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Late-onset drug-resistant epilepsy in pyridoxamine 5′-phosphate oxidase deficiency: a case report

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Abstract

Background Pyridoxamine 5′-phosphate oxidase deficiency is a rare inborn error of vitamin B_6 metabolism that presents with drug-resistant epileptic seizures. However, the condition is responsive to supplementation with the active vitamin B_6 metabolite pyridoxal 5′-phosphate and, in some cases, pyridoxine.

Case presentation In this case report, a 10-year-old Iranian male of Fars ethnicity came to a regional hospital in Tehran, Iran with a chief complaint of tic-like movement. He had a history of unintentional, repetitive, and stereotypic movements of both arms since the age of 4 years. The physical examination depicted facial dimorphism. During admission, the patient experienced habitual hypermotor seizures and generalized tonic–clonic seizures. Ictal electroencephalography demonstrated a generalized background attenuation and bursts of generalized, predominantly left-sided, biphasic spike-wave complexes. Whole-genome sequencing revealed a pyridoxamine 5′-phosphate oxidase deficiency as the underlying cause of the drug-resistant seizures, resulting in a low serum level of pyridoxal 5′-phosphate. The patient underwent pyridoxine supplementation therapy, which ultimately resolved his seizures. At 6 months, he was seizure free.

Conclusion Physicians ought to be aware of manifestations of vitamin B6 deficiency such as mimicking tic and consider it in the differential for drug-resistant epilepsy.

Keywords PNPO, Drug-resistant epilepsy, Seizure, Vitamin B_6, A case report

Introduction

Epilepsy is a neurological condition characterized by the occurrence of repetitive and transient unprovoked seizures, and it may have detrimental effects on the psychological well-being, quality of life, and work health of patients [1]. Approximately 5 million new cases of epilepsy are diagnosed annually, with between 4 and 10 per 1000 people in the general population having active epilepsy at any given time, according to the World Health Organization (WHO) [2]. Despite advancements in antiepileptic drug therapy over the past decades, over 30% of patients with epilepsy experience treatment resistance, which leads to a notable increase in epilepsy mortality and morbidity [3].

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Autosomal-recessive pyridox(am)ine 5′-phosphate oxidase (PNPO) deficiency is a rare cause of metabolic encephalopathy associated with vitamin-responsive seizures [4]. PNPO deficiency is characterized by drug-resistant epileptic seizures, but it is responsive to administration of the active vitamin B_6 metabolite pyridoxal 5′-phosphate (PLP) and, in some cases, pyridoxine (PN) supplementation [4]. In addition to epileptic encephalopathy, PNPO deficiency can present with a wide range of other clinical manifestations, including respiratory distress, metabolic acidosis, dystonia, hepatomegaly, and prematurity [5].

This case report describes a patient suffering from drug-resistant epilepsy caused by PNPO deficiency, who exhibited a favorable response to vitamin B_6 supplementation.

Case presentation

A 10-year-old Iranian male of Fars ethnicity was admitted to the neurology ward in a regional hospital in Tehran, Iran in January 2023, with a chief complaint of tic-like movement on upper extremities. The patient reported a history of unintentional, repetitive, and stereotypic movements of both arms since the age of 4 years. Notably, consciousness was maintained throughout these episodes. These movements were initially diagnosed as tics, and the patient was prescribed sertraline, aripiprazole, and sodium valproate for tic treatment. However, the abnormal movements did not resolve with this medication regimen, and the frequency of the abnormal movements increased over time, to one episode per month from 9 months ago. The patient also reported experiencing multiple episodes of transient loss of consciousness beginning ~9 months prior to hospital admission. Following the increase in frequency of the abnormal movements and loss of consciousness episodes, the patient was admitted to the neurology ward of a regional hospital in Tehran, Iran to rule out epilepsy and long-term video-electroencephalographic monitoring (LTM) for further evaluation and characterization of the events. The patient's past medical history includes episodes of forced eye deviation and nystagmus that lasted several minutes since he was 2 years old, although the precise nature of these episodes remains unclear. Additionally, he has experienced symptoms of anxiety disorder, including skin picking, insomnia, and restlessness. To manage these symptoms, fluoxetine syrup was initiated.

The patient was delivered via cesarean section at 38 weeks of gestation, resulting in a low Apgar score (5 at minute 1) and asphyxia. He was hospitalized for 2 weeks following birth. His family history was unremarkable, except for consanguinity, as his parents are first cousins. The patient's early development was normal, and there is no reported history of febrile seizures, head trauma, or central nervous system (CNS) infections. Also, his social history was negative. As well, regarding dietary history, he had a regular diet regimen.

At the time of admission, the patient had been receiving a daily dose of 2cc of fluoxetine syrup. The patient reported no history of smoking or illicit drug use.

On physical examination, the patient presented as a well-appearing male without any signs of acute distress. He was awake, alert, and oriented to person, place, and time, and he was able to respond appropriately to questions. The patient's vital signs were within normal limits, with a temperature of 36.8 °C, heart rate of 86 bpm, respiratory rate of 19 breaths per minute, blood pressure of 125/76 mmHg, and oxygen saturation of 100% on room air. His weight was 35 kg (75th percentile), and his height was 137 cm (50th percentile). The remaining physical examination did not reveal any notable abnormalities. However, the patient presented with distinctive facial features, including hypertelorism, prominent supraorbital ridges, and a depressed nasal bridge. Furthermore, the patient exhibited characteristics associated with autism, such as repetitive behaviors.

The neurological examination revealed intact strength and sensation, with no focal neurological deficits. A comprehensive assessment of the cranial nerves, motor and sensory functions, reflexes, coordination, and gait did not yield any significant findings. A brain magnetic resonance imaging (MRI) was performed, and the results were unremarkable, showing no abnormalities. The patient's laboratory test results were all within the normal reference ranges, as presented in Table 1.

During the patient's admission for long-term electroencephalographic (EEG) monitoring, he experienced three episodes of habitual tics, which were characterized by increased motor activity without loss of awareness or facial features with fear expression. Additionally, the patient had one generalized tonic–clonic seizure (GTCs) during his hospitalization. Ictal video-EEG recordings captured the semiology of the seizure activity, which began with an aura followed by a hypermotor seizure. This then progressed to a right versive seizure with loss of awareness, which ultimately evolved into a GTC. The ictal EEG findings showed a generalized background attenuation at seizure onset, followed by bursts of generalized, predominantly left-sided, biphasic spike-wave complexes (Figs. 1, 2). Observed seizure semiology and the pattern of ictal EEG onset suggested that the abnormal movements, firstly diagnosed as tics, were in fact habitual hypermotor seizures (HMS), and the seizure activity was localized to the mesial frontal lobe, with a left-sided predominance.

Table 1 Laboratory tests

WBC	10.2×10^9/L ($4.5–11.0 \times 10^9$/L)[a]	LDH	250 U/L (140–280)
RBC	4.57 million cells/mcL (4.45–5.75)	Bill. T	0.5 mg/dL (less than 1)
Hb	14.8 g/dL (14–18)	Bill. D	0.2 mg/dL (less than 0.3)
HCT	43% (40%–54%)	25-(OH) Vit D_3	36.87 ng/mL (30–50)
MCV	87.6 fL (80–100)	Sodium	137 mEq/L (135–145)
MCH	29.2 pg/cell (27–31)	Potassium	4.6 mmol/L (3.6–5.1)
MCHC	33.8 g/dL (32–36)	Magnesium	1.8 mg/dL (1.7–2.2)
PLT	357,000/µL (150,000–450,000)	Urea	20 mg/dL (6–26)
RDW	14% (12%–15%)	Creatinine	0.6 mg/dL (0.7–1.3)
PT	12.1 s (10–13)	Calcium	9.9 mg/dL (8.6–10.3)
INR	1.03 (0.8–1.1)	Albumin	3.6 g/dL (2.5–4.5)
PTT	30 s (25–35)	Corrected Ca level	10.1 mg/dL (8.5–10.2)
FBS	97 mg/dL (70–100)	PTH	< 0.4 (14–65 pg/mL)
AST	19 U/L (14–22)	Total protein	6.9 g/dL (6.0–8.3)
ALT	25 U/L (29–33)	Phosphorus	3.6 mg/dL (2.5–4.5)
ALK.P	139 IU/L (44–158)	U/A	Negative

Laboratory tests at time of admission. Laboratory normal ranges are provided in parenthesis

ALK.P alkaline phosphatase, *ALT* alanine transaminase, *AST* aspartate transaminase, *Bill.D* direct bilirubin, *Bill.T* total bilirubin, *FBS* fasting blood sugar, *Hb* haemoglobin, *HCT* hematocrit, *INR* international normalized ratio, *LDH* lactate dehydrogenase, *MCH* mean corpuscular hemoglobin, *MCHC* mean corpuscular hemoglobin concentration, *MCV* mean corpuscular volume, *PLT* platelets, *PT* prothrombin time, *PTH* parathyroid hormone, *PTT* partial thromboplastin time, *RBC* red blood cell, *RDW* red cell distribution width, *U/A* urine analysis, *WBC* white blood cell

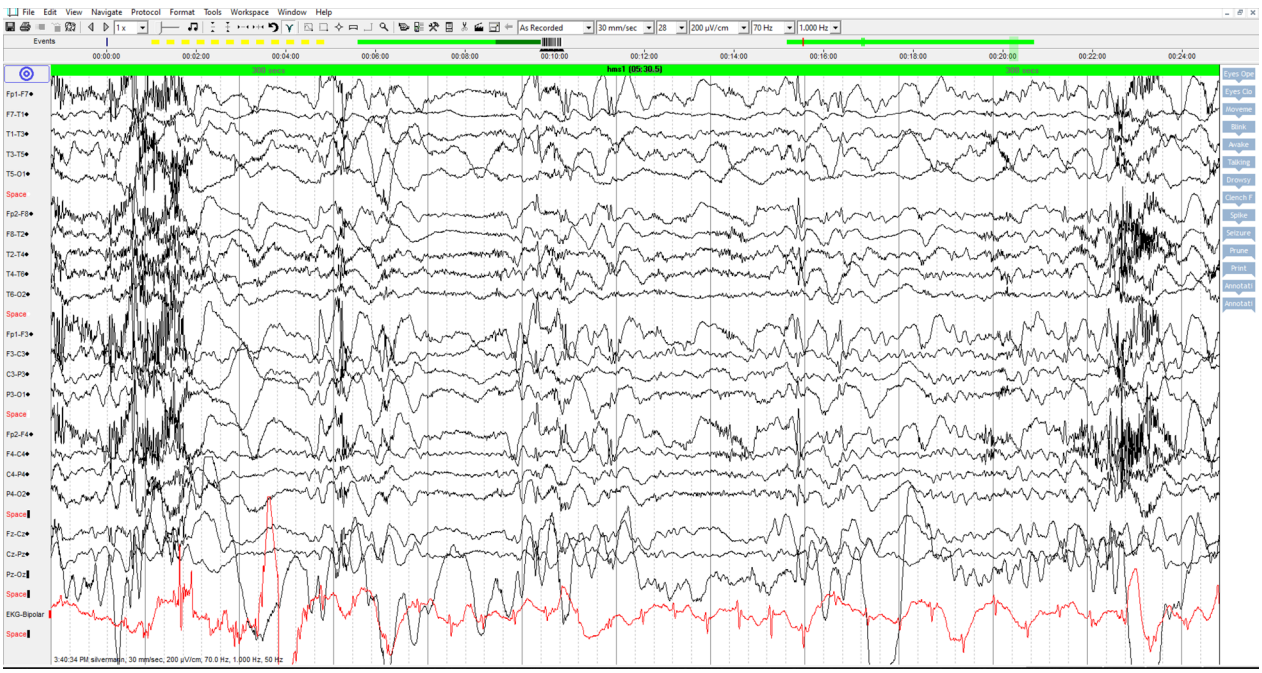

Fig. 1 The ictal electroencephalographic findings showed a generalized background attenuation at seizure onset, followed by bursts of generalized, predominantly left-sided, biphasic spike-wave complexes

Owing to coarse facial features, dysmorphic characteristics, and autistic traits of the patient, a request for genetic counseling was suggested. Whole-exome sequencing (WES) revealed a homozygous stopgain mutation (c.G358T:p.E120X) in the PNPO gene. Additionally, a hemizygous missense mutation (c.A188C:p.N63T) in the phosphatidylinositol glycan biosynthesis class A protein (PIGA) gene was also detected (Table 2).

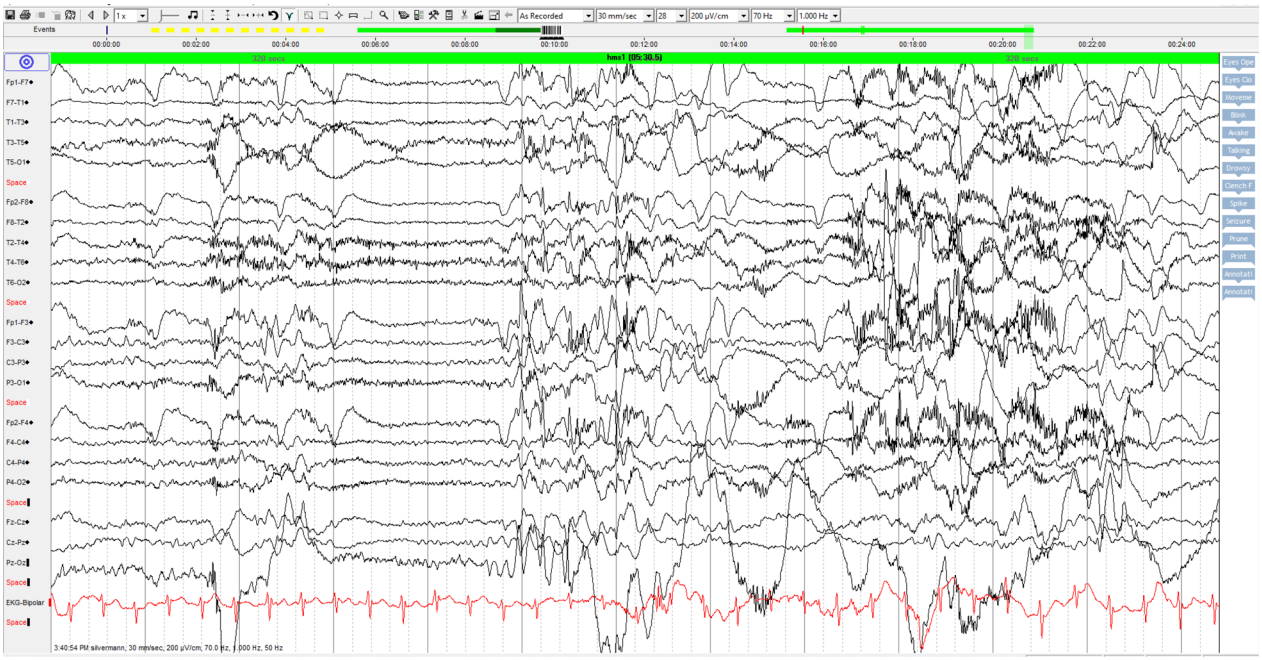

Fig. 2 The ictal electroencephalographic findings showed a generalized background attenuation at seizure onset, followed by bursts of generalized, predominantly left-sided, biphasic spike-wave complexes

Furthermore, a heterozygous missense mutation (c.C317T:pT106M) in the 6-pyruvoyltetrahydropterin synthase (PTS) gene was identified.

At the onset of admission, the patient was initiated on sodium valproate at an initial dose of 15 mg/kg/day orally, which was gradually increased to 60 mg/kg/day. Concurrently, levetiracetam was prescribed at an initial dose of 10 mg/kg twice a day orally, with subsequent increments of 10 mg/kg every 2 weeks, resulting in a maintenance dose of 30 mg/kg twice daily. Despite these interventions, the patient's epileptic seizures persisted. Subsequent WES identified PNPO deficiency, prompting the measurement of plasma PLP levels, which were found to be 0.3 µg/L (normal range 5–50 µg/L). Following the initiation of oral PN at a daily dose of 240 mg, sodium valproate and levetiracetam were tapered. Remarkably, the patient achieved a seizure-free interval of 6 months of follow-up while solely consuming PN.

Discussion

The dietary forms of vitamin B_6, PN and pyridoxamine, are ultimately converted to the biologically active form, PLP, through the action of the PNPO enzyme. PLP is essential for over 140 metabolic reactions, including those involved in the synthesis and degradation of brain neurotransmitters and neuromodulators [6]. PLP has been implicated in various physiological processes, and its deficiency has been linked to a wide range of disorders, including diabetes, cardiovascular diseases, pneumonia, coronavirus disease 2019 (COVID-19) progression,

Table 2 Gene study

Gene/transcript (RefSeq)	Variant position	Variant	Zygosity	Related phenotype	Inheritance pattern	Variant classification
PNPO: NM_018129	Chr17: 46022076: exon3	c.G358T: p.E120X	Hom	PNPO deficiency	AR	Likely pathogenic
PIGA: NM_020473	ChrX: 15343233: exon3	c.A188C: p.N63T	Hemi	Multiple congenital anomalies—hypotonia—seizures syndrome 2	XLR	VUS
PTS: NM_000317	Chr11: 112104157: exon6	c.C317T: p.T106M	Het	Hyperphenylalaninemia, BH4-deficient,A	AR	Pathogenic

The identified variant(s) related to phenotype in the proband

PNPO pyridox(am)ine 5′-phosphate oxidase, *PIGA* phosphatidylinositol glycan biosynthesis class A protein, *AR* autosomal recessive, *XLR* X-linked recessive, *VUS* variant of unknown significance, *PTS* 6-pyruvoyltetrahydropterin synthase

cancer, and seizures [7, 8]. Specifically, PLP deficiency increases the risk of seizures by reducing the production of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), because PLP is a crucial mediator in the decarboxylation of glutamate to GABA [8].

PNPO deficiency is an exceedingly rare metabolic disorder, with fewer than 100 cases diagnosed worldwide as of 2020. The key clinical features of this condition include prematurity, fetal distress, and treatment-resistant neonatal seizures [9]. Approximately 90% of PNPO-deficient patients fall into the "classic" category, characterized by seizure onset within the neonatal period, typically between 1 and 14 days after birth. The remaining 10% are classified as of "late-onset" type, experiencing seizure onset after the neonatal period. Affected individuals have been reported to exhibit a variety of seizure types, including myoclonic, clonic, and tonic seizures [10]. Individuals with PNPO deficiency may exhibit a combination of different seizure types, either within the same seizure episode or alternating between episodes [9]. Notably, these seizures are often refractory to common antiepileptic medications. However, the seizures in PNPO deficiency have been shown to be responsive to long-term treatment with PLP in 60% of cases, and to PN in 40% of patients [10]. Interestingly, our patient demonstrated a combination of HMS and GTCs, and also responded favorably to PN therapy.

A review of the literature reveals that the majority of patients with PNPO deficiency experience seizure onset on the first day of life, accounting for 48% of cases. An additional 22% of patients develop seizures during the neonatal period, while 11% have seizure onset during the embryonic period (noticed by the mother). Additionally, 15% of patients have seizure onset in the months following birth. Notably, only 4% of individuals with PNPO deficiency present with seizures years after birth [9]. A case report described two patients who experienced the onset of seizures after the first year of life. The first patient, a 20-month-old male, presented with an episode of focal clonic status epilepticus. Despite administration of three intravenous doses of midazolam, the seizures persisted. Ultimately, phenobarbital was effective in terminating the seizure activity. Interictal EEG revealed the presence of bilateral spikes, and slow waves localized to the frontotemporal region. The second patient, aged 3 years 2 months, exhibited multiple myoclonic-astatic and GTCs on a daily basis. Consistent with the findings in our patient, the initial EEG assessment revealed a slow background activity and the presence of multiple spike and wave discharges. Furthermore, the patient had experienced multiple absence, tonic, or tonic–clonic seizures since the age of 8, accompanied by similar EEG findings. The positive response to PN supplementation implies that a portion of the PNPO enzyme's function remains intact, allowing for the conversion of PN to PLP [11].

PNPO deficiency is associated with a broad spectrum of neurological complications beyond seizures, such as paroxysmal movement disorders, abnormal ocular motility (for example, gaze deviation), developmental delay, autism spectrum disorders (ASD), and attention-deficit/hyperactivity disorder (ADHD) [9]. Remarkably, our patient exhibited autistic characteristics, forced eye deviation, and nystagmus. Furthermore, PNPO deficiency can result in a variety of nonneurological symptoms, with prematurity being the most frequent manifestation [9]. However, our patient was not premature. Instead, he was affected by asphyxia and had a low Apgar score at birth, which has also been implicated in PNPO deficiency [10].

Normal brain imaging is the most common radiological finding observed in brain MRI images of patients with PNPO deficiency. However, some patients may exhibit abnormal findings, including diffuse brain atrophy, ischemic changes, and encephalomalacia. The EEG findings in patients with PNPO deficiency are quite variable: The most common EEG patterns include burst suppression, followed by multifocal spikes and sharp waves, as well as generalized spike and wave discharges. However, in contrast to brain MRI findings, normal EEG results are observed in a minority of these patients [9]. Although our patient had a normal brain MRI, the ictal EEG findings during the seizure episode showed generalized background attenuation at the onset of the seizure, followed by bursts of generalized, predominantly left-sided, biphasic spike and wave complexes.

Despite the recommendation that children with PNPO deficiency typically require PLP supplementation up to 60 mg/kg/day, and theoretically, these patients should only respond to PLP [9], our patient surprisingly responded to PN treatment. This unusual response may be attributed to the presence of residual PNPO enzyme activity, which can convert PN to PLP. Additionally, PN might have a chaperone effect that prevents premature PNPO degradation [12]. Furthermore, it has been suggested that identifying the precise gene mutation sequence may help determine treatment responsiveness in PNPO-deficient patients [13]. In our case, we did not use PLP supplementation, as our patient responded well to PN treatment alone.

In addition to the PNPO mutation, our patient also presented with a PIGA mutation. Although PNPO deficiency is not commonly associated with facial abnormalities, the distinctive facial features observed in our patients may be linked to the PIGA mutation. This mutation can lead to plagiocephaly, a short nose with anteverted nares, and a depressed nasal bridge, which

can appear as a triangular structure at the base of the nose. Notably, the PIGA mutation has also been known to cause refractory, early-onset epilepsy with suppression burst and/or hypsarrhythmia [14]. Our patient also demonstrated hypertelorism, prominent supraorbital ridges, and a depressed nasal bridge.

Clinicians should be aware of PNPO deficiency, as it can present with a broad spectrum of clinical manifestations. Timely diagnosis and appropriate treatment with vitamin B_6 supplementation can significantly improve the outcomes for patients affected by this rare metabolic disorder. This case report aims to raise awareness among healthcare providers about the need to consider PNPO deficiency in the differential diagnosis of late-onset drug-resistant epilepsy, to facilitate early intervention and optimize patient management.

Conclusion

PNPO deficiency represents a potential underlying cause in late-onset drug-resistant epilepsy. Prompt diagnosis and initiation of PLP or PN supplementation is crucial to prevent adverse neurological outcomes. Clinicians should be aware of the vitamin B_6 deficiency clinical presentations, such as mimicking tic, and consider it in the differential diagnosis of refractory epilepsy.

Abbreviations

PNOP	Pyridoxamine 5′-phosphate oxidase
PLP	Pyridoxal 5′-phosphate
PN	Pyridoxine
WHO	World Health Organization
LTM	Long-term video-electroencephalographic monitoring
CNS	Central nervous system
MRI	Magnetic resonance imaging
EEG	Electroencephalographic
GTCs	Generalized tonic–clonic seizure
HMS	Hypermotor seizures
WES	Whole-exome sequencing
PIGA	Phosphatidylinositol glycan biosynthesis class A protein
PTS	6-Pyruvoyltetrahydropterin synthase
GABA	Gamma-aminobutyric acid
ASD	Autism spectrum disorders
ADHD	Attention-deficit/hyperactivity disorder

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Author contributions

S.R., A.T., H.A., and M.R. contributed to the design of the study. M.R., S.R., A.D., I.S., and E.N. contributed to the implementation of the research. E.N., A.R.B., and A.D. participated to the writing of the manuscript. A.R.B., M.D., and S.R. edited the manuscript. All authors read the final version of the manuscript.

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Availability of data and materials

If supporting data are needed, contact the corresponding author.

Declarations

Ethics approval and consent to participate

Informed consent was obtained from the participant and the parents of the patient included in the study.

Consent for publication

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

Competing interests

The authors declare that they have no competing interests.

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