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Maple syrup urine disease: magnetic resonance imaging findings in three patients

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Abstract

Maple syrup urine disease (MSUD) is an autosomal recessive inherited metabolic disorder, caused by branched-chain alpha-ketoacid dehydrogenase (BCKD) deficiency, leading to toxic accumulation of branched-chain amino acids (BCAAs) including leucine, isoleucine and valine and their corresponding α-ketoacids. The diagnosis of MSUD is based on elevated BCAAs and allo-isoleucine in plasma, and branched-chain hydroxyacids and ketoacids in urine. The identification of alloisoleucine >5 µmol/L is considered pathognomonic. Moreover, brain magnetic resonance imaging (MRI) showing atypical signal intensity and oedema is characteristic of MSUD. Recognition of the classical neuro-radiological findings of MSUD is particularly useful in local settings as many healthcare facilities lack the resources to measure Plasma Amino Acids (PAA). We report three cases of MSUD, in whom the disorder was strongly suspected at presentation, based on classical brain MRI findings, which was urgently confirmed by PAA analysis.

Keywords: Maple Syrup Urine Disease, Magnetic Resonance Imaging, amino acids, diagnosis, inherited metabolic disorders, brain

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Introduction

Maple syrup urine disease (MSUD, OMIM #248600) is an autosomal recessive inherited metabolic disorder, caused by branched-chain alpha-ketoacid dehydrogenase (BCKD) deficiency, leading to toxic accumulation of branched-chain amino acids (BCAAs) including leucine (LEU), isoleucine (ILE) and valine (VAL) and their corresponding α-ketoacids.[1, 2] BCKD is a multi-enzyme complex, which consists of a decarboxylase, E1. E1 is composed of two-protein α2β2 structure encoded by *BCKDHA*, and *BCKDHB* respectively. The other components are a transferase, E2 encoded by DBT and a flavoprotein lipamide dehydrogenase, E3 encoded by *DLD*.[3]

MSUD is classified in five clinical phenotypes based on clinical presentation and enzyme activity: classical, intermediate, intermittent, thiamine responsive and type III form (E3 deficient).[4] The classic form, with the lowest enzyme activity (0–2%) is characterised by asymptomatic period of first few days after birth, followed by non-specific signs and symptoms such as lethargy, poor feeding, phases of hypertonia and hypotonia, convulsions, bulging fontanelle, irregular breathing, apnoea and frequently a maple syrup odour in urine or cerumen that are usually evident in the first week of life. Whereas, the intermediate form possesses up to 30% of BCKD residual activity and has a variable age of onset. Patients often appear healthy during the neonatal period, with symptoms usually appearing during the first year of life. The intermittent (5-20% BCKD residual activity) and thiamine-responsive (2-40% BCKD residual activity) forms may also manifest at any time in life, with decompensations occurring during periods of acute illness or stress.[3] E3-deficiency form may present with neonatal neurologic manifestations to late-onset hepatic disorder.[3]

The diagnosis of MSUD is based on elevated BCAAs and allo-isoleucine in plasma, and branched-chain hydroxyacids and ketoacids in urine.[5] The identification of alloisoleucine >5 μmol/L is considered pathognomonic for

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MSUD and helps in differentiating elevation of BCAAs caused by excessive vomiting or starvation.[6, 7]

In the neonatal period, brain magnetic resonance imaging (MRI) of patients with classical MSUD is diagnostic. Regions which are normally myelinated at this age, show atypical signal intensity and are oedematous. T2 weighted images (T2WI) display considerable swelling and high signal intensity in the dorsal pons, midbrain, white matter of the cerebellum, posterior limb of the internal capsule, thalamus, globus pallidus and central part of the corona radiata.[8] Diffusion MRI enables a better characterisation of the lesions demonstrated by conventional MR imaging, which demonstrates a high signal intensity due to diffusion restriction in the areas where vacuoles replace degenerating white matter.[9] In particular, high signal abnormalities shown by diffusion-weighted images related to cytotoxic or intra-myelinic oedema, secondary to branched-chain amino acids accumulation are also apparent in the late onset forms of MSUD.[10, 11] Early neuro-radiological pattern recognition, prompts urgent biochemical workup and emergency supplementation with ILE and VAL, even if they are already elevated in order to promote anabolism and lower elevated plasma LEU levels.[1]

We report three cases of MSUD, in whom the diagnosis was strongly suspected at presentation based on the classical brain MRI findings, which was urgently confirmed by plasma amino acids (PAA) analysis facilitating early introduction of ILE and VAL in the management which resulted in early recovery from metabolic decompensation. All the three cases were seen at the Department of Paediatrics and Child Health, the Aga Khan University Hospital (AKUH), Karachi, by a consultant clinical biochemical geneticist from January 2018 to June 2019. The biochemical and radiological workup was undertaken at the section of chemical pathology, Department of Pathology and Laboratory Medicine and Department of Radiology, AKUH. Informed consent was obtained from the patients' parents.

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Case Series

Case # 1: A male child was born at 37 weeks' gestation to a gravida 5, para 3+1 mother via spontaneous vaginal delivery (SVD) after an uneventful pregnancy to first-cousin parents. He presented on the fifth postnatal day with a two-day history of reluctance to feed and lethargy and a seizure-like activity. On examination, he was dull with minimal activity on handling, had normal vital signs, poor neonatal reflexes and normal anterior fontanelle. Laboratory work-up for sepsis and meningitis including complete blood count, C-reactive protein, CSF Detailed Report (DR) and Latex Particle Agglutination (LPA) were normal. The unexplained encephalopathy prompted a brain MRI, which showed abnormal signals in the basal ganglia, posterior limb of internal capsule and dorsal part brainstem including midbrain, pons and medulla (Figure 1A-1E).

The characteristic brain MRI findings in this patient prompted the doctors to actively follow PAA and results were obtained within an hour of radiological analysis. PAA showed markedly elevated levels of LEU, ILE, VAL and alloisoluecine, as shown in table 1, confirming the diagnosis of MSUD. The patient was treated with intravenous dextrose saline and oral ILE and VAL in keeping with the treatment guidelines[1] resulting in clinical and biochemical improvement with 42 hours of commencement of treatment.

Case # 2: A two-and-a-half-year-old male born to first-cousin parents was delivered at term via SVD to a gravida 3 para 2 mother after an uneventful pregnancy. He presented to the metabolic clinic with a history of two stroke-like illnesses separated by four months, each lasting for one and two-day duration respectively. Both episodes were preceded by febrile illness; he was hospitalised during both events and recovered after receiving intravenous fluids containing dextrose. His baseline developmental history and current developmental was appropriate for age. On examination, the patient had a fair complexion and blonde hair. His gait and tone were both normal and reflexes were positive in all limbs. He did not have any organomegaly.

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Brian MRI done during the last episode of stroke-like event revealed abnormal signals in the basal ganglia, posterior limb of internal capsule and brainstem including dorsal part of midbrain, pons and medulla, highly suggestive of MSUD (Figure 1F-1I). This led to urgent PAA analysis, which showed markedly elevated LEU, ILE and VAL with detection of alloisoleucine confirming the diagnosis of MSUD. The patient was started on leucine-restricted diet supplemented with leucine-free amino acid mixture. Since the commencement of the treatment, the patient has been symptom free.

Case # 3: A male child was born at 37-week gestation to a gravida 4, para 2 mother via spontaneous vaginal delivery after an uneventful pregnancy to first cousin parents. He presented on the third postnatal day to the emergency room with a two-day history of reluctance to feed, hypotonia and lethargy. On examination, he was dull with minimal activity on handling, poor neonatal reflexes and bulging fontanelle. The baby was intubated and shifted to neonatal intensive care unit. Laboratory work-up for sepsis and meningitis including complete blood count, C-reactive protein, CSF DR and LPA were normal. The unexplained encephalopathy prompted a brain MRI, which showed symmetrical diffusion restriction in bilateral perirolandic white matter, thalami, and posterior limbs of internal capsules, cerebral peduncles, dorsal midbrain, posterior pons, medulla, central cerebellar white matter and posterior aspect of cervical spinal cord (Figure 1J-1N). MR spectroscopy showed inversion of the lactate peak, elevated choline as well as an inverted peak at 0.9-1 ppm. The characteristic brain MRI findings prompted the team to request for urgent PAA analysis, which showed markedly elevated levels of LEU, ILE, VAL and alloisoleucine pointing towards a diagnosis of MSUD. The patient was treated with intravenous dextrose saline and oral ILE and VAL to promote anabolism and to facilitate rapid removal of neurotoxic metabolites; peritoneal dialysis was started, as facility of haemodialysis is not available for neonates at our centre.

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Clinical and biochemical improvement was achieved in 36 hours of commencement of the treatment.

Discussion

As early recognition and timely emergency intervention of MSUD significantly determines the outcome of affected individuals, MSUD is part of the recommended uniform screening panel (RUSP), which is a list of metabolic disorders for which screening is recommended for all new-borns.[12,13] Although, Pakistan lacks a comprehensive new-born screening programme, a few studies from the country including high-risk cases by selective metabolite screening, have reported varying frequencies of MSUD, i.e. 9.1%, 6.66% and 25%.[14-16] However, to the best of our knowledge, this is the first study from Pakistan that has reported neuro-radiological findings in MSUD.

In all the three cases reported here, the classical brain MRI findings consistent with the diagnosis of MSUD prompted active and urgent analysis of PAA, which confirmed the diagnosis of MSUD and aided in the timely emergency management. The distinct radiological pattern was recognised not only in two neonates with an early onset classical presentation but also in the toddler with the late onset form.[11]

Recognition of classical neuro-radiological findings of MSUD is particularly useful in local setting as many healthcare facilities lack the resources to measure PAA, which is often sent to AKUH laboratory in Karachi, which requires time for sample transportation, especially from other cities of Pakistan. PAA analysis is a sophisticated biochemical test, which requires both time and technical expertise for sample preparation and analysis. Most tertiary care hospitals in major cities of Pakistan have brain MRI facilities available either within the hospital or within the city. Brain MRI can be viewed on the console while the imaging is being performed and radiologist and clinicians can recognise the classical pattern and make a quick radiological diagnosis of MSUD.[17]

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Recognition of classical brain MRI finding consistent with the diagnosis of MSUD in our local setting allows initiation of critical early management including early introduction of ILE and VAL and commencement of dialysis, thus allowing to achieve better clinical outcome by reducing morbidity and mortality caused by neuro-intoxication in acute metabolic decompensation. [18, 19]

Conclusion

Neuro-imaging plays an important role in early diagnosis of MSUD in our local setting, allowing timely intervention in the form of coordinating with laboratory to get urgent PAA results and early introduction of emergency treatment, thus improving the outcome of the disease.

Ethical Approval: The study was approved by the Institutional Ethics Committee and written informed consent was obtained from the parents of all the babies.

Disclaimer: None to declare.

Conflict of interest: None to declare.

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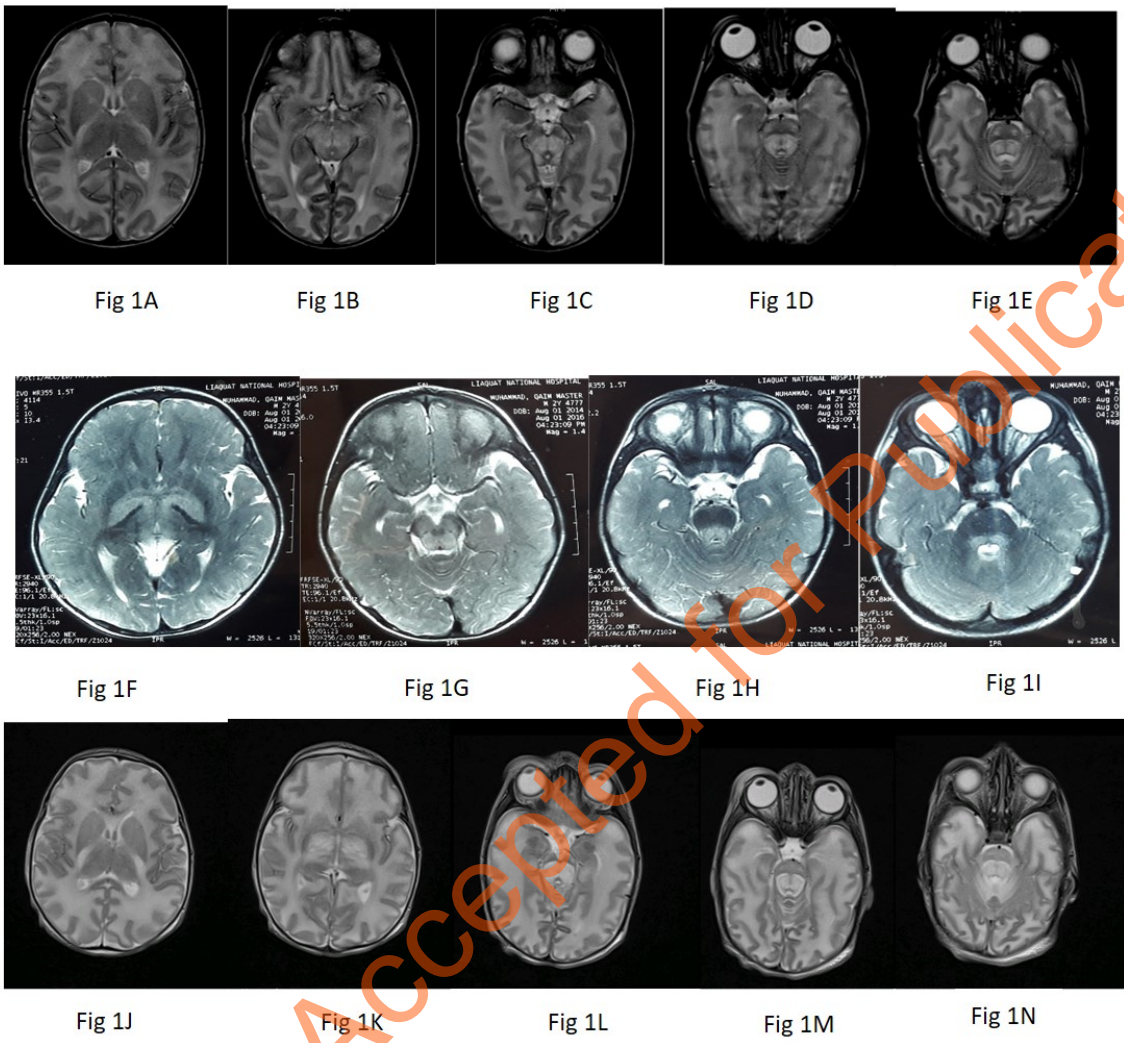

Figure 1:

Figure 1A- 1E; Case 01

Figure 1A: MRI Brain T2WI showing hyperintense signals and swollen posterior limb of internal capsule.

Figure 1B&C: MRI Brain T2WI showing hyperintense signals and swelling in the dorsal part of midbrain.

Figure 1D: MRI Brain T2WI showing hyperintense signals and swelling in dorsal part of the pons.

Figure 1E: MRI Brain T2WI showing involvement of dorsal part of medulla

Figure 1F-1I; Case 02

Figure 1F: MRI Brain T2WI showing hyperintense signals and swollen basal ganglia.

Figure 1G: MRI Brain T2WI showing hyperintense signals and swelling in the dorsal part of midbrain.

Figure 1H: MRI Brain T2WI showing hyperintense signals and swelling in dorsal part of the pons.

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Figure 1I: MRI Brain T2WI showing involvement of dorsal part of medulla

Figure 1J- 1N; Case 03

Figure 1J: MRI Brain T2WI showing hyperintense signals and swollen posterior limb of internal capsule.

Figure 1K: MRI Brain T2WI showing hyperintense signals and swollen basal ganglia.

Figure 1L: MRI Brain T2WI showing hyperintense signals and swelling in the dorsal part of midbrain.

Figure 1M: MRI Brain T2WI showing hyperintense signals and swelling in dorsal part of the pons.

Figure 1N: MRI Brain T2WI showing involvement of dorsal part of medulla

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Table 1: Table 1: Clinical & Biochemical Parameters

Case	**1**	**2**	**3**
Age at presentation	7 Days	2 ½ years	3Days
Height (cm)	50	89.5	51
Weight (kg)	2.6	10.9	2.9
BMI (kg/m^2)	10.4	13.6	11.1
Leucine (N: 47-167 µmol/L)	2067	530	> 2500
Isoleucine (N: 22-94 µmol/L)	683	249	334
Valine (N: 69-199 µmol/L)	586	580	294
Alloisoluecine (N:undetectable µmol/L)	411	31	400

N: normal

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