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CASE REPORT

Epilepsy due to pyridoxine dependence: a case report

Larissa Magalhães de Paiva[1], Luigi Neves Reis[2], Rinara Grossi de Andrade[3], Shaira Salvadora Cunha Brito[4], Giulia Antunes Chieppe[4], Isabela Bernardino Freire[4]

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Abstract

Pyridoxine-dependent epilepsy (EDP) is an autosomal recessive disease clinically represented by recurrent seizures. The diagnosis is made by clinical observation, and may be assisted by electroencephalography (EEG) and biochemical and genetic tests. The aim of this work was to report the case of an infant patient with epilepsy due to pyridoxine dependence, using the methods of analysis of clinical history data, physical examination, therapeutic response, with simultaneous laboratory investigation and image analysis. In the face of a neonatal convulsive crisis immune to the instituted anticonvulsants and, with laboratory and imaging exams without changes, the introduction of pyridoxine brought clinical improvement, allowing the discontinuation of the other drugs in use. The reported case reinforces the importance of investigating neonatal seizures for the correct diagnosis and treatment.

[1] Hospital Municipal de Governador Valadares, Residente de Pediatria - Governador Valadares - Minas Gerais - Brazil.
[2] Hospital Municipal de Governador Valadares, Neurologista Pediátrico - Governador Valadares - Minas Gerais - Brazil.
[3] Hospital Municipal de Governador Valadares, Pediatra - Governador Valadares - Minas Gerais - Brazil.
[4] Universidade Vila Velha, Graduanda do curso de Medicina - Vila Velha - Espírito Santo - Brazil.

Correspondence to:
Giulia Antunes Chieppe.
Universidade Vila Velha. Avenida Comissário José Dantas de Melo, nº 21, Boa Vista II, Vila Velha, ES, Brazil. CEP: 29102-920. E-mail: giulia.antunesc@hotmail.com

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INTRODUCTION

Pyridoxine-dependent epilepsy (PDE), classified as a vitamin-responsive neonatal epileptic encephalopathy[1], is a rare autosomal recessive disease, clinically represented by recurrent seizures, unresponsive to antiepileptics[2]. In most cases, the administration of parenteral or oral pyridoxine quickly results in seizure control and encephalopathy improvement[3]. The diagnosis is made by clinical observation, with the aid of electroencephalography (EEG), biochemical and genetic tests[3]. This neurological condition is characterized by erratic myoclonus (an obligatory type of fit), which can be focal or involve limbs and the axial trunk, sporadic or almost continuous, during wakefulness and sleep, which migrate from one body segment to another and, generally, it begins in the early neonatal period[1]. They are frequently associated with focal ocular or non-motor fits and, finally, tonic spasms, in the neonatal period or in the first months of life. There is a significant global and neurological development delay, accompanied by marked hypotonia[1], and sleep disorders may also occur[2,4].

Atypical presentations of the disorder include late-onset PDE, which can begin as early as two months of age[3]; other forms that include patients who previously had seizures controlled by small doses of pyridoxine, but who end up needing higher doses for control; or patients who responded to general anticonvulsants, and evolve to a selective response to pyridoxine[5].

Therefore, the choice of anticonvulsant for treatment, as well as the early initiation of pyridoxine treatment, must be made based on the type of fit, the effectiveness of the medication and the side effects on the patient[6]. This report aims to depict a case of pyridoxine-dependent epilepsy, diagnosed in the neonatal period, with seizures that were difficult to control with anticonvulsants. The results showed that pyridoxine ended the convulsive fits.

CASE REPORT

Infant, male, 1 month and 16 days old, resident and from Itaobim – Minas Gerais – Brazil; already under treatment for seizures, he was referred to the Municipal Hospital of Governador Valadares (HMGV) after being admitted to the emergency room in his city of origin, because of four episodes of tonic-clonic seizures. During his outpatient treatment, he was weaning from medications, in which clonazepam had been reduced a week before and phenobarbital the day before. Hospitalization was carried out for investigation and control of the seizures, without success at the hospital of origin. Therefore, the patient was transferred to HMGV. When investigating his past medical history, the mother reported that she was unaware of the pregnancy until the moment of birth, making it impossible to carry out medical and prenatal care. The mother stated that she did not experience any complications during pregnancy. At the time of delivery, maternal quick tests for syphilis and HIV were negative. Born preterm, cesarean section, with Apgar scores of 9 and 10 in the 1st and 5th minutes, respectively, birth weight of 3,415 grams, head circumference of 34 centimeters, height of 49 centimeters.

At 6 days of life, the patient presented his first seizure with gaze eversion, crying and myoclonus, which is why he was hospitalized for 26 days in the neonatal ICU of Teófilo Otoni – MG. The investigation was unsuccessful, and the patient was discharged with outpatient follow-up.

At HMGV, computed tomography (CT) of the skull, magnetic resonance imaging of the brain (MRI) and analysis of cerebrospinal fluid were performed, which showed no changes. Laboratory tests showed blood VDRL of 1:1. One day after admission to the HMGV, the patient developed a generalized seizure with nystagmus, crying, myoclonus, after a further reduction in clonazepam (we decided to maintain scheduled weaning for in-hospital observation). The seizure improved after 2 doses of midazolam, and he was then admitted to the semi-intensive ward for continued care.

Upon physical examination, he was hypoactive but reactive, flushed, hydrated, afebrile, acyanotic, anicteric, good peripheral capillary perfusion, normotensive palpable anterior fontanelle, 2 digital pulps, palpable posterior fontanelle with 1 digital pulp. Regular heart rhythm in 2 beats with systolic murmur (2+/6+), heart rate of 110 beats per minute. Bladder murmur universally audible, without adventitious sounds, eupneic, breathing effortless. Laboratory tests were carried out, which showed no changes, and a serological test for toxoplasmosis and cytomegalovirus - the results of which were negative. In addition to Doppler echocardiography, which showed a patent foramen ovale and stenosis of the left pulmonary branch (normal findings in newborns).

Medication adjustment was performed and, even when using phenobarbital 21 mg/day, levetiracetam 40 mg/kg/day and topiramate 5 mg/kg/day, the patient maintained a progressive increase in fits throughout the day. Therefore, we started a treatment trial with pyridoxine 100 milligrams every 8 hours. The patient continued to experience a significant improvement in his level of consciousness after the administration of the vitamin, maintaining longer periods of wakefulness and activity, and no seizures. Due to the good response to Pyridoxine, phenobarbital was reduced to 3 drops/day with good tolerance. Treatment was followed up in the pediatric ward and a buccal swab was collected for DNA analysis. After five days without new episodes of fits, the patient was discharged from the hospital with outpatient follow-up with a pediatric neurologist.

The PDE diagnosis was confirmed by molecular analysis by next generation sequencing, being identified as homozygosity, of a pathogenic variant in the ALDH7A1 gene.

DISCUSSION

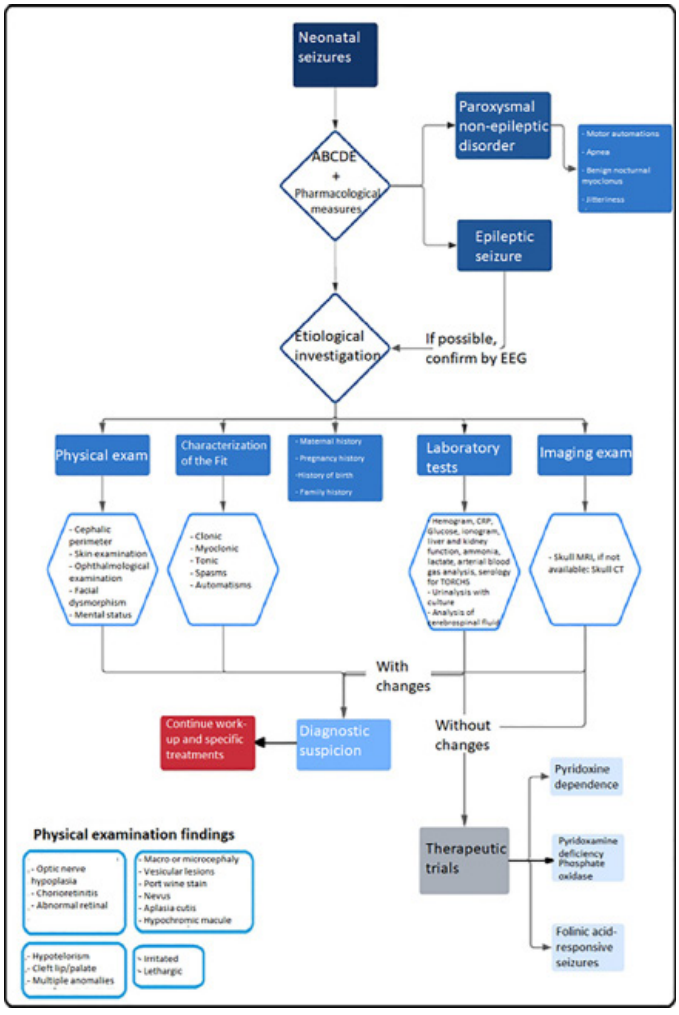
PDE is the best understood of the vitamin-responsive neonatal epileptic encephalopathies, due to the discovery of its underlying biochemical and genetic basis[3]. Its phenotype

is due to defects in multiple genes, with unique disease mechanisms and treatment implications. PDE can be caused by a defect in the conversion of pyridoxine into pyridoxal phosphate (PLP), by defects in PLP homeostasis (PLP-binding protein deficiency), with the most common cause being the enzymatic defect in lysine oxidation (deficiency of PLP). of a-aminoadipic semi-aldehyde dehydrogenase), caused by mutations in the ALDH7A1[7] gene. Most patients with EDP-ALDH7A1 have developmental delay or intellectual disability, therefore, its early diagnosis and personalized treatment regimens hold promise for treating epilepsy and neurodevelopmental delay in this disease[7].

The EEG can be quite heterogeneous and non-specific. Abnormal baseline activity, burst-suppression, lack of sleep organization, spike and poly-tip foci are described. It is difficult to evaluate the EEG due to the fact that it is typically performed after several seizure spells and anticonvulsant drugs have already been administered. In many patients with PDE, normal or minimal epileptiform activity is not uncommon.

After establishing the suspicion of PDE, the diagnosis can be confirmed by therapeutic testing, in which in most cases there is a clinical response to the administration of pyridoxine via intravenous infusion within 15 minutes[8]. In suspected cases without an immediate response, the diagnosis of PDE[9] should not be excluded, and oral treatment should be continued for one to three weeks[8].

Treatment should be initiated in an intensive care environment with ventilatory support available, cardiopulmonary and, if possible, electroencephalographic monitoring, as patients may develop apnea, central hypotonia and hypotension in response to the administration of pyridoxine[10,11]. An initial dose of 100 mg of pyridoxine should be administered, which may be repeated every 5 to 15 minutes, not exceeding 500 mg, under careful supervision[11-13]. Treatment should be continued with oral pyridoxine supplementation of 15 or 30 mg/kg/day divided into three daily doses. The dosage of pyridoxine is empirical; therefore, adequate treatment causes remission of seizures, and, if pyridoxine is interrupted, the seizure condition will be reestablished[8]. In Brazil, diagnosis based on chemical and genetic tests, as well as the assistance of EEG, may be unfeasible, due to the scarcity of these resources in the Brazilian Public Healthcare System (SUS). The case presented did have some of these obstacles. Therefore, adequate clinical reasoning is essential to carry out the differential diagnosis



Algorithm 1. Investigation of neonatal seizures[1,8,9].

of neonatal epileptic encephalopathies. The algorithm 1[1,8,9] presents the clinical reasoning that must be implemented for diagnosis.

PDE has a good prognosis for controlling seizures in the majority of patients[3], being initially controlled with the administration of pyridoxine as a medication, and subsequently, in the majority of affected individuals, antiepileptic medications can be discontinued and suspended[2]. The patient will still need pharmacological doses of Pyridoxine for life[3], and annual dosage monitoring is recommended to assess any possibility of abnormalities[12].

CONCLUSION

PDE is a rare autosomal recessive condition, characterized by recurrent epileptic seizures that are easy to control and improvement in encephalopathy when the correct diagnosis is made, based on clinical evidence and complementary tests. The attention of pediatricians is necessary in cases with this diagnostic hypothesis and its investigation through symptoms, electroencephalogram and biochemical and genetic tests.

Keeping this diagnosis in mind is extremely important for providing adequate treatment and improving the prognosis of newborns with seizures.

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