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*Case Report*

# Diffusion Weighted Imaging and MR Spectroscopic Findings in Maple Syrup Urine Disease: The Importance of Early Radiological Diagnosis in the Prevention of Cerebral Parenchymal Damage

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**Abstract** Maple Syrup Urine Disease is a very rare autosomal recessive inherited disease that results from the defect in the catalytic activity of the alpha ketoacid dehydrogenase enzyme complex. The deficiency in the catabolism of branched chain amino acids naturally results in the accumulation of these amino acids (leucine, isoleucine and valine) and toxic metabolic end products in human blood and urine. In this study, the importance in early diagnosis of cranial DWI imaging and MR spectroscopy and evaluation of treatment efficacy in a newborn who was referred to the emergency room with ketoacidotic coma was reported.

**Key words** *Diffusion weighted imaging; Maple syrup urine disease; MR spectroscopy*

## Introduction

Maple Syrup Urine Disease (MSUD) is a very rare autosomal recessive inherited disease that results from the defect in the catalytic activity of the alpha ketoacid dehydrogenase enzyme complex. The deficiency in the catabolism of branched-chain amino acids (BCAA) naturally results in the accumulation of these amino acids (leucine, isoleucine and, valine) and toxic metabolic end products in human blood and urine.[1,2] The estimated frequency of MSUD in the world varies from 1: 185.000 to 1:940.000.[3] The very rare occurrence of the disease causes it not to be included in routine a screening programs in many countries. However, it is thought that the real incidence is higher because of the undiagnosed death causes as the disease is not in screening program. Autosomal recessive genetic diseases such as MSUD are more common in countries like in Turkey where consanguineous marriages are frequent and screening programs are limited.[4,5]

Accumulating BCAA and their metabolites in MSUD disease are markedly neurotoxic. If the patient is not treated with BCAA-free formulation, irreversible brain damage will occur. In untreated case of MSUD, ketoacidosis, hypoglycaemia, lethargy and epileptic seizures are seen over time. If patient can survive, the developmental and mental retardation develop in later stage of life.[6]

In this study, we aimed to discuss the importance of Diffusion Weighted-Magnetic Resonance Imaging (DW-MRI) and Magnetic Resonance Spectroscopy (MRS) in the diagnosis and in the early treatment of the disease as a 9 day old male with MSUD who was admitted to emergency department with ketoacidotic coma and treated in the neonatal intensive care unite.

## Case Report

A male, 9 days old, term newborn with birth-weight of 2800 grams, and born by cesarean section was brought to our emergency service by his family. He was found immobile in his bed and with purple colour. The family

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stated that the baby is the second child of the family and that there was no perinatal problem in pregnancy follow up and the first baby is healthy. There was no family history for consanguinity. On physical examination, the general condition of the baby was bad, unconscious, body temperature was 37.2ºC and wasn't spontaneously breathing. Pulse rate of the baby was 140 beats/min and had a pulsating and bulging anterior fontanelle. Fontanel size was 2x2 cm. Liver and spleen were normal and no pathological findings were found in other systems. At the time of the examination, generalised tonic seizures were observed. Complete blood count test was normal and toxic granulation was detected in peripheral blood smear examination. Metabolic acidosis was detected in the blood gas test. Chest X-ray was normal. Liver and kidney function tests, blood sugar, amylase, lipase, calcium, and other electrolyte levels were normal. C-reactive protein level was 6 mg/dL(normal 0-0.5 mg/dL). Sugar 60 mg/dL (concurrent blood sugar 94 mg/dL, normal 70-100 mg/dL), protein 40 mg/L(normal 64-83 mg/L) and 1-2 leukocytes were detected in cerebrospinal fluid (CSF). Abdominal ultrasonography and transfontanelle cranial ultrasonography examinations were normal. There were no reducing substances in urine and urine and blood ketone were negative. Serum ammoniac level was 268 mcg/dL (normal 27-86.9 mcg/dL) and lactate level was 4.2 mmol/L (normal 0.5-1.6 mmol/L).

Cefotaxime and vancomycin were started to the infant with a prediagnosis of neonatal sepsis-meningitis. The infant was supported by mechanical ventilator due to respiratory failure and encephalopathy. He was screened for metabolic disorders and before screening results come out, DW-MRI was performed. DW-MRI showed marked diffusion restriction in bilateral frontal deep white matter, putamen, brain stem and cerebellar dentate nuclei (Figure 1a,b,c). MRI findings were consistent with MSUD. Single-voxel MRS was performed on pathological areas of the patient and showed decreased N-acetylaspartate (NAA) levels and increased myoinositol and lactate levels. Also, MRS revealed a broad peak at 0.9 ppm (Figure 1d). As previously reported in the literature, the metabolites which contribute to the peak level at 0.9 ppm, are BCAA and branched-chain α-ketoacids (BCAK). With all these findings, MSUD was diagnosed radiologically. Immediately after screening tests were done (tandem mass spectrometry, tests for urine and blood amino acids),

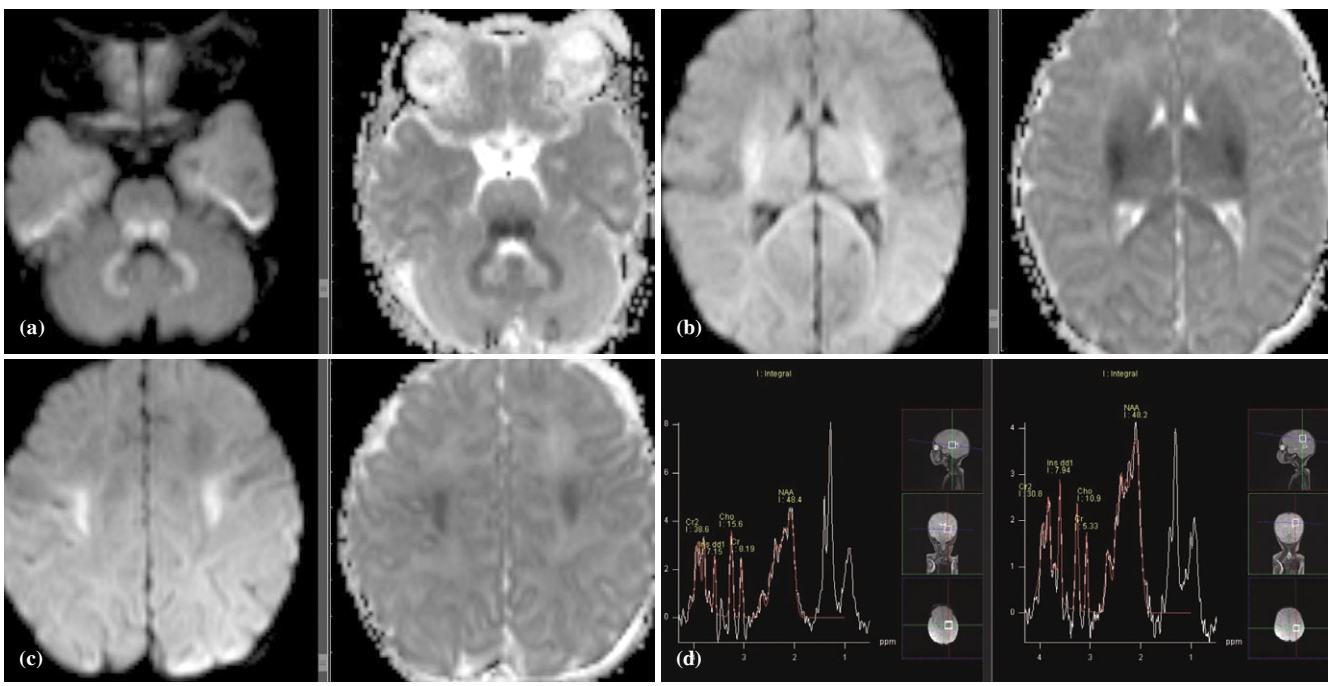


**Figure 1** Axial DWI (B=1000) on the left side and ADC maps in the right side. There are diffusion restriction in the bilateral dentate nucleus, putamen and frontal deep white matter (a, b, c). There is a broad peak at 0.9 ppm at short TE (30 ms) MR spectroscopic images in the bilateral putaminal and frontal deep white matter's lesions (d). The metabolites which contribute to the peak level at 0.9 ppm, are branched chain amino acids and branched chain α-ketoacids.

acidosis treatment was started with peritoneal dialysis. Also due to the encephalopathic crisis; total parenteral nutrition (TPN) was started with protein-restricted, high calorie and lipid content. The level of leucine and isoleucine found in tandem mass spectrometer was very high. Level of valine 477 µM/L (normal: 64-294) and leucine 371 µM/L (normal: 47-155) were detected in evaluation of plasma quantitative amino acid levels. All of these findings confirmed the diagnosis of MSUD, which was radiographically diagnosed to the patient. After appropriate treatment, the finding of the disease improved rapidly. The patient's metabolic acidosis regressed in the blood gas test (pH: 7.40), blood sugar improved (95 mg/dL), serum ammonia level (30 mcg/dL) and lactate level decreased (1.5 mmol/L). After 5 days, mechanical ventilation and peritoneal dialysis were terminated. After his acute treatment, he was referred to a third level centre that has a metabolism specialist for diet adjustment and lifelong care planning.

## Discussion

The most common type of MSUD is the classic type which the most severe symptoms occur like in our case. MSUD has an insidious clinical pattern and newborns with this disease are normal at birth. Clinically, during the first week of life, symptoms usually seen, are; a reduction in sucking reflex, lethargy, no weight gain and vomiting. In undiagnosed and untreated patients, BCCA and BCAK accumulate in the blood and urine, and metabolic acidosis and coma develop with cerebral encephalopathic crisis.[7,8] Early diagnosis and treatment are very important in this disease. Most of the patients who are diagnosed and treated early are survived from death and the neurological problems that may arise in the future are either completely lost or minimised.[9]

In the acute phase of the disease, on MRI, diffuse oedema is observed in cerebellar white matter, posterior brain stem, cerebral pedicles, posterior limb of the internal capsule and posterior centrum semiovale. Recent studies have reported that this is a reversible intramyelinic cytotoxic oedema, which causes diffusion restriction (brightening on DWI) in the affected regions and decrease in the ADC level.[9] In most of the studies on DWI imaging in MSUD, reported that cytotoxic oedema reverses with early diagnosis and appropriate treatment.[5,6,9,10] Also in our case, there was cytotoxic oedema along the pyramidal tract, cerebellar dentate nuclei, in posterior brain stem and due to this, there was diffusion restriction and reduced ADC levels. DW-MRI was performed a few days after the appropriate treatment and showed a decrease in cytotoxic oedema, resulting in a decrease in brightening due to diffusion restriction and an increase in ADC levels (Figure 2). All of these findings have shown that intramyelinic cytotoxic oedema is reversible and rapidly regressed with early diagnosis and appropriate treatment and found to be consistent with the literature.

Another radiological examination with significant contribution to MSUD is the MRS. Terek et al and Cakmakci et al described MR spectroscopy findings in the literature in encephalopathic cases. These studies showed

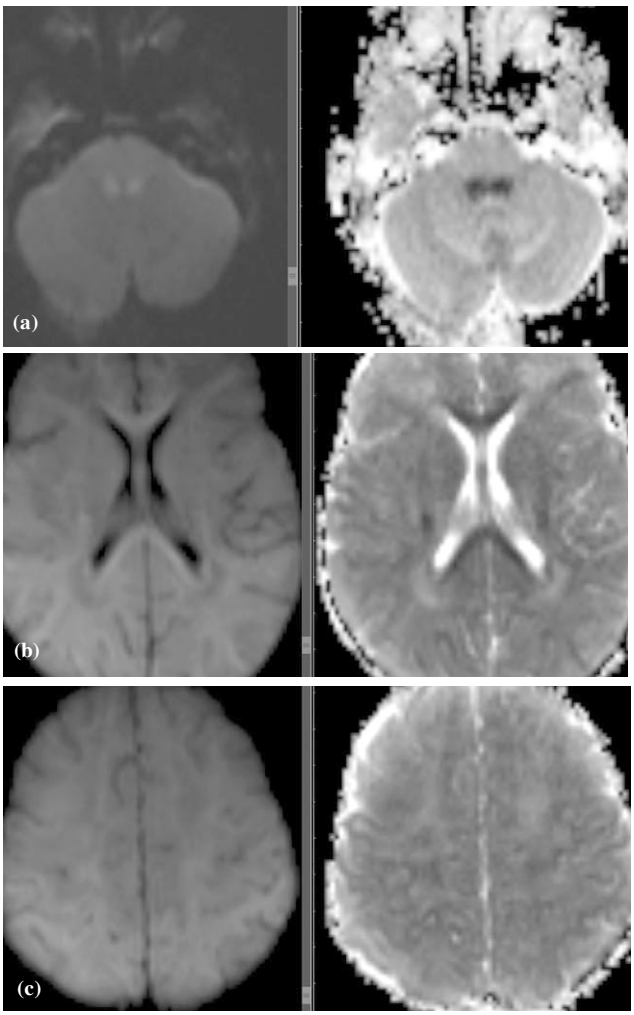


**Figure 2** Axial DWI (B=1000) on the left side and ADC maps in the right side (a, b, c). On the 4th day after treatment, the areas showing diffusion restriction are seen to be regrese significantly.

a decrease in NAA peak and an increase in the lactate and myoinositol peak in involved areas and an abnormally increased broad peak due to BCAA and BCAK accumulation at 0.9 ppm.[5,11] Our patient also has a large MR spectroscopic peak at 0.9 ppm at low TE (TE 30) single-voxel MR spectroscopy.

## Conclusion

As a result, reversible cerebral parenchymal injury and neurotoxicity in MSUD, if not diagnosed early and untreated, become irreversible and cause severe neurological deficits in the future. DWI and MR spectroscopy are important MR techniques in early diagnosis of the disease. Additionally, DWI seems to be radiologically important in evaluating the efficacy of treatment and therefore, follow up of regression of cerebral parenchymal intramyelinic cytotoxic oedema.

## Declaration of Interest

No conflict of interest was declared by the authors.

## Financial Disclosure

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