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Pyridoxine-Dependent Seizures: Magnetic Resonance Spectroscopy Findings

ABSTRACT

Pyridoxine-dependent seizures are an extremely rare genetic disorder. Early diagnosis and treatment are important for the prevention of permanent brain damage. Elevated levels of glutamate and decreased levels of γ-aminobutyric acid (GABA) in the frontal and parietal cortices are among the characteristic features of this disorder. These metabolic abnormalities eventually lead to seizures and neuronal loss. In this case report, we present magnetic resonance spectroscopy findings of a 9-year-old girl with pyridoxine-dependent seizures with mental retardation. The *N*-acetylaspartate-to-creatine ratio was found to be decreased in the frontal and parieto-occipital cortices, which could indicate neuronal loss. Magnetic resonance spectroscopy could be a useful tool in the neuroimaging evaluation for assessment of parenchymal changes despite a normal-appearing brain magnetic resonance image in patients with pyridoxine-dependent seizures. (*J Child Neurol* 2004;19:75–78).

Pyridoxine-dependent seizures are an extremely rare autosomal recessive genetic disorder caused by an inborn abnormality in the pyridoxine-dependent synthesis of γ-aminobutyric acid (GABA) that presents as generalized seizures in the first few days of life.[1,2] Owing to the lack of specific neuroimaging findings of this disorder, the diagnosis is very difficult and depends on clinical suspicion. If the diagnosis could not be made or is made late, permanent brain damage is inevitable.[2] Autopsy studies showed elevated glutamate and decreased GABA concentrations in the frontal and occipital cortices, and an imbalance of cerebral levels of GABA was thought to be responsible for the seizures.[3]

Magnetic resonance spectroscopy is a noninvasive tool to investigate the biochemical alterations in neural structures caused by various brain disease processes.[4,5] It could provide information reflecting metabolite changes in the brain of patients with pyridoxine-dependent seizures. In this case report, we present magnetic resonance spectroscopy findings of a 9-year-old girl who had mental retardation with delayed diagnosis and treatment of pyridoxine-dependent seizures. To our knowledge, this is the first report of magnetic resonance spectroscopy findings of pyridoxine-dependent seizures in the literature.

Case Report

A 9-year-old girl who was the first child of healthy consanguineous parents was born of a normal delivery and an uneventful prenatal period and experienced generalized myoclonic convulsions on the 3rd day of life. Physical examination, routine laboratory tests, and neuroimaging studies were normal. Electroencephalographic (EEG) examination at 13 months revealed diffuse bioelectrical depression. She had been treated with various antiepilepsy drugs with additional pyridoxine to some of them, which then turned out to have been administered at insufficient doses. Although generalized tonic-clonic convulsions responded to antiepilepsy drugs to a certain extent, they have recurred. At age 6 years, a definite diagnosis of pyridoxine-dependent seizures was made and supplemental pyridoxine was immediately started, and she has been seizure free to date. The IQ test showed mental retardation.

Magnetic resonance imaging (MRI) and spectroscopy of the brain were performed on a 1.5 Tesla system (Philips, Gyroscan Intera, Best, The Netherlands). Axial and sagittal T_1-weighted images (TR: 560, TE: 15 msec) and axial and coronal T_2-weighted images (TR: 4530, TE: 100 msec) were obtained. Single-voxel proton magnetic resonance spectroscopy was performed by using the point-resolved spectroscopy sequence (TR: 1500, TE: 31 ms). Voxels ($2 \times 2 \times 2$ cm) were placed, including the frontal and parieto-occipital subcortical white and cortical gray matter. After automatic shimming and gradient tuning, water suppression with a water-selective excitation pulse was interactively optimized on the display console. Analysis of the spectra was performed with the manufacturer-supplied spectroscopy software package of the magnetic resonance system. The spectra were referenced to creatine (3.02 ppm). The signals from choline, creatine and phosphocreatine, *N*-acetylaspartate, and myo-inositol were integrated. Short-echo single-voxel proton magnetic resonance spectroscopy was used owing to its ability to show *myo*-inositol, glutamate, lactate, and lipid in addition to *N*-acetylaspartate, creatine, and choline. Peak area metabolite ratios (*N*-acetylaspartate-to-creatine, choline-to-creatine, and *myo*-inositol-to-creatine) were calculated. Control spectra were obtained from five age-matched healthy children. Table 1 shows the metabolite ratios obtained from the patient and a corresponding control group.

Discussion

Pyridoxine-dependent seizures were first described by Hunt et al in 1954,[6] and about 100 cases have been reported since then.[7] It is an abnormality in the pyridoxine-dependent synthesis of GABA.[2] Four criteria have been suggested to make the diagnosis of pyridoxine-dependent seizures: seizures resistant to traditional antiepilepsy treatment, demonstrated cessation of clinical seizures with parenteral or oral pyridoxine administration, complete seizure control on pyridoxine monotherapy, and recurrence of seizures on pyridoxine withdrawal.[1] Clinical diagnosis is often delayed, and severe neurologic sequelae are common.[7]

Pyridoxal phosphate is the coenzyme for glutamic acid decarboxylase and GABA transaminase, which are the enzymes necessary in the production and metabolism of brain GABA.[2,8] Insufficient activation of glutamic acid decarboxylase will lead to reduced glutamate-to-GABA conversion and, as a consequence, will result in an excess of glutamate and a depletion of GABA in the central nervous system. Normally, the brain tissue has glutamate concentrations 800-fold higher than in those in the cerebrospinal fluid.[9] Glutamate does not cross the blood–brain barrier significantly. High-affinity uptake systems exist that transport glutamate into nerve endings and glial cells. It is quite reasonable to expect that lower GABA concentrations in the brain might result in excessive neuronal excitation and thus in seizures.

Table 1. Magnetic Resonance Spectroscopy Findings of Pyridoxine-Dependent Seizures in a 9-Year-Old Girl

	Frontal Cortex		*Parieto-occipital Cortex*	
Metabolite Ratios	*Case*	*Control (n = 5)*	*Case*	*Control (n = 5)*
NAA/Cr	1.55	1.84 ± 0.14	1.45	1.75 ± 0.12
Cho/Cr	0.70	0.72 ± 0.18	0.74	0.78 ± 0.14
MI/Cr	0.56	0.63 ± 0.12	0.62	0.66 ± 0.12

Cho = choline; Cr = creatine; MI = *myo*-inositol; NAA = *N*-acetylaspartate.

Seizures could begin either in the intrauterine period or during the first few days of life. In our case, generalized tonic-clonic seizures were started on the 3rd day of life. Seizures do not usually respond to anticonvulsant medication but cease within minutes following parenteral administration of pyridoxine. They recur within days after withdrawal of supplementation.[7]

Brain imaging studies described gray- and white-matter atrophy to some extent in patients with pyridoxine-dependent seizures.[2] The progressive MRI changes seen in pyridoxine-dependent seizures can be due to chronic excitotoxicity caused by an imbalance of cerebral levels of GABA and glutamate, which could lead to selective neuronal loss.[2,10] Hypodense white matter in frontal and occipital lobes on computed tomography suggestive of a retarded or defective myelination has been reported.[11] In our case, MRI findings were normal (Figure 1).

Progressive encephalopathy with mental retardation, intractable seizure, and progressive neurologic signs and symptoms develops in untreated patients; even death within days or months could occur in these cases. This feature of pyridoxine-dependent seizures necessitates early diagnosis and treatment for stopping the seizures and preventing the encephalopathy. Lifelong supplementation with vitamin B_6 is an effective choice of treatment. Withdrawal of pyridoxine even after several years of effective therapy results in the reappearance of seizures within days or weeks. But it is reported that despite early treatment, many patients could develop mental retardation.[7] In our patient, the diagnosis was made when she was about 6 years old. Although she has taken supplemental vitamin B_6 for approximately 3 years, she has been moderately mentally retarded.

Magnetic resonance spectroscopy is a noninvasive, complementary imaging modality to MRI that has the ability to show the presence of various metabolites in the sampled tissues and thereby helps in the understanding of abnormalities detected by MRI or clinical examination. Information on neuronal/axonal viability, cellular energetics, and cellular membrane status can be obtained from magnetic resonance spectroscopy studies. The clinical utility and importance of this information are to narrow the diagnostic possibilities and guide treatment.[4,5] The prominent resonances detected on magnetic resonance spectroscopy in normal brains include *N*-acetylaspartate, choline, and creatine. *N*-Acetylaspartate, which is present in neuronal cells and made in mitochondria, is considered to be a marker for neuronal development. It is the most sensitive central nervous system metabolite, and neuronal damage or loss will result in decreased *N*-acetylaspartate levels. Phosphocreatine content provides information regarding cell energy metabolism and is associated with the degree of cell viability. In our case, magnetic resonance spectroscopy revealed a decrease in the *N*-acetylaspartate-to-creatine ratio in the frontal and parieto-occipital cortices, which may indicate neuronal loss (Figure 2). These findings could depend on an increased glutamate level that leads to neurotoxicity during the early period of pyridoxine-dependent seizures. Additionally, a lactate peak was detected in the frontal cortex, which might reveal cellular anaerobic glycolysis. Magnetic resonance spectroscopy findings in our case with pyridoxine-dependent seizures with mental retardation could explain the neuronal loss in the brain cortex, which was reported in pathologic studies.[3]

Choline is a constituent of the phospholipid metabolism of cell membranes and reflects membrane turnover. Major components of the choline resonance are choline-containing compounds with small molecular weight, such as phosphorylcholine and glycerophosphorylcholine, that form a pool involved in membrane synthesis and degradation. The *myo*-inositol peak represented an osmolyte of plasma membranes. The increased choline-to-creatine and *myo*-inositol-to-creatine levels, which could indicate increased membrane turnover and myelin breakdown and astrocytosis,

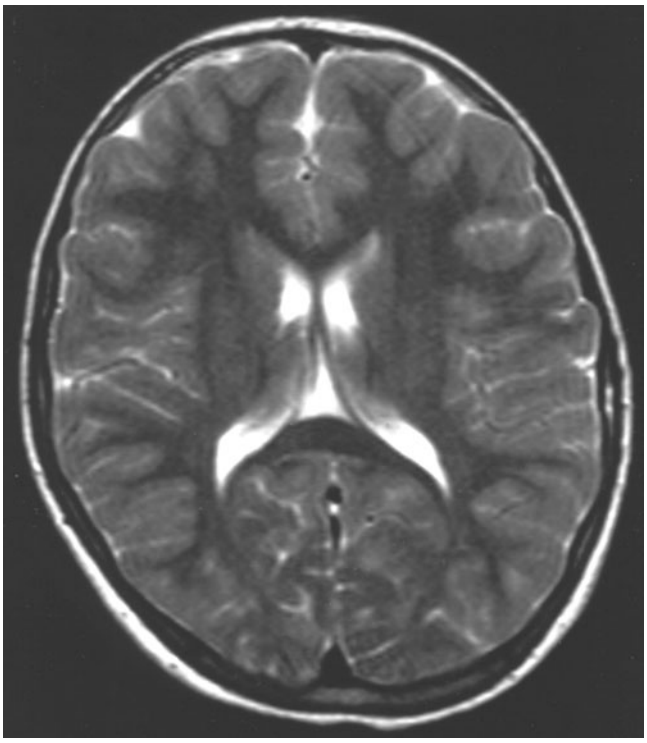

Figure 1. Axial T_2-weighted TSE (4530/100) magnetic resonance image shows normal brain findings.

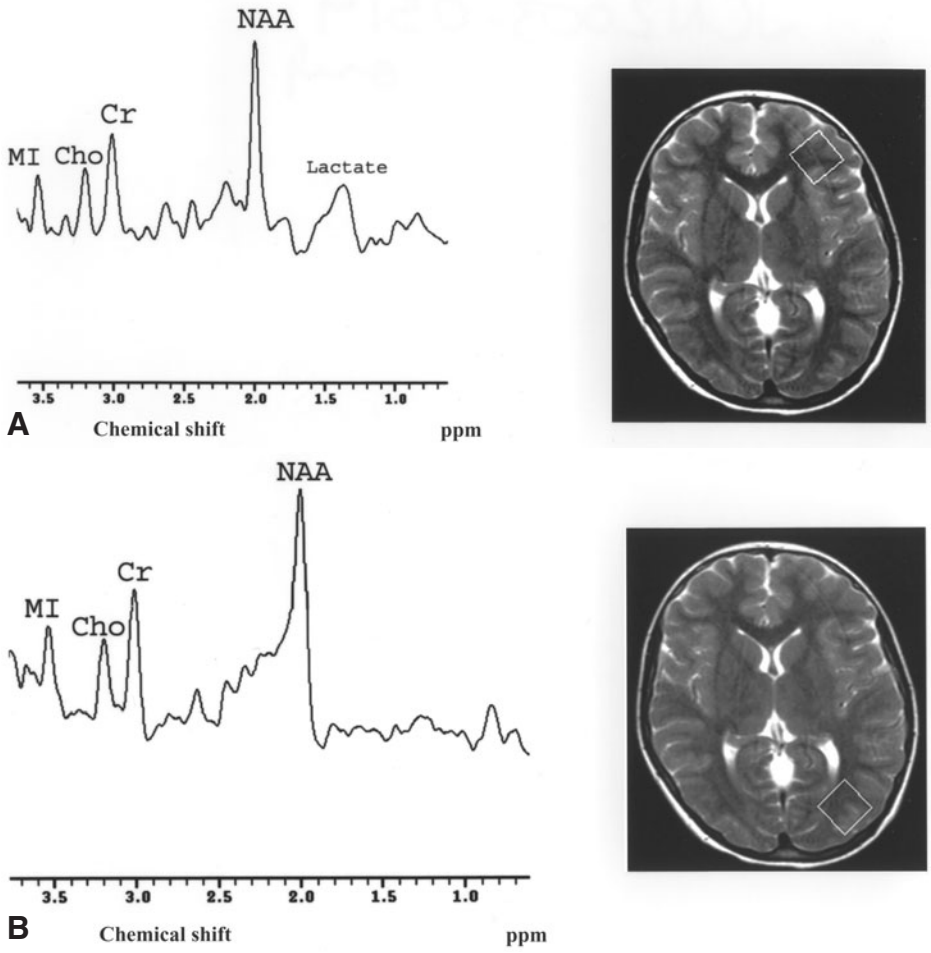

Figure 2. *A,* Single-voxel magnetic resonance spectrum (point-resolved spectroscopy sequence [1500/31/256]) obtained from the frontal cortex shows a decrease in the *N*-acetylaspartate-to-creatine ratio and a lactate peak, which could indicate neuronal loss and cellular anaerobic glycolysis. *B,* Magnetic resonance spectrum (point-resolved spectroscopy sequence [1500/31/256]) obtained from the parieto-occipital cortex shows a decrease in the *N*-acetylaspartate-to-creatine ratio.

respectively, might correspond to glial cell proliferation.[4,5] In our patient, choline-to-creatine and *myo*-inositol-to-creatine ratios in the frontal and parieto-occipital cortices were normal when compared with those of control subjects. These findings could reveal an absence of demyelination and glial proliferation.

Conclusion

In our case, magnetic resonance spectroscopy demonstrated the characteristic metabolic features of pyridoxine-dependent seizures as a decreased *N*-acetylaspartate-to-creatine ratio in the frontal and parieto-occipital cortices that could represent neuronal loss. For that reason, inclusion of magnetic resonance spectroscopy in the neuroimaging evaluation for assessment of parenchymal changes despite a normal-appearing brain MRI in pyridoxine-dependent seizures could be useful.

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Notice

As described in a recent journal article by Painter, Capute, and Accardo,[1] the American Board of Psychiatry and Neurology has now begun certification in the subspecialty of Neurodevelopmental Disabilities. The individuals who have completed this certification are:

Neurodevelopmental Disabilities Diplomates Certified April 3, 2001 thru December 31, 2011

Timothy Patrick Bohan
Jodie Lynn Bolt
Joseph Herbert Donnelly
Murray Engel
Marvin A. Fishman
Yitzchak Frank
William David Graf
Michael V. Johnston
David Ezra Mandelbaum
John F. Mantovani
Geoffrey Miller
Mark Ivan Mintz
Michael J. Painter
Marc Clayton Patterson
Steven George Pavlakis
Alan K. Percy
Dorothy M. Pietrucha
Isabelle Rapin
Sanford Schneider
Donald A. Taylor
Doris A. Trauner
Barbara Lois Trommer
Robert Pearce Turner
Jan Brian Wollack

Neurodevelopmental Disabilities Diplomates Certified April 9, 2002 thru December 31, 2012

Roman Oleh Bilynsky
Steven Lloyd Kugler
Nancy L. Kuntz
Diana Leticia Rodriguez
Romaine S. Schubert
Jay E. Selman
Michael Shevell
Charles N. Swisher

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