for the delineation of the syndrome. The final clinical series comprised 21 patients.

Seven patients were available from the original study by Salonen et al. [1] and 14 additional patients were found later. Nineteen patients were studied also by neuradiological and/or neuropathological methods. Altogether, there have been 14 sibships with 19 PEHO patients. Five of these families (including 11 siblings) had earlier been described by Riikonen when publishing data of families with infantile spasms in siblings [2]. The other half of Somer's patients were called PEHO-like patients.

PEHO-like patients had a clinically similar disorder, but they had neither the cerebellar atrophy nor the optic atrophy. Clinical features alone are not sufficient for diagnosing the PEHO syndrome. The PEHO syndrome seems to be over represented in Finland. The minimum incidence was estimated to be 1:74 000 [3]. There are also reports from other countries [4–7] but never from Italy.

Clinical, Ophthalmological and Radiological Features

The PEHO syndrome is a progressive encephalopathy with edema, hypsarrhythmia, and optic atrophy. It is a severe progressive encephalopathy with onset in early infancy. The distinct clinical criteria for the PEHO syndrome are the following: (a) Infantile, usually neonatal, hypotonia; (b) Convulsions, seizure onset at 2–52 weeks of life: myoclonic jerking and infantile spasms and/or hypsarrhythmia; (c) Early arrest of mental development: absence of motor milestones (no head support or ability to sit unsupported), no speech, and later profound psychomotor retardation; (c) Poor or absent visual fixation from the first months of life with atrophy of the optic disks by 2 years of age, normal electroretinogram, extinguished visual evoked potentials; (d) Progressive brain atrophy, as shown by computed tomography (CT) or magnetic resonance imaging (MRI), particularly of the cerebellum and brain stem, milder supratentorial atrophy. Additional features present in most patients included (e) subcutaneous peripherial and facial edema; (f) microcephaly developing at 12 months; (g) dysmorphic features consisting in: narrow forehead, epicanthal folds, short nose, open mouth, small chin, midfacial hypoplasia, protruding lower parts of auricles, and tapering fingers [1-8]

Patient **Presentation**

C.S. was born by normal vaginal delivery at 38 weeks of gestation. All his growth parameters were between 50° and 75° percentile. In the neonatal period he presented generalized hypotonia. He had feeding difficulties in the newborn period and developed intractable clonic seizures by 3 months of age. There were marked truncal hypotonia, limb hypertonicity, clonus and hyperreflexia by the age of 6 months. Since the first months of life the baby presented profound psychomotor retardation with absence of motor milestones and speech. Visual inattention with poor visual responsiveness was also noted in the firs months of life and at 6 month of age optic discs were slightly pale. By 7 months of age were evident delayed visual evoked potentials and delayed brainstem potentials.
An electroencephalogram (EEG) showed hypsarrhythmia by 3 months of age. Tonic seizures devoloped by 10 months of age and multifocal clonic seizures continued. Dysmorphic features included an opened mouth appearance, bitemporal narrowing, pear shaped face, oedema of face and limbs (Figure 1 and 2). MRI performed at 6 months of age was referted as normal with only a mild dysmielination, at 16 months was evidence of diffuse atrophy of supratentorial and infratentorial structures (Figure 3 A-B).

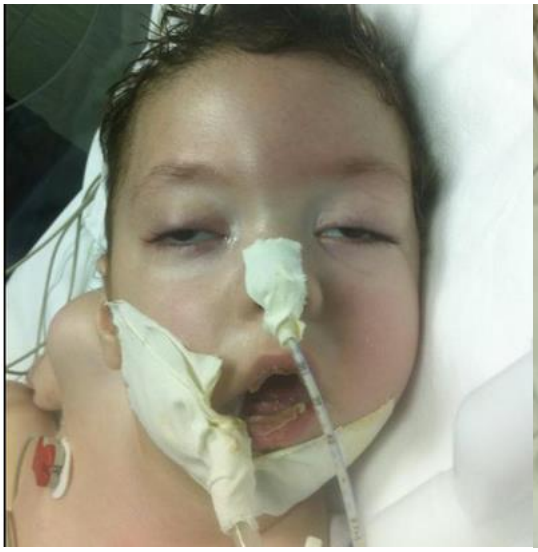

Fig. 1 *Opened mouth appearance, bitemporal narrowing, pear shaped face*

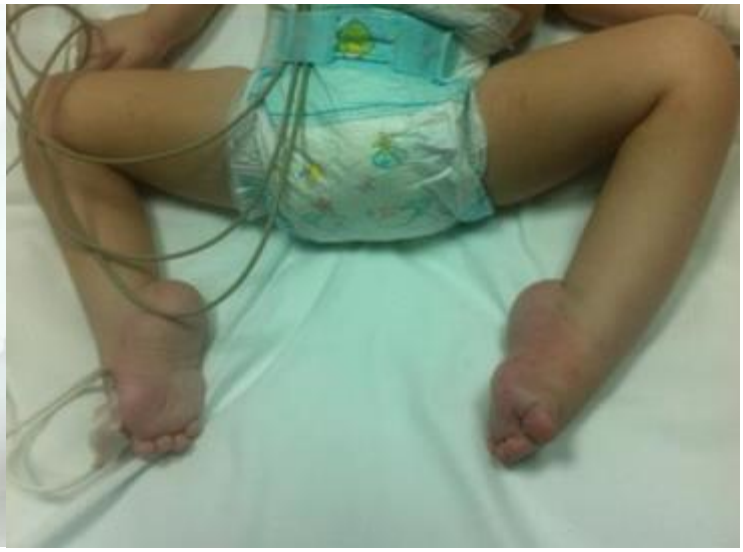

Fig.2 *Limbs and feet oedema*

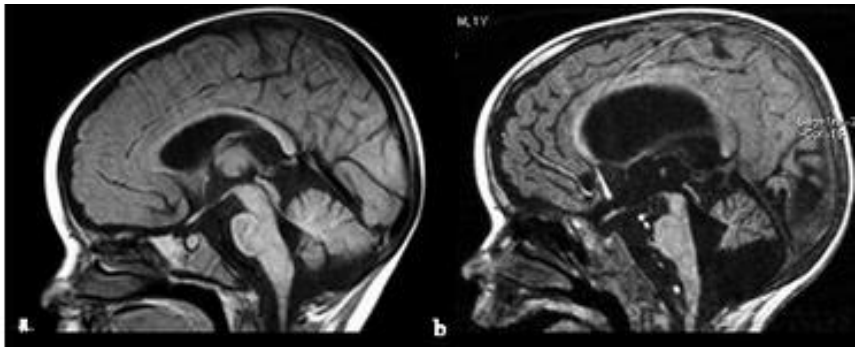

Fig.3 *Sagittal T1-weighted images performed at six-months age (a) and sixteen-months age (b) Supratentorial and infratentorial atrophy is well depicted*

The following investigations in Carmelo were normal: full blood count (FBC), liver function tests (LFTs), plasma urea, electrolyte, creatinine levels, creatinine kinase (CK), urine amino and organic acids, phytanic acid, 7-dehydrocholesterol (7-DHC), white cell lysosomal enzymes, whole blood and cerebrospinal fluid (CSF) lactate and pyruvate levels. CSF cells, protein and glucose retrivied no results. Blood lymphocyte chromosome analysis (karyotype) and serum transferrin isoform pattern were both normal. CGH array and skin biopsy for fibroblasts colture were negative. There was a mild elevation of serum very long chain fatty acids (VLCFAs), likely related to his diet or endogenous synthesis. Muscle and skin biopsies were performed and no abnormalities were seen on light or electron microscopy. Electromyogram (EMG), and nerve conduction velocity (NCV) showed a peripheral neuropathy. There was no optic atrophy at 20 months of age at ophtalmological examination (the sister developed optic nerve atrophy at 3 years of age).

Clinical features, EEG, neuroradiological pattern and laboratory results of the sister (Figure 4), were overlapping the above reported case (also in the natural history of the disease) exception for the presence of optic nerve atrophy at 3 years of age. She died at 8 years age. No other probands have been never referred in this family (Figure 5).

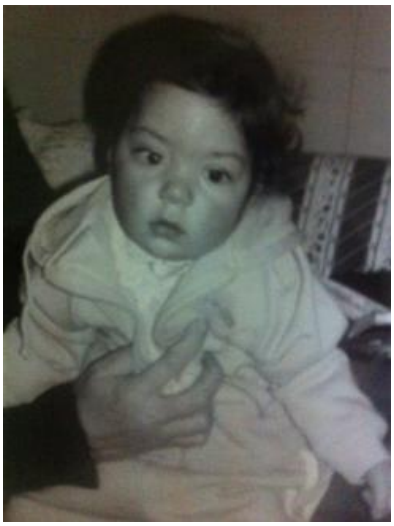

Fig. 4 *Sister at 9 months already presented profound psychomotor retardation with absence of motor milestones and speech. At that time visual inattention with poor visual responsiveness were also noted.*

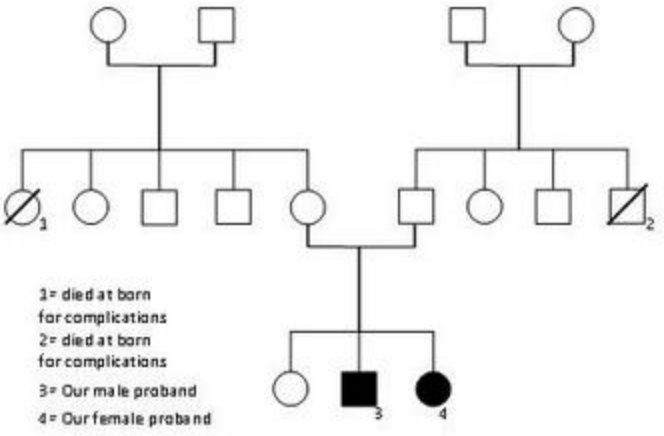

Fig.5 *Family Tree*

Discussion

These italian siblings were affected by an unvarying disorder which is most likely to be due to an autosomal recessive gene defect. The condition has the clinical, visual, neurodevelopmental, neuroradiological and electrodiagnostic features of PEHO syndrome. The occurrence of affected siblings of both sexes suggests an autosomal recessive inheritance for this rare neurodegenerative disorder [3]. Clinical criteria need to be applied, because no chromosomal abnormalities or biochemical markers have yet been recognized. Strict diagnostic guidelines should require the presence of characteristic, progressive clinical and neuroradiologic findings, to avoid misdiagnoses and incorrect genetic counseling. Moreover, patients with PEHO-like syndrome should not be considered as having PEHO syndrome because those patients are heterogeneous and do not exhibit a common underlying etiology [6, 9-10]. An ethnic background other than Finnish may be observed in patients with PEHO syndrome more often than previously thought [5, 11-12]. Our cases could be regarded as the first description of this rare neurodegenerative disorder in italian patients. Further molecular investigations of this family by exome sequencing are in process and could lead in a near future to identify the causative gene of this devastating syndrome. Moreover, this syndrome probably occurs more frequently than suspected in the past, and we emphasize that this entity should be considered in patients with progressive encephalopathy with neonatal hypotonia, epileptic spasms associated with hypsarrhythmia, typical dysmorphic features, and progressive cerebellar and brainstem atrophy in the absence of chromosomal and biochemical abnormalities. Conventional neuroradiologic studies, and especially MRI, are fundamental for demonstrating the progressive cerebellum and brainstem atrophy. Early diagnosis is important, to offer correct genetic counseling.

References

[1] Salonen R, Somer M, Haltia M, Lorentz M, Norio R. Progressive encephalopathy with edema, hypsarrhythmia, and optic atrophy (PEHO) syndrome. Clin Genet 1991;39:287–293.
[2] Riikonen R. Infantile spasms in siblings. J Pediatr Neurosci 1987;3:235–244.
[3] Somer M. Diagnostic criteria and genetics of the PEHO syndrome. J Med Genet 1993;30:932–936.
[4] Fujimoto S, Yokochi K, Nakano M, Wada Y. Progressive encephalopathy with edema, hypsarrhythmia, and optic atrophy (PEHO syndrome) in two Japanese siblings. Neuropediatrics 1994;26:270–272.
[5] Shevell M, Colangelo P, Treacy E, Polomeno R, Rosenblatt B. Progressive encephalopathy with edema, hypsarrythmia, and optic atrophy. Pediatr Neurol 1996;15:337–339.
[6] Chitty L, Robb S, Berry C, Silver D, Baraitser M. PEHO or PEHOlike syndrome? Clin Dysmorphol 1996;5:143–152.
[7] Korkepek R, Katalin H, Katalin K. PEHO syndroma (progressiziv encephalopathia, oedema, hypsarrhythmia, opticus atrophia). Orvosi Hetilap 1997;138:425–428.
[8] Riikonen R. The PEHO syndrome. Brain Dev. 2001 Nov;23 (7):765-9. Review.
[9] FieldMJ, Grattan-Smith P, Piper SM, et al. PEHO and PEHO-like syndromes: Report of five Australian cases. Am J Genet 2003;122A:6-12.
[10] Arrigo S, Bruzzone M, Faravelli F, Riva D. Progressive encephalopathy with edema, hypsarrhythmia, and optic nerve atrophy (PEHO)-like syndrome: Diagnostic characteristics are defining? J Child Neurol 2005;20:454-6.
[11] Klein A, Schmitt B, Boltshauser E. Progressive encephalopathy with edema, hypsarrhythmia and optic atrophy (PEHO) syndrome in a Swiss child. Eur J Paediatr Neurol 2004;8:317-21.
[12]Caraballo RH, Pozo AN, Gomez M, Semprino M. PEHO syndrome: a study of five Argentinian patients. Pediatr Neurol. 2011 Apr;44 (4):259-64.

www.thechild.it Four-monthly Journal of Pediatrics edited by Genetics and Pediatric Association (APIG)
The Child, a journal of pediatrics - Law March 7th, 2001, n. 62 - Press Register Court of Messina n. 4/2012
Director manager: Giuseppe Micali - Scientific manager: Giorgio Ciprandi - Editor in chief: Carmelo Salpietro
Secretariat writing: Basilia Piraino - Piera Vicchio - Italia Loddo
Editorial staff from Genetics and Pediatric Unit - University of Messina