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PYRIDOXINE-DEPENDENT EPILEPSY IN NEWBORN – A RARE AND CHALLENGING DIAGNOSIS

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ABSTRACT

Pyridoxine-dependent epilepsy (PDE) is a developmental, epileptic encephalopathy historically characterized by seizures that are resistant to the standard anti-seizure medications. The administration of pharmacological doses of pyridoxine (vitamin B6) often results in a dramatic clinical response, with many patients achieving complete seizure remission. However, a significant delay between seizure onset, diagnosis of PDE due to ALDH7A1 mutations, and the initiation of pyridoxine therapy is common. Such delays can lead to prolonged periods of poorly controlled seizures and, in rare instances, may result in mortality. Even when seizure control is eventually achieved, the majority of patients exhibit intellectual or developmental impairments.

In this report, we describe a case of pyridoxine-responsive neonatal seizures in a newborn who initially responded to conventional anti-seizure medications but subsequently experienced a relapse characterized by recurrent seizures, ultimately leading to a diagnosis of PDE. The whole exome sequencing identified a homozygous mutation, c.328C>T (p.Arg110Ter), in exon 4 of the ALDH7A1 gene, confirming the diagnosis. Given the established association between the early diagnosis and treatment of PDE and the improved neurological outcomes, we emphasize the critical importance of the timely recognition and initiation of pyridoxine therapy in affected neonates, in order to optimize long-term neurodevelopmental outcomes.

Keywords: newborn, seizures, pyridoxine-dependent epilepsy, outcome

INTRODUCTION

Pyridoxine-dependent epilepsy (OMIM 266100) is a rare autosomal recessive inherited disorder of the lysine metabolism, with an estimated prevalence of 1:65 000 to 1:250 000 live births [1–3]. It is characterized by epileptic encephalopathy, usually starting in the neonatal period, with variable degrees of intellectual disability or developmental delay [3]. PDE is caused by the deficiency of alpha aminoadipic semialdehyde (α-AASA) dehydrogenase as a result of a mutation in the antiquitin (ALDH7A1) gene [1-3]. The loss of α-AASA dehydrogenase activity results in accumulation of pipecolic acid (PIP), α-AASA and its cyclic equilibrium partner Δ(1)-piperideine-6-carboxylate (P6C), that causes a subsequent imbalance between the excitatory and inhibitory neurotransmitters (γ-aminobutyric acid - GABA) and increases the risk of seizure

activity [3]. In addition, accumulation of intermediate metabolites such as α-AASA can contribute to adverse neurological outcomes [1].

Classical onset of PDE is in the neonatal period with drug-resistant seizures [3]. Seizure semiology is diverse, from partial or generalized, clonic, tonic, myoclonic jerks or infantile spasms, including development of status epilepticus [1, 4]. Due to the diverse clinical picture and signs overlapping with other, more common causes of neonatal convulsions, the diagnosis is sometimes difficult to establish [2, 4]. There should be a high index of suspicion, especially when neonatal seizures are partially responsive to anti-seizure medications [3]. The diagnosis is made by determining elevated values of metabolic markers (PIP, α-AASA, P6C) in biological fluids, and molecular genetic testing [2]. A spectrum of structural brain malformations has been described in the affected patients, but normal MRI, however, does not exclude PDE [1]. No specific pattern of EEG abnormalities has yet been documented in patients with PDE [5]. In the current published data there is no apparent relationship between biochemical (α-AASA) or genetic mutation and MR or EEG findings [6].

The treatment of PDE is with lifelong pharmacological pyridoxine replacement, in combination with lysine reduction therapy (LRT), and arginine supplementation to reduce the risk of adverse neurological outcomes [1, 3]. Pyridoxine usually provides seizure control, but a small percentage of patients with resistant epilepsy need additional anticonvulsive therapy [1, 2]. Approximately 75 % of the patients have some degree of neurodevelopmental disability [2].

In this case report we seek to draw attention to this long-known but often difficult to recognize cause of neonatal seizures. The clinical diagnosis can be challenging because some patients partially respond to antiepileptic drugs, the presentation may be multi-systemic, or there is no immediate or obvious response to pyridoxine. In addition, the structural brain anomalies identified may mislead us as the sole cause of seizures, even though they are in fact the consequence of antiquitin deficiency. Our case report shows the very broad clinical presentation of PDE in a newborn, with many laboratory and neuroimaging findings that greatly expand the differential diagnosis, although, after reviewing the literature, most of the findings have already been described in patients with PDE.

CASE REPORT

In our case we describe a full-term girl infant, born after an eventful pregnancy and delivery, with birth weight 3,015 g (10-50th percentile), head circumference 35.5 cm (50-90th percentile) and Apgar score 9.9 who developed hypertonia and grunting six hours after birth. Antibiotic therapy was started until bacterial infection was ruled out. In addition, congenital cytomegalovirus and herpes viral infection were also excluded. The initial blood work showed metabolic acidosis and elevated lactates, which normalized spontaneously. The basic metabolic workup was normal, and newborn tandem mass spectroscopy screening was negative. The family history for epilepsy and inborn errors of metabolism was negative.

During the first hours of observation irritability and hypertonia persisted, but there were no apparent clinical or electroencephalographic seizures seen on amplitude-integrated electroencephalography (aEEG). Nonetheless, due to suspected seizures the infant received phenobarbital, with partial improvement of her neurological status. Approximately 24 hours after the first neurological symptoms started, another paroxysmal episode was noted with eye deviation, extremity jerks and lip smacking. One dose of pyridoxine was also given with no clinical effect. The maintenance therapy with pyridoxine was discontinued. Brain magnetic resonance imaging (MRI) performed one day after the symptoms started revealed a hypoplastic corpus callosum, a hypoplastic anterior part of the falx cerebri, with rightward deviation of the medial sulcus of the frontal lobe across the midline, mild ventriculomegaly, and enlarged cisterna magna. On diffusion-weighted imaging (DWI) restricted diffusion of the posterior limb of the capsula interna was seen. The high intensity signal of the medial thalamus and the lentiform nucleus on T1-weighted scans was suggestive of hypoxic-ischemic injury. The interictal conventional electroencephalogram (cEEG) at that time was normal.

Between the 3rd and 9th days of life the infant was hypotonic and lethargic without apparent seizures or feeding disturbances. Another neurological deterioration followed 9 days after birth. She presented with tremor and rhythmical jerks of the extremities, hypertonia, opisthotonus, a high-pitch cry, and eye deviations. After an additional dose of phenobarbital, the seizures

persisted. Due to these drug-resistant seizures she was transferred to the neonatology department for further diagnostic and therapeutic workup. She was hemodynamically stable and breathing spontaneously. We observed hypertonia, rhythmical jerks of the extremities suggestive of convulsive activity, eye deviation, and a high-pitch cry. A cEEG was performed immediately. There were clinically and electroencephalographic signs of convulsive activity, so another loading dose of phenobarbital was given, followed by a loading dose of pyridoxine. Several minutes after the drug administration the cEEG improved and the seizures subsided. No adverse cardiorespiratory event was noticed during during pyridoxine administration.

Further metabolic and genetic workups were performed for etiological evaluation of the neonatal seizures. The plasma amino acids were normal, lactate and ammonium levels were negative. The serum and urine levels of PIP were markedly elevated (urine PIP/creatinine ratio was 113.63 μmol/mmol; normal value: 0.52 to 7.00 μmol/mmol, and serum PIP was 27.6 μmol/l; normal value: 0.6 to 4.1 μmol/l). The diagnosis of PED was confirmed by genetic analysis. The whole exome sequencing (WES) revealed homozygotic mutation c.328C>T (p.Arg110Ter) in exon 4, which the girl inherited from her mother and father, who are heterozygous carriers.

With maintenance anticonvulsive therapy with phenobarbital and pyridoxine, the infant's clinical condition slowly improved and seizures did not recur. Before the discharge her cEEG was still mildly abnormal, and her neurological status still demonstrated axial and limb hypotonia and spontaneous clonus of the lower limbs.

DISCUSSION

It is important to consider pyridoxine-responsive seizures in the differential diagnosis of neonatal seizures, especially when targeted treatment is important for seizure cessation. Neonatal seizures are one of the most common neurological emergencies in the neonatal period, with a reported frequency of 1.5 to 3 in 1,000 live births [7]. While the most frequent cause of seizures is hypoxic-ischemic encephalopathy (HIE), other known etiological factors include: ischemic stroke, intracranial hemorrhage, genetic epilepsy syndromes, central nervous system infection, congenital brain malformation, transient metabolic or electrolytes disturbances, and inborn errors of the metabolism, which are well recognized in the newborn period [7, 8]. Although PDE is a very rare cause of neonatal seizures, a high level of suspicion is required, especially when seizures are refractory to conventional antiepileptic therapy and more common causes of seizures have been excluded [1, 5].

The classical onset of PDE is in the neonatal period. Newborns develop drug-resistant seizures within a few days of life [3]. Besides seizures, many other neurological symptoms have been reported in patients with PDE, including: hypotonia/hypertonia, lethargy/encephalopathy, strabismus, dystonia, tremor, irritability, hyper-alertness, and sleep disturbances [4]. Our patient developed neurological symptoms within the first day of life and presented with hypertonia, opisthotonus and irritability, which are all described in the literature. The semiology of epileptic seizures in patients with PDE can be very diverse. In our patient we observed partial seizures (lip smacking) and myoclonic jerks, but seizures in PDE can also be generalized, multifocal and prolonged tonic seizures, or epileptic spasms [1,4]. These manifestations should be regarded as clinical red flags that warrant prompt diagnostic evaluation and immediate initiation of appropriate therapeutic interventions. Newborns can sometimes present with status epilepticus, which may be clinically obscured by the administration of multiple anticonvulsive medications, but seizures persist electroencephalographically [1]. Rarely, the onset of the disease is multi-systemic with respiratory distress, vomiting, poor feeding and abdominal distension [4].

Brain imaging is crucial during diagnostic workup, as it is used to rule out the most common causes of neonatal seizures. MRI scans showed a hypoplastic corpus callosum, a hypoplastic anterior part of the falx cerebri, with rightward deviation of the medial sulcus of the frontal lobe across the midline, mild ventriculomegaly, and enlarged cisterna magna. Apart from the hypoplastic falx, all the other findings have already been described in the literature [8, 10, 11]. Similar to our case, other authors have described a wide spectrum of pathological imaging findings in PDE, including hypoplasia of the corpus callosum, mega cisterna magna, intracerebral hem-

orrhages, ventriculomegaly and hydrocephalus, cerebellar hypoplasia, incomplete/delayed myelination, white matter lesions, subependymal cysts, hypoplasia of the optical chiasm, and cortical dysplasia and atrophy [1, 2, 4, 9]. A normal MRI image, however, does not exclude PDE [1, 10]. It is hypothesized that structural brain malformations result from dysfunction of antiquitin expressed in the glial cells during the early fetal period, resulting in impaired neurogenesis and migration disorders [10,12]. Antiquitin is also expressed in the choroid plexus and ependyma, and thus most likely contributes to ventriculomegaly [10, 12].

Even though researchers have reported many electroencephalographic (EEG) characteristics of PDE patients, no specific pattern of EEG abnormality has yet been documented [5]. EEG can be completely normal, or mildly slower background activity can be seen [1, 13]. The first interictal EEG in our case was normal, and the second EEG during clinical seizures showed electroencephalographic signs of seizure activity. In our case we did not observe any markedly pathological EEG patterns (high voltage delta waves, burst-suppression activity or hypsarrhythmia), which are rarely described in the literature in patients with PDE [1].

In patients with PDE many non-specific laboratory findings are reported in the literature including: lactate acidosis, electrolyte disturbance (hypocalcaemia, hypomagnesaemia), hypoglycemia, coagulopathy, abnormal plasma and CSF amino acid concentrations, and endocrine abnormality (hypothyroidism) [4]. Our patient had only lactic acidosis that resolved after a few hours. Elevated metabolic markers (PIP, α-AASA, P6C) in the biological fluid help guide the diagnosis [1]. PIP is elevated in urine, plasma and cerebrospinal fluid (CSF) in most patients with PDE [3]. Our patient had markedly elevated serum and urine levels of PIP. Although this was a clue to the final diagnosis in our case, it is important to emphasize that increased levels of PIP are not a specific marker of PDE, as they can be elevated in other metabolic diseases (peroxisome dysfunction, hyperlysinemia, hyperprolinemia, liver dysfunction), so molecular genetic testing is warranted to confirm or exclude diagnosis. Moreover, α-AASA can be elevated in patients with molybdenum cofactor deficiency and isolated oxidase deficiency, that may also present with neonatal seizures [1, 2]. Evaluation of the ALDH7A1 gene can be done through specific gene testing, multiple gene panels, and comprehensive genomic testing [1]. A biallelic pathogenic variant in the ALDH7A1 gene is consistent with a diagnosis of PDE [3]. In the Caucasian population around 60 % of the mutations in ALDH7A1 currently known are located in exons 4, 6, 9, 11, 14 [4]. In our case, we identified mutation c.328C>T (p.Arg110Ter) in exon 4, which is not a novel mutation, since it has already been described in the literature [10, 11].

The treatment of PDE is with lifelong pharmacological pyridoxine replacement, in combination with lysine reduction therapy (LRT) and arginine supplementation to reduce the risk of adverse neurological outcomes [1,3]. It is important to start targeted therapy in a timely manner to reduce long-term neurodevelopment disabilities. Patients with PDE actually do not have pyridoxine deficiency, but they are metabolically dependent on it [2, 3]. Seizures in PDE patients are usually resistant to classical anticonvulsive drugs [9]. In our case, there was only a partial response to the therapy with phenobarbital, but none to the loading dose of pyridoxine, even though the infant received it early in the course of the disease. The inadequate response to treatment with pyridoxine can be misleading, as it was in our case, because it is known that generally in individuals with PDE, clinical seizures cease in several minutes after the administration of a loading dose of pyridoxine. In line with our case, there are reports in the literature that the response to pyridoxine was delayed, or that patients initially responded well to classical anticonvulsant therapy, although this is rare [16-18]. With this in mind, it is important to emphasize that in the case of a poor clinical response to the initial loading dose of pyridoxine and a high clinical suspicion of PDE, the dose can be repeated up to a maximum of 500 mg, and treatment should be continued until the final diagnosis is confirmed or excluded [1, 3]. During the pyridoxine administration we need to be aware of the negative cardiorespiratory events, because a sudden increase in GABA, the main inhibitory neurotransmitter, can cause a diffuse inhibitory state and apnea, but this did not happen in our case. Sometimes this may aid the final diagnosis [1, 3].

In a recent study, Falsaperla et al. demonstrated a significant association between the delayed diagnosis and the adverse neuromotor

outcomes observed during the long-term follow-up, underscoring the critical importance of the early recognition and the timely intervention in the management of pyridoxine-dependent epilepsy. Furthermore, a prolonged interval between the initiation of anti-seizure medication therapy and the administration of pyridoxine was correlated with poorer neurological outcomes at follow-up [19].

Maintenance treatment with pyridoxine usually provides seizure control, but in a small percentage of patients seizure activity is not fully controlled with pyridoxine alone, and patients with intractable seizures need additional anticonvulsive therapy to control their epilepsy [1, 2]. Some explanations have been postulated as to why epileptic seizures may not completely respond to pyridoxine. In patients with delayed diagnosis recurrent epileptic episodes may cause additional brain damage, resulting in epileptogenic focus. The development of brain dysgenesis that is reported in some patients with PDE, may also be the cause [1]. In our case, the therapy with pyridoxine and phenobarbital was necessary to control the seizures. In addition to the phenobarbital and pyridoxine, the patient started LRT and pharmacological doses of arginine after confirmation of the diagnosis of PDE. It is known that LRT and arginine reduce the levels of toxic lysine degradation intermediates (PIP, α-AASA, P6C), which may have neurotoxic effects on developing brains [3].

CONCLUSION

Due to its rarity, varied clinical picture, and non-specific laboratory and neuroimaging findings, the diagnosis of PDE is sometimes challenging. In a newborn with seizures of unexplained cause, we should always consider PDE and start the treatment with pyridoxine, which should be continued until the final diagnosis is confirmed or excluded, because response can sometimes be delayed or partial.

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Резиме

ЕПИЛЕПСИЈА ЗАВИСНА ОД ПИРИДОКСИН КАЈ НОВОРОДЕНЧЕ – РЕТКА И ПРЕДИЗВИКУВАЧКА ДИЈАГНОЗА

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Епилепсијата зависна од пиридоксин (ПДЕ) е развојна епилептична енцефалопатија, која историски се карактеризира со напади што се отпорни на стандардните антиепилептични лекови. Администрацијата на фармаколошките дози на пиридоксин (витамин Б6) често резултира со драматичен клинички одговор, при што многу пациенти постигнуваат комплетна ремисија на нападите. Меѓутоа, значително доцнење меѓу појавата на нападите, дијагнозата на ПДЕ поради мутации во генот ALDH7A1 и иницирањето на терапијата со пиридоксин е честа појава. Таквите доцнења можат да доведат до продолжени периоди на слабоконтролираните напади и, во ретки случаи, може да резултираат со смрт. Дури и кога контролата на нападите на крајот ќе се постигне, поголемиот број од пациентите покажуваат интелектуални или развојни нарушувања.

Во оваа статија опишуваме случај на неонатални конвулзии зависни од пиридоксин кај новороденче што првично реагираше на конвенционалните лекови против конвулзии, но потоа доживеа повторно појавување, карактеризирано со повторувачки напади, што на крајот доведе до дијагноза на ПДЕ. Комплетното секвенционирање na егзомот идентификува хомозиготна мутација, c.328C>T (p.Arg110Ter), во ексон 4 на генот ALDH7A1, потврдувајќи ја дијагнозата. Имајќи ја предвид воспоставената врска меѓу раната дијагноза и лекување на PDE и подобрени невролошки исходи, ја нагласуваме критичната значајност на навременото признавање и иницирање на терапијата со пиридоксин кај новороденчињата за да се оптимизираат долгорочните невроразвојни исходи.

Клучни зборови: новороденче, конвулзии, епилепсија зависна од пиридоксин, исход