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CASE REPORT

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Pyridoxine-dependent epilepsy caused by an ALDH7A1 mutation in an infant girl: the first case report in Syria

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Abstract

Background Pyridoxine-dependent epilepsy is primarily characterized by early-onset refractory seizures. This condition can be caused by alpha-aminoadipic semialdehyde dehydrogenase deficiency due to a mutation in the ALDH7A1 gene, leading to the accumulation of certain substances that impact the production of various brain neurotransmitters and enzymes.

Case presentation Our report presents the first documented case of pyridoxine dependency in Syria. The female infant, born to consanguineous parents, exhibited seizures on the second day of life. Despite the administration of multiple antiepileptic medications, seizures persisted. A comprehensive assessment, including metabolic evaluation, electroencephalography, and phenotypic characteristics of seizures, prompted genetic testing for pyridoxine-dependent epilepsy, which identified a homozygous likely pathogenic variant in the ALDH7A1 gene, confirming the diagnosis of this condition. Subsequently, the baby was put on oral pyridoxine, resulting in complete cessation of seizures.

Conclusions Due to its rarity, this condition was initially overlooked and led to an inappropriate therapeutic approach. Pyridoxine dependency should be considered after the manifestation of refractory seizures, as increased awareness can enable early diagnosis, appropriate treatment, and avoid unnecessary use of antiepileptic drugs. However, predicting the long-term outcome remains challenging.

Keywords Pyridoxine-dependent epilepsy, Antiquitin, Genetic disorder, Rare genetic disorders, Case report

Background

Pyridoxine-dependent epilepsy (PDE) is a rare condition (OMIM: 266100) with an estimated incidence ranging from 1:400,000 to 1:750,000 [1]. This incidence rate may be underestimated globally, as many patients might be underdiagnosed, particularly in under-reported and resource-limited regions like Syria, where access to genetic testing and specialized diagnostics is limited. In 2006, mutations in ALDH7A1, which encodes antiquitin (ATQ), were identified as the primary cause of PDE [2]. Since then, multiple variants have been identified within the ALDH7A1 gene [2–5], and more than 340 cases have been confirmed via genetic analysis [6]. This genetic anomaly precipitates a deficiency in the enzyme alpha-aminoadipic semialdehyde (α-AASA) dehydrogenase (ATQ), an integral part of the lysine catabolic pathway, leading to the accumulation of α-AASA, piperidine-6-carboxylate (P6C), and pipecolic acid [3]. P6C hampers

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the function of pyridoxal 5'-phosphate (PLP), the active form of pyridoxine. PLP serves as a cofactor for glutamic acid decarboxylase, which is responsible for converting glutamate into the inhibitory neurotransmitter gamma-amino butyric acid (GABA). Moreover, it acts as a cofactor for numerous other enzymes in the brain [7].

Although ATQ deficiency is not adequately addressed by daily oral pyridoxine intake, it has been shown to significantly improve seizure management and prevent neurological development impairment or even reverse it [4]. However, awareness of PDE remains low, often leading to delays in diagnosis, inappropriate management, and poorer neurological outcomes. This underscores the crucial importance of early identification, diagnosis, and treatment of this condition. In this context, we present the first reported case of PDE in Syria involving a female baby who began experiencing seizures on her second day after birth, as we aim to shed light on PDE in an under-reported region and highlight the need for increased awareness and access to diagnostic tools.

Case presentation

This report highlights a compelling case involving a female infant born to a consanguineous family. The maternal history revealed a G2P2L2 previously healthy non-smoker non-worker mother. The first gestation resulted in a premature baby who had lower limb deformities, who his loss was evident several days after birth at 35 weeks of gestation. The current newborn, who was delivered naturally at term (birth weight: 3.1 kg, length: 49 cm, head circumference: 34.5 cm) without notable complications, suffered from a 1-minute episode of abnormal eye movements prior to discharge on the second day of life. Patient also had another episode of abnormal movement of both hands, and was hypotonic outside those episodes. The medical team promptly administered midazolam, levetiracetam, and phenytoin, due to their broad-spectrum efficacy in neonatal seizures, resulting in slight improvements.

On day 7, a head computed tomography (CT) revealed bilateral calcifications surrounding the caudate nucleus alongside the noted cavum septum pellucidum (Fig. 1). Notably, examinations of other systems showed no abnormalities. Concerns regarding congenital infections prompted antibody testing for toxoplasmosis, cytomegalovirus, and rubella, which yielded unpredictably negative IgM and positive IgG results. After several days with no seizures, the infant relapsed on day 12, necessitating readmission. She experienced respiratory distress, requiring assisted ventilation, and exhibited muscle hypotonia. An electroencephalogram (EEG) revealed persistent abnormal patterns with generalized epileptic discharges (Fig. 2). Polymerase chain reaction (PCR) testing for toxoplasmosis and cytomegalovirus returned negative results. By day 20, the infant was successfully weaned off ventilation but needed topiramate and levetiracetam after seizure recurrence.

Subsequent magnetic resonance imaging (MRI) at 1 month revealed the surprising absence of calcifications, with well-defined basal ganglia, demonstrating a natural shape and signal (Fig. 3). The cerebral cortex presented a typical normal appearance, and differentiation between grey and white matter was noted. The ventricles appeared completely normal, and no signs of lesions or hemorrhage were observed. The cavum septum pellucidum persisted. A metabolic consultation was sought at this

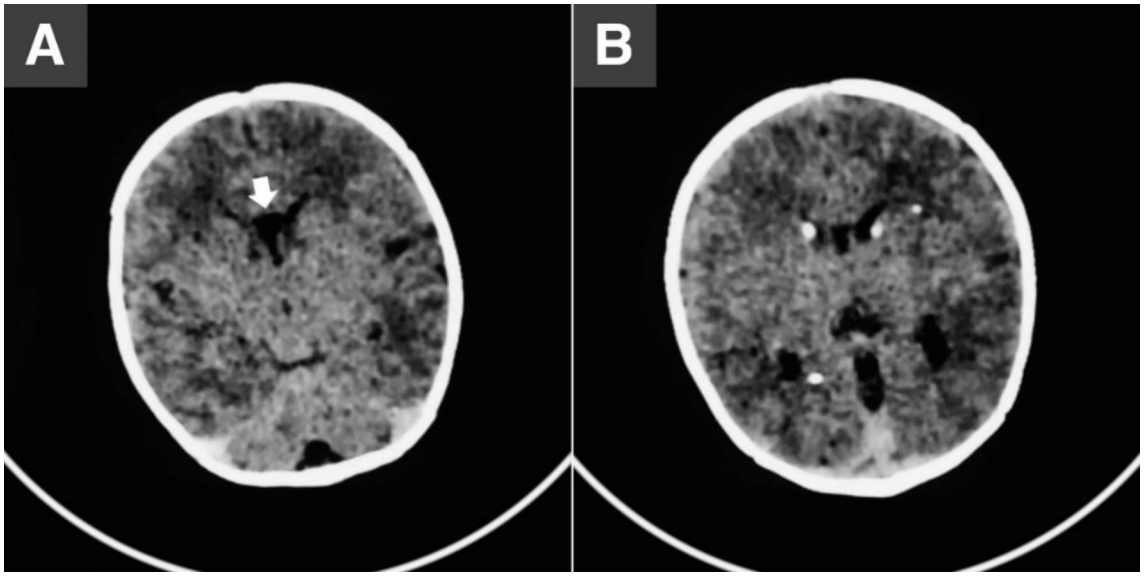

Fig. 1 Initial CT scan at one week showing (**A**) cavum septum pellucidum (arrow) and (**B**) multiple calcifications predominantly surrounding the caudate nucleus

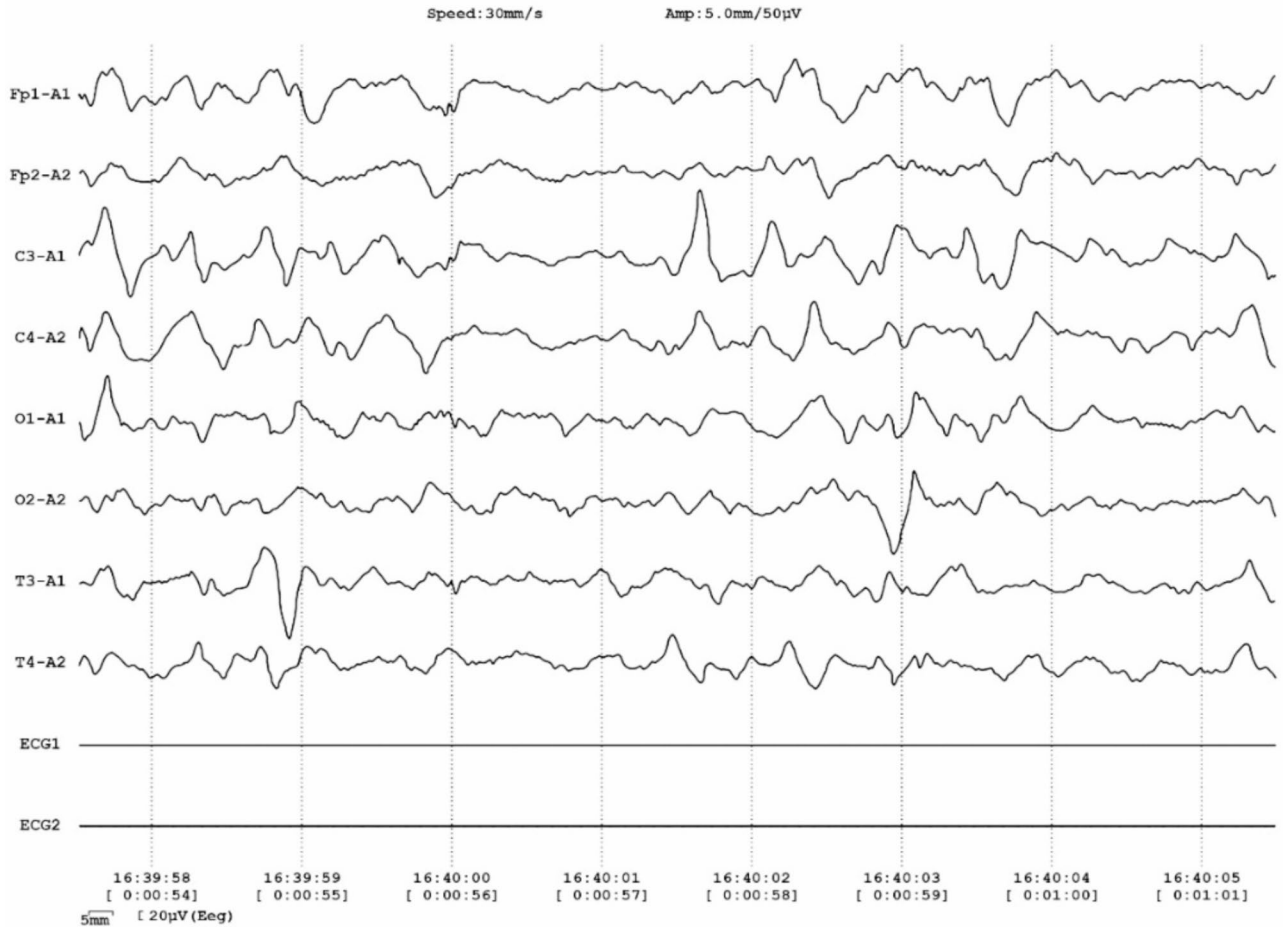

Fig. 2 Abnormal pattern with continuous epileptiform discharges on EEG at two weeks

point. Assessment revealed elevated levels of lactic acid and ammonia (35 mg/dl and 135.8 mcg/dl, respectively), indicating a potential enzymatic deficiency. Gas chromatography of urine organic acids (GC-OAs) detected elevated levels of β-hydroxybutyric acid and slightly elevated levels of acetoacetic acid and β-ketovaleric acid. These results lack specificity but may suggest an anomaly within the Krebs cycle. Based on these findings, L-carnitine, arginine hydrochloride, and thiamine were prescribed. Despite this, the seizures persisted, occurring two to three times daily, even with the administration of multiple anticonvulsants.

By 5 months, developmental delays became apparent, with poor head control and delayed social interaction. A suspicion arose regarding ATQ deficiency, commonly referred to as pyridoxine-dependent epilepsy (PDE). Genetic testing via whole exome sequencing at seven months of age confirmed a homozygous frameshift likely pathogenic variant c.1597del p.(Ala533Profs*109) in the ALDH7A1 gene, indicating early-onset vitamin B6-dependent epilepsy-4 (EPEO4), otherwise known as PDE. The infant was discharged on clonazepam (1 oral drop daily of 2.5 mg/ml solution), sodium valproate (100 ml/day of 57.64 mg/ml syrup) and oral pyridoxine (250 mg/day). Parental genetic counseling was recommended before any future pregnancy.

At ten months, the infant remained seizure-free. Developmental assessment revealed some improvement, with the infant now able to sit with support and engage in social smiling, though some motor delays persisted. A neurologic follow-up guided the discontinuation of clonazepam and gradual tapering of sodium valproate (reducing 25 ml every 10 days until it eventually stopped after one month). At one year of age, the baby has been free from seizures for five consecutive months and is currently receiving sole oral pyridoxine treatment at a dosage of 250 mg/day. Muscle tone improved, but she still had delayed motor milestones, being unable to pull to stand.

Discussion and Conclusions

Pyridoxine dependency in children typically commences at birth, resulting in resistance to traditional anticonvulsants, while rare instances of seizure onset occur in

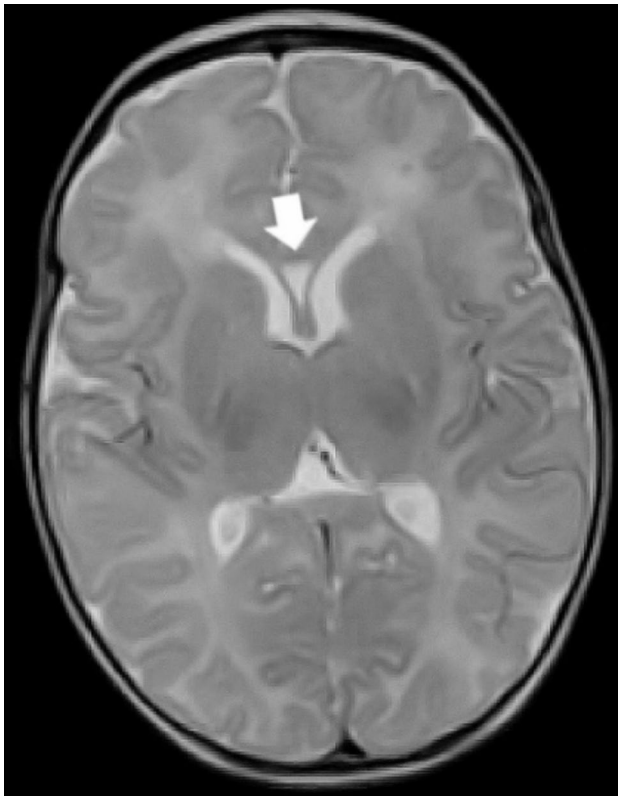

Fig. 3 Normal MRI findings with persistence of the cavum septum pellucidum (arrow) at one month

the second or third year [8]. Seizures manifest diversely, spanning from prolonged generalized tonic–clonic seizures evolving into status epilepticus to various other seizure types, such as atonic, myoclonic, visual seizures, and infantile spasms [5, 9]. A recent review reported that 67.8% of all PDE cases experienced seizure onset before the age of 1 month, often resistant to traditional antiepileptic medications, as seen in our case [6]. Additionally, generalized motor seizures are the most commonly observed seizure type at onset (29.7%) [6]. In contrast, our case primarily exhibited frequent focal and tonic-clonic seizures.

MRI findings present variability, showcasing callosal dysgenesis, either hypoplastic or dysplastic corpus callosum, cortical dysplasia, hydrocephalus, ventriculomegaly, and subependymal cysts [10]. Moreover, EEG in pyridoxine-dependent patients commonly shows abnormal sleep patterns, slow-high voltage activity, generalized rhythmic slow-waves, and paroxysmal sharp elements [8, 11]. In 81.1% of PDE cases caused by ALDH7A1 deficiency, abnormal initial EEG patterns are observed [6]. Similarly, our patient's initial EEG showed continuous abnormal background with generalized discharges of epileptiform spikes and sharp waves. On the other hand, no notable abnormalities were found on the newborn's head MRI, as in 82,1% of cohorts with ALDH7A1 mutations, revealed a recent review [6]. This underscores the variability in PDE imaging findings, where most patients, even with severe clinical presentations, may present with normal MRI results.

Pyridoxine dependency warrants consideration as a potential cause of intractable seizures in specific scenarios, including seizures of unknown origin in otherwise healthy infants with no abnormal gestational or perinatal history, prolonged focal or unilateral seizures, medication-resistant seizures, or parental consanguinity [4, 12, 13]. Thus, recommendations suggest that all neonates experiencing unexplained seizures should undergo a trial of intravenous (IV) pyridoxine to evaluate responsiveness [12]. Despite our patient presenting the scenarios above, the consideration of PDE was inadvertently overlooked. Neonates might also initially exhibit symptoms akin to birth asphyxia or intrauterine infection, which can lead to mistaking seizures for part of hypoxic ischaemic encephalopathy [13]. This can potentially lead to a misinterpretation of clinical findings. In this case, although the patient showed no infection-related symptoms, cerebral calcifications on the initial CT scan raised a suspicion of infectious encephalopathy.

The pathophysiology of PDE associated with ALDH7A1 mutations involves three main components: the primary accumulation of α-AASA and its derivative P6C due to ATQ deficiency, subsequent PLP deficiency resulting from this accumulation, and the secondary accumulation of pipecolic acid [4]. Diagnosing PDE linked to α-AASA dehydrogenase (ATQ) deficiency currently relies on measuring α-AASA levels in urine, which is considered the optimal diagnostic procedure [14]. However, it is important to highlight that other mutations, such as pyridoxamine 5'-phosphate oxidase (PNPO) and PLP-binding protein (PLPBP) deficiencies, can lead to pyridoxine dependency, meaning that only cases caused by ATQ deficiency (ALDH7A1 gene mutation) will lead to elevated α-AASA levels. Confirming the diagnosis involves mutation analysis of the ATQ gene (ALDH7A1) [4]. In our case, the consideration of PDE as a potential diagnosis occurred later in the clinical timeline relative to the onset of seizures; consequently, the parents sought a definitive diagnosis, prompting their choice of genetic analysis via whole exome sequencing over conventional molecular testing. Historically, PDE diagnosis involved withdrawing pyridoxine to observe seizure recurrence and then administering it again to confirm responsiveness before biomarkers were identified [4]. Although this initiative carries a significant amount of risk to the baby's life, it was not applied here.

The standard treatment for PDE involves lifelong supplementation with pyridoxine at pharmacologic doses [4]. In acute seizure episodes, immediate administration of pyridoxine is recommended [15]. The recommended

dose of oral pyridoxine is 30 mg/kg/day, which was equivalent to approximately 250 mg/day in our case [16]. This dose may be doubled during acute infections that can provoke seizure exacerbations. Once seizures are effectively controlled through daily pharmacologic doses of pyridoxine, all antiepileptic medications can be discontinued in most individuals [16]. It was reported that 55.4% of pediatric patients with PDE respond well to pyridoxine therapy, achieving complete seizure freedom, while significant seizure reduction occurred in 12.2% of the cases [6]. Adjunctive therapies, such as lysine reduction through dietary modification or use of lysine-reducing agents, have shown potential in improving cognitive and developmental outcomes by limiting the accumulation of neurotoxic intermediates such as pipecolic acid and α-AASA, which contribute to neurodevelopmental impairment [17]. Evidence suggests that combining pyridoxine therapy with lysine reduction may optimize both seizure control and cognitive development, although further longitudinal studies are needed to validate these effects [6]. Our patient was able to remain seizure-free after weaning off all antiepileptic medication and keeping oral pyridoxine.

Several genetic mutations are associated with PDE, each adding complexity and variability to clinical presentations and treatment approaches. Common mutations, besides ALDH7A1 deficiency, include PNPO and PLPBP deficiencies, hyperprolinemia type II (ALDH4A1 gene), and hypophosphatasia (ALPL gene) [6]. While most PDE cases present with neonatal-onset seizures, ALDH4A1-related seizures typically begin after the neonatal period [6]. Specific clinical features vary across these disorders, such as dystonia in ALDH7A1 and PNPO deficiencies, behavioral disturbances in ALDH4A1 mutations, and dysmorphisms or skeletal abnormalities in hypophosphatasia [6]. Additionally, these conditions are managed effectively with pyridoxine at pharmacologic doses, even cases like PNPO, previously considered responsive exclusively to PLP therapy [18].

One of the challenges in managing PDE, particularly in cases associated with ALDH7A1 mutations, is the scarcity of long-term follow-up data. Seizure types during follow-up were reported for only 10.2% of ALDH7A1 patients with molecular genetic diagnosis, and longitudinal EEG patterns were available for just 22.1% of them [6]. Although pyridoxine therapy can control seizures in many patients, as stated previously, long-term neurological and developmental prognosis remains uncertain due to the variability reported across cases. Available data show that some patients continue to experience developmental delays or intellectual disabilities despite early treatment, while others may achieve near-normal development [4, 9, 19]. This lack of comprehensive data underscores the need for systematic follow-up of PDE patients to optimize management strategies.

Pyridoxine dependency could have been considered earlier in the management after initial anticonvulsants were found to be ineffective. However, the diagnosis was made at a relatively early stage in the baby's life, allowing timely commencement of the correct therapy. Future research is essential to better understand the long-term cognitive outcomes in PDE patients, particularly in regions with limited access to early genetic testing. Improved awareness, alongside the development of more accessible diagnostic tools, will be crucial in optimizing management strategies and minimizing neurological damage.

Abbreviations

PDE	pyridoxine-dependent epilepsy
ATQ	antiquitin
α-AASA	alpha-aminoadipic semialdehyde
PLP	pyridoxal 5'-phosphate
P6C	piperidine-6-carboxylate

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Author contributions
RJ curated the data. RJ and HS participated in writing, editing and reviewing the manuscript. MZ, AJ and HF participated in writing the original draft. DA supervised and performed the final review. All the authors have read and approved the final manuscript.

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Data availability
All datasets generated and/or analysed during this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
Ethical approval was received from the Ethics Committee of Children's University Hospital.

Consent for publication
Written informed consent was obtained from the patient's parent for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal upon request.

Competing interests
The authors declare no competing interests.

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