Pediatric Neurology 60 (2016) 83–87

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Clinical Observations

PEHO Syndrome May Represent Phenotypic Expansion at the Severe End of the Early-Onset Encephalopathies

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ABSTRACT

BACKGROUND: Progressive encephalopathy with edema, hypsarrhythmia and optic atrophy (PEHO) syndrome is a distinct neurodevelopmental disorder. Patients without optic nerve atrophy and brain imaging abnormalities but fulfilling other PEHO criteria are often described as a PEHO-like syndrome. The molecular bases of both clinically defined conditions remain unknown in spite of the widespread application of genome analyses in both clinic and research. **METHODS:** We enrolled two patients with a prior diagnosis of PEHO and two individuals with PEHO-like syndrome. All four individuals subsequently underwent whole-exome sequencing and comprehensive genomic analysis. **RESULTS:** We identified disease-causing mutations in known genes associated with neurodevelopmental disorders including *GNAO1* and *CDKL5* in two of four individuals. One patient with PEHO syndrome and a *de novo* *GNAO1* mutation was found to have an additional *de novo* mutation in *HESX1* that is associated with optic atrophy. **CONCLUSIONS:** We hypothesize that PEHO and PEHO-like syndrome may represent a severe end of the spectrum of the early-onset encephalopathies and, in some instances, its complex phenotype may result from an aggregated effect of mutations at two loci.

Keywords: PEHO, encephalopathy, whole-exome sequencing, optic atrophy, neurodevelopmental disorder

Pediatr Neurol 2016; 60: 83-87

Conflicts of Interest: J.R.L. has stock ownership in 23andMe and Lasergen and is a paid consultant for Regeneron. J.R.L. is a coinventor on multiple U.S. and European patents related to molecular diagnostics for inherited neuropathies, eye diseases, and bacterial genomic fingerprinting. The Department of Molecular and Human Genetics at Baylor College of Medicine derives revenue from the chromosomal microarray analysis and clinical exome sequencing offered in the Baylor Medical Genetics Laboratories (http://www.bcm.edu/geneticlabs/). Other authors have no disclosures relevant to the article.

Article History:
Received February 1, 2016; Accepted in final form March 20, 2016

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http://dx.doi.org/10.1016/j.pediatrneurol.2016.03.011

Introduction

Progressive encephalopathy with edema, hypsarrhythmia and optic atrophy (PEHO) syndrome (Mendelian Inheritance in Man [MIM]#260565) is a rare genetic disorder that was originally described in the Finnish population.[1] The cardinal features of PEHO syndrome include (1) infantile hypotonia, (2) seizure disorder, (3) profound delay in motor and intellectual development, (4) progressive brain atrophy, and (5) atrophy of the optic disc by the age of 2 years. The aforementioned criteria are considered necessary for a diagnosis of PEHO syndrome and together with supportive findings that may include subtle dysmorphic features, edema of the face and limbs, evidence of dysmyelination on brain magnetic resonance imaging studies and slowing of nerve conduction velocities have been used to identify patients with this condition.[2-4] Patients who are lacking neuroradiologic and/or ophthalmologic signs have been referred to as PEHO-like syndrome. Families with multiple affected siblings were reported; therefore, an autosomal recessive mode of inheritance has been proposed; however, most PEHO-spectrum patients represent sporadic patients.[3,5,6]

Material and Methods

Study subjects

Subjects were selected on the basis of their phenotype and, with their written consent, were studied via protocols approved by the institutional review boards for the protection of human subjects of Baylor College of Medicine.

Genomic DNA preparation

DNA was isolated from clotted whole blood by using the Clotspin Baskets and the Gentra PureGene Blood Kit (Qiagen, Germantown, MD) according to the manufacturer's instructions.

Whole-exome sequencing

After obtaining informed consent, we applied whole-exome sequencing (WES) to the probands at Baylor College of Medicine Human Genome Sequencing Center through the Baylor Hopkins Center for Mendelian Genomics.[7]

Results

We have enrolled two patients with the prior diagnosis of PEHO syndrome (IMD1 and IMD2) and two with PEHO-like syndrome (IMD3 and IMD4).

Patients IMD1 and IMD2 underwent comprehensive evaluation by genetics at 6 years and 4.5 years of life and were found to fulfill clinical criteria required for the diagnosis of PEHO syndrome (Table). Patients were born to nonconsanguineous parents, and their family history was noncontributory. Comparative genomic hybridization (array CGH) studies did not reveal any pathogenic copy number variants. WES studies for the patients and their parents were performed using a trio approach searching for sequence variants in known and candidate genes. In patient IMD1, we identified two *de novo* mutations: ch16: 56226501G>A (c.134G>A, p.Gly45Glu) in *GNAO1* and chr3:57233922G>A (c.25G>A, p.Ala9Thr) in *HESX1* that potentially contributed to the observed phenotype; the mutations were confirmed by Sanger sequencing (Fig 1). Both *GNAO1* and *HESX1* are genes associated with known human disorders. The *GNAO1* mutation has not been identified in available mutation databases including Exome Sequencing Project (ESP), 1000 Genomes, Exome Aggregation Consortium (ExAC), and internal Baylor Hopkins Center for Mendelian Genomics database.[8-10] The *HESX1* mutation was not recorded in the aforementioned databases except for ExAC where it was found in three of 60,703 individuals, all coming from South Asia (minor allele frequency = 0.00002471). The *GNAO1* p.Gly45Glu mutation was predicted to be pathogenic or likely pathogenic by available bioinformatics tools including Sorting Intolerant From Tolerant, MutationTaster, PolyPhen, whereas *HESX1* p.Ala9Thr variant was called benign by the same algorithms. WES analysis for patient IMD2 failed to identify mutation in either a known or candidate gene that could potentially explain the existing phenotype.

Two patients, IMD3 and IMD4, had clinical findings suggestive of PEHO-like syndrome (Table). Brain-imaging studies for patient IMD3 showed cerebral atrophy but no signs of cerebellar abnormalities (Fig 2) and normal brain imaging studies in IMD4. Both patients were born to nonconsanguineous couples with no prior family history of

TABLE.
Clinical Characteristic of Patients With PEHO Syndrome (IMD1, IMD2) and PEHO-Like Syndrome (IMD3, IMD4)

Patient ID	IMD1	IMD2	IMD3	IMD4
Diagnosis	PEHO	PEHO	PEHO-like	PEHO-like
Mutated gene	*GNAO1* *HESX1*	–	*CDKL5*	–
Sex	F	F	M	F
Age at evaluation	6 yr	4.5 yr	6 yr	1 yr
Age of onset	Infancy	Infancy	Infancy	Infancy
Severe hypotonia	+	+	+	+
Seizures (age of onset)	+ (4 days)	+ (8 days)	+ (6 wk)	+ (6 mo)
Profound psychomotor delay with lack of developmental progress	+	+	+	+
Abnormal/loss of visual fixation with optic atrophy by the age of 2 years	+	+	–	+
Cerebral atrophy	+	+	+	–
Cerebellar atrophy	+	+	–	–
Dysmorphic features including narrow forehead, epicanthal folds, short nose, open mouth, receding chin, tapering fingers	+	+	+	+
Edema of the face and limbs	+	+	+	+
Abnormal ABER	+	+	+	NA
Array CGH	normal	normal	normal	normal

Abbreviations:
ABER = auditory brainstem evoked response
PEHO = Progressive encephalopathy with edema, hypsarrhythmia and optic atrophy