Ann Med Res 2021;28(4):842-6

Annals of Medical Research

DOI: 10.5455/annalsmedres.2020.04.290

Case Report

Classical Maple Syrup Urine Disease successfully treated with living donor liver transplantation

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Abstract

Maple syrup urine disease (MSUD) is a disease that causes ketoacid accumulation in body. Diffusion-weighted imaging (DWI) is an important imaging modality for the diagnosis. Two children were diagnosed with MSUD at the neonatal period. They had uncontrolled ketosis and epileptic seizures although they were in compliance with their medical nutrition. Their DWIs were similar and showed high signal intensity localized within the myelinated white matter areas. Both of the patients were treated with living donor liver transplantation. The patients with classic form of MSUD are normal at birth. If the disease is not diagnosed and treated early, it can lead to serious neurological complications. Most researchers conclude that, the best choice for detecting MSUD encephalopathy in newborns is DWI. The traditional treatment of MSUD had been a protein-restricted diet until the liver transplantation became an alternative and better option for the cure of the patients..

Keywords: Liver transplantation; magnetic resonance imaging; maple syrup urine disease

INTRODUCTION

Maple syrup urine disease (MSUD) is a disease that causes the ketoacids to accumulate in plasma, urine, and cerobro spinal fluid (CSF) due to the deficient activity of the enzyme which is responsible for the catabolism of leucine, isoleucine and valine containing branched chain amino acids (BCAA) named branched-chain a-ketoacid dehydrogenase complex. This autosomal recessive disease is seen approximately 1:120.000-500.000 in newborns. Diffusion-weighted imaging (DWI) is an important imaging modality for the diagnosis of MSUD (2). In the first line treatment of MSUD, a strict low protein diet containing a formula without BCAA is recommended. Since the early 2000s, the importance of liver transplantation in treatment has been mentioned in the literature (3).

We report here preoperative and follow up Magnetic Resonance Imaging (MRI) findings of two cases with classical MSUD that were treated with liver transplantation.

CASE REPORT

Case 1

A 3-year-old male patient was diagnosed with MSUD in our hospital at the neonatal period, and was followed up in the Pediatric Nutrition and Metabolism Department of a different university hospital. Ketosis and epileptic seizures of the patient could not be controlled although he was in compliance with his medical treatment and nutrition. The patient applied to our clinic for liver transplantation due to frequent ketosis and epileptic seizures. In the physical examination, no pathology other than neuromotor development retardation was detected. Liver synthesis functions were normal. We examined the DWI of the patient at the 8th day of his life retrospectively. DWI showed high signal intensity localized within the myelinated white matter (WM) areas, including the cerebellar WM (Figure 1a), pons, cerebral peduncles (Figure 1b), lentiform nucleus, posterior limbs of the internal capsules (Figure 1d), bilateral thalamus (Figure 1c), corona radiata and bilateral perirolandic cortex. Also, there were restricted diffusions at the same localizations at apparent diffusion coefficient (ADC) images (Figure 2a-d). The father of the patient was then evaluated for donor suitability and found appropriate. The left lateral segment of the live donor was used for liver transplantation. There was no complication related to surgery after transplantation. Nutritional therapy had been initiated with a special formula that is low in natural protein and BCAAs. The amount of natural protein gradually increased at the end of 14 days. The patient was discharged with a good general condition. At the

Received: 02.04.2020 **Accepted:** 18.05.2020 **Available online:** 26.04.2021
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end of the 18th month after transplantation, the general condition of the patient was found to be good. Although there was mild neuromotor development retardation in his physical examination, the liver function tests were all in normal limits. No metabolic attack had been observed in the patient, who was fed with a normal diet after the transplantation. In his control MRI, there was a significant atrophy in the cerebral parenchyma and the lateral ventricles were dilated (Figure 3a-d). In the DWI, there was no restriction in the areas that were previously restricted (Figure 3d). In addition, there was cortical laminar necrosis in the posterior parietal parenchyma, which was seen as T1 and FLAIR intens cortical- subcortical areas (Figure 3a, Figure 3c).

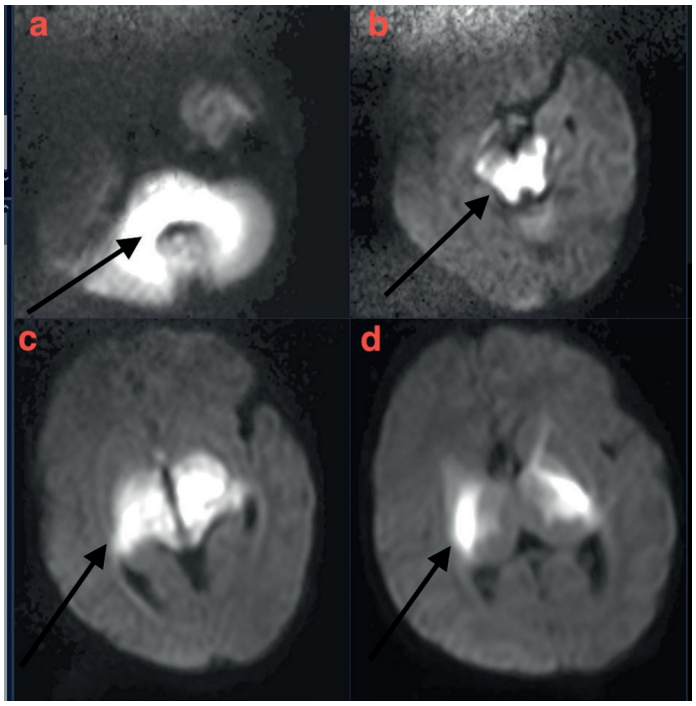

Figure 1. Diffusion Weighted Brain Magnetic Resonance Imaging Restricted diffusion marked with arrow **a.** cerebellum **b.** cerebral peduncles **c.** thalamus d. posterior limbs of the internal capsules

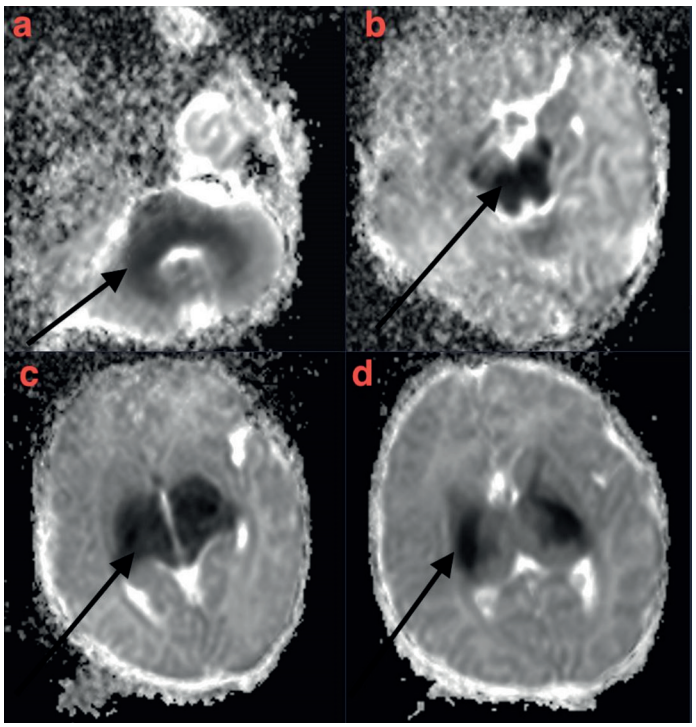

Figure 2. Apparent diffusion coefficient (ADC) Images Restricted diffusion marked with arrow a. cerebellum b. cerebral peduncles **c.** thalamus **d.** posterior limbs of the internal capsules

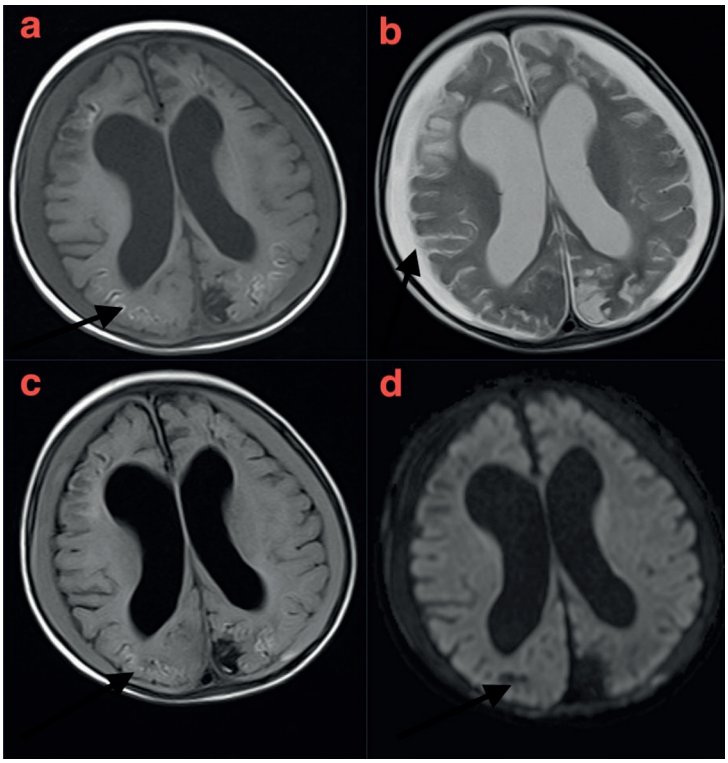

Figure 3. a. T1-Weighted axial b. T2-W axial c. FLAİR axial d. DWI Brain MRI Atrophy in the cerebral parenchyma, the lateral ventricles are dilated. T1 (a) and FLAIR (c) intense cortical-subcortical areas in the posterior parietal parenchyma, which do not have restricted diffusion in DWI (d). Fronto-parietal subdural effusion, that is intense in T1-W images according to cerebrospinal fluid (CSF) and iso-intense with CSF in T2-W images (b).

Case 2

A 1.5-year-old girl was diagnosed with MSUD in the different center in the neonatal period and was followed by Pediatric Nutrition and Metabolism Clinics of our hospital. In the physical examination of the patient at the time of admission, lethargy, difficult breathing, and opisthotonos were observed. In addition, the smell of maple syrup was detected in the urine. The leucine, valine and isoleucine levels in the serum were extremely high. Diffusion restriction was observed in the cerebellar white matter (Figure 4a), cerebral peduncles (Figure 4b), posterior limbs of the internal capsules (Figure 4c), and the perirolandic cortex (Figure 4d) in the DWI. Also, there were restricted diffusions at the same localizations at ADC images (Figure 5a-d). His father donated left lateral segment and the patient underwent living donor liver transplantation. The explanted liver was used in another patient for domino liver transplantation. Postoperative course of all three patients were uneventful. The patient, who was given a low protein diet after transplantation, was discharged approximately 2 months later without any neurological and surgical complications. Her physical examination was normal at her last control 16 months after the transplantation, and her ketosis attacks completely regressed. Neither diffusion restriction, nor other pathologies were observed in her brain MRI.

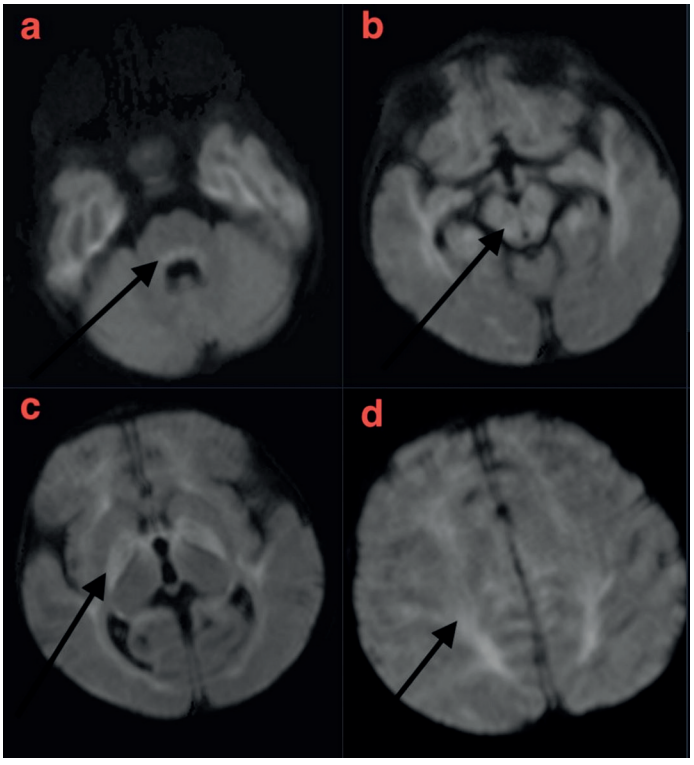

Figure 4. Diffusion Weighted Brain Magnetic Resonance Imaging Restricted diffusion marked with arrow a. cerebellum b. cerebral peduncles c. posterior limbs of the internal capsules d. perirolandic cortex.

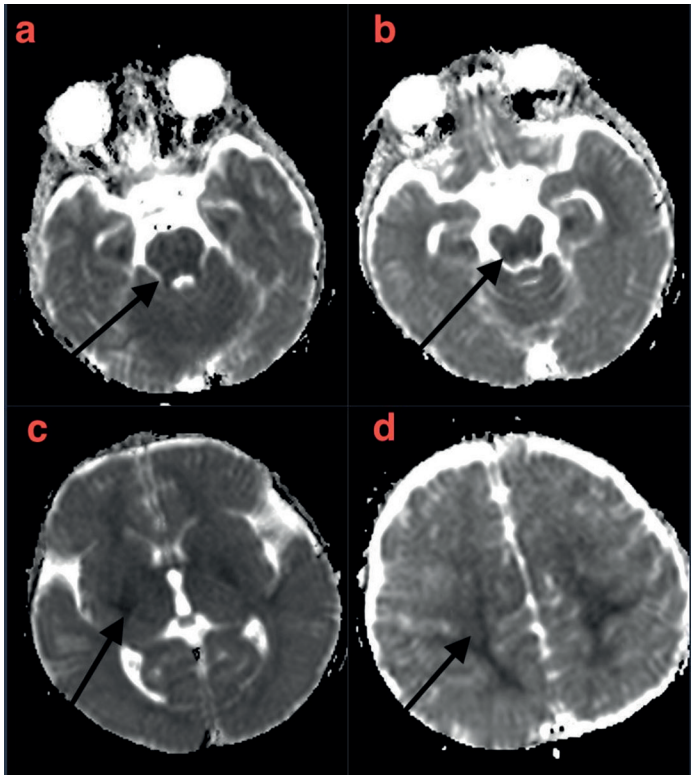

Figure 5. Apparent diffusion coefficient (ADC) Images Restricted diffusion marked with arrow a. cerebellum b. cerebral peduncles c. posterior limbs of the internal capsules d. perirolandic cortex

DISCUSSION

The age of the onset of the disease, the clinical presentation of the patient at first admission, and the response to thiamine replacement therapy have an important role on the classification of MSUD as classical, intermediate, intermittent, sensitive to thiamine, and deficient E3 forms (4). The patients classified in its most common classic form are normal at birth, but usually symptoms appear suggesting a metabolic crisis at the end of the first week of life (5). Symptoms of the disease can be counted as drowsiness, irritability, nutritional problems, vomiting, and specific urine odor due to the accumulation of amino acids. If the disease is not diagnosed and treated early, it can lead to serious neurological complications. Two of our patients were diagnosed and treated in the neonatal period. One of them had severe neuromotor development retardation and the other had moderate at the time of admission.

It is mentioned in the literature that the reason for this is the cytotoxicity of the BCAAs, especially leucine, to brain cells (6). The most important diagnostic test for MSUD is to show high levels of BCAA (leucine, isoleucine and valine) and alloisoleucine (leucine metabolite), which is done by measuring plasma amino acid concentrations. However, an increase in plasma amino acid levels may not appear until the first week of life. Therefore, radiological diagnosis plays an important role especially in the early diagnosis of MSUD. Most researchers conclude that, the best choice for detecting MSUD encephalopathy in newborns is DWI (7,8). Newborns with MSUD encephalopathy have both a dense localized edema called widespread cerebral edema and MSUD edema. This is a cytotoxic edema and can be shown very clearly with DWI. The cause of cytotoxic edema is the shift of fluid in the intracellular compartment due to the decrease in Na+/K+ ATPase activity. Fluid shift is also defined as high signal on DWI. The most common places of edema are the cerebellar white matter, brainstem, globus pallidus, internal capsule and the thalamus (9) and typically occur in areas that are myelinated in normal full-term neonates (10). Diffusion restricting areas showed very typical involvement in both of our patients.

The traditional treatment of MSUD had been a protein-restricted diet until the liver transplantation became an alternative and better option for the cure of the patients. Although, metabolic cure could be achieved with transplantation, it was shown that the brain damage was arrested but not reversed (11). In the preliminary liver transplantations done for MSUD, only non-relative deceased donor whole grafts were used. After the first living donor partial graft transplantation done to a MSUD patient which was reported to be unsuccessful because of the death of the recipient from vascular complications, many successful cases have been reported in the literature (11,12). Transplanting a partial graft from a related donor to a MSUD patient was the main concern of this era, since all the donors were carriers of the disease. It was shown that, although the transplanted livers were from disease carrier donors, the recipients did not experienced severe metabolic complications as they had before the transplantation and there was no difference in survival when compared to non-disease carrier donors (11,13). Both of our patients who had partial liver grafts from their relatives were done well after liver transplantation and they did not have any surgical or metabolic complications. The recipient of the domino liver of the second case also had no surgical or medical complication after transplantation.

Neurological pathologies seen in this disease can be reversed with appropriate treatment, but if the treatment is not carried out in the first years of life and delayed, marked cerebral atrophy may develop (10). In our patient, who was transplanted when she was 1.5-years-old, cerebral edema regressed completely in brain MRI and normal myelinization developed. However, in our patient who was transplanted when he was 3-years-old, cortical laminar necrosis developed in addition to prominent cerebral atrophy. This shows that treatment of the disease was late in this patient for regresion of brain pathology although cerebral edema had resolved completely. This supports that liver transplantation stops brain damage progressing, but if structural changes have evolved, it cannot reverse it (11).

CONCLUSION

In conclusion, it can be said that, radiologists have an important role in the diagnosis of MSUD if they have a detailed clinical knowledge. DWI is a very useful MRI sequence for the diagnosis. Liver transplantation is a curative treatment for MSUD and should be done as early as possible to prevent permanent brain damage.

Conflict of interest: The authors declare that they have no competing interest.
Financial Disclosure: There are no financial supports.
Informed Consent: Additional informed consent was obtained from the patient's wife since the patient is dead.

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