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Case Report

CASE REPORT

A case of pyridoxine-dependent epilepsy with novel *ALDH7A1* mutations

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Abstract

Pyridoxine-dependent epilepsy (PDE) is a rare autosomal-recessive disorder typically presenting with neonatal seizures and is sometimes difficult to diagnose, because the clinical features mimic those of birth asphyxia. A Japanese newborn boy presented with pulmonary haemorrhage and convulsions on the day of birth. Brain computed tomography showed diffuse, but mild, low-density cerebral white matter and a thin subdural hematoma in the posterior fossa. He did not have thrombocytopenia or coagulopathy. His respiratory status improved with conservative treatment, but his convulsions were persistent even after prescription of several antiepileptic drugs. His serum and cerebrospinal fluid showed decreased vitamin B6 vitamers and increased upstream metabolites of α-aminoadipic semialdehyde dehydrogenase, strongly suggesting a diagnosis of PDE; the epileptic spasms ceased after administration of intravenous pyridoxal phosphate hydrate. Gene analysis revealed novel compound heterozygous mutations in *ALDH7A1* that included NM_001182.4:[c.1196G > T] and [c.1200 + 1G > A]. Atypical birth asphyxia with persistent neonatal seizure should prompt vitamin B6/metabolite screening.

INTRODUCTION

Pyridoxine-dependent epilepsy (PDE; no. 266100 in the Online Mendelian Inheritance in Man [OMIM] Database) is a rare autosomal-recessive disorder, typically presenting as neonatal seizures. It is unresponsive to conventional antiepileptic drugs but can be controlled by continuous supplementation with pyridoxine [1]. Historically, PDE has been diagnosed by its clinical responsiveness and dependency on pyridoxine. The causative gene was eventually identified as *ALDH7A1* and mapped to 5q31, which encodes α-aminoadipic semialdehyde (α-AASA) dehydrogenase [2]. PDE is sometimes difficult to diagnose, because the clinical features mimic those of birth asphyxia. Here, we report a patient with PDE and novel compound heterozygous mutations.

CASE REPORT

A Japanese newborn boy was transferred to our hospital due to respiratory distress and convulsions. He was born at a gestational age of 39 weeks, 2865-g weight (−0.5 standard deviations [SD]), 49.0-cm long (+0.0 SD), 34.5-cm occipito-frontal circumference (+0.8 SD), and Apgar scores of 7 at 1 min and 9 at 5 min. He was the first baby of non-consanguineous parents with no family history of neurological or metabolic disorders.

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Table 1: Laboratory data at birth

White blood cells	25.8×10^3	/μl	pH	7.164	
Red blood cells	4.23×10^6	/μl	$paCO_2$	37	mmHg
Haemoglobin	16.1	g/dl	paO_2	61	mmHg
Haematocrit	50.1	%	HCO_3	12.8	mmol/L
Platelet cells	323.0×10^3	/μl	Base excess	-15.1	mmol/L
			Lactate	10.2	mmol/L
Total protein	5.3	g/dl			
Albumin	3.6	g/dl	PT s	16.0	s
Total bilirubin	2.35	mg/dl	PT%	56.3	%
AST	125	IU/L	PT-INR	1.39	
ALT	8	IU/L	APTT	39.6	s
LDH	785	IU/L	Fibrinogen	105.4	mg/dl
CK	2845	IU/L	Hepaprastin	43.1	%
BS	103	mg/dl	Antithrombin-III	45.6	%
BUN	7.3	mg/dl	FDP	14.2	μg/ml
Creatinine	0.97	mg/dl	D-dimer	7.2	μg/ml
Na	136	mmol/L			
K	4.0	mmol/L			
Cl	104	mmol/L			
Ca	10.1	mmol/L			
P	6.4	mmol/L			
NH_3	81	μg/dl			

AST, aspartate aminotransferase; ALT, alanine transaminase; LDH, lactate dehydrogenase; CK, creatine kinase; BS, blood sugar concentration; BUN, blood urea nitrogen; PT, prothrombin time; PT-INR, prothrombin time-international normalized ratio; APTT, activated partial thromboplastin time; FDP, fibrin/fibrinogen degradation products.

He experienced haemoptysis and convulsions immediately after birth. He repeatedly cried, fluttered and deviated his eyes, with abnormal amplitude-integrated EEG monitoring. The convulsions persisted for 2 h before phenobarbital was prescribed. Radiography revealed ground-glass opacifications in both lungs suggestive of pulmonary haemorrhage. No significant coagulopathy was evident (Table 1). Four hours after the birth, brain computed tomography was performed, which showed diffuse, but mild, low-density cerebral white matter and a thin subdural hematoma along the tentorium cerebelli of the posterior fossa. At 1 day, brain magnetic resonance imaging (MRI) showed a thin corpus callosum, diffuse,but mild, cerebral white-matter signal abnormalities, delayed myelination and a thin hematoma within the posterior fossa (Fig. 1). He was intubated for 2 days. Seizures decreased with midazolam, levetiracetam and phenobarbital but did not cease completely. Interictal electroencephalography showed no abnormalities. At the age of 1 month, he developed epileptic spasms, which were confirmed by ictal electroencephalography and were immediately responsive to 60 mg intravenous pyridoxal phosphate hydrate (the typical dose is 50–100 mg) [1]. Oral pyridoxal phosphate maintenance dose was started (18 mg kg^{-1} day^{-1}; the typical dose is 15 mg kg^{-1} day^{-1}), and all antiepileptic drugs were discontinued with no seizure recurrence. We measured vitamin B6 vitamers and PDE-related metabolites in the cerebrospinal fluid and serum [2, 3, 4]. The results, findings of decreased vitamin B6 vitamers and increased upstream α-AASA dehydrogenase metabolites, strongly suggested an α-AASA dehydrogenase deficiency (Fig. 2; Table 2). After obtaining informed parental consent, we performed direct sequencing of *ALDH7A1* sampled from the patient's peripheral blood cells. Sequencing revealed two *ALDH7A1* mutations, namely NM_001182.4:[c.1196G > T(;)c.1200 + 1G > A]. A paternal specimen could not be obtained. Therefore, TA cloning was performed, and the mutations were confirmed on each allele. The patient's genotype was determined as NM_001182.4:[c.1196G > T];[c.1200 + 1G > A] (Fig. 3). These mutations were not listed in public databases such as Exome Variant Server (https://evs.gs.washington.edu/) and Human Genetic Variation Browser (http://www.hgvd.genome.med.kyoto-u.ac.jp/). According to an analysis published in the Berkeley Drosophila Genome Project (https://www.fruitfly.org/), the c.1196G > T (p.Glu399Val) mutation is a missense mutation in exon 13 that alters a highly conserved position in the catalytic domain. According to the same analysis, the c.1200 + 1G > A mutation is a point mutation of the first base of the intron next to exon 13 and leads to a splicing mutation.

Interictal electroencephalography performed at the age of 19 months showed positive sharp waves at bilateral occipital lobes. Cerebral MRI performed at the age of 24 months revealed signal abnormalities at the ventricular trigones (Fig. 1). Motor developmental milestones were delayed without regression, but his psychosocial development was almost normal according to the Enjoji developmental test (Table 3) [5].

DISCUSSION

We reported novel *ALDH7A1* mutations, presenting as neonatal pulmonary haemorrhage and a subdural hematoma, which have not been previously reported. Foetal and neonatal abnormalities resembling hypoxic-ischemic encephalopathy are relatively common in PDE [6]. Our patient did not have a low Apgar score but experienced acidosis and severe respiratory distress due to pulmonary haemorrhage. Status epilepticus immediately after birth might cause neurogenic pulmonary oedema, as neurogenic pulmonary haemorrhage is known to be induced by epileptic seizures [7]. We found no primary disease that could have caused the pulmonary haemorrhage or subdural hematoma. Pulmonary haemorrhage is not a reported complication of PDE; however, it could be a symptom of PDE and may lead to severe respiratory distress.

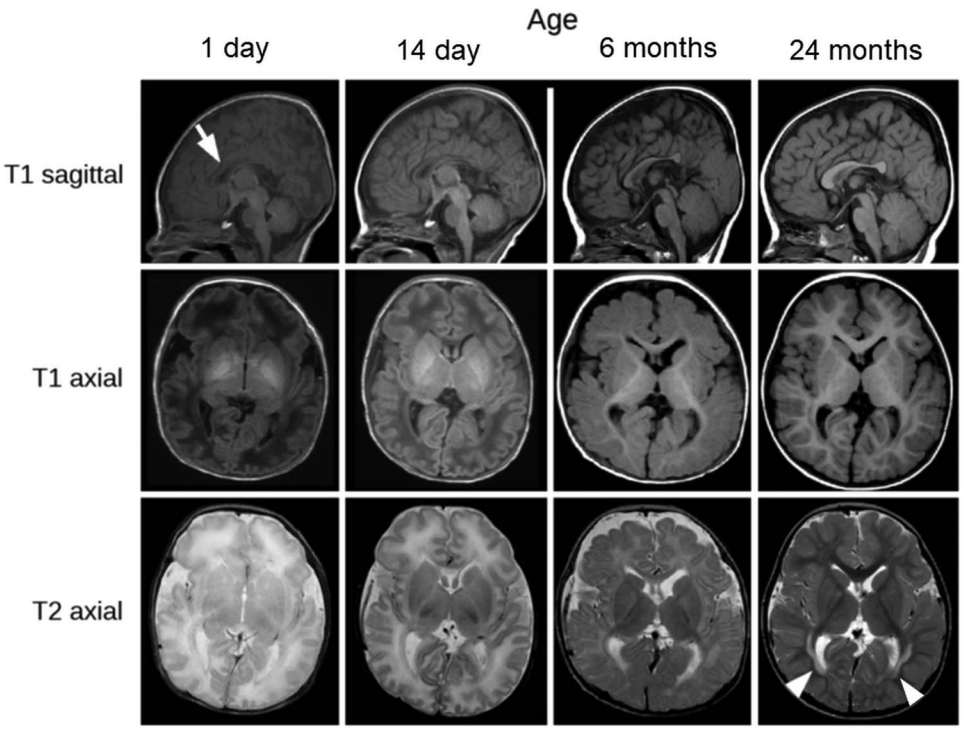

Figure 1: MRI findings obtained at 1 day, 14 days, 6 months and 24 months. The images shown are in the first to third rows, respectively, T1-weighted mid-sagittal, T1-weighted axial at the basal ganglia level and T2-weighted axial at the same level. The early images show a thin corpus callosum (arrow), diffuse white-matter signal abnormalities and delayed myelination. As the patient matures, the corpus callosum thickens and myelination gradually progresses. White-matter signal abnormalities persist along the ventricular trigones (arrowhead). The hyperintense white matter surrounded by hypointense area might be gliosis with oedema or 'terminal zones' that is a normal feature of late-stage myelination.

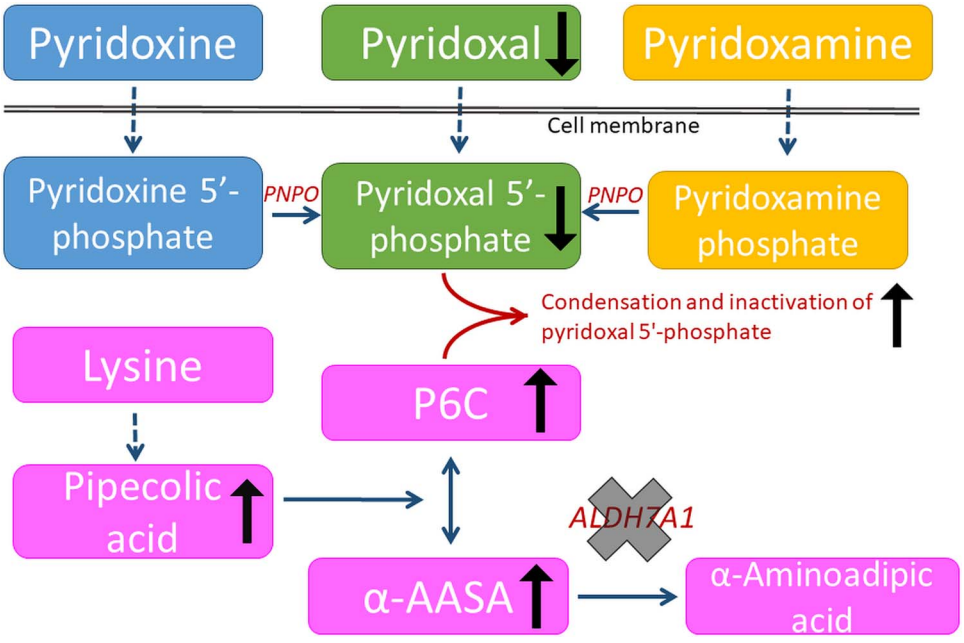

Figure 2: The pyridoxine metabolic map. When α-AASA dehydrogenase is inactivated, the vitamin B6 vitamers, which is synthesized by α-AASA dehydrogenase, decrease including pyridoxal 5′-phosphate, pyridoxal and 4-pyridoxic acid. Upstream metabolites, such as pipecolic acid and α-AASA, increase. PNPO, pyridoxine 5′-phosphate oxidase; P6C, piperidine-6-carboxylate.

Brain MRI findings in PDE are non-specific [8]. Signal abnormalities of the white substance that persist along the ventricular trigones are suggestive of gliosis surrounded by oedema, as previously reported [9]. The hyperintense white substance may be associated with the abnormal discharge in the occipital lobes.

The c.1200 + 1G > A mutation leads to a splicing mutation that has a greater impact on the gene product than an amino

Table 2: Vitamin B6 vitamers and upstream metabolites of α-AASA dehydrogenase

			Specimen			
			Cerebrospinal fluid		Serum	
	Item	Unit	Measured value	Reference range	Measured value	Reference range
Vitamers	PLP	nmol/L	<3.5	26–69	7.7	20.5–151
	PL	nmol/L	<2	16.1–55.7	<4	8.8–58.7
	4-PA	nmol/L	<1.2	<3.1	2.7	8.8–104
Upstream metabolites	Pipecolic acid	μmol/L	5.6	<0.12	23.7	1–3.2
	α-AASA	μmol/L	8.1	<0.1	7.5	<0.2

PLP, pyridoxal 5′-phosphate; PL, pyridoxal; 4-PA, 4-pyridoxic acid; α-AASA, α-aminoadipic semialdehyde.

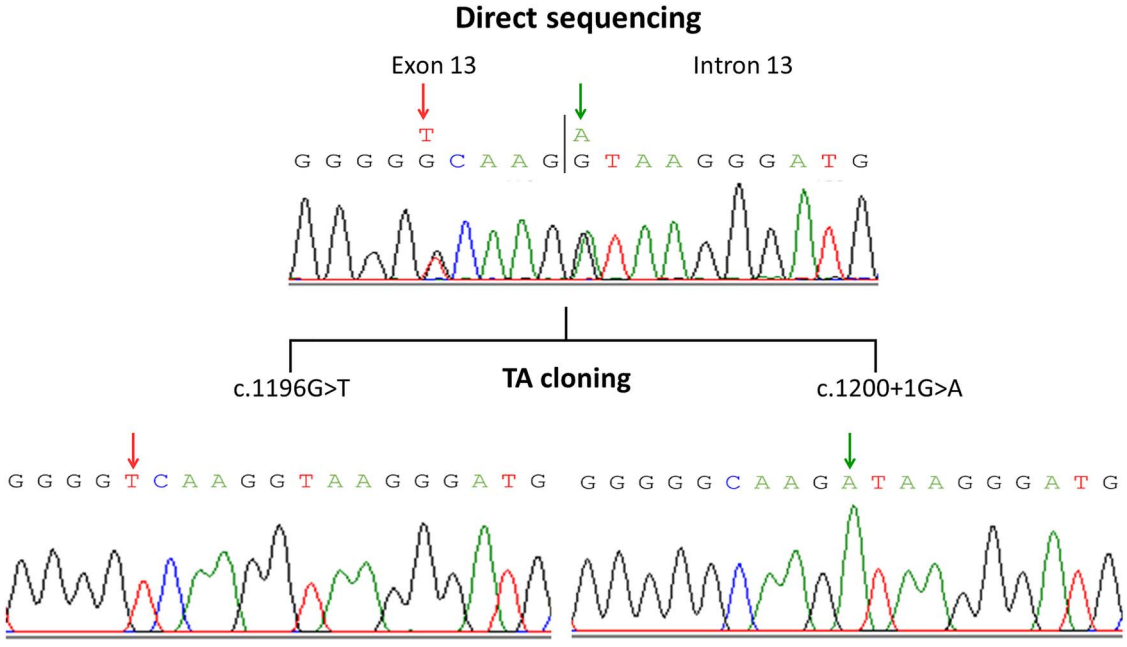

Figure 3: Genetic findings. Upper row: direct sequencing of *ALDH7A1* exon 13 and its intron boundary. Lower row: TA cloning methods confirm the presence of the compound heterozygous mutations NM_001182.4:[c.1196G > T];[c.1200 + 1G > A].

Table 3: Developmental quotient at 2 years and 9 months of age

		DQ
Motor movement	Gross	48
	Fine	73
Social skill	Daily habits	79
	Interpersonal skills	100
Language	Speech	82
	Comprehension	73
Average DQ		75

DQ, developmental quotient.

acid substitution. Moreover, the missense mutation c.1196G > T (p.Gly399Val) is predicted to be pathogenic by its Polyphen 2 score (= 1.000, 'probably damaging') and its SIFT score (= 0, 'damaging'). These scores should be interpreted as 'likely pathogenic' by the standards and guidelines of the American College of Medical Genetics and Genomics [10]. We did not perform a functional analysis of these mutations, but we consider both as pathogenic for the above-mentioned reasons.

We found that vitamin B6 vitamer and PDE-related metabolite analyses represent an effective alternative method of measuring α-AASA dehydrogenase activity [2, 3, 4]. *ALDH7A1* encodes the enzyme α-AASA dehydrogenase, and its dysfunction causes piperidine-6-carboxylate (P6C) accumulation. P6C inactivates pyridoxal 5′-phosphate (the only active form of vitamin B6), and the lack of activated vitamin B6 leads to seizures. We did not perform an enzyme assay, deducing that we could rely on the metabolite analysis to confirm an *ALDH7A1* mutation.

We promptly diagnosed neonatal PDE by determining vitamin B6 vitamers and PDE-related metabolites, even though the associated mutations in *ALDH7A1* were novel. Early treatment can potentially improve neurodevelopmental outcomes. Therefore, clinicians should not hesitate to screen for PDE by measuring vitamin B6 vitamers and/or PDE-related metabolites. Further research into PDE aimed at providing earlier diagnoses and better treatments is warranted.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

FUNDING

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ETHICAL APPROVAL

The study design and methodology were approved by the ethics committees of Okayama University (1809–003) and Gunma Children's Medical Centre (GCMC2018–6).

CONSENT

Informed consent was obtained from the patient's parent for publication of this case report.

GUARANTOR

YD is the Guarantor of this paper.

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