May PEHO Syndrome be a Clinical Entity Associated with Early Onset Encephalopathies?

Sir,

Progressive encephalopathy with edema, hypsarrhythmia and optic atrophy (PEHO) syndrome is a rare neurodegenerative condition. The cardinal and supportive features for PEHO syndrome have been described. Infantile hypotonia, seizure disorder, profound delay in motor and intellectual development profound developmental delay, abnormality of visual fixation, optic atrophy by the age of 2 years, and progressive brain atrophy are the cardinal clinical features of PEHO syndrome. The supportive criteria of PEHO syndrome include microcephaly at birth hypotonia, dysmorphic features with narrow forehead, epicanthic folds, short nose, open mouth, receding chin, tapering fingers and oedema of the face and limbs.[1] PEHO-like syndrome patients who look similar to infants with PEHO syndrome, but who may have milder clinical features without neuroradiologic and/or ophthalmologic signs has been identified.[2]

Our patient is a 18-month-old boy was followed due to intractable epilepsy and developmental delay. He was born by normal vaginal delivery at 38 weeks of gestation with normal antenatal period. He was the first child of consanguineous parents. He was hospitalized in a neonatal intensive care unit because of respiratory distress, poor feeding and decreased activity on the first day after his birth. In the second day of life, he had a seizure which was interrupted by phenobarbital. From age of one month, progressive seizures were observed. He also became lethargic with generalized muscular hypotonia, poor feeding and developmental delay.

Complete blood count, serum electrolytes and liver function test were normal. Blood lactate, ammonia, serum amino acids, tandem mass spectrometry, urinary organic acids and cerebrospinal fluid analysis were normal. Karyotype was also normal. At the age of 18 months, his weight and head circumference was 15 kg (97 percentile) and 44.8 cm (3 percentile), respectively. His neurological examination revealed severe development delay, truncal hypotonia, microcephaly, and brisk tendon reflexes. He was not able to follow objects. At 6 months, fundoscopy was normal. At 18 months of age, the ophthalmological evaluation revealed bilateral optic nerve pallor. He was feeding with nasogastric feeding tubes. Dysmorphic features included narrow forehead and short nose. There was prominent edema in the face and limbs [Figure 1]. He had multiple seizure types, including myoclonic seizures, limb spasm and tonic seizures. Multiple antiepileptic medications were tried with poor control, including phenobarbital, sodium valporoate, levertiracetam, clobazam, vigabatrin, and topiramate. At the age of four months, an electroencephalogram revealed hypsarrhythmia. He was treated with adrenocorticotrophic hormone (ACTH). After ACTH use for 4 times, seizures were nearly controlled,

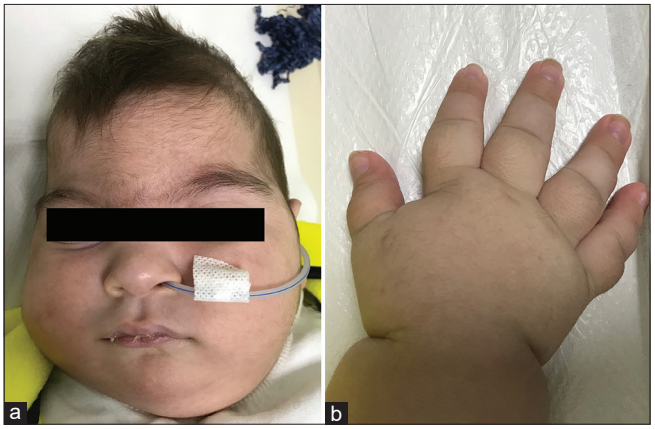

Figure 1: (a) Dysmorphic features included narrow forehead and short nose, (b) prominent edema in the hand

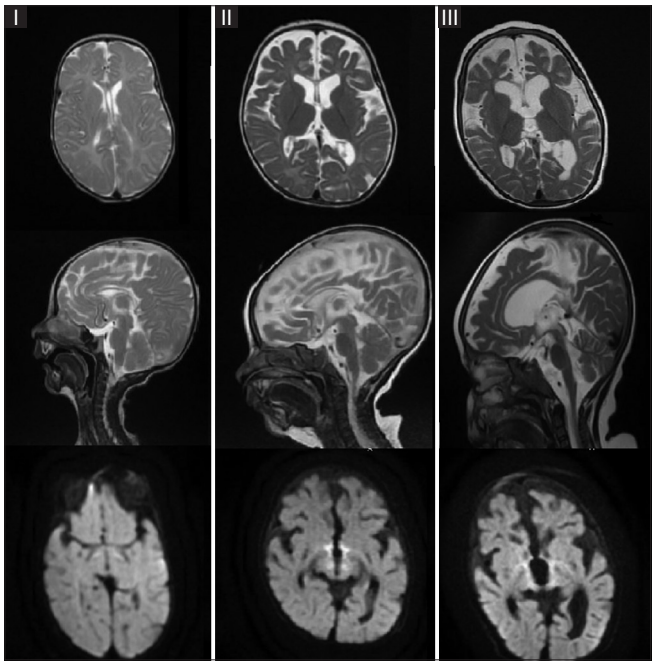

Figure 2: Serial T2-FSE and isotropic DWI images at 2 months (I), at 5 months (II), and 16 months (III). Initial MR imaging showed a thinned corpus callosum with no diffusion abnormality. Follow-up MR imaging showed a cerebral atrophy. The occipital cortex, basal ganglia and cerebellum appear spared. Bilaterally significant restricted diffusion was seen in the medial inferior thalami and extending into the central tegmental tracts. Final MR imaging showed a marked cerebral atrophy, mild cerebellar and brainstem atrophy and diffusion abnormalities remains

but it was interrupted due to infection. Initial cranial MRI at age 2 months showed a thinned corpus callosum with no diffusion abnormality. Follow-up MRI at 5 months showed a cerebral atrophy. Final MRI at 16 months showed a marked cerebral atrophy, mild cerebellar and brainstem atrophy [Figure 2]. The patient was clinically diagnosed with PEHO syndrome. Clinical exome sequencing and Sanger sequencing were done. Next generation sequencing showed a heterozygous missense variation, *c.4022T > C, p.Leu1341Pro*, in *SCN2A* (NM_001040142) gene. This condition showed that the mutation was de novo in the *SCN2A* gene.

In our patient, hypotonia beginning in the newborn period, myoclonic seizure and infantile spasm refractory to multiple antiepileptic drugs, hypsarrhythmia, loss of of visual fixation, microcephaly, progressive cerebral atrophy, dysmorphic features and oedema of the face and limbs has been seen He was clinically diagnosed with PEHO syndrome. Our patient's fundoscopy was normal at 6 months of age, and bilateral optic nerve pallor were detected at 18 months of age. Huisman *et al*. reported a case whom optic disk became pale at 18 months of age and optic nerve atrophy was seen at 30 months. Our patient's fundoscopic examination follow-up was planned. Cerebellar and brainstem atrophy, progressive cerebral atrophy was detected in our patient. Bilaterally significant restricted diffusion was seen in the medial inferior thalami and extending into the central tegmental tracts. It was suggested that the absence of cerebellar atrophy in some children may represent early timing of investigations.[3]

Chitre and *et al*.[4] concluded that PEHO and PEHO-like syndrome are clinically and genetically diverse entities and questioned whether the diagnostic criteria for MRI and ophthalmic findings should be altered. In addition to cerebral and cerebellar atrophy, abnormal neuronal migration, abnormal myelination and abnormal signal intensity of the cerebral white matter was demonstrated.[4] The diagnosis of PEHO and PEHO-like syndrome depends on the presence of the clinical and radiologic findings. PEHO syndrome was thought to be inherited as an autosomal recessive trait.[5] It has been demonstrated different inheritance patterns of their PEHO/PEHO-like syndrome including autosomal recessive, dominant and X linked dominant.[4] The different genes including ZNHIT3, CDKL5, CCDC88A, PRUNE1, TBCD, KIF1A, PCLO, PLAA, UBA5, CASK, CCDC88A, SCN1A reported in association with a PEHO/PEHO-like phenotype,[4-6] along with mutations in GNAO1 associated with early-onset epileptic encephalopathy type 17 (EIEE17), have been reported to show significant clinical overlap with PEHO syndrome. It was suggested that PEHO syndrome may represent phenotypic expansion at the severe end of the early-onset encephalopathies.[7]

Heterozygous mutation in the SCN2A gene on chromosome 2q24 cause infantile epileptic encephalopathy-11 (EIEE11) and benign familial infantile seizures type 3. It is characterized by infantile onset of refractory seizures with resultant delayed neurologic development and persistent neurologic abnormalities.[8] In our patient, next generation sequencing showed a heterozygous missense variation, c.4022T > C, p.Leu1341Pro, in SCN2A (NM_001040142) gene. Our patient has a novel mutation in the SCN2A gene. Our findings expand the spectrum of causative mutations, and clinical findings in EIEE11. It has been previously reported first child with PEHO syndrome was found to have a heterozygous SCN2A mutation c.743T > C p.Leu248Pro. PEHO syndrome has been concluded the endpoint of different genetic epilepsies.[4] Our patient is the second case associated with SCN2A mutation in PEHO syndrome.

Apart from PEHO syndrome, progressive brain atrophy and optic atrophy have been reported with SN2A encephalopathy and also the other epileptic encephalopathies.[9,10] PEHO syndrome can be diagnosed when it is considered. We consider that PEHO syndrome may be a concomitant clinical entity which accompanying with early onset encephalopathies.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published

and that due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Arzu Ekici, İlyas Yılmaz[1], Orhan Görükmez[2], Cengiz Gökhan Orcan[3], Sevil Dorum[4]

Departments of Pediatric Neurology, [1]Pediatrics, [2]Medical Genetics, [3]Radiology, and [4]Metabolism, University of Health Sciences, Bursa Yüksek İhtisas Training and Research Hospital, Bursa, Turkey

Address for correspondence: Dr. Arzu Ekici, Mimar Sinan Avenue, Yıldırım, Bursa, Turkey.
E-mail: drarzuekici@gmail.com

References

1. Somer M. Diagnostic criteria and genetics of the PEHO syndrome. J Med Genet 1993;30:932-6.
2. Chitty LS, Robb S, Berry C, Silver D, Baraitser M. PEHO or PEHO-like syndrome? Clin Dysmorphol 1996;5:143-52.
3. Field MJ, Grattan-Smith P, Piper SM, Thompson EM, Haan EA, Edwards M, *et al*. PEHO and PEHO-like syndromes: Report of five Australian cases. Am J Med Genet A 2003;122A:6-12.
4. Chitre M, Nahorski MS, Stouffer K, Dunning-Davies B, Houston H, Wakeling EL, *et al*. PEHO syndrome: The endpoint of different genetic epilepsies. J Med Genet 2018;55:803-13.
5. D'Arrigo S, Grazia BM, Faravelli F, Riva D, Pantaleoni C. Progressive encephalopathy with edema, hypsarrhythmia, and optic nerve atrophy (PEHO)-like syndrome: What diagnostic characteristics are defining? J Child Neurol 2005;20:454-6.
6. Salpietro V, Zollo M, Vandrovcova J, Ryten M, Botia JA, Ferrucci V, *et al*. The phenotypic and molecular spectrum of PEHO syndrome and PEHO-like disorders. Brain 2017;140:e49.
7. Gawlinski P, Posmyk R, Gambin T, Sielicka D, Chorazy M, Nowakowska B, *et al*. PEHO syndrome may represent phenotypic expansion at the severe end of the early-onset encephalopathies. Pediatr Neurol 2016;60:83-7.
8. Ogiwara I, Ito K, Sawaishi Y, Osaka H, Mazaki E, Inoue I, *et al*. De novo mutations of voltage-gated sodium channel alphaII gene SCN2A in intractable epilepsies. Neurology 2009;73:1046-53.
9. Syrbe S, Zhorov BS, Bertsche A, Bernhard MK, Hornemann F, Mütze U, *et al*. Phenotypic variability from benign infantile epilepsy to ohtahara syndrome associated with a novel mutation in SCN2A. Mol Syndromol 2016;7:182-8.
10. Baasch AL, Hüning I, Gilissen C, Klepper J, Veltman JA, Gillessen-Kaesbach G, *et al*. Exome sequencing identifies a de novo SCN2A mutation in a patient with intractable seizures, severe intellectual disability, optic atrophy, muscular hypotonia, and brain abnormalities. Epilepsia 2014;55:e25-9.

Submitted: 15-Jun-2019 **Revised:** 23-Jun-2019 **Accepted:** 23-Jun-2019
Published: 10-Jun-2020

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

DOI: 10.4103/aian.AIAN_331_19