case report

Brain magnetic resonance imaging and proton MR spectroscopic findings after metabolic crisis in 3-methylcrotonylglycinuria

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Magnetic resonance imaging (MRI) and magnetic resonance spectroscopic (MRS) findings in 3-methylcrotonylglycinuria presenting with acute metabolic decompensation in a previously healthy 7-year-old female are described. The patient was hospitalized with fever, irritability, gastrointestinal problems, drowsiness, signs of upper motor neuron deficit, and rapidly progressive respiratory distress requiring assisted ventilation. Laboratory workup showed severe metabolic acidosis, and the diagnosis of 3-methylcrotonylglycinuria was established by the mass spectrometry analysis of urine sample. Although initial CT imaging workup was found to be gross normal, subsequent MRI of the brain in the early chronic stage of the disease showed symmetrical ill-defined signal abnormalities within medulla oblongata, pons, inferior cerebellar peduncles, and periventricular white matter in cerebral hemispheres. Diffusion-weighted images were unremarkable. Single-voxel proton MRS showed elevated levels of lactate, branched-chain amino acids, as well as glutamine and glutamate. To the best of our knowledge, this is the first reported case of late onset 3-methylcrotonylglycinuria with complete MRI and MRS workup in the early chronic phase after metabolic crisis.

We report conventional magnetic resonance imaging (MRI), diffusion-weighted imaging (DWI), and single-voxel proton magnetic resonance spectroscopic (MRS) findings in a 7-year-old female patient with 3-methylcrotonylglycinuria (OMIM ID: 210200) 10 weeks after the first metabolic decompensation of her life. Our conventional MRI findings are different from those already published, and to the best of our knowledge, no advanced imaging data (including DWI and MRS) in this disease have been reported yet. Therefore, our data may contribute to broadening our knowledge of the spectrum of imaging phenotypes of the disease, especially with regard to the late onset clinical form.

CASE

A 7-yearold female patient was initially admitted to a peripheral hospital with a few days' history of fever, cough, and vomiting. Her perinatal and past medical history were unremarkable. The parents were consanguineous, but her siblings were normal.

On initial clinical evaluation, the patient was comatose with both pupils symmetrical and reacting. She had tall stature (125 cm) for her age with arachnodactyly. Her weight was 22 kg. Chest and cardiovascular examination revealed severe chest retraction and pansystolic murmur. She was afebrile and her pulse rate was 180/min, respiratory rate 70/min, and blood pressure 130/80 mm Hg. Apart from drowsiness, she was found to have no focal neurological abnormalities. She, however, rapidly developed hypotonia and exaggerated deep tendon reflexes. Subsequently, she developed severe respiratory distress requiring intensive care unit admission.

Blood gas analysis indicated severe metabolic acidosis. Tandem mass spectroscopy screening performed using blood and urine samples) was diagnostic for 3-methylcrotonyl glycinuria. Echocardiography con-

firmed the presence of mild mitral valve regurgitation. The chest X-ray examination revealed bilateral hyperinflation and signs suggestive of viral respiratory infection. Ultrasound and CT of the abdomen showed a left solitary kidney. CT scan of the brain was reported as normal.

The patient was treated with the intravenous infusion of sodium bicarbonate at the rate of 1 mmol/(kg × h), and metabolic acidosis gradually improved to normal. She needed assisted ventilation for about a month, and a tracheostomy tube was inserted afterwards. She was kept on a leucine-restricted diet in addition to glycine 1.25 gm orally every 8 hours and carnitine 3.5 mL orally twice per day.

The patient was transferred to our hospital 6 weeks after the initial metabolic decompensation for further specialized workup and management. At this time, she was in a stable condition both metabolically and neurologically. She was alert, cooperative, obeying commands, with no facial asymmetry or signs of cranial nerve palsy. She was walking independently but with a wide-based gait. She had mild hypotonia and exaggerated deep tendon reflexes with grossly normal muscle power. There was no tremor or abnormal eye movements. However, for an unknown cause, she was unable to speak.

On the 71st day post-onset of the metabolic decompensation, an MRI examination of the brain was performed in our hospital on a scanner of 1.5 Tesla (Siemens, Magnetom Vision Magnetom vision, Siemens Medical Solutions, Erlangen, Germany). The study included sagittal T1-weighted spin-echo, axial proton density and T2-weighted fast spin echo, axial fluid-attenuated inversion recovery (FLAIR), axial T1-weighted inversion recovery, and axial echo-planar diffusion-weighted (b: 0, 500, and 1000) imaging sequences. The long TR (T2-weighted FLAIR) images showed abnormal symmetrical high signal intensities within posterolateral medulla oblongata and inferior cerebellar peduncles as well as patchy hyperintensities within pons (**Figure 1**). Additional subtle signal abnormalities were present supratentorially in frontal periventricular white matter bilaterally (**Figure 2**). A few scattered non-specific hyperintense foci were also noted within the cerebral hemispheric white matter on FLAIR images (**Figure 2**). The lesions were not associated with swelling or restricted water diffusion, suggesting a burned-out, early chronic state of the underlying histopathological processes (**Figure 3**). As an incidental finding, the study also showed persistent cavum septi pellucidi.

Single-voxel proton MRS study was also performed during the same session. The sampling voxels were placed on deep gray matter structures within the right cerebral hemisphere. A short echo-time study (STEAM, TE: 20 ms) showed a prominent positive peak doublet at the 1.3 to 1.4 ppm level (**Figure 4a**), which with a long echo-time (PRESS, TE: 135 ms) almost totally disappeared (**Figure 4b**). This was consistent with the elevated cerebral lactate. Another prominent abnormal positive peak was also seen at around the 0.8 to 0.9 ppm level on the short echo-time spectrum, which was not conspicuous either on the long echo-time spectrum. This was believed to correspond to branched-chain amino acids (in particular, leucine), perhaps overlapping with additional lipid degradation products. The short echo-time spectrum also showed a broad peak complex at the 2.2 to 2.4 ppm level. These peaks may correspond to small amounts of glutamine and glutamate. Additional smaller peaks were also seen at 2.5 and 2.6 ppm levels, which could not be assigned to any known metabolites. Another peak was identified at the 3.56 ppm level; since it disappeared on the longer

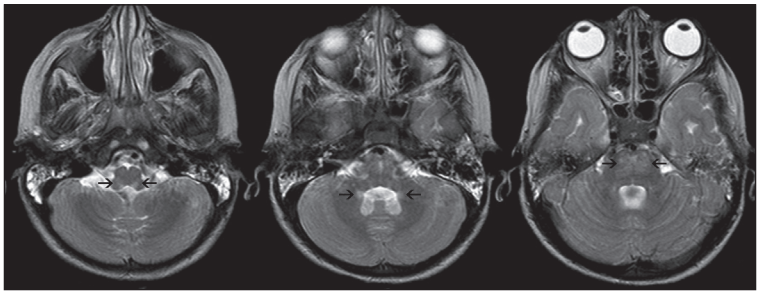

Figure 1. Axial T2-weighted image of the brainstem shows symmetrical abnormal signal within posterolateral medulla oblongata and inferior cerebellar peduncles bilaterally as well as ill-defined, more diffuse high signal intensities in pons (arrows).

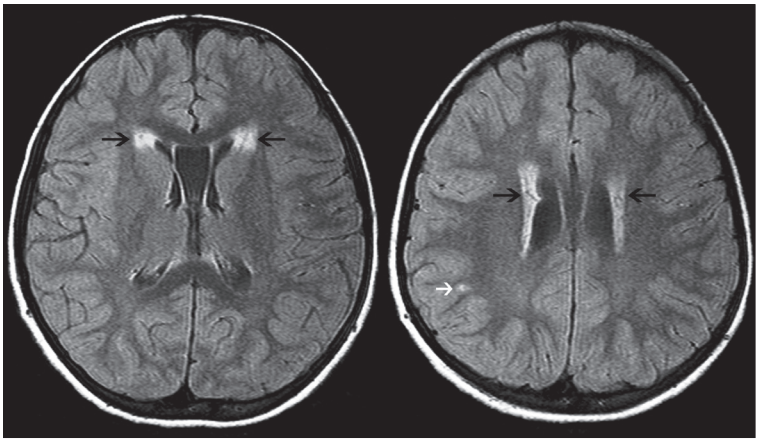

Figure 2. Axial FLAIR image showing symmetrical high signal intensity periventricular bands in both cerebral hemispheres (black arrows). A small subcortical white matter lesion is also noted (white arrow). Note incidental persistent cavum septi pellucidi.

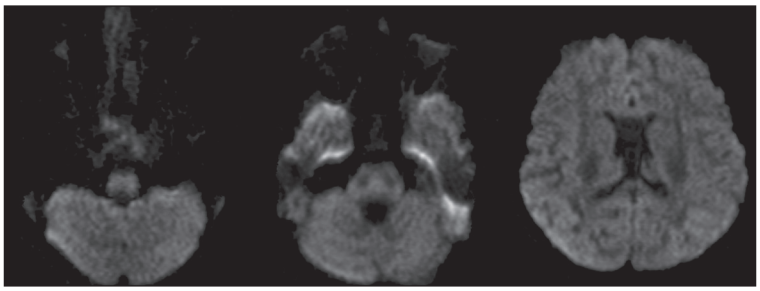

Figure 3. Axial echo-planar diffusion-weighted images of brainstem and cerebral hemispheres. No definite signal abnormalities are seen in lesion areas identified by conventional long TR images.

echo-time spectrum, it was interpreted as myo-inositol. The N-acetylaspartate, creatine, and choline peaks were found to be grossly normal on both short and long echo-time spectra.

DISCUSSION

3-Methylcrotonylglycinuria is a rare inborn error of leucine catabolism characterized by autosomal recessive inheritance. The cause of the disease is deficiency of 3-methylcrotonyl-coenzyme A carboxylase (EC 6.4.1.4), an enzyme converting 3-methylcrotonyl-coenzyme A to 3-methylglutaconyl-coenzyme A, which is the fourth step in the leucine breakdown pathway.[1,2] Since biotin is a cofactor of the enzyme, in cases of impaired biotin metabolism, the disease may present as part of the multiple carboxylase deficiency complex, and hence may be responsive to biotin supplementation.[2] The isolated biotin-resistant form of the disease is very rare; to date, less than 50 cases of the disease have been reported.

The typical clinical presentation of the disease is acute metabolic crisis, including metabolic acidosis, ketonuria, and hyperammonemia, between 6 months and 3 years of age. However, the known clinical phenotypes of the disease range from asymptomatic patients living in adulthood to severe systemic metabolic and neurological abnormalities or even death in early infancy.[3,4] Metabolic decompensation is often triggered, as in many other organic and amino-acidopathies, by intercurrent viral illness, excessive physical effort, or protein overload. Routine laboratory workup of patients may be normal or non-specific; hence, the diagnosis in suspected cases relies on the demonstration of excessive amounts of alternate leucine breakdown products in urine samples by mass spectrometry (notably 3-hydroxyisovalerate and 3-methylcrotonylglycine) due to the accumulation of 3-methylcrotonyl coenzyme A and 3-methylcrotonic acid.[2,3]

In this case report, we described a female patient with true, isolated 3-methylcrotonylglycinuria. Our patient was somewhat peculiar because she was clinically asymptomatic till the age of 7 years, when she presented with the first episode of Reye syndrome-like metabolic decompensation in a context of upper respiratory viral infection. Apart from the age of onset,

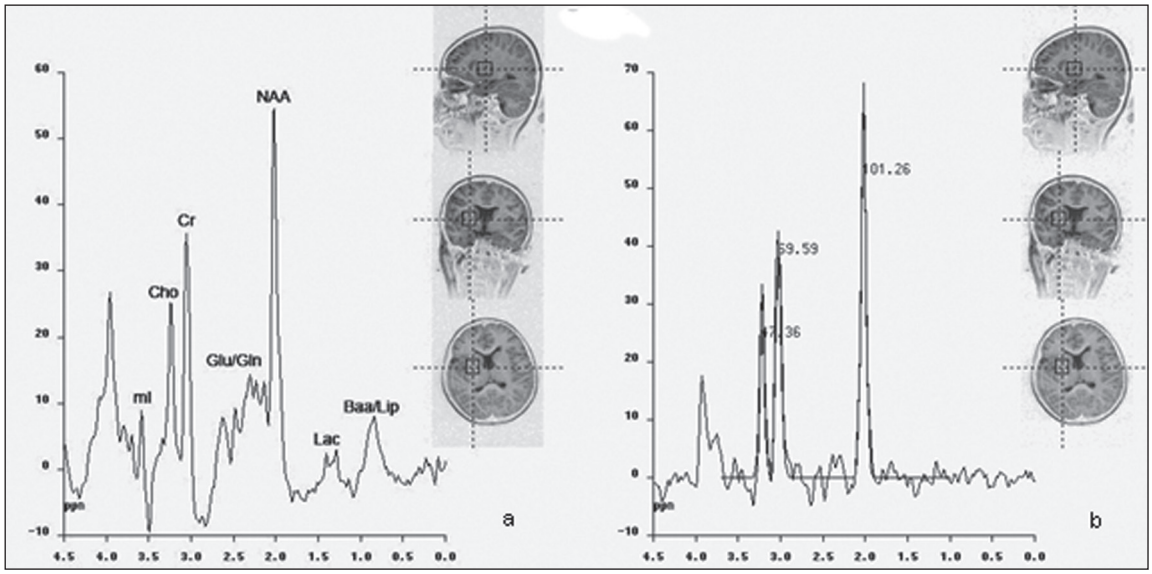

Figure 4. Single-voxel proton MR spectroscopic findings. The spectrum with short echo time (STEAM, TE: 20 ms) demonstrates (from right to left) elevated levels of branched-chain amino acids and lipids (Baa/Lip), lactate (Lac), normal N-acetylaspartate (NAA), elevated glutamate and glutamine (Glu/Gln), normal creatine (Cr), choline (Cho), and myoinositol (mI) peaks (a). On long echo-time spectrum (PRESS, TE: 135 ms), the abnormal peaks all disappear (b).

the overall clinical picture was quite similar to those described in other patients. Solitary kidney and mitral valve regurgitation revealed in our patient are not known associated manifestations of this disorder and probably represent coincidental findings. As in most reported cases with the late onset form, our patient responded well to treatment and showed a fairly good neurological recovery.

Reports of neuroimaging findings in 3-methylcrotonylglycinuria are limited to a few cases only. In the neonatal onset form, the reported abnormalities included severe encephalomalcia, leukodystrophy-like changes leading to severe brain atrophy, and rapidly necrotizing encephalopathy.[3] In a case of late infantile onset, brain atrophy and parietal-occipital periventricular leukodystrophy-like white matter disease was described.[4] Imaging abnormalities presumably representing metabolic stroke have also been observed.[5] Occasionally atrophy may be the only detected imaging abnormality in the chronic phase of the disease.[2,6] In some other cases, however, no imaging abnormalities could be detected at all.

We believe that MRI findings in our case are unique, presenting dominantly with lesions in the brainstem, and their combination with supratentorial periventricular white matter involvement has also not been reported before. Since these imaging abnormalities were observed in the early chronic phase of the disease, it is possible that additional, perhaps reversible, lesions were also present earlier. Therefore, the imaging lesion pattern may have been more complete during the acute phase after the metabolic crisis.

MRS in our patient showed several definite and possible abnormalities. A small amount of lactate was suggested within the brain parenchyma, which is always considered to be abnormal in term infants or any time later during life. Our patient did not have an elevated serum lactate level, likely reflecting persistently impaired energy metabolism within the brain several weeks after the episode of metabolic decompensation. A possible dissociation between serum and brain tissue lactate levels is well-known; therefore, MRS has been considered as the most reliable method to monitor lactic acidosis in the brain.[7] Elevated levels of other unusual metabolites in the brain were also detected in our patient. We believe that the peak at the 0.9 ppm level on the short echo-time spectrum likely corresponds to leucine and/or its early metabolites on its breakdown pathway (2-oxoisocaproic acid, isovaleryl-coenzyme A). The reason behind this is that leucine seems to be the strongest contributor to the typical abnormal peak in the same location in patients with maple syrup urine disease, which is another classical disease entity on the branched-chain amino acid metabolic pathway.[7,8] A contribution to this peak by lipid degradation products (secondary to myelin breakdown during metabolic decompensation) is, however, also possible. The significance of the suspected small amounts of glutamine and glutamate in brain is unclear. An increase of these metabolites in brain parenchyma is known in various abnormal metabolic conditions presenting with hyperammonemia, such as urea cycle defects.[9] Although hyperammonemia is a common laboratory abnormality associated with 3-methylcrotonylglycinuria and because this is the first ever case of 3-methylcrotonyl glycinuria with combined MRI-MRS workup, we can only speculate that increased glutamine and glutamate levels could be part of the pattern of metabolic changes shown by MRS in this disorder, especially as we do not have laboratory data to indicate hyperammonemia at the time of the examination.

Reviewing our and other reported cases with 3-methylcrotonylglycinuria, we can conclude clear that the imaging phenotype of the disease is quite heterogeneous. It seems, however, that neonatal and early infantile forms are more likely to present with a severe, rapidly progressive leukodystrophy-like findings, consistent with the known increased vulnerability of the developing brain to any noxious insult (metabolic or other) and the poorer prognosis of these clinical forms. In late-onset forms, the imaging findings may be different and less consistent. While the periventricular white matter in cerebral hemispheres may remain prone to damage, as was found in our case, additional structures, in particular brainstem and cerebellum may be vulnerable, too. Factors possibly explaining this quite peculiar late selective vulnerability pattern are yet unknown. While the overall MRS pattern described in our patient does not seem to be specific to the disease, in an appropriate clinical setting it may be considered suggestive.

In conclusion, we describe the brain MRI and MRS findings in a patient with 3-methylcrotonylglycinuria. The MRI may show symmetrical ill-defined signal abnormalities within medulla oblongata, pons, inferior cerebellar peduncles and periventricular white matter. The MRS findings include elevated levels of lactate, branched-chain amino acids, as well as glutamine and glutamate.

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