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Case Report

Epileptic apnea in a patient with inherited glycosylphosphatidylinositol anchor deficiency and *PIGT* mutations

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Abstract

We report an 11-month-old boy with acetazolamide-responsive epileptic apnea and inherited glycosylphosphatidylinositol (GPI)-anchor deficiency who presented with decreased serum alkaline phosphatase associated with compound *PIGT* mutations. The patient exhibited congenital anomalies, severe intellectual disability, and seizures, including epileptic apnea with epileptiform discharges from bilateral temporal areas. Brain magnetic resonance imaging revealed delayed myelination and progressive atrophy of the brainstem, cerebellum, and cerebrum. Whole-exome sequencing revealed compound heterozygous mutations in *PIGT* (c.250 G > T, p.Glu84X and c.1096 G > T, p.Gly366Trp), which encodes a subunit of the GPI transamidase complex. Flow cytometry revealed decreased expression of CD16 (a GPI anchor protein) on granulocytes, supporting the putative pathogenicity of the mutations. Phenobarbital, clonazepam, and potassium bromide decreased the frequency of tonic seizure and acetazolamide decreased epileptic apnea. To our knowledge, this is the first reported case of intractable seizures accompanied by epileptic apnea associated with GPI anchor deficiency and a compound *PIGT* mutation.

Keywords: Epileptic apnea; Gamma-aminobutyric acid; Glycosylphosphatidylinositol anchor deficiency; Multiple congenital anomalies-hypotonia-seizures syndrome-3

1. Introduction

Deficiencies in glycosylphosphatidylinositol (GPI) anchor biosynthesis and protein attachment typically present with intractable epilepsy, severe intellectual disability, and diverse congenital anomalies, including

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skeletal, urogenital, cardiovascular, and gastroenterological anomalies. Recent advances in next-generation sequencing technology have led to the discovery of genetic causes of GPI deficiency and revealed a broad range of phenotypes [1]. The phosphatidylinositol glycan anchor biosynthesis class T (PIGT) enzyme is a component of the GPI transamidase complex that catalyzes GPI anchor attachment to proteins via carbonyl intermediates [2].

Apnea is a manifestation of localization-related epilepsy, which can necessitate resuscitation and may underlie sudden unexpected death. Experimental evidence indicates the presence of dense interconnections between the limbic system and respiratory center in the brainstem [3]. Moreover, ictal electroencephalography (EEG) has suggested that epileptic apnea can be caused by epileptic discharges originating in the temporal lobes [4]. Here, we presented a case of with inherited GPI anchor deficiency and compound *PIGT* mutations, presenting with refractory epileptic apnea.

2. Case report

The patient was an 11-month-old boy, born by cesarean section due to breech presentation, as the first child of healthy non-consanguineous parents. At birth, he presented with distinctive external features, including micrognathia, high arched eyebrows, epicanthus, telecanthus, a depressed nasal bridge, a short anteverted nose, a long philtrum, a tented lip, and a high arched palate. He had skeletal abnormalities (pectus excavatum, clinodactyly, middle phalanx defect, and delayed bone age), urogenital abnormalities (nephrocalcinosis, cryptorchidism, and perineal groove), and duplication of the esophagus, as gastroenterological feature. There were no cardiovascular abnormalities. After aspiration pneumonia, aspiration and dysphagia were confirmed on videofluoroscopic examination of swallowing, and tube feeding was introduced. Frequent epileptic apnea, associated with severe oxygen desaturation, occurred at 2 months of age and was successfully controlled with sodium valproate; however, epileptic apnea recurred with additional tonic and myoclonic seizures at 8 months of age. The patient exhibited psychomotor regression and increased frequency of epileptic apnea during sleep. The seizures were refractory to carbamazepine, zonisamide, and levetiracetam.

The patient was admitted to our hospital at 11 months of age. He was bedridden, in a frog-leg position, and could only move his arms and feet in response to noxious stimuli. Height and weight growth were in the normal range. Multiple congenital skeletal malformations were observed (Fig. 1A). Laboratory test results were normal except for an extremely low serum alkaline phosphatase levels (105 IU/L; normal range, 395–1339 IU/L). At 1 year of age, delayed myelination and progressive atrophy of the brainstem, cerebellum, and cerebrum were identified on brain magnetic resonance imaging (Fig. 1B, C). Inter-ictal EEG revealed high-amplitude diffuse slow-wave background activity as well as multifocal spikes and sharp waves in bilateral temporal areas (Fig. 1D). Ictal EEG during epileptic apnea revealed rhythmic sharp activity arising from the left temporal area, spreading to the ipsilateral frontal and contralateral temporal regions. Oxygen saturation monitoring showed that the apneic episode coincided temporally with discharges on ictal EEG (Fig. 1E).

Whole-exome sequencing revealed compound heterozygous mutations (c.250G > T, p.Glu84X and c.1096G > T, p.Gly366Trp) in *PIGT* (NM_015937.5), which were confirmed using Sanger sequencing (Fig. 2A). Flow cytometry revealed decreased expression of CD16, a GPI anchor protein, on granulocytes (Fig. 2B). Therefore, inherited GPI anchor deficiency associated with these *PIGT* mutations was diagnosed. The seizures were intractable and required the patient's hospitalization for 6 months. High-dose phenobarbital, clonazepam, and potassium bromide treatment decreased the frequency of the tonic seizures. Additionally, acetazolamide was effective for epileptic apnea. Pyridoxine and pyridoxal phosphate had no effect.

3. Discussion

We described a case with compound *PIGT* mutations associated with epileptic apnea and seizures. We diagnosed the present case as having multiple congenital anomalies-hypotonia-seizures syndrome-3 (MCAHS3) due to *PIGT* mutations. *PIGT* mutations characteristically present with severe intellectual disability, the seizure before the age of 2 years, congenital anomalies, including skeletal, cardiac, or genitourinary anomalies, and decreased alkaline phosphatase expression. To date, only four reports have described families with *PIGT*-associated MCAHS3 [5–8]. Different *PIGT* mutations have been associated with several different seizure types, including myoclonic, tonic, tonic-clonic, dyscognitive, and autonomic seizures (Table 1); no previous report has described such cases with associated epileptic apnea. Only a single Japanese study has reported apneic episodes with tonic seizures [6]. To our knowledge, we are the first to report a case of intractable epileptic apnea confirmed by the observation of ictal epileptic discharges in a patient with MCAHS3.

In our case, sodium valproate was initially effective for controlling epileptic apnea, but the patient showed tonic, tonic-clonic, and myoclonic seizures in addition to the resurgence of epileptic apnea at 8 months of age. Treatment with phenobarbital, clonazepam, and potassium bromide decreased the frequency of tonic and tonic-clonic seizures, and the subsequent addition of acetazolamide was effective for epileptic apnea. In

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