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Case Report

MRS features during encephalopathic crisis period in 11 years old case with GA-1

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Abstract

Glutaric aciduria type-1 (GA-1) is a disorder of amino acid metabolism. The usual clinical-onset is an acute encephalopathic crisis in early childhood. There are only a few cases diagnosed in older age groups. MRI features of the disease are well defined. However, there are limited number of studies concerning advanced neuroimaging findings. We present DWI and MRS findings of an 11 year-old GA-1 patient admitted with an encephalopathic crisis. Diffusion restrictions in bilateral basal ganglia, corpus callosum and periventricular deep white matter were observed. In left occipital periventricular white matter and left basal ganglia, mild increased Cho/Cr and MI/Cr ratios and decreased NAA/Cr ratio were detected. Also inverted double lactate peak (TE: 135 ms) was present at 1.33 ppm in the left basal ganglia. In addition to these findings, a peak at 1.56 ppm above the baseline was seen on both short and long echo-time MRS in left occipital lobe deep white matter which may show accumulation of degradation products of amino acids in the GCDH enzyme deficiency.

Keywords: Glutaric aciduria type-1; Magnetic resonance spectroscopy; Encephalopathic crisis

Glutaric aciduria type I (GA-1) is an inherited autosomal recessive disorder caused by glutaryl-CoA dehydrogenase (GCDH) enzyme deficiency. The estimated prevalence of GA-1 is 1 in 100,000 newborns [1]. GCDH enzyme plays a role in the breakdown of lysine, hydroxylysine, and tryptophan amino acids to acetyl-CoA by transformation of the glutaryl-CoA to crotonyl-CoA which is the intermediate step in the catabolic pathway. The enzyme deficiency results in blockage of catabolism of these three essential amino acids and accumulation of Glutaric acid, 3-hydroxyglutaric acid and glutaconic acids in the urine and the other body fluids particularly during acute illnesses [2].

It is associated with poor clinical outcome including; spastic cerebral palsy, dystonia, choreoathetosis and rarely mental retardation which is a serious metabolic disorder and often with a fatal outcome [3]. Most of the patients present acute encephalopathic crisis in the early childhood. There are only a few cases that had been diagnosed in older age groups. Early diagnosis of the disease is crucial prognostic determinant because timely treatment with dietary restriction of lysine and tryptophan prevents permanent neurological damage.

MRI features of the disease are typical and well established including: frontotemporal atrophy with bat wing-like middle cranial fossa, bilateral temporal

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arachnoid cysts, sylvian fissure enlargement, signal changes in the basal ganglia [4,5].

MR spectroscopy (MRS) is a noninvasive imaging modality that provides valuable information regarding in vivo brain metabolism and neuronal functions. Although basic MRS findings and diffusion weighted imaging (DWI) characteristics in GA-1 patient have been presented [6,7], in our knowledge, accumulation of break down products, occured in the metabolic pathway of lysine, hydroxylysine, and tryptophan amino acids, have not been identified on MRS, in a child with GA-1 during acute encephalopathic crisis.

1. Case report

A 11 years old male patient admitted to pediatric neurology department with an epileptic attack. His parents have a third degree consanguinity marriage. At 5 months of age, he was presented with neuromotor developmental delay and followed up as dyskinetic cerebral palsy. On admission to our hospital, neurological examination revealed an increase muscle tone in four extremities especially more seriously pronounced on the upper and also increase the deep tendon reflexes. Deficiency in thin motor coordination, involuntary, athetotic movements during speaking were noticed. He had no walking ability. He had a story of upper respiratory infection a week ago. Laboratory investigations showed metabolic acidosis (pH: 7.24, HCO_3: 15.5, pCO_2: 32). Urine organic acid analysis by gas chromatography and mass spectrometry revealed increased excretion of 3-OH Glutaric acid (1220 mg/g creatinine), and lactate (250 mg/g creatinine) in the urine. Marked blood lactate level (28.2 mg/dl) was also noted. Enzymatic assay in cultivated skin fibroblasts revealed complete absence of GCDH activity.

Magnetic resonance imaging (MRI) and spectroscopy of the brain were performed on a 1.5-T system.

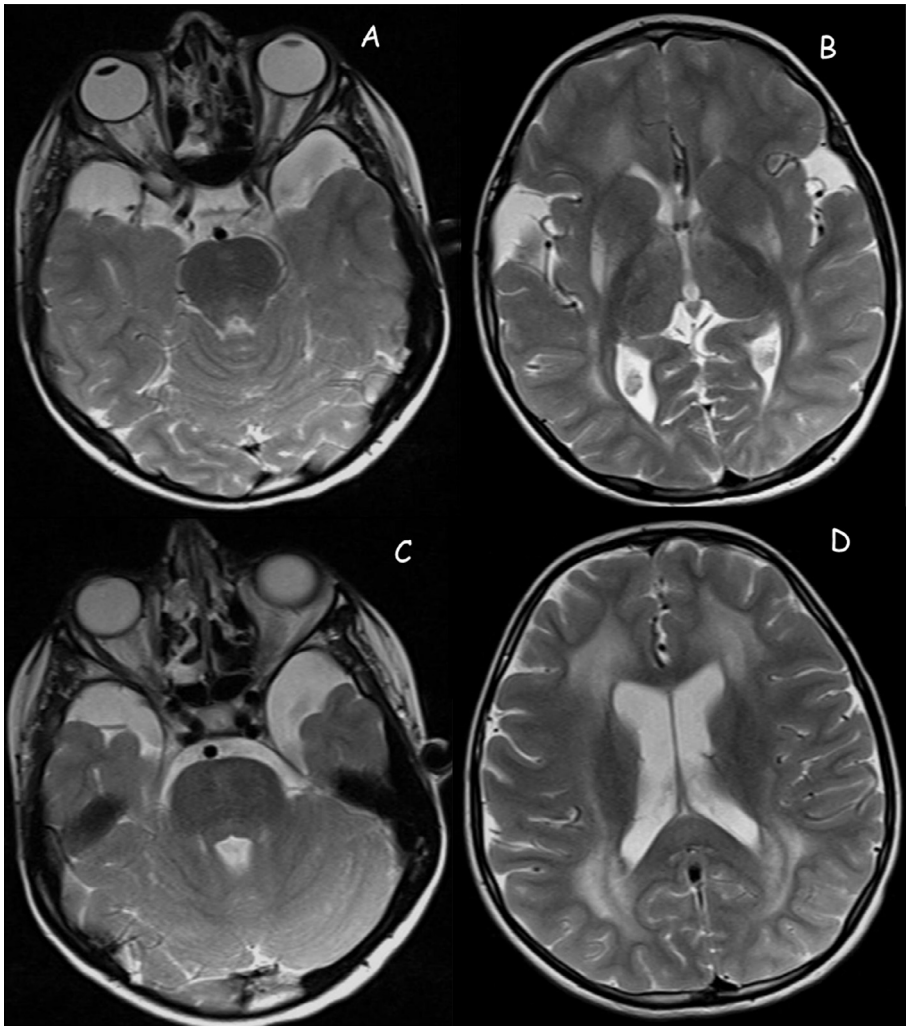

Fig. 1. Axial T2W images show widening cerebrospinal fluid spaces anterior to temporal lobes enlargement of the sylvian fissures and increased signal intensities in bilateral lentiform nuclei and periventricular deep white matter (A–D).

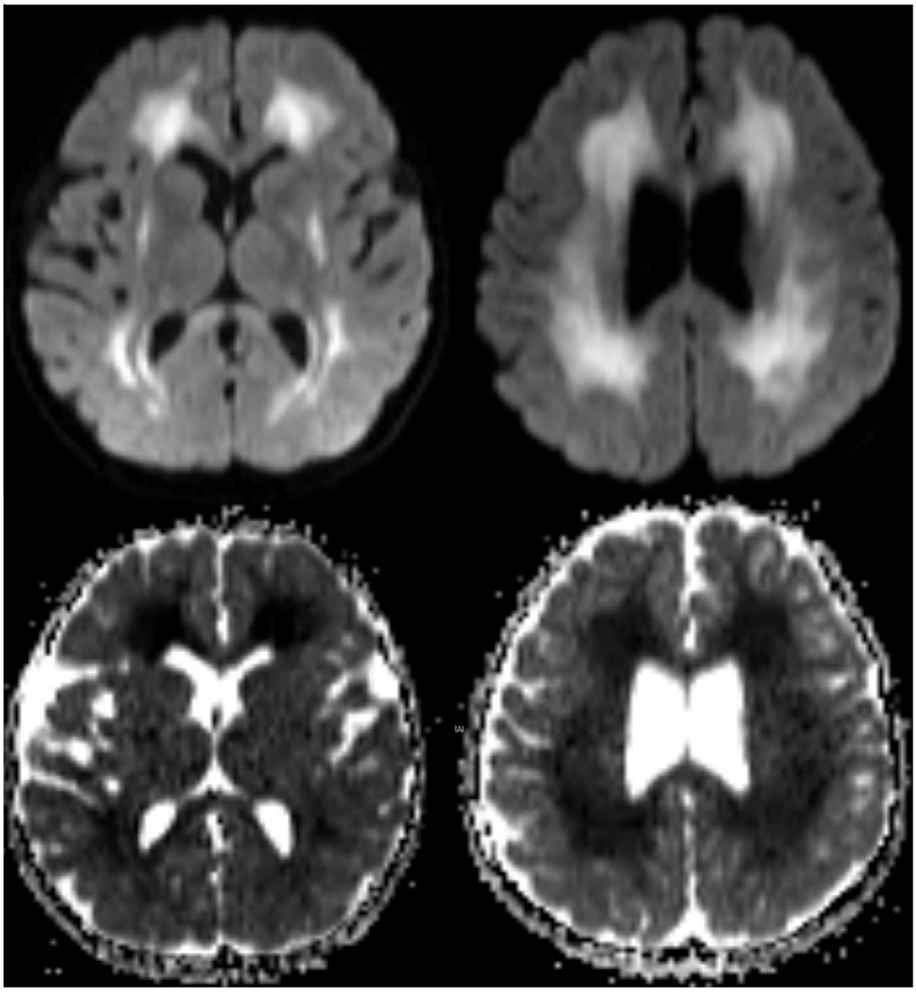

Fig. 2. On DWI, hyperintensities in bilateral nucleus lentiformis, corpus callosum and periventricular deep white matter reflecting restricted diffusion (ADC maps).

MRI disclosed frontotemporal atrophy including; widening cerebrospinal fluid spaces anterior to temporal lobes and enlargement of the sylvian fissures. Increased signal intensities in bilateral lentiform nuclei and deep white matter on T2 images (Fig. 1). Diffusion restrictions were also observed in bilateral globus pallidum, putamen, corpus callosum and periventricular deep white matter on DWI (Fig. 2).

Multivoxel MRS was performed by using the point-resolved two-dimensional chemical shift imaging (CSI) (TR: 1500; TE: 135/35 ms). Voxels were placed in deep white matter of frontal and occipital lobes and basal ganglions. N-acetylaspartate (NAA), choline (Cho), creatine (Cr), myo-inositol (MI) and lactate peaks were analyzed. Peak area metabolite ratios (NAA/Cr, Cho/Cr and MI/Cr) were calculated. Mild increased Cho/Cr and MI/Cr ratios detected in deep white matter of left occipital lobe and left basal ganglia. NAA/Cr ratio was mild decreased. Inverted double lactate peak (TE: 135 ms) was seen at 1.33 ppm in the left basal ganglia (Fig. 3). Increased peak at 1.56 ppm above the baseline was seen on both short and long echo-time MRS (TE: 135/35 ms) in left occipital lobe deep white matter which may show accumulated of degradation products of amino acids in the GCDH enzyme deficiency (Fig. 4).

We report 11 years old boy, presented with psychocomotor dysfunction, who have not been diagnosed yet. According to clinical symptoms, laboratory results, and neuroimaging features, he was diagnosed glutaric aciduria type 1 with acute encephalopathic crisis.

2. Discussion

Although the basic radiological findings of GA-1 are well defined, there are limited number of studies concerning advanced neuroimaging findings [6,7]. DWI provides information about changes in water molecules diffusion. DWI is dependent on the random motion of water molecules and offers a chance to evaluate the structural characteristics of tissues. DWI shows restriction of water diffusion of the vital brain structures with low ADC indicating a shift of fluid into the intracellular

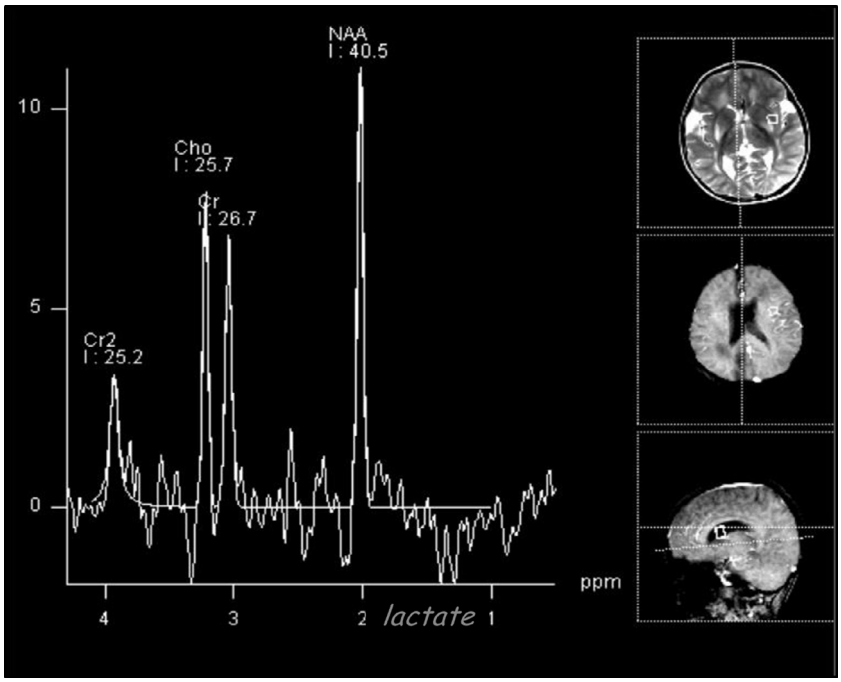

Fig. 3. The MR spectrum (TE: 135 ms) obtained from left nucleus lentiformis show the inverted double lactate peak at 1.33 ppm.

compartment in cytotoxic edema. It is known that cytotoxic or cellular edema is the abnormal uptake of fluid in the cytoplasm because of abnormal cellular osmoregulation. Such an edema may occur together with various processes that may give harm to cells, such as ischemia, trauma, toxic metabolic disease, demyelination, and even the beginning phase of degeneration. In the gray matter, cytotoxic edema appears meanly in neurons and glial cells. Nevertheless, in the white matter, it is usually seen in glial cells, axons (axonal swelling) and myelin sheaths (intramyelinic edema) [8].

On DWI, diffusion restriction is seen during the episodes of acute encephalopathic crisis in a patient with GA-1. The usual clinical presentation of GA-1 is acute encephalopathic crises precipitated by gastroenteritis, intercurrent febrile illnesses, immunization and surgical intervention. At the same time, acute encephalopathic crisis can be seen with a diet rich in tryptophan, lysine and hydroxylysine and when there is no dietary control. For this reason, accumulation of metabolites, acting as neurotoxins, may lead to cytotoxic edema like intramyelinic edema and restricted diffusion. Our case have not received a diagnosis until the age of 11 and experienced no dietary control. In our case, decreased signal intensities on ADC maps were observed in bilateral lentiform nuclei, corpus callosum and periventricular deep white matter which shows restricted diffusion in acute encephalopathic period.

MRS is a useful imaging modality which maintain data by studying metabolic composition of tissue and by probing their variations during the disease process. It provides information about neuronal/axonal viability, cellular metabolism and membrane status. Major MRS resonances of normal brain tissue include NAA, Cho, Cr, and MI. Resonance peaks were assigned as follows: NAA; 2.0 ppm, Cr; 3.02 ppm, Cho;3.2 ppm, and MI; 3.56 ppm. In vivo accumulation of intermediate breakdown products of amino acids (1.6–1.7 ppm) can be identified in short-echo time (TE: 35 ms) spectrum.

K. Oguz et al. reported DWI and MRS findings in a GA-1. Diffusion restriction areas were showed in the periventricular white matter and corpus callosum. MRS revealed lactate peak at 1.3 ppm, decreased NAA level in affected basal ganglia and normal appearing white matter. They explained findings by oxidative stress due to deficiency of mitocondrial proteins in GA-1 and neuronal death [6]. In another research, diffusion restriction and decreased NAA peak were showed in the affected basal ganglia in acute encephalopathic crisis period [5]. The increased Cho/Cr and MI/Cr ratios and lactate peak may be an indication of myeline breakdown products due to increased membrane turnover, astrocytosis and anaerobic glycolysis respectively which correspond to neuronal loss and glial cell proliferation. Besides, Heyes [9] reported in his study that the accumulation of quinolinic acid, a breakdown product of tryptophan, is a potent neurotoxicity in cases with GA-1.

In our case, mildly increased Cho/Cr and MI/Cr and decreased NAA/Cr ratios at the left occipital lobe deep white matter and left basal ganglia could represent demyelinization and gliotic process at that areas. The inverted double lactate peak (TE: 135 ms) at 1.33 ppm

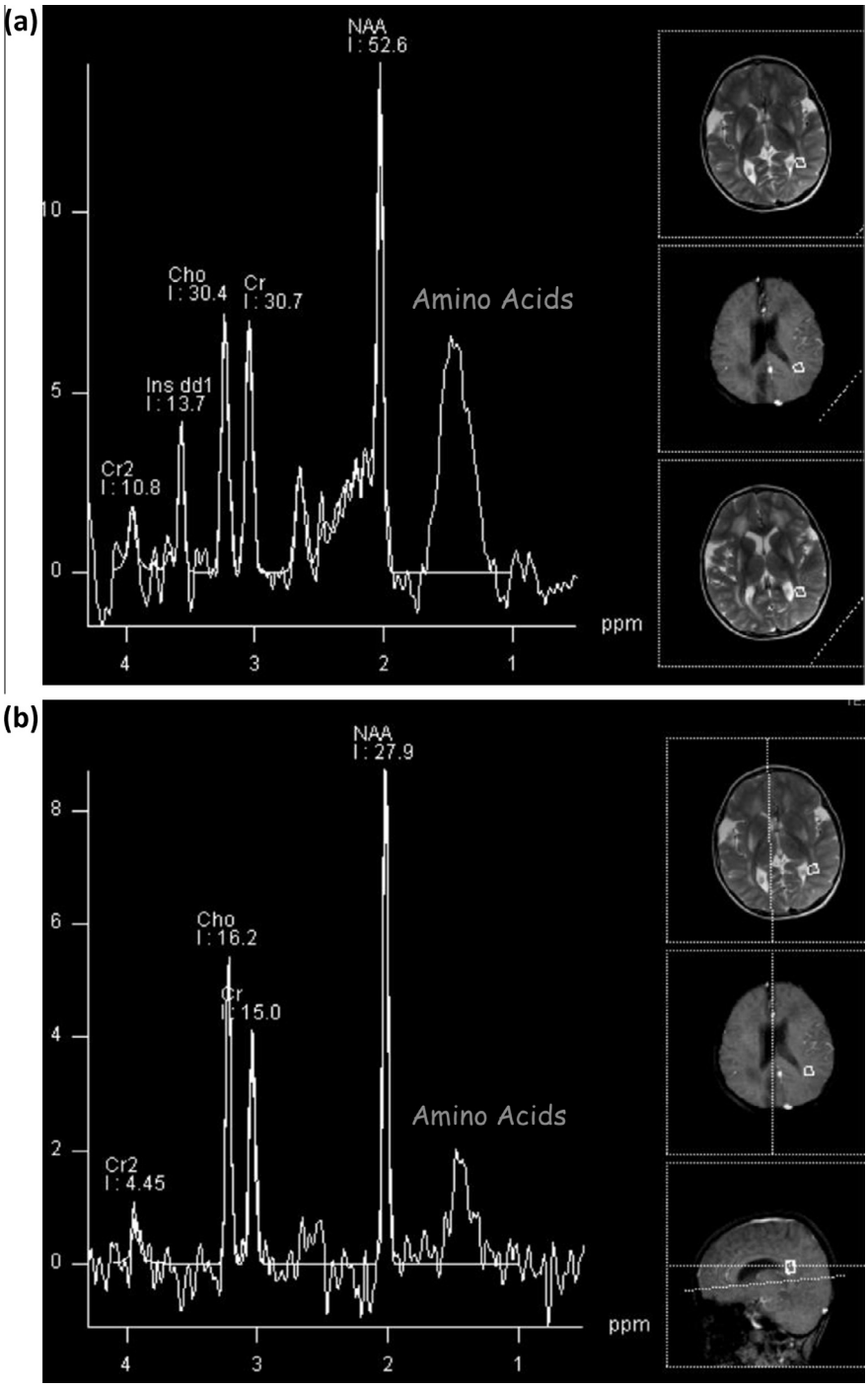

Fig. 4. The MR spectrum obtained from left occipital lobe deep white matter show mild increased Cho and MI peaks. Note the increased peak at 1.56 ppm above the baseline on both short and long echo-time MRS (TE: 30 and 135 ms) shows intermediate products of the amino acids.

in left basal ganglia was thought to be due to oxidative metabolism damage. The peak observed at 1.56 ppm in left occipital lobe deep white matter on both short and long echo-time spectrums may show accumulation of degradation products of amino acids at the cellular level in brain. Besides, this peak was not observed in basal ganglia. This may have resulted from the prominent observation of diffusion restriction in periventricular white matter due to intramyelinic edema on DWI while diffusion restriction is observed less in basal ganglia.

The nearest resonances to this peak we have detected on MRS can be seen as alanine, lactate and lipid peaks. Alanine is known as a metabolite having a doublet peak at 1.48 ppm, but its existence may be overshadowed by lactate peak at 1.33 ppm. There is a very short relaxation time of membrane lipids and they are not usually

visualized on intermediate or long TE, although they are visualized on short TE. Their peaks are usually between 0.8 and 1.4 ppm.

In our case, these metabolic alterations detected on MRS may be associated with neuronal loss. As a conclusion, it can be said that short and long echo time MRS may provide significant information in cases with GA-1 in the acute encephalopathic period.

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