

The clinical and EEG features and mutation analysis in a Chinese patient with severe hypoplasia of the cerebellum and pons

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Abstract

We report here a Chinese female infant with severe hypoplasia of the cerebellum and pons, and heterozygous mutation (c.18G >T, p.E6D) in the TSEN54 gene. This mutation was not present in her parents and the 100 Chinese controls, which proved to be a *de novo* missense mutation. MR imaging of the patient revealed severe hypoplasia of the bilateral cerebellar hemispheres and vermis with moderate flattening of the pons. A video EEG during hospitalization demonstrated abnormal background activities and generalized burst and attenuation patterns during interictal stage. The spasms and tonic spasms occurred frequently in clusters with generalized voltage attenuation.

INTRODUCTION

Pontocerebellar Hypoplasia (PCH) is a group of very rare, inherited progressive neurodegenerative disorders affecting the pons and cerebellar hemispheres. Up to now seven different subtypes have been reported (PCH1-7). Progressive microcephaly and variable cerebral involvement are common features in all subtypes. Severe cognitive, motor handicaps and seizures are often reported.¹ In the previous reports, details of the seizure type and electroencephalography (EEG) changes are seldom described. We report here a Chinese female infant with PCH and with characteristic EEG and seizure. We also described the clinical features and mutation analysis of this patient.

CASE REPORT

This is a female infant born full term by normal vaginal delivery, and weighed 2.5 kg. Her growth was stunted soon after birth. When she was admitted to our hospital at 4 months of age, her body weight was 5.0 kg, height 60.0 cm and head circumference 38.6cm. She was unable to lift her head, roll over and follow objects. She had marked dyskinetic movement, spasticity, impaired swallowing and progressive microcephaly. The other abnormalities include blepharophimosis, abnormal startle response and hyperreflexia. Familial history of febrile seizures and epilepsies

were absent. She started to have seizures at the age of 3 months. Her epileptic spasms occurred daily, more on awakening, often in clusters, and involved proximal extremities, neck and trunk. Administration of clonazepam, phenobarbital and topiramate did not control the seizures.

The investigation protocols were approved by the Ethical Committee of Beijing Sanbo Brain Hospital. We took blood samples from the infant and her parents after informed consent. DNA was extracted by standard protocols. Each exon of the TSEN54, TSEN2, TSEN34, RARS2 and VRK1 gene (including B30 bp of flanking intronic sequence) were amplified by PCR. Purified PCR products were sequenced in both directions by using PCR primers as sequencing primers. The sequencing results were analyzed by FinchTV Version 1.4.0. To confirm that the alterations were mutations, but not polymorphisms, genomic DNAs from 100 healthy controls of Han Chinese ethnicity were analyzed.

A video electroencephalogram (EEG) during hospitalization showed abnormal background activities and generalized burst and attenuation patterns during interictal stage during awake and sleep. The spasms and tonic spasms may occur in clusters or singly with generalized voltage attenuation (Figure 1), in both wakefulness and sleep. The duration of epileptic spasms was 2 to 5 seconds, sometimes it was longer on the right side of body. The interval between spasms

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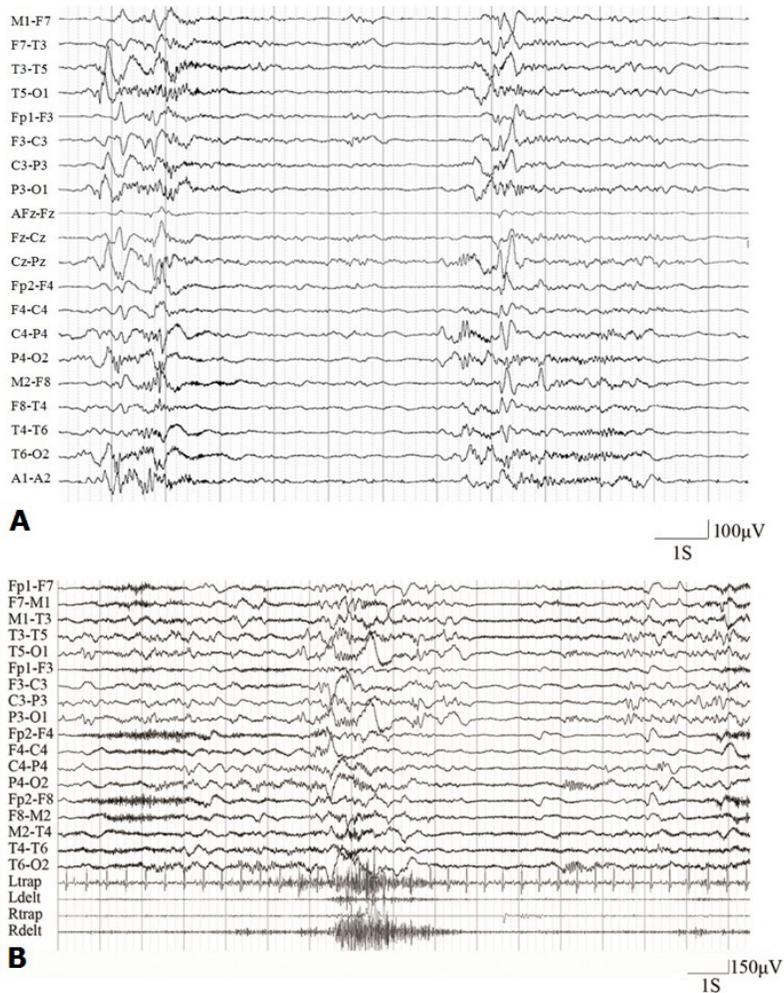


Figure 1: Interictal and ictal EEG. (A) An atypical burst and attenuation pattern in this 4 months infant during sleep: bursts of fast activities mixed with irregular generalized polyspikes or spike and waves (150-200µV) lasting from 2 to 5 seconds and alternating with flat periods of 2 to 6 seconds. (B) Cluster of tonic spasms recorded in this 4 months baby: Ltrap and Rtrap are surface EMG recording on left and right trapezius muscles; Ldelt and Rdelt are surface EMG recording on left and right deltoid muscles.

within cluster ranged from 6 to 10 seconds. MR imaging of the patient showed severe hypoplasia of both cerebellar hemispheres and vermis with moderate flattening of the pons. Mild atrophy of the cerebral cortex was also seen (Figure 2).

Sequencing of TSEN54 revealed one heterozygous mutation (c.18G >T, p.E6D) and one heterozygous SNP (rs7216673, c.12G>T, p.E4D) in exon 1, and two heterozygous SNPs (rs9911502, c.1041G>C, p.K347N; rs17854519, c.1121G>C, p.R374P) in exon 8. The missense mutation (c.18G >T, p.E6D) did not present in the parents of this infant and the 100 Chinese controls. No mutations were found in the other four genes.

DISCUSSION

The clinical and neuroradiological findings in our patient ruled out other conditions associated with pontocerebellar hypoplasia, such as progressive cerebello-cerebral atrophy, infantile cerebral and cerebellar atrophy, subtypes of the congenital glycosylation disorders, phosphoserine aminotransferase deficiency and VLDLR-associated cerebellar hypoplasia.¹ Based on the clinical manifestation, we thought that PCH is the most probable diagnosis. However, the subtype cannot be determined, but most likely it is PCH2. Dyskinesias are the major features of PCH2. Pure spasticity is reported in a minority of patients. Other clinical features include impaired swallowing from birth, jitteriness in the neonatal

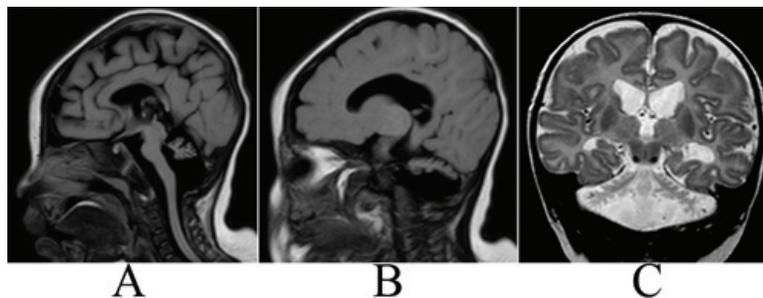


Figure 2: MRI sections of our case. (A) Mid-sagittal section (T2 FLAIR) shows vermal hypoplasia and ventral pontine flattening. (B) Lateral sagittal section (T2 FLAIR) shows severe hypoplasia of the cerebellar hemispheres. (C) Coronal section (T1) shows extremely small and flattened cerebellar hemispheres and moderate vermal hypoplasia. Immaturity of cerebral cortex, enlarged ventricles and thin corpus callosum are also visible.

period, central visual failure and seizures. Typical brain MR imaging findings are a dragonfly-like cerebellar pattern on coronal sections, where the cerebellar hemispheres are flat, severely reduced in size, and the vermis is relatively spared. Mild or severe atrophy of the cerebral cortex is observed in 40% of the PCH2 cases.^{2,3} Hypotonia, contractures, primary hyperventilation were not presented in our patients, which did not support the diagnosis of PCH1 and PCH4.

An amino acid change of an alanine into a serine at the position 307 (p.A307S) in the TSEN54 gene is the basic and common variant of PCH2. Most alleles with the homozygous p.A307S TSEN54 mutation were reported from the patients of Northern European descent. Exceptional cases were from Israeli, Arab, Turkish and Ibero-American descent.⁴ Similarly, we did not find p.A307S in this Chinese infant. In 2014, a Chinese extended familial case of late-onset hereditary ataxia mimicking PCH is described. By means of direct sequencing, a novel heterozygous mutation was found in the TSEN54 gene by c.254A > T (+) (p.E85V). However, this subtype was found to have late onset, differing from PCH with prenatal onset and predominantly affecting the growth of neurons.⁵ Therefore, race may be an important factor in the genotype of PCH.

During interictal phase of our patient, EEG demonstrated short atypical bursts of fast activities mixed with irregular generalized polyspikes or spike and waves lasting from 2 to 5 seconds, alternating with flat periods of 2 to 6 seconds. The clusters of tonic spasms could be found during the ictal phase. These features are not fully identical to that of the Ohtahara syndrome (OS)^{6,7}, because there are no typical high enough voltage (150-350 μ V) slow waves intermixed with irregular spikes/polyspikes alternating with

periods of suppression of electrical activity. The diagnostic workup of OS remains a challenge because of frequent difficulties in EEG analysis and determining the etiologies. The EEG features of this patient with PHC may evolve, similar to other patients with early epileptic encephalopathy, requiring further observations on its evolution.

TSEN54 is one of four different tRNA splicing endonuclease genes. The missense mutation in this gene would not abrogate tRNA splicing completely, but lead to reduction of certain amino acids, which would hinder the development of telencephalon and metencephalon from eight weeks of gestation.⁸ Hence, not only the pons and cerebellum had hypoplasia, but the cerebral cortex was also immature, which may lead to early epileptic encephalopathy.

In conclusion, the atypical burst and attenuation patterns of EEG with spasm and tonic spasm seizures can be demonstrated in the patient with PCH. There may be differences in the genotype and phenotype of PCH between Chinese and European descent. Further observations on a larger number of cases are needed to accumulate electro-clinical data on this rare disease.

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DISCLOSURE

Conflicts of interest: None

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