Imaging in a Rare Case of Maple Syrup Urine Disease

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INTRODUCTION

Maple Syrup Urine Disease (MSUD) is also known as Leucine encephalopathy. It is an autosomal-recessive metabolic disorderr involving catabolic pathway of the branched-chain amino acids (leucine, isoleucine, valine). There is decreased activity of branched chain α-keto acid dehydrogenase complex resulting in increased brain levels of leucotoxic metabolites which in turn induce cytotoxic or intramyelinic oedema. This build-up of ketoacids gives rise to the classic 'maple syrup' or burnt sugar smell of urine.

MSUD affects about 1 in 1,85,000 infants all over the world. Classic type is the most common and severe form of disease, which becomes apparent soon after the birth. Patients with this condition presents with poor feeding, vomiting, lethargy and developmental delay since early infancy. If left untreated, it can lead to seizures, coma, and death.[1] Without treatment the infant often dies during the first few weeks of life. Those surviving the first weeks develop severe brain damage.[2]

Here we describe the Magnetic Resonance Imaging (MRI) findings in classic type of MSUD.

PRESENTATION OF CASE

Baby of patient X, born of a 2nd degree consanguineous marriage at term had a birth weight of 3.5 Kg & was non-asphyxiated.

1. His sibling was 6 years old and was neurologically normal.
2. The child presented to MVJ hospital on day 11 of birth, with complaints of 4 day history of lethargy and rapid breathing for a day.

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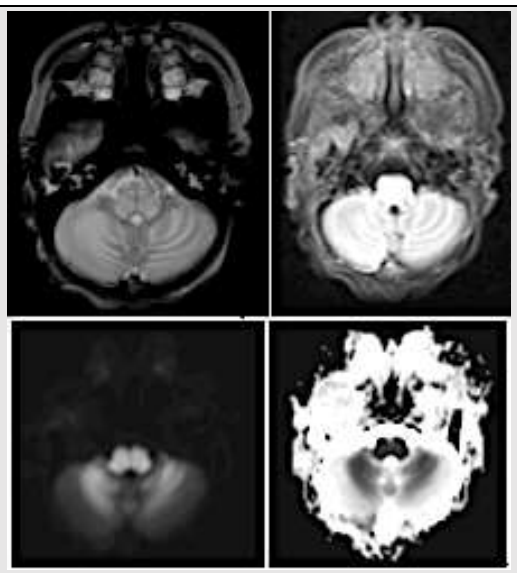

Figure 1. MRI Images in Axial Sections Demonstrating T2 and FLAIR Hyperintensities and Diffusion Restriction (Hyperintense on DW and Low ADC Value) Involving the Bilateral Cerebellar White Matter

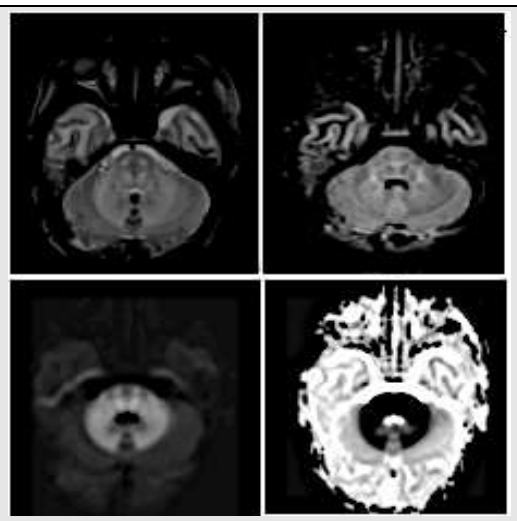

Figure 2. MRI Images in Axial Sections Demonstrating T2 and FLAIR Hyperintensities and Diffusion Restriction (Hyperintense on DW and low ADC Value) Involving the Dorsal Brainstem, the Pyramidal and Tegmental Tracts

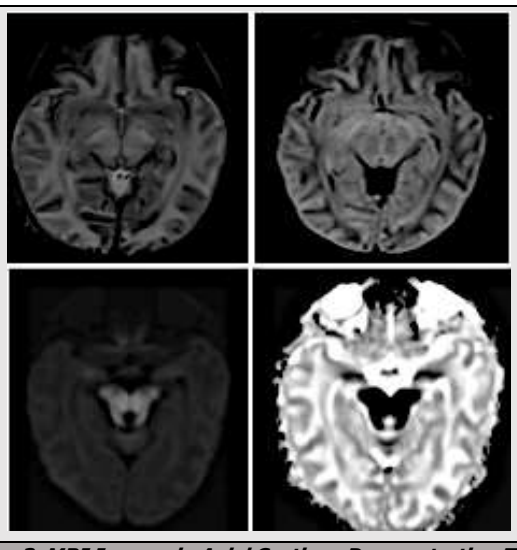

Figure 3. MRI Images in Axial Sections Demonstrating T2 and FLAIR Hyperintensities and Diffusion Restriction (Hyperintense on DW and low ADC Value) Involving the Cerebral Peduncles

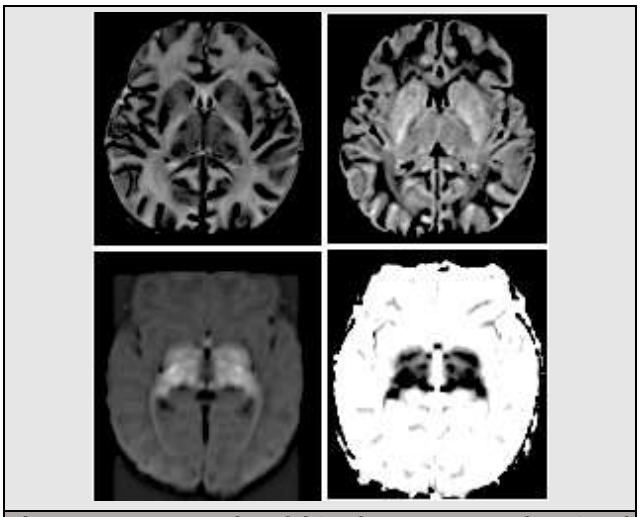

Figure 4. MRI Images in Axial Sections Demonstrating T2 and FLAIR Hyperintensities and Diffusion Restriction (Hyperintense on DW and Low ADC Value) Involving Bilateral Globi Pallidi, Posterior Limb of Internal Capsule and Thalami

Course in Hospital

- In ER, child was having seizure (cycling movements with tachycardia and desaturation), had normal sugar and ionized calcium & was loaded with phenobarbitone & required 2 mini boluses of phenobarbitone & loading with fosphenytoin. Serum Sodium & CSF was normal.
- Blood gas revealed high anion gap metabolic acidosis, with normal ammonia, lactate, uric acid, liver enzymes, urine ketones. CRP was negative & blood c/s was sterile. Child was managed with nil per oral with glucose infusion rate of 8, aminoacid at 0.5 g/kg/day with vitamin cocktail comprising of B12, pyridoxine, thiamine, levocarnitine & biotin.
- MRI brain on D13 (3rd day of admission) showed altered T1W & T2 signal intensities in bilateral peri rolandic region (sensorimotor cortex) extending inferiorly involving centrum semiovale, corona radiata, posterior limb of internal capsule, thalamus, posterior putamina, midbrain, medulla oblongata and cerebellum. These areas also showed high signal intensity on DWI and low ADC values suggestive of diffusion restriction. Overall, they were suggestive of severe hypoxic ischemic injury.
- Tandem mass spectrometry sent at time of admission revealed elevated leucine 2905 U (control 64-328 U) & Valine 720 U (control 57-212 U) suggestive of Maple syrup urine disease.

CLINICAL DIAGNOSIS

In view of clinical history with normal ammonia and high anion gap, metabolic acidosis, aminoaciduria was suspected.

DIFFERENTIAL DIAGNOSIS

1. Hypoxic-ischemic encephalopathy (HIE): Positive history of periparturitional distress (birth asphyxia) is given and no significant symptom-free period present.

Cerebellum and brain stem usually not involved, no characteristic involvement of myelinated white matter tracts, history. Blood gas analysis will be abnormal in MSUD.
2. Sepsis where brain MR appears to be normal.
3. Alexander disease shows T2 hyperintensity of the frontal WM and enhancement on contrast studies.
4. Mitochondrial cytopathy where episodic stroke-like clinical events of varied severity depending on the genotype of the disorder is seen.

DISCUSSION OF MANAGEMENT

- Child was started on formula milk free of branched chain amino acid (metanutrition) & breast feeds alternating with each other.
- Acidosis which normalized by D4 did not recur on oral feeds for next 4 days and was discharged on oral thiamine at 200 mg/day & oral clonazepam for athetoid movements.
- At discharge child neurologically had good state to state variability with axial hypotonia with normal appendicular tone.

MSUD was first described in 1954 by Menkes et al.,[3] who described a family that had lost four of six infants during their first week of life, each of whom displayed symptoms of vomiting, increased muscular tone, and urine that smelled like maple syrup. It is now known that the disease is inherited as an autosomal recessive trait, and from large screening series its frequency has been estimated to be about 1:224,000[4]

In the maple syrup urine disease, there is an enzymatic defect which blocks one of the first step in the common metabolic pathway which helps in the catabolism of the branched-chain amino acids (BCAA) that is leucine, isoleucine, and valine. This results in the accumulation of its corresponding keto acids and then results in the urinary excretion of a metabolite with a characteristic odour, hence the name was given as maple syrup urine disease.

MSUD shows two forms of oedema-

1. Intramyelinic Oedema- Is believed to be formed by myelin splitting as a result of branched-chain key acids and water molecules accumulation between the layers of myelin.[5]
2. Vasogenic Oedema- Is due to acute metabolic crisis or decompensation causing disruption of the blood-brain barrier.[5]

Characteristic Oedema Pattern of MRI Brain in MSUD

T1: Low signal intensity seen predominantly in the posterior limb of the internal capsule, globe pallidi, thalami, perirolandic cerebral white matter, cerebellar white matter, cerebral peduncles and dorsal brainstem.[5]

T2: High signal intensity in the corresponding regions as described above.[5]

DWI: High diffusion signal is seen in the posterior limbs of the internal capsules, optic radiations and central corticospinal tracts within the cerebral hemispheres.

MR Spectroscopy: During metabolic crisis MR spectroscopy may show the presence of branched-chain amino acids and branched-chain alpha-keto acids resonating at 0.9-1.0 ppm.[6,7]

Our case showed characteristic intramyelinic oedema involving myelinated fibers. Neuroimaging plays a key role in suggesting the probable diagnosis, limiting the differential diagnosis, and may consequently allow early initiation of targeted metabolic and genetic laboratory investigations and treatment. Grey matter signal abnormalities are more common with Urea cycle disorders & Pyruvate dehydrogenase deficiency while both grey and white matter signal abnormalities are common with Maple syrup urine disease, Propionic academia & sulphite oxidase deficiency.

Maple syrup urine disease and propionic acidaemia has propensity to involve myelinated white matter in comparison to other IEMs thus narrowing the differential diagnosis.

Treatment

1. Dietary management is the main stay in therapy.
2. Thiamine may help and liver transplantation has shown promising results.

FINAL DIAGNOSIS

Maple Syrup Urine Disease

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