Case Reports

Pyridoxine-dependent Seizures: Long-term Follow-up of Two Cases with Clinical and MRI Findings, and Pyridoxine Treatment

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Summary

Pyridoxine-dependency is a rare autosomal recessive disorder causing a severe seizure disorder of neonatal onset. There are a few reports including neuroimaging studies, such as cranial CT and MRI, and one report with longitudinal MRI findings in two cases with pyridoxine-dependent seizures (PDS). We report long-term follow-up of two siblings with PDS in the light of clinical, EEG, CT and MRI findings, and pyridoxine treatment. The first patient, an 8-year-old female who had neonatal seizures, has sequential cranial CT and MRIs which are normal except for mega cistema magna thus far. She still has mild mental retardation, although the accurate diagnosis was made when she was 6 years old and pyridoxine treatment was initiated. The second patient, a 1-year-old female, who is the younger sibling of the first patient, presented with neonatal seizures and PDS was diagnosed immediately, with resulting pyridoxine treatment (10 mg/kg/day). She is now neurologically normal, seizure-free, and has sequential normal CT and MRIs. These patients show rather benign clinical courses.

Introduction

Pyridoxine-dependency is a rare autosomal recessive disorder causing a severe seizure disorder of prenatal, neonatal or postneonatal onset, psychomotor retardation and death in untreated patients. The underlying defect is currently unknown and treatment requires life-long supplementation with pyridoxine.[1] Longitudinal findings of MRI and other neurophysiological and neuroimaging studies in some cases have recently been reported.[2,3] These reports concluded that patients with pyridoxine-dependent seizures (PDS) showed progressive diffuse structural abnormalities and/or functional derangement in the brain if they had not been treated, or had had ineffective treatment, and this progressive course stopped and also partly reversed when they began to take effective treatment.[2,3] In the present study, we report the long-term follow-up of two siblings with PDS.

Case Reports

Patient 1

A female patient, aged 8 years at the time of this report, is the first child of healthy consanguinous parents, and was carried full-term with a normal pregnancy and delivery. She presented on the third day of life with crying, irritability, and then generalized myoclonic convulsions. Convulsions of the patient, who had normal physical examination and routine laboratory tests, ceased soon after administration of i.v. diazepam (0.2 mg/kg). She had right focal and then secondary generalized clonic convulsions at the age of 1 month, which did not respond to diazepam, but immediately ceased after i.v. administration of pyridoxine (50 mg). She presented again at the age of 3 months with generalized tonic-clonic seizures (GTCS). Physical examination and routine laboratory tests were normal, and seizures had subsided but not fully ceased with i.v. diazepam and subsequently clonazepam. They ceased after 100 mg of pyridoxine i.v. in a few minutes. Thereafter she received 15 mg/day of phenobarbital and 25 drops/day of Dapta 12® (a multivitamin preparation where each drop contains 1 mg of vitamin B_6); the seizures did not recur while receiving these drugs. Seizures recurred during the periods when Dapta 12® was discontinued for any reason, for example at the age of 5 months secondary generalized tonic-clonic seizures showed diffuse bioelectrical slowing with left hemisphere dominance on EEG, and at 13 months GTCS showed diffuse bioelectrical depression on EEG. Both seizures were immediately controlled after 100 mg of pyridoxine, i.v. Cranial CT performed at the age of 13 months was normal,

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except for mega cisterna magna (MCM), and sodium valproate (20 mg/kg/day) was added to the treatment. She was admitted to hospital in generalized convulsive status epilepticus during the period where Dapta 12® was discontinued at the age of 4 years, with diffuse ictal discharges on EEG, and normal CT except for MCM. The patient continued to have seizures despite 0.2 mg/kg of midazolam, 15 mg/kg of phenytoin, and 20 mg/kg of phenobarbital, i.v. We then began giving 1 μg/kg/min of midazolam infusion over 12 h. Seizures disappeared within 2 h. Status epilepticus recurred on the 4th day in hospital and ceased within minutes upon administration of 100 mg of pyridoxine i.v. The patient recovered totally in a few hours. MRI was found to be normal except for MCM at the age of 5 years (Fig. 1). During the period between 4.5 and 6 years of age she sometimes had brief focal or generalized tonic or clonic seizures, and also visual seizures characterized by bright objects moving in front of the eyes, images like flashes of lightning, and distortion of the objects in the surroundings. Two of the visual seizures evolved into secondary generalized seizures. The next day EEG showed diffuse disorganized background activity, and bilateral synchronous 2.5 Hz spike-slow wave bursts with anterior dominance on hyperventilation (Fig. 2). The definite diagnosis of PDS was made when she was 6 years old, and pyridoxine (10 mg/kg/day) was immediately started while gradually discontinuing her oral anticonvulsants. She now has normal MRI, except for MCM, and EEG. She continues to be seizure-free and has mild mental retardation.

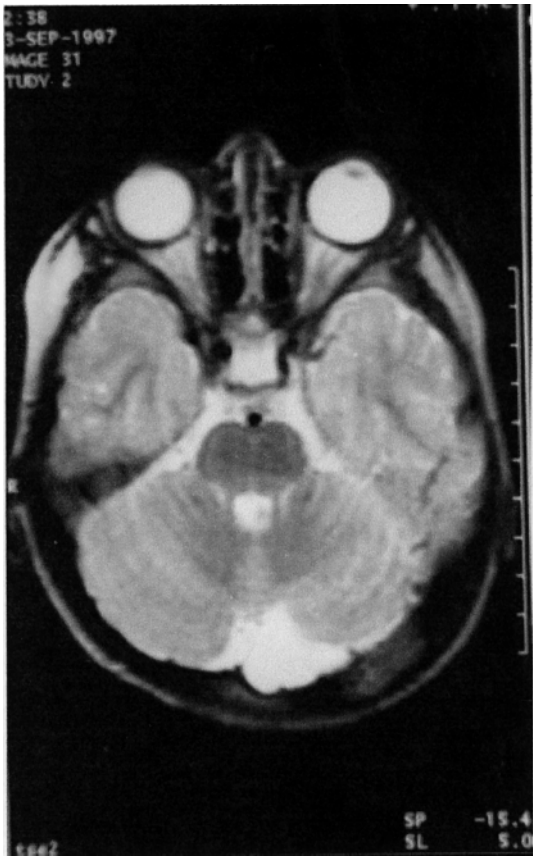


FIG. 1. First patient's T2-weighted cranial MR images demonstrating normal findings except for MCM at the age of 5 years.

Patient 2

This female patient is the younger sibling of patient 1. She was the product of a full-term normal pregnancy and delivery and was normal for the first 2 days of life. She had two generalized clonic seizures on the third day, with normal physical examination and routine laboratory tests, and diffuse bioelectrical depression on EEG. She also had a generalized tonic seizure on the 5th day, with normal routine laboratory tests and cranial CT. She was diagnosed with PDS and subsequently treated with pyridoxine (10 mg/kg/day). The parents were unwilling to undergo a trial of pyridoxine withdrawal and refused to pursue follow-up testing. The patient had normal cranial MRI at age 1 month and normal EEGs at age 1 and 3 months. As a 1-year-old she was neurologically normal, seizure-free, and had normal MRI.

Discussion

Four criteria have been suggested to make the diagnosis of PDS: seizures resistant to traditional antiepileptic treatment; demonstrated cessation of seizures with pyridoxine administration; complete seizure control on pyridoxine monotherapy; and recurrence of seizures upon pyridoxine withdrawal.[1] Our first patient fulfilled all the criteria. The second patient fulfilled the first three of the criteria but not the fourth since the parents refused to undergo a trial of pyridoxine withdrawal. Our first patient had the diagnosis of PDS at the age of 6 years. We believe that the seizure recurrence with intervals as long as 2 months after stopping pyridoxine supply might have had a role in the delay of diagnosis for this patient.

There are several non-specific abnormalities on EEG during periods where patients do not use pyridoxine and undergo seizures, although EEG is usually normal in those using pyridoxine and are seizure-free as in the case of our patients.[1,2,4,5]

To the best of our knowledge, there are a few cases with neuroimaging studies (CT and MRI) in the literature, and a study presenting longitudinal MRI findings.[2] In these studies, MRIs performed at the neonatal or postneonatal periods had no abnormal-



FIG. 2. First patient's EEG showing bilateral synchronous 2.5 Hz spike-slow wave bursts with anterior dominance on hyperventilation.

ity or mild cerebral atrophy although MRIs taken at later periods showed an increase in cerebral atrophy. Patients in these studies suffered mild or severe neurological sequelae compatible with cerebral atrophy. However, our patients had normal CTs and MRIs (except for MCM in the first patient) obtained at not only early but also later periods, with mild mental retardation for the first patient and normal neurological status for the second patient at present. It is not clear why patients might have clinically and radiologically different courses. We speculate that this difference may be due to a mild or severe course of the disease.

MCM has been demonstrated in most of the cases published in literature and also in our first case on CT and MRI. The incidence of this benign developmental brain anomaly in the general population is 4:1000,[6] suggesting that the incidence is increased in patients with PDS. It is not clear why this is so.

An increased concentration of glutamate has been demonstrated in the cerebral cortex[7] and CSF[8] in cases with PDS. Glutamate does not cross the blood–brain barrier significantly and is synthesized as non-essential amino acid in the brain.[9] In the brain tissue the glutamate concentration is 800-fold higher than in the CSF.[10] High-affinity uptake systems exist that transport glutamate into nerve endings and glia cells.[9,10] Glutamate is an excitatory neurotransmitter,[9,11] and at sustained elevated levels glutamate acts as a neurotoxin.[11,12] Glutamate hyperexcites the *n*-methyl D-aspartate receptor, the most likely mediator of the cascade of events leading to nerve cell death.[11,13] Raised levels of glutamate in the cerebral cortex and CSF in cases with PDS suggest that the progressive atrophic changes demonstrated by neuroimaging studies may be a consequence of increased levels of glutamate.

Gamma-aminobutyric acid (GABA) levels have been found to be decreased in the CSF[14] and cerebral cortex[7] in the cases with PDS. It has been suggested that reduced synthesis of GABA in pyridoxine dependency is responsible for the lowered seizure threshold.[7,14]

The optimal dose of pyridoxine to prevent brain damage and to allow normal development is higher than the dose needed to prevent recurrence of

convulsions. The seizures reported in the study by Baumeister, *et al*.[8] were controlled and the EEG became normal with 5 mg/kg/day of pyridoxine. At this dosage the CSF glutamate was still 10 times normal. The dose of pyridoxine was increased to 10 mg/kg/day and the CSF glutamic acid level was normalized. With this dose, mental development in their patient was reported to be normal. The authors concluded that the development of mental retardation might be prevented by adjusting the dose of pyridoxine to achieve not only remission of epilepsy but also normalization of CSF glutamate.[8] They also concluded that it is important to adjust the vitamin B_6 dosage according to the results of repeated measurements of glutamate in the CSF for the optimal treatment of PDS.[8] In our opinion, it is an objective and reliable, but not practical method. We think it may be sufficient to give each patient pyridoxine (10 mg/kg/day) without measuring glutamate levels in the CSF. Our patients use pyridoxine at this dosage and are still neurologically normal.

Some cases published in the literature showed good clinical course without taking effective pyridoxine treatment. Although our first patient started taking pyridoxine at an effective dosage when she was 6 years old, she still has mild mental retardation. However, some cases have shown severe neurological sequelae in spite of early diagnosis and pyridoxine treatment. The reasons for such differences are not known. There may be point mutations in patients with PDS inherited as an autosomal recessive trait, although no point mutation has been detected so far.[1] Different point mutations in cases with PDS can be responsible for different clinical pictures, such as typical or atypical cases, and mild or severe courses. We believe further genetic studies will broaden our knowledge and horizon in this field.

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Internal Jugular Phlebectasia: Usefulness of Color Doppler Ultrasonography in the Diagnosis

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Summary

Jugular phlebectasia (JP) is an entity that has been increasingly recognized in recent years. It is a rare entity. This paper reports three new cases presenting with swelling on the right side of the neck, and reviews all cases of internal JP published in English literature up to 2001. This article also discusses the usefulness of color Doppler ultrasonography for the diagnosis of internal jugular venous ectasia.