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A 9-year follow-up of a girl with pyridoxine (vitamin B6)-dependent seizures: magnetic resonance spectroscopy findings

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Abstract. – Being an extremely rare condition makes the diagnosis of pyridoxine-dependent seizures (PDS) difficult. Early diagnosis of PDS is very important to prevent unwanted clinical outcomes. Elevated levels of glutamate and decreased levels of γ-aminobutyric acid (GABA) in the frontal and parietal cortices are detected in this disorder. Here we present an 18 year old girl with PDS, who was reported 9 years ago with Magnetic Resonance Spectroscopy (MRS) findings. Present and past MRS findings showed a decrease in N-acetyl-aspartate-to creatine ratio on MRS. In this case it is surprising that neuronal damage has been preceded despite the administration of accurate treatment. That can be because of delay in treatment and/or under treatment.

Key Words:

Pyridoxine-dependent seizures, PDS, Magnetic resonance spectroscopy, MRS.

Introduction

Pyridoxine dependent seizure (PDS) is an uncommon disease caused by the pyridoxine-dependent synthesis of γ-aminobutyric acid (GABA) and inherited recessively. The disease currently manifests itself at prenatal or neonatal ages that do not usually countered with anticonvulsants and results in severe seizures[1]. There are not any particular findings of this disease detected on neuroimaging techniques. Therefore, the diagnosis of this disorder is very difficult and must be assessed together with clinical findings. The disease can be fatal in the absence of proper treatment when the diagnosis is delayed and/or the condition is underdiagnosed[2].

Magnetic resonance spectroscopy (MRS) is a non-invasive valuable modality for detecting some useful informations about neuronal integrity and function, cell membrane turnover and energy status of brain by measuring several metabolites. It can provide information reflecting metabolite changes in the brain of patients with PDS[3]. Here we compare MRS findings of an eighteen year old patient with PDS after long term treatment with pyridoxine who was also appraised and defined by Alkan et al[3] nine years ago. To our knowledge, although long term follow-up is lacking, this case report represents the first attempt to asses MRS findings of the pyridoxine dependency seizure patient at long term interval.

Case Report

An 18-year-old girl was the first child born to a healthy consanguineous parent. She was delivered normally and had an uneventful prenatal period. Within the third days of life she was manifested with generalized myoclonic convulsions. Until the diagnosis of a definite PDS, she was treated with various antiepileptic drugs. When she was 6 years old the supplemental pyridoxine treatment was started and she has been seizure free to date. She was diagnosed with learning disorder and attention-deficit, hyperactivity disorder according to Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria. There were findings suggesting especially frontal lobe damage in brain on neuropsychiatric examination.

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Magnetic resonance imaging (MRI) containing axial and sagittal T1-weighted images (TR: 560, TE: 15 msec) and axial and coronal T2-weighted images (TR: 4530, TE: 100 msec) and spectroscopy were employed on a 1.5 Tesla system (Philips, Gyroscan Intera, Best, The Netherlands). The point-resolved spectroscopy sequence (TR: 1500, TE: 31 ms) was used to perform single-voxel proton MRS. The volume of interests was placed to frontal and parieto-occipital lobe locations including both 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 MRS. The choline (Cho), creatine (Cr), and phosphocreatine, N-acetylaspartate (NAA), and myo-inositol (MI) signals were evaluated, with signals from creatine (3.02 ppm) being reference for spectra. Short-echo single-voxel proton MRS was used for being able to measure other metabolites like MI, glutamate, lactate, and lipid other than NAA, Cr, and Cho. Metabolite values derived automatically from the area under each metabolite peak was used to calculate metabolite ratios (NAA/Cr, Cho/Cr, and MI/Cr). The spectra obtained by examining five age matched healthy children were used as control group. Table I shows the metabolite ratios obtained from the patient and a corresponding control group nine years ago and now.

Discussion

PDS is a recessively inherited rare genetic disorder and abnormality is exhibited on chromosome 2q3[1]. After its first description in 1954, to the best of our knowledge, only more than a hundred cases exist in the reported literature[4,5]. An abnormality of brain glutamic acid decarboxylase-1 (GAD1) is responsible from the genetic defect. Glutamate decarboxylase is used to convert glutamate into GABA which has also rate limiting effect. An active metabolite of pyridoxine known as pyridoxal phosphate, is a coenzyme for glutamate decarboxylase. GABA is a major inhibitory mediator of neural transmission in the central nervous system. The decrease in GABA level of the brain tissue causes excessive neuronal excitation with resultant seizures[6].

Being an extremely rare condition makes the diagnosis of PDS difficult. Underdiagnosis or delay in diagnosis often bring severe neurological damage and may be fatal[7]. Early diagnosis of PDS is very important to prevent unwanted outcomes and is especially based on clinical suspicion. There are no specific imaging findings in the diagnosis of PDS. However, Gospe et al[8] described progressive brain atrophy on MRI in two cases. According to Jardim et al[9] there were hypodensities concerning abnormality in the myelination of the brain especially on frontal and occipital lobes on CT imaging. In our patient, MRI examination revealed any pathological findings.

MRS is a new non-invasive imaging modality that can provide completely independent biochemical information to complement MRI findings and can be easily integrated into a clinical MRI protocol without changing any hardware or the patient's position. This technique is used in different diseases of the central nervous system, supplies informations about neuronal integrity and function, cell membrane turnover and energy status of the brain. Due to non-invasive nature of this modality, neuronal tissue can be examined and followed sequentially over the entire life span. The metabolites that can be detected on MRS are NAA, Cho and Cr, with Cr being the putative internal standard against the others[3]. NAA is an important predictor of neuronal dys-

Table I. Magnetic resonance spectroscopy of pyridoxine-dependent seizures in a 18 year-old girl.

Metabolite rations	Frontal cortex			Parieto-occipital cortex		
	9 years ago	Present	Control (n = 5)	9 years ago	Present	Control (n =5)
NAA/Cr	1.55	1.33	1.77 ± 0.14	1.45	1.28	1.75 ± 0.14
Cho/Cr	0.70	0.73	0.74 ± 0.16	0.74	0.76	0.77 ± 0.16
MI/Cr	0.56	0.66	0.65 ± 0.13	0.62	0.67	0.68 ± 0.12

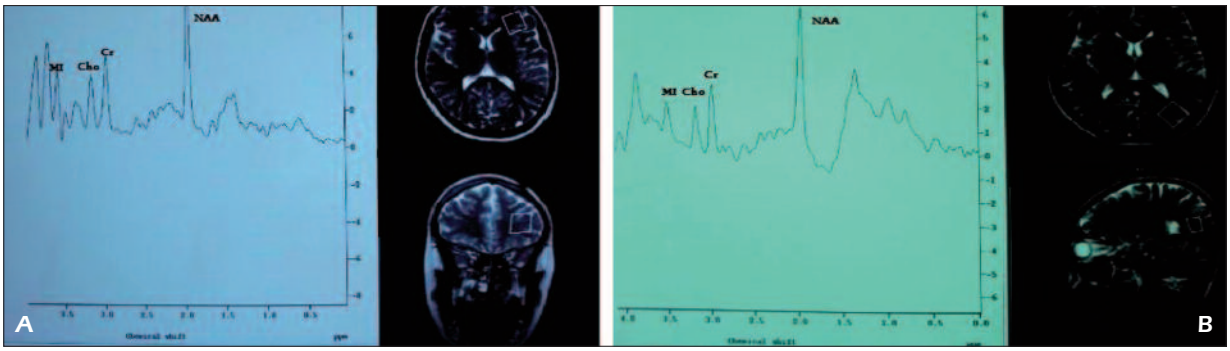

Figure 2. ***A,*** Single-voxel magnetic resonance spectrum (point-resolved spectroscopy sequence [1500/31/256]) obtained from the frontal cortex shows a decrease in the N-acetylaspartate-to-creatine ratio indicate neuronal loss. ***B,*** Magnetic resonance spectrum (point-resolved spectroscopy sequence [1500/31/256]) obtained from the parietooccipital cortex shows a decrease in the N-acetylaspartate-to-creatine ratio.

function and the decrease in NAA level is consistent with decrease in neuronal density or viability. Cr which is more concentrated in glia than in neurons indicate cellular energy metabolism. Cr is a stable metabolite whose level remains constant except in trauma, stroke, tumor, and Cr deficiency syndromes[3].

In this case, detected NAA/Cr ratio was lower in the patient than in control group those measured from frontal and parieto-occipital lobe locations, suggesting going on neuronal damage in respect to treatment (Figure 1). Our MRS findings supported that the neuronal loss depending on chronic excitation resulted with decrease in GABA and glutamate levels in brain which was also reported by the Meldrum et al[6]. On neuropsychiatric examination, there were findings concerning brain damage especially in frontal lobes which supported MRS findings. There was even a decrease in NAA/Cr ratio on MRS examination compared to those findings detected 9 years before from the same regions of the brain in the same patient. It is surprising that neuronal damage has been preceded despite the administration of accurate treatment. This can be because of delay in treatment and/or undertreatment.

Major components of the Cho resonance are Cho containing compounds with small molecular weight, such as phosphocholine and glycerophosphocholine that form a pool involved in membrane synthesis and degradation. The MI peak showed an osmolyte of plasma membranes. The increased Cho/Cr and MI/Cr levels, which could indicate increased membrane turnover and myelin breakdown and astrocytosis, respectively might correspond to glial cell proliferation[10]. In these either present or past MRS findings assessed 9 years ago, Cho/Cr and MI/Cr ratios detected in the frontal and parieto-occipital lobes were normal comparing with control group. These findings could reveal an absence of demyelination and glial proliferation.

Conclusions

The decrease in NAA/Cr ratio on present MRS examination compared to those findings detected 9 years before from the same regions of the brain in the same patient supports the proceeded neuronal damage which is being consistent. There is a need to a growing body of literature including comprehensive follow up studies to contribute the treatment and prognosis of this disease.

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