Original article

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Early infancy-onset stimulation-induced myoclonic seizures in three siblings with inherited glycosylphosphatidylinositol (GPI) anchor deficiency

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ABSTRACT – Inherited glycosylphosphatidylinositol anchor deficiency causes a variety of clinical symptoms, including epilepsy, however, little information is available regarding seizures as a symptom. We report three siblings with inherited glycosylphosphatidylinositol anchor deficiency with *PIGL* gene mutations. The phenotypes of the subjects were not consistent with CHIME syndrome or Mabry syndrome, as reported in previous studies. All shared some clinical manifestations, including transient apnoea as neonates, dysmorphic facial features, and intellectual disability. Between one week and 3 months of life, all patients developed myoclonic seizures. Myoclonic jerks were easily evoked by sudden unexpected acoustic or tactile stimuli. None showed elevation of serum alkaline phosphatase. Vitamin B_6 was given to one of the three siblings, but failed to suppress seizures. The presence of early infancy-onset stimulation-induced myoclonic seizures combined with dysmorphic facial features should lead physicians to consider the possibility of inherited glycosylphosphatidylinositol anchor deficiency.

Key words: inherited GPI anchor deficiency, *PIGL*, epilepsy, stimulation-induced myoclonic seizure

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Glycosylphosphatidylinositol (GPI) is a glycolipid that anchors proteins to the cell membrane (Kinoshita and Fujita, 2016). More than 150 kinds of GPI-anchored proteins have been reported in humans. GPI is synthesized and transferred to proteins in the endoplasmic reticulum. This biosynthesis pathway of GPI involves over 20 genes, called *PIG* (phosphatidyl inositol glycan) genes. After the attachment of GPI to the protein, both lipid and glycan moieties of GPI are structurally remodelled in the endoplasmic reticulum and Golgi apparatus prior to the surface expression of GPI-anchored proteins. Five genes, called *PGAP* (Post GPI Attachment to Protein) genes, are involved in this remodelling of GPI.

GPI-anchored proteins play essential roles in embryogenesis, neurogenesis, immune responses, and fertilization. Recent studies have indicated that germ-line mutations in these genes lead to inherited GPI anchor deficiencies with various symptoms, including intellectual disability, dysmorphic facial features, deafness, hyperphosphatasia, and epilepsy (Murakami *et al*., 2012). However, little is known about epilepsy associated with inherited GPI anchor deficiency, because many previous reports refer to events as merely "seizures" or provide extremely limited descriptions of epilepsy.

Epileptic myoclonic jerks provoked by stimuli are extremely rare seizures. Herein, we report three siblings with inherited GPI anchor deficiency (PIGL) who developed stimulation-induced myoclonic seizures in early infancy.

Case studies

The clinical manifestations of the three affected siblings are shown in *table 1*. Pregnancy was uneventful in the youngest sister (proband; Case 1) and her elder brother (Case 2), while congenital hydronephrosis was detected by foetal ultrasound in the eldest brother (Case 3). All were full-term (38-40 gestation weeks) neonates born to non-consanguineous parents with no asphyxia. The body weight, length, and head circumference at birth were normal in one (Case 1) and large for gestational age in two (Case 2 and 3). All patients had ichthyosiform dermatosis at birth, and shared similar dysmorphic facial features, such as hypertelorism, brachycephaly, epicanthal folds, flat broad nasal root, full lips, widely spaced teeth, overfolded helices, and thickened palms and soles. However, our patients did not have retinal coloboma, congenital heart defects, or hearing loss. Their clinical courses after birth were as follows.

Case 1

A 2-year-old girl developed apnea on Day 1. Her routine blood test (for *e.g.* glucose, electrolytes) was normal, and apnea disappeared without treatment on Day 3. At the age of one week, she developed myoclonic jerks, which involved mainly head and upper limbs. Myoclonic seizures occurred spontaneously, and were also easily evoked by sudden unexpected acoustic or tactile stimuli. Subsequently, focal seizures, manifesting as tonic seizures involving bilateral upper limbs with a stiffness on the right side of the face, occurred on Day 10. Initial EEG showed multifocal spikes. Ictal EEG revealed identical diffuse irregular spike-and-wave complexes (or sometimes high-voltage diffuse slow waves without spikes), corresponding to spontaneous or stimulation-induced myoclonic jerks (*figure 1 A, B*). Brain MRI was normal. Metabolic screening, *e.g.* for amino acids, lactate, pyruvate, and organic acids, was unremarkable. Her focal seizures were controlled with zonisamide at 5 months of age. In contrast, myoclonic seizures were resistant to valproic acid (VPA), and the seizure frequency gradually increased up to 70 times a day at the age of 6 months. Interictal EEG showed both a diffuse spike-and-wave complex and multifocal spikes. After informed consent was obtained, a high dose of vitamin B_6 (pyridoxine at 30 mg/kg/day, tid.) was given at 6 months of age. However, myoclonic seizures persisted without obvious effects. At 18 months of age, the seizure frequency decreased after administration of clobazam.

The patient achieved head control and sat at five and 10 months of age, respectively. Developmental assessment (using the revised Kyoto Guidance Clinic Developmental Scale for Children) at 18 months of age showed moderate delay (DQ: 41). At the final evaluation, she was able to walk along a wall, but speech had not been achieved. She continued to have a few myoclonic seizures per day despite combination treatment with clobazam, VPA, and vitamin B_6. The EEG considerably improved and showed no definite epileptiform activities. Her serum alkaline phosphatase (ALP) levels ranged from 856 to 1,620 IU/l, which did not exceed the age-adjusted upper limit for normal Japanese female children (1,150-1,630 IU/l) (Tanaka *et al*., 2008).

Case 2

A 9-year-old boy presented with apnea, which started a few hours after birth. His routine blood test was negative. Apnea disappeared spontaneously on Day 2. At two months, he developed spontaneous and stimulation-induced myoclonic seizures, similar to those of Case 1. Initial EEG showed single spikes and spike-and-wave complexes within the bilateral central area. Ictal EEG revealed diffuse irregular spike-and-wave complexes (or sometimes high-voltage diffuse slow waves without spikes), corresponding to myoclonic jerks. Brain MRI revealed no

Table 1. Clinical manifestations of the siblings and reported cases with mutations in the *PIGL* gene.

	Present study			**Ng *et al.* (2012) CHIME syndrome (*n*=6)**	**Fujiwara *et al.* (2015) Mabry syndrome (*n*=1)**
	Case 1	**Case 2**	**Case 3**		
Age	2y 2m	9y 4m	13y 3m	1-18 (16?) y	3y 6m
Sex	f	m	m	3m, 3f	f
Gestational age/body weight	38w/3,260g (AFD)	40w/3,855g (LFD)	39w/3,702g (LFD)	2 LFD, 3 AFD, 1 unknown	33w/2,510g (LFD)
Coloboma	-	-	-	6/6	-
Heart defects	-	-	-	3/6	-
Ichthyosiform dermatosis	+	+	+	6/6	-
Intellectual disability	Severe	Severe	Severe	6/6	Severe
Developmental milestones					
Head control	5m	2y	5m	ND	5m
Sitting	10m	2y 6m	1y 6m	ND	2y 3m
Standing	NA	6y	2y	ND	NA
Gait	NA	7y	3y	6/6	NA
Speech	NA	Only few words	NA	2/6	NA

Table 1. Clinical manifestations of the siblings and reported cases with mutations in the *PIGL* gene (*Continued*).

	Present study			**Ng *et al*. (2012) CHIME syndrome (*n*=6)**	**Fujiwara *et al*. (2015) Mabry syndrome (*n*=1)**
	Case 1	**Case 2**	**Case 3**		
Facial dysmorphic features	+	+	+	6/6	+
Ear anomalies	+	+	+	6/6	+
Hearing loss	-	-	-	6/6	+
Renal abnormalities	-	-	+	3/6 (1 unknown)	-
Apnea (onset)	Transient (1d)	Transient (0d)	Transient (2d)	-	-
Seizure Seizure type (onset)	+ Myoclonic seizure (1w) Focal seizure (10d)	+ Myoclonic seizure (2m) Focal seizure (3m)	+ Myoclonic seizure (3m) Focal seizure (10m) Absence seizure (1y) Atonic seizure (4y)	6/6 ND (3w-14m; 1 unknown)	+ Twitching (4m)
Serum ALP(IU/l)	Normal (856-1,620)	Normal (414-1,620)	Normal (782-1,401)	ND	Elevated (3,000-4,500)
Brain imaging	Normal	Normal	Normal→Periventricular lateralis T1/T2 high intensity	1 normal, 3 atrophy, 2 unknown	Dilatation of the bilateral ventricles, hypoplasia of the cerebellar vermis

Y: year(s); m: month(s); w: week(s); d: day(s); f: female; m: male; AFD: appropriate for date; LFD: large for date; NA: not achieved; ND: not described.

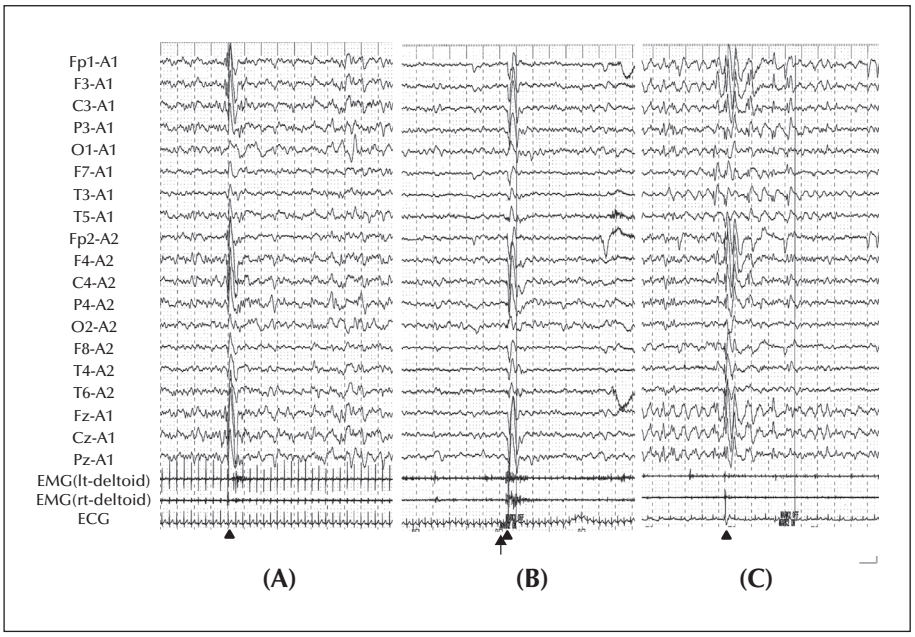

Figure 1. Ictal EEG of Case 1 (A, B) and Case 3 (C). All patients developed myoclonic seizures between one week and three months of age. Myoclonic seizures (▲) occurred spontaneously, and also appeared in response to sudden unexpected acoustic or tactile stimuli (↑). Representative ictal EEGs are shown. In Case 1, ictal EEG reveals a diffuse irregular spike-and-wave complex corresponding to spontaneous myoclonic jerks (A) and high-voltage diffuse slow waves corresponding to stimulation-induced myoclonic jerks (B). The ictal EEG of Case 3 shows spike-and-wave complexes corresponding to spontaneous myoclonic jerks (C).

abnormalities. Metabolic screening (using blood, urine, and CSF) and ophthalmological examination were unremarkable. Myoclonic seizures did not respond to VPA. Focal seizures, characterized by an abrupt arrest of motion with blinking, occurred at 3 months of age. Myoclonic seizures were controlled with antiepileptic drugs (zonisamide and nitrazepam) at the age of one year, whereas focal seizures persisted after infancy. Follow-up brain MRI revealed no abnormalities.

Developmental milestones were severely delayed, with head control and sitting at 26 months and 30 months of age, respectively. At the last visit, the patient showed unsteady gait and uttered only a few words. Focal seizures presented monthly. EEG showed multifocal spikes. The patient's serum ALP levels (414 to 1,620 IU/l) were below the age-adjusted upper limit for normal Japanese male children (1,200-1,630 IU/l) (Tanaka *et al*., 2008).

Case 3

A 13-year-old boy developed apnea on Day 2. His routine blood tests were normal. Apnea lasted for a few days and disappeared spontaneously. He developed spontaneous myoclonic seizures at the age of 3 months, which also occurred in response to sudden unexpected acoustic or tactile stimuli. The myoclonic seizures did not respond to VPA. The initial EEG showed multifocal spikes. Ictal EEG revealed identical diffuse irregular spike-and-wave complexes (or sometimes high-voltage slow waves without spikes), corresponding to spontaneous or stimulation-induced myoclonic jerks (*figure 1C*). Initial brain MRI revealed no abnormalities. At 10 months of age, he developed focal seizures, sometimes evolving to secondary generalized tonic-clonic seizures. Subsequently, absence and atonic seizures occurred at the age of one year and 4 years, respectively. During follow-up, all seizures were refractory to antiepileptic drugs. At the age of 5 years, brain T2-weighted MRI revealed high-intensity signal lesions in the left posterior periventricular white matter (*figure 2*). Metabolic screening, a chromosome test, and funduscopic findings were unremarkable. Peripheral nerve conduction velocity was within the normal range.

Developmental milestones were severely delayed, with head control and sitting at 5 months and 18 months of age, respectively. At the final evaluation, development was profoundly delayed. The patient had unsteady gait and no speech. He continued to have several daily myoclonic and tonic seizures. EEG revealed left hemisphere-dominant multifocal spikes during wakefulness and sleep. His serum ALP levels, ranging from 782 to 1,401 IU/l, were within normal range for corresponding age (Tanaka *et al*., 2008).

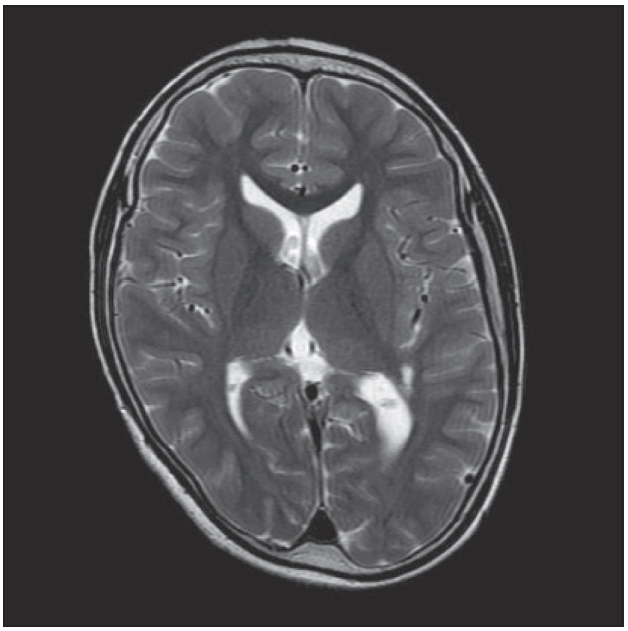

Figure 2. Brain MRI of Case 3. Initial brain MRI was normal. At five years of age, however, MRI T2-weighted images revealed high-intensity signal lesions in left posterior periventricular white matter.

Fluorescence-activated cell sorter (FACS) analysis (*figure 3*)

As described in our previous study (Chiyonobu *et al*., 2014), the surface expression of GPI-anchored proteins was determined by staining cells with Alexa488-conjugated inactivated aerolysin (FLAER; Protox Biotech, Victoria, BC, Canada) and appropriate primary antibodies: mouse anti-DAF (IA10), CD16 (3G8), CD24 (ML5), and CD59 (5H8), followed by phocoerythrin (PE)-conjugated anti-mouse IgG antibody (3G8, ML5, and secondary antibodies; BD Biosciences). Cells were analysed by flow cytometry (Cant II; BD Biosciences) with FlowJo software (Tommy Digital Inc., Tokyo, Japan).

In this study, FACS analysis was performed at 11 years, eight years, and six months for Case 1, 2, and 3, respectively. Data revealed a clear decrease in CD24 and CD16 in granulocytes and CD14 in monocytes. These results suggested a diagnosis of inherited GPI anchor deficiency.

Identification of *PIGL* mutations

To investigate gene mutations, we obtained informed consent from the parents of the siblings and ethical approval from the Osaka University Review Board. Based on exome analysis of 40 GPI-related genes (HaloPlex kit, Agilent Technologies), the heterozygous *PIGL* mutation, NM_004278.3 c.701G>A p.Arg234His, was detected in the three siblings and their mother. Based on quantitative polymerase chain reaction of the gene, the level of expression of exon 3 in the three siblings and the father was half that of the mother. This therefore confirmed a diagnosis of inherited GPI anchor deficiency (*PIGL*).

Discussion

Of more than 27 genes involved in the biosynthesis of GPI-anchored proteins, 15 have been shown so far to cause inherited GPI anchor deficiencies (Edvardson *et al*., 2016). The affected genes include *PIGA, PIGC, PIGQ, PIGY, PIGL, PIGW, PIGM, PIGV, PIGN, PIGO, PIGG, PIGT, PGAP1, PGAP2,* and *PGAP3*. Among these genes, *PIGL* is involved in the second stage of GPI-anchor synthesis. To date, only seven cases with mutations in the *PIGL* gene have been reported in the literature (*table 1*). Ng *et al*. (2012) demonstrated that mutations in the *PIGL* gene were detected in six patients with CHIME syndrome, characterized by colobomas, heart defects, ichthyosiform dermatosis, intellectual disability, and ear anomalies, including conductive hearing loss (Shashi *et al*., 1995; Schnur *et al*., 1997; Sidbury and Paller, 2001; Tinschert *et al*., 1996). Other clinical manifestations include distinctive facial features, abnormal growth, genitourinary abnormalities, seizures, and feeding difficulties. More recently, mutations in *PIGL* were detected in a patient with Mabry (HPMRS) syndrome, characterized by increased serum ALP levels, severe developmental delay, intellectual disability, and seizures (Fujiwara *et al*., 2015). Our siblings lacked three symptoms of CHIME syndrome (eye colobomas, heart defects, and ear anomalies). None of the patients showed elevated serum ALP. These findings indicate that the genotype/phenotype relationship for the *PIGL* gene is not straightforward.

Our siblings developed episodes of recurrent apnea as neonates, in addition to the common symptoms of inherited GPI anchor deficiency. All our patients were full-term infants. Routine blood tests revealed no abnormalities. Apnea lasted for only a few days, and remitted spontaneously without antiepileptic drugs. However, we could not determine whether the transient apnea attacks were of epileptic origin, because EEG was not performed during the neonatal period. Apnea attacks have been reported in a boy carrying *PIGO* mutations (Kuki *et al*., 2013) and a girl with *PIGN* mutations (Nakagawa *et al*., 2015). Recently, Kettwig *et al*. (2016) reported that dizygotic male twins with mutations in *PGAP1* displayed recurrent prolonged apnea at 3 months of age. Their apnea occurred mainly during sleep. The EEG did not show epileptic activity during these episodes which persisted for two years. Taken

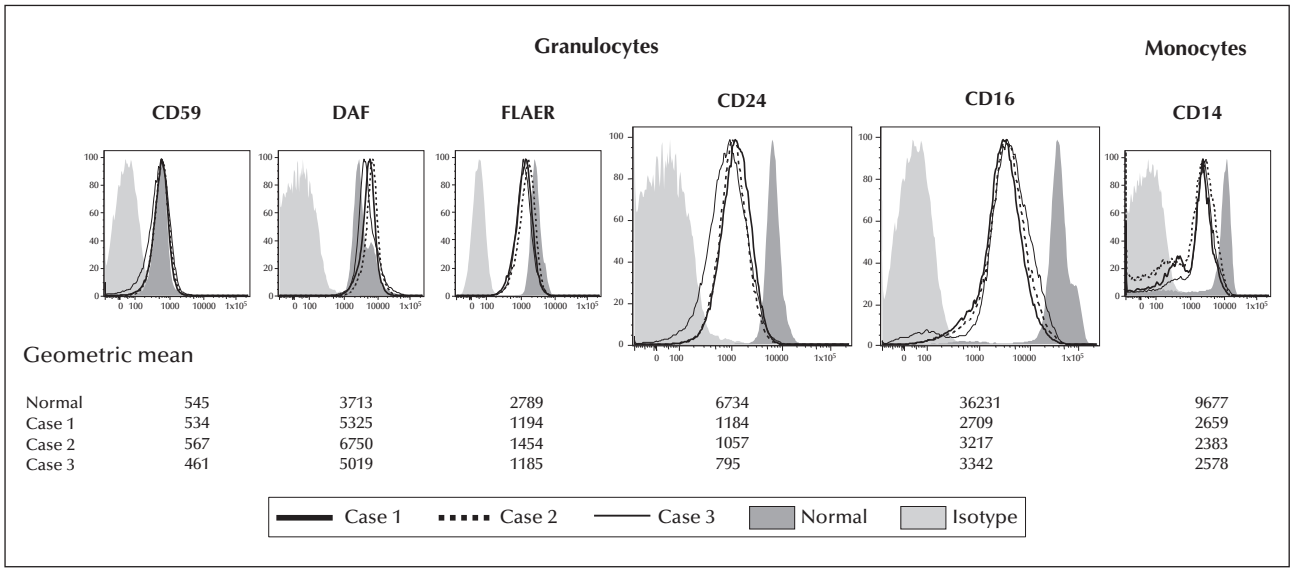

Figure 3. FACS analysis (GPI anchor proteins at neutrophil membranes). Data reveal a clear decrease of CD24 and CD16 in granulocytes and CD14 in monocytes.

together, these data provided a possibility that apnea might be one of the clinical symptoms of inherited GPI anchor deficiency.

Although the detailed descriptions of epilepsy are very limited in the majority of reports in the literature, early-onset epilepsy is one of the clinical manifestations of inherited GPI anchor deficiency (Kato *et al.*, 2014). Between one week and 3 months of life, our patients developed daily myoclonic jerks which were associated with irregular spike-and-wave complexes on EEG. During the course of the disease, a variety of seizures, including generalized seizures (tonic, atonic, and absence seizures) and/or focal seizures, occurred in all patients. All seizures were refractory to antiepileptic drug treatment. Of note, the myoclonic seizures occurred mostly spontaneously, but sometimes appeared in response to sudden unexpected acoustic or tactile stimuli.

Myoclonic jerks provoked by stimuli are extremely rare events. Based on ictal EEG abnormalities, the myoclonic seizures of our patients could be easily distinguished from non-epileptic excessive startle responses of hyperekplexia. Ricci *et al*. (1995) first reported six normal infants (aged 6-21 months) who developed epileptic myoclonic jerks in response to sudden unexpected tactile or acoustic stimuli. They proposed the term "reflex myoclonic epilepsy of infancy" (RMEI) as a new age-dependent idiopathic generalized epileptic syndrome. To date, 80 cases with RMEI have been reported in the literature (Verrotti *et al*., 2013). However, some authors claim that this group of infants with reflex myoclonic seizures should be considered as a variant of myoclonic epilepsy in infancy rather than a distinct epileptic syndrome (Verrotti *et al*., 2013). Our patients demonstrated stimulation-induced myoclonus, similar to the reflex myoclonic seizures of RMEI. In our patients, however, the onset of myoclonic seizures was much earlier in infancy (between one week and 3 months of age), compared with RMEI (between 4 months and 3 years of age). In addition, all our patients had a poor response to VPA and severe intellectual disability, in contrast to cases of RMEI.

Children with congenital metabolic diseases, such as mitochondriocytopathies, non-ketotic hyperglycemia, storage disorders, and infantile hexosaminidase deficiency, may present with myoclonic seizures. However, these myoclonic seizures are usually spontaneous (Verrotti *et al*., 2013). In inherited GPI anchor deficiency, myoclonic seizures are likely to be one of the most common seizure types. To our knowledge, myoclonic seizures have been reported in patients with mutations in *PIGA, PIGL, PIGV, PIGN, PIGT, PGAP1, PGAP3,* and *PGAP2* (Ng *et al*., 2012; Krawitz *et al*., 2013 ; Horn *et al*., 2014; Kato *et al*., 2014; Nakashima *et al*., 2014; Jezela-Stanek *et al*., 2016; Kettwig *et al*., 2016; Knaus *et al*., 2016). In the majority of these patients, myoclonic seizures developed before 3 years of age. Among them, we found only one boy with mutations in the *PIGA* gene, who developed stimulation-sensitive myoclonus (Swoboda *et al*., 2014). However, detailed clinical information and EEG findings were not described in this report. Our patients are the first published cases of inherited GPI anchor deficiency with stimulation-induced epileptic myoclonic seizures, confirmed by ictal EEG.

ALP is a GPI-anchored protein and is present in all tissues throughout the body (Murakami *et al*., 2012). ALP in neurons has an enzymatic action that dephosphorylates pyridoxal phosphate (PLP) to pyridoxal (PL), a membrane-permeable form, which is converted to PLP intracellularly. We previously demonstrated that ALP is released from cells defective in late-stage GPI biosynthesis (Murakami *et al*., 2012). Elevated serum ALP levels, termed hyperphosphatasia, are seen in some inherited GPI anchor deficiencies, such as Mabry syndrome. Thompson *et al*. first reported a pyridoxine-responsive seizure in a case of Mabry syndrome, although the underlying gene was not identified (Thompson *et al*., 2006). The authors speculated that one of the underlying mechanisms for seizures is a decrease in brain γ-aminobutyric acid (GABA) levels due to an intraneuronal shortage of PLP, a cofactor of GABA synthase (glutamate decarboxylase), which is caused by a loss of membrane-anchored ALP (Thompson *et al*., 2006). Thereafter, several studies have reported on the efficacy of vitamin B_6 (pyridoxine) treatment in patients diagnosed with Mabry syndrome, clinically and genetically. Kuki *et al*. described a boy with *PIGO* mutations who responded to daily oral administration of pyridoxine (20 mg/kg). Complete cessation of seizures with improvement of interictal EEG was achieved one week after treatment, and interruption of pyridoxine administration induced recurrence of habitual seizures (Kuki *et al*., 2013). On the other hand, there was no reduction in seizure frequency after oral pyridoxine treatment in two patients with *PIGV* mutations (Marcelis *et al*., 2007; Krawitz *et al*., 2010; Thompson *et al*., 2012). A more recent report described a transient response to pyridoxine in two patients with mutations of the *PIGV* and *PIGO* genes (Xue *et al*., 2016); intractable seizures were controlled with intravenous or oral pyridoxine for a few weeks. Thus, the pathogenesis of epilepsy in inherited GPI anchor deficiency remains unknown. At the time this manuscript was prepared, a high dose of pyridoxine (30 mg/kg) was given to only one of our siblings (Case 1) at the age of 6 months, but failed to suppress her seizures. When compared to her two brothers, however, her developmental milestones may have been less delayed. In addition, EEG showed a remarkable improvement after starting vitamin B_6 therapy. Further studies, including seizure response, EEG changes, and developmental outcome, are necessary to elucidate the efficacy of vitamin B_6 treatment.

In conclusion, we report three siblings with inherited GPI anchor deficiency (*PIGL*) who had myoclonic seizures starting in early infancy. Myoclonic seizures were easily evoked by sudden unexpected acoustic or tactile stimuli. To date, epileptic myoclonic jerks provoked by stimuli have been reported exclusively in infants with RMEI (Verrotti *et al*., 2013). Here, we report the first case of stimulation-induced epileptic myoclonic seizures in infants with GPI anchor deficiency. None of our patients showed elevated serum ALP which is a useful marker of inherited GPI anchor deficiency. The presence of early infancy-onset stimulation-induced myoclonic seizures, combined with dysmorphic facial features, should lead physicians to consider the possibility of inherited GPI anchor deficiency, even when serum ALP level is normal. □

Disclosures.
None of the authors have any conflict of interest to declare.

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TEST YOURSELF

(1) What symptoms should lead physicians to consider the possibility of inherited glycosylphosphatidylinositol (GPI) anchor deficiency in patients with epilepsy?

(2) What types of seizure may occur in patients with inherited GPI anchor deficiency?

(3) Is there any potentially effective regimen other than antiepileptic drugs for the treatment of seizures associated with inherited GPI anchor deficiency?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".