



Review Article

MRI Findings of Maple Syrup Urine Disease-A Metabolic Central Nervous System Disease

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Abstract

Maple syrup urine disease (MSUD) is a rare inherited autosomal recessive disease. It is characterized by impaired metabolism of branched-chain amino acids, which is caused by deficiency of branched chain α -ketoacid dehydrogenase enzymes complex. This leads to accumulation of branched chain amino acids includes leucine, isoleucine, and valine and their toxic by-products (ketoacids) in blood, urine and cerebrospinal fluid. The usual clinical presentation of patient is irritability, lethargy, poor feeding, vomiting, poor growth, and developmental symptoms. MSUD is characterized by radiological imaging features of cytotoxic brain edema affecting the white matter, and involving the corticospinal tracts, thalami, globus palladi, midbrain, dorsal brain stem and cerebellum. Here we present MRI features of classic MSUD in neonate which was later confirmed on biochemical investigations.

Keywords: Maple syrup urine disease, autosomal recessive inherited disorder, branched-chain amino acids, α -ketoacid dehydrogenase enzymes complex, metabolic central nervous system disease.

Abbreviations: MRI: Magnetic resonance imaging; MSUD: Maple syrup urine disease; APLA: Anti-phospholipid antibody; ER: Emergency room; CRP: C-reactive protein; ABGA: Arterial blood gases analysis; BCAA: Branched chain amino acids; Urine DR: Urine detailed report; CPAP: Continue positive airway pressure; CSF: Cerebrospinal fluid; TLC: Total leucocyte count; FLAIR: Fluid attenuated inversion recovery; DWI: Diffusion weighted imaging; ADC: Apparent diffusion coefficient.

Introduction

Maple syrup urine disease also called branched chain keto-aciduria is an uncommon autosomal recessive inherited disorder of branched chain amino acids metabolism caused by the deficiency of branched chain α -ketoacid dehydrogenase enzymes complex [1-5]. This disease gets its name because of its sweet odour of affected infant's urine [4]. It is characterized by life threatening reversible

cytotoxic brain edema and dysmyelination in affected individual [2,6]. MSUD is classified into the four major categories includes classic, intermediate, intermittent and thiamine responsive [1-4,7]. The clinical presentation of disease depends on classic and non-classic MSUD. The usual symptoms are irritability, lethargy, poor feeding, vomiting, poor growth, and developmental symptoms. In classic MSUD form of the disease which is most common and severe one, if it is untreated can leads to progressive neurological deterioration, seizures, coma and eventually death [2,3,7].

Case Report

We present a case of neonate, product of consanguineous married parents born in 37 weeks of gestation by emergency caesarean section because of APLA positive mother. He was brought in E.R with complaints of fever, seizures, irritability, poor feeding and excessive crying. His systematic examination was performed by a neonatologist and showed hypotonic baby with poor neonatal reflexes, temperature of 101F, respiratory examination showed respiratory distress with bilateral crepitus and heavy breathing and respiratory rate of 55 breath/minute, cardiovascular examination showed heart rate of 130 beats/minute with normal S1 and S2 and

abdominal examination was unremarkable. Baseline biochemical investigation showed magnesium levels 1.9 (1.4-2.5 mg/dl), serum electrolytes: Potassium 3.9 (3.5-5.3 mEq/L), chloride 111 (98-106 mEq/L), sodium 135 (133-145 mEq/L), calcium 8.9 (7.7-10.4 mEq/L), urea 21, creatinine 0.44, lactic acid 10, CRP 0.03, were non-contributory and his Complete blood count showed raised TLC of 15.3 (4.0 – 11.0⁹/L). He was initially diagnosed as Meningitis and sepsis on the basis of clinical history, examination and baseline investigations. Patient was kept on parenteral nutrition and intravenous antibiotics and CPAP for respiratory distress. His Lumbar puncture was performed, CSF analysis and blood culture turned out to be sterile. He was sent to the radiology department for MRI Examination to see the cause of CNS symptoms. His MRI demonstrated high signal intensity on T2w and FLAIR images in bilateral posterior limbs of internal capsules, globus pallidi, thalami, hypothalamus, brain stem, medial parts of both cerebellar hemispheres, and bilateral middle cerebellar peduncles. They also showed restriction diffusion with high signal on DWI and low signal on ADC (Figure 1, 2, and 3). On the basis of MRI findings the diagnosis of MSUD was given and biochemical analysis was suggested.

ABGA and urine DR demonstrated metabolic ketoacidosis (serum HC03= 12 mmol/L), (urine ketones 77 mg/dl), blood serum demonstrated hyper-ammonemia 78 (> 50 μ mol/L), and random blood sugar showed hypoglycaemia 55 (109 mg/dl).

Urine organic acids by GCMS (CHROMATOGRAM) showed marked excretion of 2-ketoisocaproic (double peak) 4-hydroxyphenyllactic acid, 2-hydroxyisovaleric acid along with moderate excretion of lactic acid and mild excretion of indolelactic acid, vanillactic acid, are noted. Large peak of 2-hydroxy-3-methylevaleric (double peak) along with moderate peak of phenyllactic acid and small peak of 2-ketoisocaproic acid, 2-keto-3-methylvaleric acid are identified. Blood serum showed increase level of leucine, isoleucine, and valine. All these biochemical parameters were in favour of diagnosis of MSUD. Patient was started on MSUD formula feed with restricted amount of branched chain amino acid. Gradually he improved on his oral intake and became symptoms free. He was followed on the basis of outpatient department.

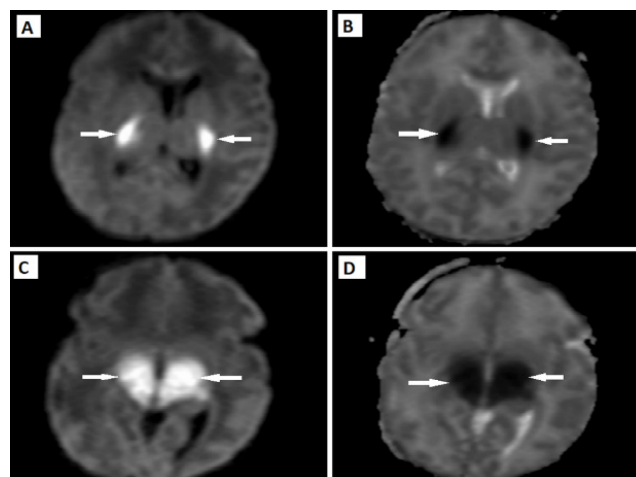


Figure 1: Shows restriction with high signal on DWI (A and C) and low signal on ADC (B and D) in posterior limb of internal capsule, globus pallidi (A and B) and Thalami (C and D).

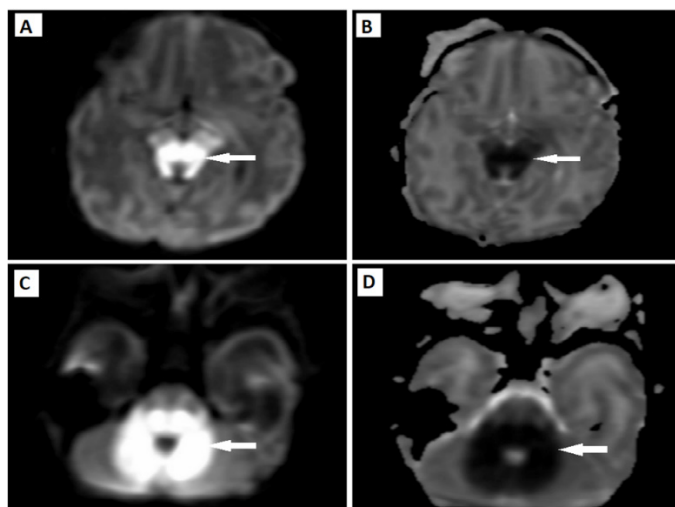


Figure 2: Shows restriction with high signal on DWI (A and C) and low signal on ADC (B and D) in midbrain (A and B), dorsal brain stem and medial cerebellum (C and D).

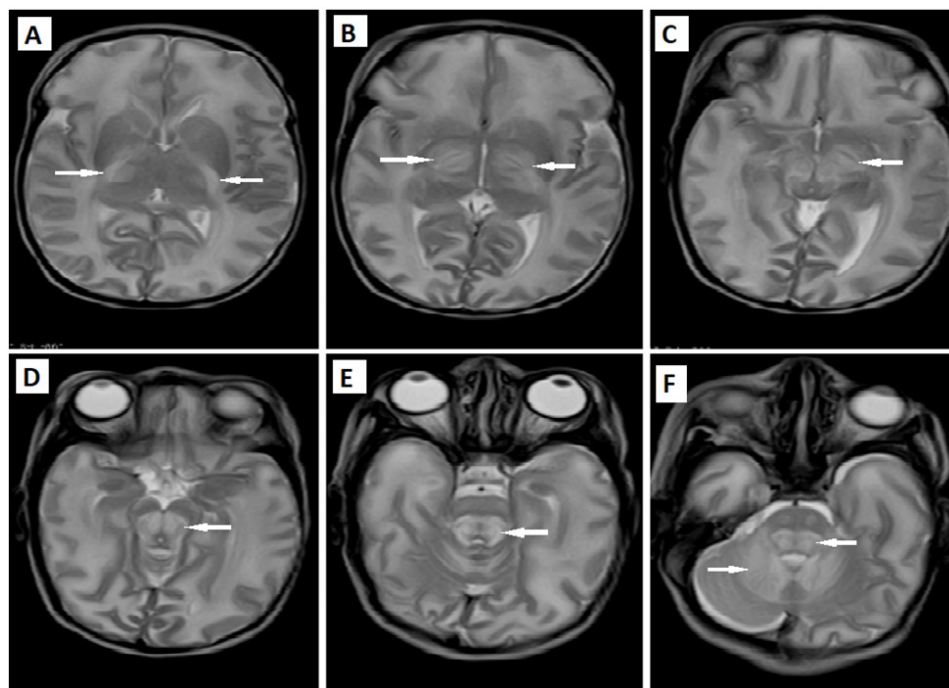


Figure 3: Axial T2 weighted images show high signal in posterior limb of internal capsule (A), thalami (B), midbrain (C, D), dorsal pones (E), dorsal pons and medial cerebellum (F).

Discussion

MSUD is uncommon autosomal recessive metabolic disorder caused by the deficiency of branched chain α -ketoacid dehydrogenase enzymes complex [2,7]. The annual incidence of the disease is 1 in 180000 live births in worldwide [3]. It is classified into the four major categories (1) classic, (2) intermediate, (3) intermittent and (4) thiamine responsive with varying symptoms and prognosis [2,3]. The classic form of MSUD is most common and severe one [3]. The cause of brain injury in MSUD is still uncertain [4]. There are two mechanisms described in literatures (1) deficiency of neurotransmitters and restriction of growth due to BCAA accumulation within the brain parenchyma. (2) Accumulation of branched chain ketoacids associated with Krebs cycle disturbance resulting in energy deprivation [2,4,5]. Accumulation of leucine in particular causes the brain injury and neurological symptoms and maple syrup odour of urine attributed to increased plasma level of isoleucine [2,4,5]. New-borns are disease free at birth [3,4] and develop ketonuria within 48 hours of life and become symptomatic with poor feeding, irritability, vomiting, lethargy, and dystonia [3]. Neurological abnormalities and signs of cerebral edema manifest at the age of 4-7 days of life [3]. One of the literature mentioned that clinical presentation of disease depends on severity of BCKAD deficiency [2]. In classic form of MSUD enzyme activity is less than 2%. If this patient

is untreated, he can develop the severe progressive neurological disease, coma, respiratory failure and eventually death. In non-classical form of MSUD enzyme activity varies from 2% to 30% with delayed clinical presentation in infancy and childhood [2]. There are different method of investigations used to diagnose the disease includes tandem mass spectrometry and liquid chromatography-tandem mass spectrometry and radiological imaging [7]. Radiological imaging investigation play an important role in early diagnosis and follow up of the disease [2,3,7]. Imaging findings of brain on MRI and CT scan in MSUD usually secondarily to acute metabolic decompensation (in classical, and intermittent forms of the disease) [8]. Classic MSUD can involves the corticospinal tracts, deep cerebellar white matter, midbrain, dorsal brain stem, thalamus, and cerebral peduncles [2,3]. MRI brain can show restriction with bilateral symmetrical high signal on DWI and low on ADC to suggest the MSUD intracellular cytotoxic edema [2,3,8]. Intermittent form of MSUD can also show abnormal signals on MRI without acute crisis [8]. DWI/ADC is more sensitive than conventional MRI [2,4]. Non-Contrast CT scan may also show diffuse bilateral and symmetrical hypodensities within the brain parenchyma but it has low specificity and sensitivity than MRI [2,3]. Treatment of the disease includes (I) metabolically appropriate protein modified diet (low BCCAs) [2,3]. (II) Peritoneal haemodialysis in cases of acute crisis to

prevent the MSUD cerebral cytotoxic edema and neurological toxicity and damage [2,3]. (III) Liver transplant is definitive and curable treatment for patients who fail to response the conservative management and metabolically appropriated modified diet [3].

Conclusion

MSUD is a rare autosomal recessive disease of BCAA metabolism. We should aim to early diagnose this disease by radiological imaging tool which can prevent the progress of neurological deficits and help the physician in prompt and appropriate management of the disease. MRI is a useful tool for early diagnosis and follow up of the disease. MRI can also confirm the reversal and resolution of the disease by typical imaging features. The biochemical markers are also used for diagnosis of disease and followed to evaluate the response of treatment.

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