

## ORIGINAL ARTICLE

# The clinico-radiological findings of MSUD in a group of Egyptian children: Contribution to early diagnosis and outcome

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## Abstract

**Background:** Maple syrup urine disease (MSUD) is an autosomal recessive inborn error of amino acid metabolism, with unique clinico-radiological findings. This study aims to show the benefit of using the clinico-radiological findings for early diagnosis of children with MSUD, and confirming this diagnosis using the tandem mass spectrometry (MS/MS), in order to avoid deleterious outcome.

**Methods:** A prospective cohort study conducted in the period from August 2016 to December 2020. Twenty-one children were included either by selective screening or by high-risk screening. All children had clinical and neurodevelopmental evaluation, brain magnetic resonance imaging (MRI) assessment, and blood amino acids analysis at diagnosis. Patients were followed clinically.

**Results:** Most children had acute onsets neuro-developmental symptoms, with wide range of brain parenchyma involvement on MRI (hyperintensity). Diagnosis of MSUD was confirmed by detecting high serum levels of leucine/isoleucine (mean value 2085.5  $\mu\text{mol/L}$ ) in all patients, and elevated levels of serum valine in (81%) of children. In addition, all children showed elevated leucine: alanine ratio, and leucine: phenylalanine ratio.

**Conclusions:** The characteristic clinico-radiological features can help in the early diagnosis of MSUD children, thus preventing the delay in laboratory diagnosis and improving their outcomes.

## KEYWORDS

clinico-radiological, diagnosis, Egypt, MSUD, outcome

## 1 | INTRODUCTION

Maple syrup urine disease (MSUD) is a rare inborn error of amino acid metabolism. It has an autosomal recessive pattern of inheritance that runs in families (Patil et al.,

2020). It occurs due to a deficiency in an enzyme complex [branched chain  $\alpha$ -keto acid dehydrogenase (BCKAD)] that results in defects in the catabolism of the branched chain amino acids (BCAAs): leucine, isoleucine, and valine. The accumulation of these BCAAs has a toxic effect

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on the brain cells (Chimbili et al., 2020), as they inhibit the activity of pyruvate dehydrogenase and  $\alpha$ -ketoglutarate, leading to interruption of the citric acid cycle and consequently affecting the synthesis of amino acids, causing cerebral edema and abnormal myelination (Li et al., 2021).

Clinical symptoms and signs of MSUD varies in severity according to the BCKAD residual activity (Blackburn et al., 2017). The onset of symptoms can occur within the first week of life, which can be non-specific, variable and can be easily misdiagnosed. The clinical picture may present as poor feeding, poor activity, irritability, or vomiting. Without a proper management of this condition, these symptoms and signs would proceed to muscular rigidity, convulsions, coma, and even death (Kathait et al., 2018).

MSUD is classified according to age of onset, clinical manifestations and its severity. The subtypes include classic, intermediate (mild), intermittent, MSUD caused by a deficiency of E3 subunit, and thiamine-responsive type. Classic subtype of MSUD is the commonest type (75%) and the most severe form (Blackburn et al., 2017).

Infants with MSUD can be identified early through newborn screening programs using the tandem mass spectrometry (MS/MS). Abnormal elevation of BCAAs in plasma and increased the urine organic acids are confirmatory. Tandem mass spectrometry (MS/MS) can provide the leucine–isoleucine concentration, in addition to its ratio with other amino acids including glutamate, glutamine, tryptophan, methionine, histidine, alanine, phenylalanine, and tyrosine. Organic acid analysis by gas chromatography (GC)–MS/MS also can provide qualitative assessment for the presence of branched chain  $\alpha$ -hydroxyacids and branched chain  $\alpha$ -ketoacids (BCKAs) in urine in patients with MSUD which is absent in normal individuals (Strauss & Morton, 2003; Strauss et al., 2010).

MRI brain findings in cases of classic MSUD are unique, in which characteristic patterns of edema occurs especially at diffusion-weighted imaging, and so it provide a useful tool for early diagnosis (Li et al., 2021). The characteristic types of brain edema that can be seen with MSUD are intramyelinic edema (typical pattern) and vasogenic edema. The intramyelinic edema is an intense form that affects the myelinated white matter (cerebral peduncles, perirolandic cerebral white matter, cerebellar white matter, dorsal brain stem, posterior limb of the internal capsule), the thalami and globi pallidi, both of which have a high density of myelinated fibers. The intramyelinic edema has a high signal intensity on T2-weighted & diffusion-weighted MR images, low signal intensity on T1-weighted MR images, and decreased ADC and fractional anisotropy values (Reddy et al., 2018).

Early diagnosis of infants with classic type MSUD and its proper management by lifelong diet restriction of BCAAs and supplementation with vitamin B1 (thiamine)

could decrease the morbidity, mortality and provide better outcome.

The MSUD screening by tandem mass spectrometry (MS/MS) is currently incorporated in NBS programs throughout the United States, 5 Canadian provinces, 22 European countries, 2 Latin American countries (Costa Rica and Uruguay), and 8 countries in the Asia-Pacific region; accordingly, the NBS for MSUD is not available in many regions worldwide (Therrell et al., 2015). Egypt like many developing countries, lacks mass newborn screening (NBS) program for in-born errors of metabolism, and the current Egyptian NBS is limited to hypothyroidism and phenylketonuria (Hassan et al., 2016; Zayed et al., 2019). Therefore, this study aims to show the benefit of using the clinico-radiological findings for early diagnosis of children with MSUD, and confirming this diagnosis using the tandem mass spectrometry (MS/MS), in order to avoid deleterious outcome.

## 2 | METHODS

### 2.1 | Ethical compliance

The “Sohag University Medical Research Ethics Committee” approved this study with reference number (Soh-Med-21-04-34), Egypt.

### 2.2 | Study population

From August 2016 to December 2020, we conducted a prospective cohort study in our pediatric department, at a tertiary level university hospital. The study included all consecutive children suspected to have symptoms and signs of MSUD, aged 1-day to 2-years old, admitted to the inpatient department and willing to participate in the study. Selective screening was done for: (a) any newborn presenting with neurological symptoms (e.g., coma, lethargy, and persistent of one or more of the following: convulsions, vomiting, diarrhea, metabolic acidosis, and hypoglycemia); (b) child with one or more of the following: delayed developmental milestones, altered level of consciousness, recurrent convulsions, metabolic acidosis with increased anion gap, recurrent attacks of hypoglycemia, or electrolyte imbalance (with no specific cause to explain this symptoms and signs). In addition, a high-risk screening was performed to symptomatic family members of a known index child with MSUD or a family history of previous sibling death without a definite diagnosis.

Exclusion criteria were patients known to have definite history of perinatal brain injury, CNS infection, brain trauma or tumors, and intoxication. In addition, patients diagnosed with any chromosomal abnormalities.

## 2.3 | Clinical and neuro-developmental evaluation

All participants experienced thorough history taking, clinical examination, and neuro-developmental assessment, focusing on patient's demographics, onset and details of symptoms, lag time between initial symptoms and establishing the diagnosis, manifestation severity and outcome related to MRI finding and management.

## 2.4 | Neuroimaging assessment

Children underwent brain MRI using a 1.5-T magnet system (different models and manufacturers) at various imaging centers. Available sequences were axial T2-W fast spin echo (repetition/echo times: 3600–5540/100–110 ms) and T1-W spin echo (480–565/14–15) with a slice thickness of 4–6 mm; sagittal T1-W spin echo and axial fluid attenuation inversion recovery [FLAIR] (6000–11,000/120–146; inversion time 2000–2800 ms); coronal T1-W spin echo or T2-W fast spin echo; and diffusion-weighted image. The MRI scan focused on the supratentorial area (including the frontal, temporal, parietal and occipital hemisphere regions, the centrum semiovale, and corona radiata), the internal capsule, corpus callosum, basal ganglia, thalamus, mesencephalon, pons, and cerebellum. Brain tissue manifesting with high signal on DWI can be identified as cytotoxic or intramyelinic edema. Affected areas with increased signal in T2-FLAIR were recognized as dysmyelination or disturbed water content of the white matter.

An experienced pediatric neuro-radiologist interpreted the MRI scans of the patients, while he was blinded to the clinical and laboratory data of them.

## 2.5 | Biochemistry examinations

Arterial blood gas, serum glucose level, and ketonuria were assessed. In addition, the patient's blood levels of ammonia, lactic acid, and  $\beta$ -hydroxybutyric acid were measured. Confirmatory testing of highly increased branched chain amino acid (BCAAs) levels in plasma via quantitative amino acid analysis was performed.

## 2.6 | Blood amino acids and acylcarnitines analysis

Patients' blood samples (2 ml) were obtained on a Guthrie card (Whatman 903 filter paper; GE Healthcare Ltd). Acylcarnitines and amino acids were analyzed by using ACQUITY TQD Tandem Quadrupole UPLC/MS/MS

(Waters Corporation) with a positive electrospray ionization probe according to the manufacturer's instructions.

## 2.7 | Statistical analysis

Data were expressed as frequency and percentage or means and standard deviations as appropriate. A *p* value  $\leq 0.05$  was considered significant for all statistical operations. Analyses were done using SPSS software 22.0 release, SPSS Inc., Chicago, USA.

## 3 | RESULTS

The demographic and clinical characteristics of the studied population are shown in Table 1. There were 21 children (14 males and 7 females) diagnosed to have MSUD (the classic subtype). They belongs to 18 unrelated families (case 7 and 21 were sisters; case 4 and 11 were sister and brother; while case 12 and 13 were cousins).

All the symptomatic cases (20 child, 95.2%) were normal at birth; but the symptoms of MSUD appeared after a variable disease-free interval (mean  $8.3 \pm 6.9$  days; range: 3–75 days), and were included in the selective screening. Nineteen cases (90.4%) developed these symptoms acutely, one case (4.8%) had insidious onset, whereas one case (4.8%) was asymptomatic.

For the acute onset cases, they did the MRI at mean age of  $16.5 \pm 15.4$  days (range 5–75 days), while their mean age at which the diagnosis was confirmed by MS/MS was  $38.8 \pm 22.7$  days (range: 8–360 days).

Acute onset symptomatic children (total = 19 children) were presented with poor feeding, lethargy in 17 children (89.5%), irritability with excessive crying in 2 children (10.5%), disturbed conscious level in 15 children (78.9%), generalized seizures in 14 children (73.7%). Three cases (15.8%) presented by acidotic breathing, and 14 children (73.7%) developed generalized hypotonia and need mechanical ventilation support. The insidious onset symptomatic child (case no. = 20) presented with generalized developmental delay.

All the children with acute onset presentation received supportive management in the form of IV fluids, oxygen, and were fed on special formula with low-branched chain amino acids.

The outcome of the acute symptomatic group showed 12 children (63.2%) who died before completing their first year, while the outcome of the insidious onset symptomatic child (case no. = 20) died at age of 10 months.

The brain parenchyma of all patients (*n* = 21) was analyzed by MRI and the findings are summarized in Table 2. All children with acute onset disease showed involvement

TABLE 1 Demographic, clinical characteristics, and outcome of 21 children with maple syrup urine disease

Case	Sex	Screening	Onset of symptoms	Age of onset of symptoms	Age at MRI done	Age at diagnosis by MS/MS	Consanguinity	Family history	Seizures	DCL	Acidotic breathing	Ventilation support	The outcome
1	F	Selective	Acute	6 days	25 days	45 days	+	+	+	+	-	+	Died
2	M	Selective	Acute	75 days	75 days	105 days	+	-	-	+	+	+	Died
3	M	Selective	Acute	9 days	30 days	45 days	+	+	+	+	-	+	Severe delay
4	F	Selective	Acute	7 days	15 days	40 days	+	-	+	-	-	-	Died
5	F	Selective	Acute	5 days	12 days	30 days	+	-	+	+	-	+	Died
6	M	Selective	Acute	7 days	15 days	35 days	+	+	+	+	-	-	Died
7	F	Selective	Acute	7 days	8 days	365 days	+	-	+	-	-	-	Severe delay
8	F	Selective	Acute	3 days	5 days	8 days	+	+	+	+	-	-	Moderate delay
9	M	Selective	Acute	6 days	8 days	10 days	+	-	-	+	-	+	Died
10	M	Selective	Acute	15 day	20 days	35 days	+	+	+	-	-	+	Died
11	M	Selective	Acute	3 days	13 day	25 days	+	+	+	+	-	+	Died
12	M	Selective	Acute	8 days	10 days	30 days	+	+	+	+	+	+	Died
13	M	Selective	Acute	5 days	7 days	20 days	+	+	+	+	-	+	Severe delay
14	M	Selective	Acute	7 days	13days	30 days	+	+	+	-	+	+	Died
15	M	Selective	Acute	6 days	11 days	25 days	+	+	+	+	-	+	Died
16	M	Selective	Acute	8 days	12 days	30 days	-	-	-	+	-	+	Moderate delay
17	M	Selective	Acute	9 days	13 days	35 days	-	-	-	+	-	-	Sever delay
18	M	Selective	Acute	5 days	10 days	27 days	+	+	-	+	-	+	Moderate delay
19	M	Selective	Acute	7 days	13 days	24 days	+	-	+	+	-	+	Died
20	F	Selective	Insidious	35 days	105 days	135 days	-	+	-	-	-	-	Died
21	F	High risk	Asymptomatic	NA	300 days	360 days	+	+	-	-	-	-	Slight delay

Abbreviation: DCL, disturbed conscious level.

TABLE 2 MRI alteration in different anatomic brain regions

Case	Supratentorial area	Corticospinal tract	Central portion of centrum semioval	Basal ganglia	Thalamus	Pones	Mesencephalon	Cerebellum
1	+	+	+	-	-	+	+	+
2	+	+	+	+	+	+	+	+
3	+	+	+	-	-	+	+	+
4	+	+	+	+	-	+	+	+
5	+	+	+	-	-	+	+	+
6	+	+	+	-	-	+	+	+
7	+	+	+	+	+	+	+	+
8	+	+	+	+	-	+	+	+
9	+	+	+	-	-	+	+	+
10	+	+	+	+	-	+	+	+
11	+	+	+	+	-	+	+	+
12	+	+	+	-	-	+	+	+
13	+	+	+	+	+	+	+	+
14	+	+	+	+	+	+	+	+
15	+	+	+	+	+	+	+	+
16	+	+	+	+	+	+	+	+
17	+	+	+	+	+	+	+	+
18	+	+	+	+	+	+	+	+
19	+	+	+	+	+	+	+	+
20	+	+	+	-	-	+	+	+
21	-	+	-	+	-	+	+	+

of wide range of the brain parenchyma. Involvement of the basal ganglia occurred in 13 children (68.4%), the thalamus in 9 children (47.4%), and the internal capsule in 15 children (78.9%). The involvement of the optic chiasm, optic tracts, and optic radiations was reported in 5 children (26.3%), See Figures 1–3. The child (no. = 20) with the insidious onset presentation of the disease showed similar MRI findings like the acute onset children; with preservation of the basal ganglia and the thalamus. Asymptomatic child (no.= 21) which was diagnosed through high-risk screening showed involvement of the dorsal brain stem and globus pallidus on both sides only, see (Figure 4).

Laboratory investigations of the cohort study are summarized in Table 3. An elevation of the serum ammonia level was reported in 14 children (66.7%) (Normal value = up to 85  $\mu\text{g}/\text{dl}$ ), 4 children out of them showed extremely high serum levels ( $>200 \mu\text{g}/\text{dl}$ ). In addition, there was 6 children (28.6%) who showed high plasma lactate levels (Normal values =4.5–19.8  $\text{mg}/\text{dl}$ ), 14 children (66.7%) presented with metabolic acidosis, and 6 children (28.6%) with hypoglycemia. Ketonuria was reported in 14 children (66.7%).

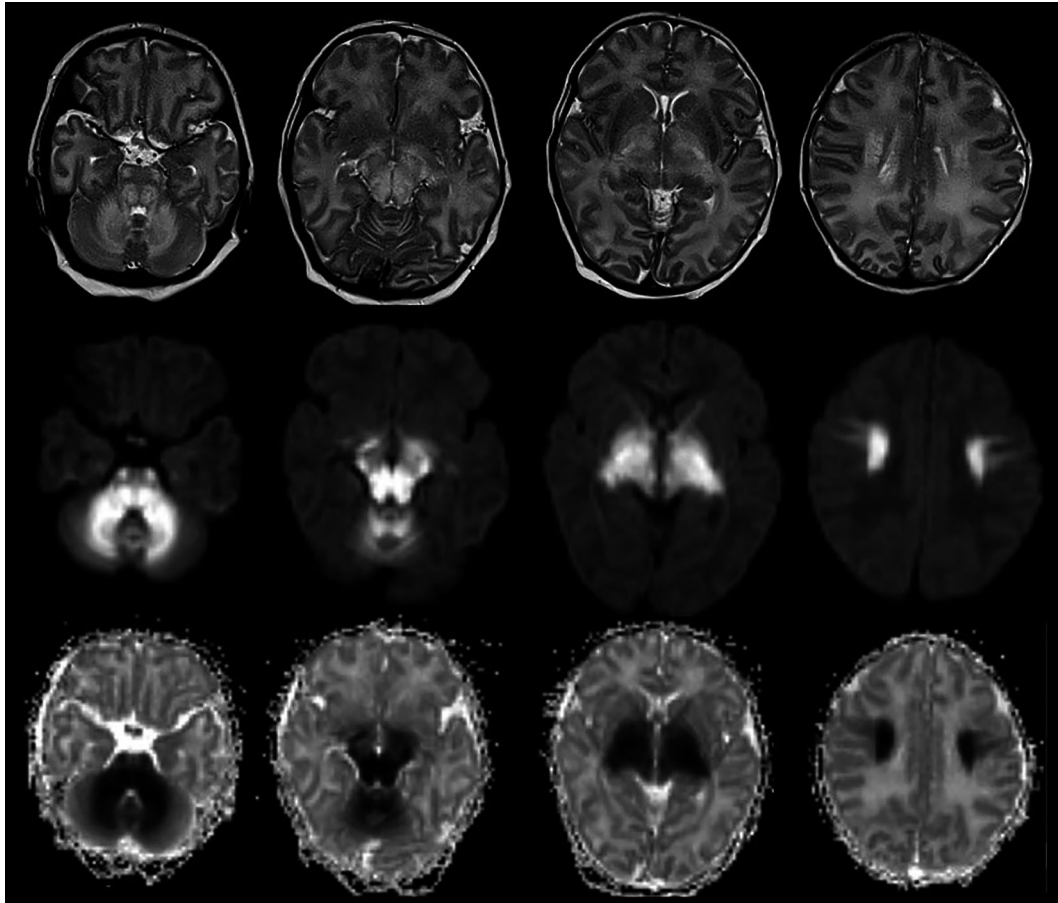
Diagnosis was confirmed by detection of elevated plasma levels of BCAAs using quantitative amino acid analysis and the tandem mass spectrometry. All children showed elevated serum levels of leucine/isoleucine

with mean value 2085.5  $\mu\text{mol}/\text{L}$  (ranging from 1006 to 3800  $\mu\text{mol}/\text{L}$ ) (Normal values = up to 270  $\mu\text{mol}/\text{L}$ ). Elevated serum valine was reported in 17 children (81%) (Normal values = up to 198  $\mu\text{mol}/\text{L}$ ); while the remaining 4 children (19%) had normal or low levels of serum valine as a result of starting protein restriction outside our center before testing with tandem mass spectrometry. In addition, all children showed elevated leucine: alanine ratio, and leucine: phenylalanine ratio.

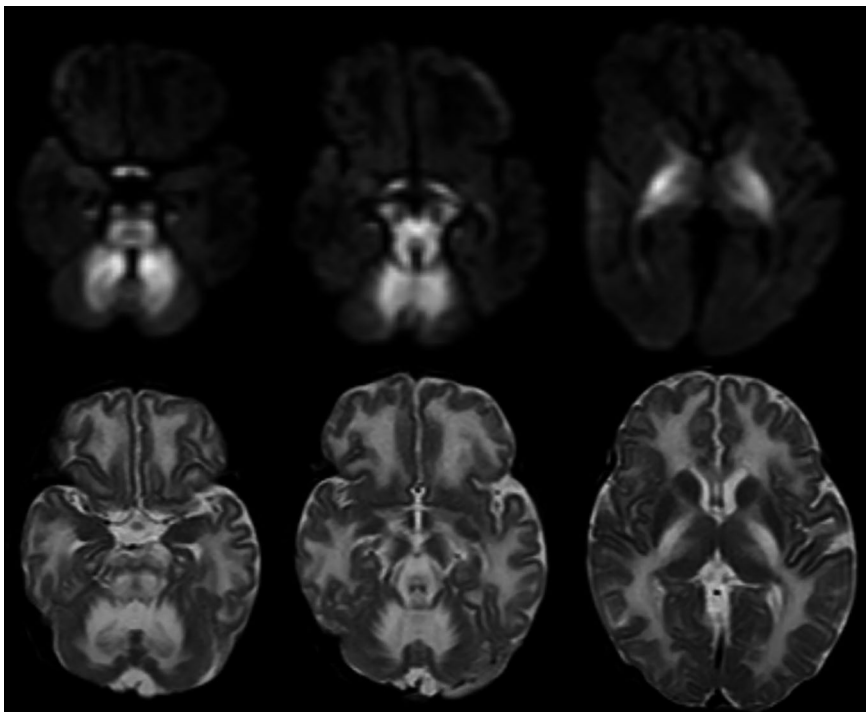
## 4 | DISCUSSION

MSUD is an inherited error of metabolism involving the BCAAs. The imaging features of this disease are very typical. The early clinico-radiological correlations in MSUD could have an important role in the diagnosis, prevent the progress of neurological deficits, and help in appropriate management of this condition (Shah et al., 2018).

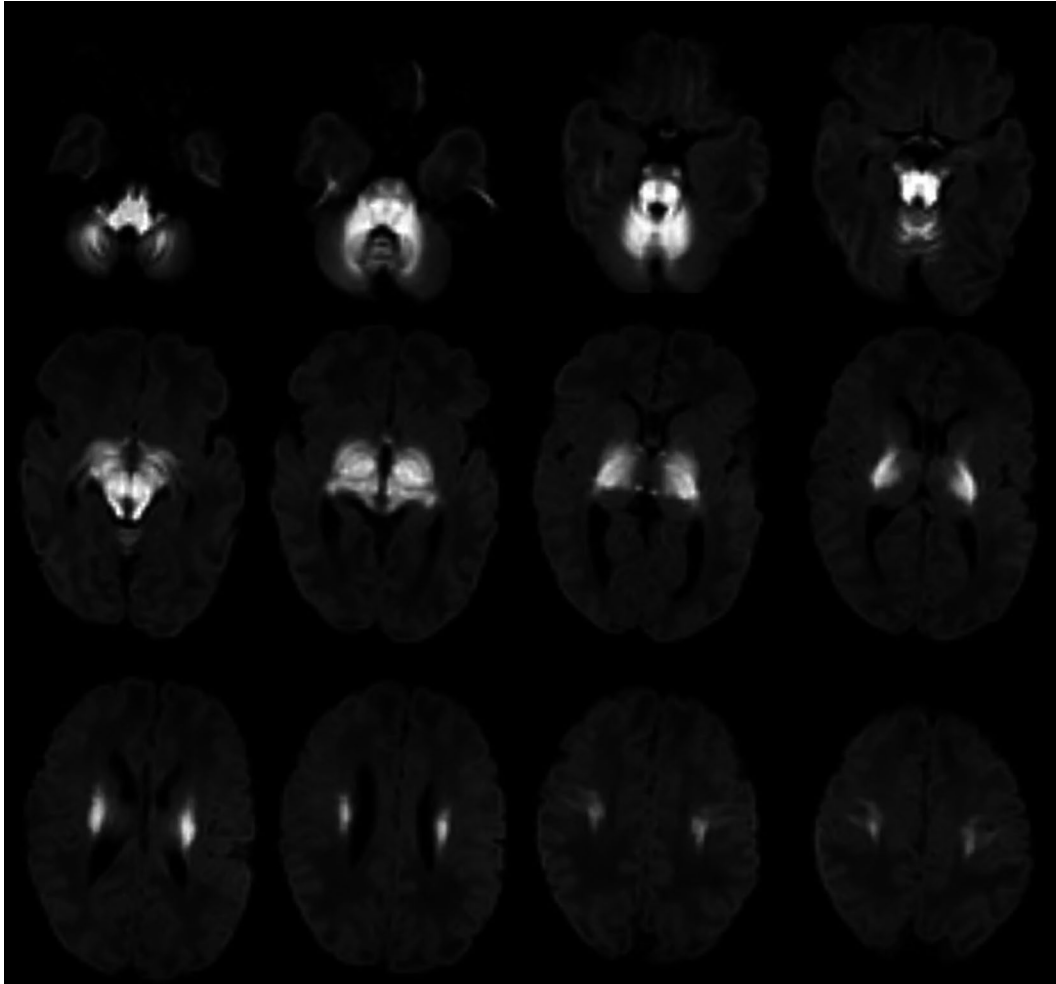
This study cohort included 21 MSUD patients (classic subtype). Other studies included nearly similar numbers of children with MSUD (classic subtype) ranging from 6 to 37 children (Cheng et al., 2017; Lee et al., 2008; Margutti et al., 2020; Yunus et al., 2012). The largest study for MUSD children was the one done by Strauss et al. who reported



**FIGURE 1** MRI of child 12 days with MSUD. Top row is axial T2, middle row is axial DWI and the bottom row is axial ADC map. There is bilateral symmetrical abnormal high T2 signal with related restriction in DWI and in ADC map involving cerebellar WM, brainstem tracts, optic tracts, cerebral peduncles, anterior, and posterior limbs of internal capsules, thalami, globus pallidus, and perirolandic WM



**FIGURE 2** MRI of child 35 days with MSUD. The upper row is axial DWI and the lower row is axial T2. There is bilateral symmetrical abnormal high T2 signal with related restriction in DWI involving cerebellar WM, brainstem tracts, optic chiasm and tracts, cerebral peduncles, anterior, and posterior limbs of internal capsules, thalami, and globus pallidus



**FIGURE 3** Axial diffusion-weighted MRI of child 11 days with MSUD. There is bilateral symmetrical abnormal restriction involving cerebellar WM, brainstem tracts, cerebral peduncles, posterior and to less degree anterior limbs of internal capsules, thalami, globus pallidus, and perirolandic WM

184 MSUD children {including 176 children (95.7%) having the classic subtype} (Strauss et al., 2020).

In this study, the mean age of onset of symptoms to appear was mean  $8.3 \pm 6.9$  days (range: 3–75 days). This consists with Lee et al. who reported that the mean age of onset of symptoms was 5 days (ranged from 2 to 14 days of life) (Lee et al., 2008), Cheng et al. who reported mean age of 10.5 days (Cheng et al., 2017), and Yunus et al. reported that all classic MSUD children developed initial symptoms within first week (Yunus et al., 2012).

In our study, we confirmed the diagnosis of MSUD by MS/MS at a mean age of  $38.8 \pm 22.7$  days (range: 8–360 days). This delay in the diagnosis can be caused by: (1) the vague clinical manifestations at initial assessment resembling neonatal sepsis; especially in the absence of a positive family history for inborn errors of metabolism. Definitive laboratory diagnosis is needed to confirm clinical suspicion of MSUD, (2) Delay in referral from primary units, (3) time consumed on samples transfer and results

receipt as there are limited number of tandem mass spectrometry in our locality. In other studies, there was variable delay (ranging from 3 to 12 months) in confirming the diagnosis of MSUD either by MS/MS or by genetic studies. The need for a rapid diagnostic test or implementation of MSUD newborn screening program to help pre-symptomatic diagnosis was mandatory to avoid that delay (Cheng et al., 2017; Lee et al., 2008; Margutti et al., 2020; Strauss et al., 2020; Yunus et al., 2012). This time lag between age of symptoms and confirming the diagnosis of MSUD; allows MRI brain to be a great diagnostic tool that saves time and gives chance to start early a specific management for these children which may improves their outcome.

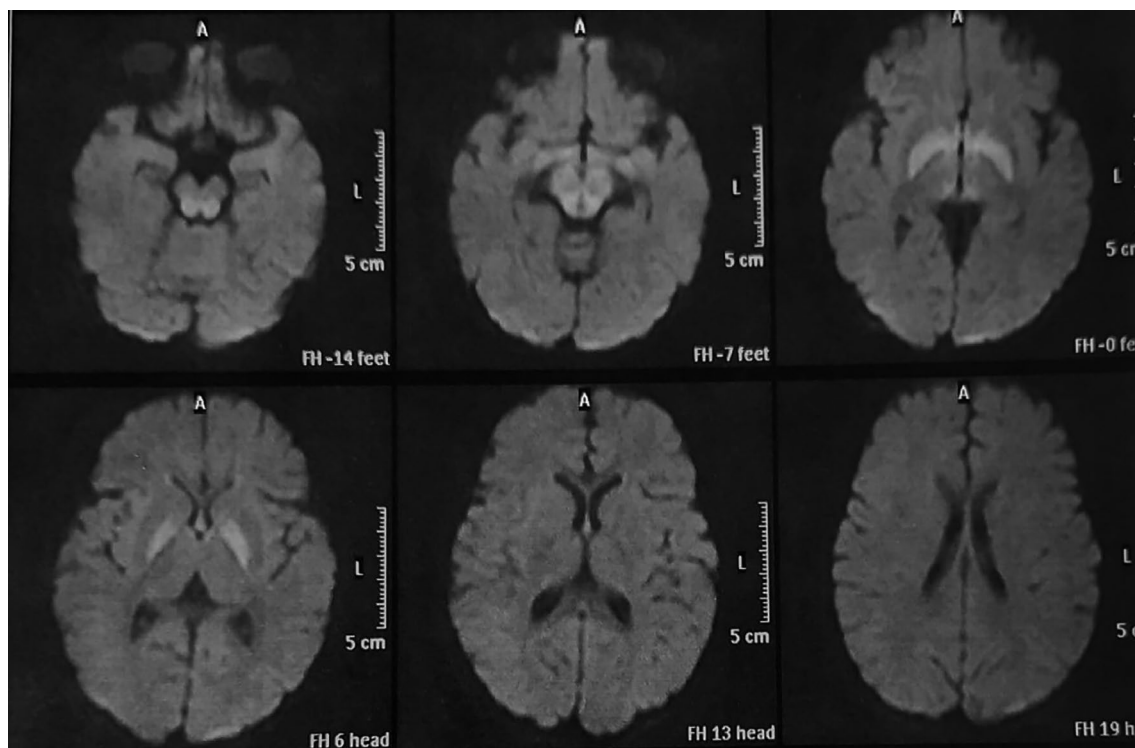
The main clinical findings in this study include poor feeding, poor activity, seizures, and disturbed conscious level. A common finding in almost children was positive consanguinity in 18 children (85.7%) and positive family history in 13 children (61.9%), which are consistent with the autosomal recessive mode of inheritance that was

TABLE 3 Laboratory characteristics for diagnosis of children with MSUD

Case no.	Leu/isoleu serum levels (normal up to 270 $\mu\text{mol/L}$ )	Leu:alan ratio (normal up to 2.28)	Leu:phe ratio (normal up to 8)	Valine serum level (normal up to 198 $\mu\text{mol/L}$ )	Ammonia serum level (normal up to 85 $\mu\text{g/dl}$ )	Lactate serum level (normal up to 19.8 mg/dl)	Ketonuria	Hypo-glycemia	Metabolic acidosis
1	2672	28	47	345	331	13	++	+	+
2	1146	5.4	15	261	80	70	+	+	+
3	1130	5.2	16	77	101	74	+	-	+
4	1068	3.7	24.6	368	125	21	++	-	+
5	2903	10.3	70.5	235	219	10	-	+	+
6	2943	21.8	51.8	424	85	18.9	-	-	-
7	2004	48.4	60.4	374	150	29	-	-	-
8	2730	21.9	75	188	104	10.2	+++	-	-
9	3800	39.6	66.9	369	55	28	+	+	-
10	1133	5.2	16	76.7	110	15	+	-	+
11	1243	13.5	25.3	167.5	112	17.5	+	-	+
12	2672	27.7	47.1	354	138	9.5	+	-	+
13	2766	35.9	51.5	442	160	14	+	+	+
14	2800.0	28.0	46.0	325.0	230	23	+	-	+
15	2608.0	27.0	45.0	312.0	149	15.7	+	-	+
16	1234.0	5.8	17.0	273.0	63	53	-	+	+
17	1079.0	3.9	19.0	284.0	134	17	+	-	+
18	1006.0	4.2	23.3	296.0	72	12	-	-	-
19	2856.0	19.4	65.5	407.0	59	11.7	+	-	+
20	2900	28	42	319	215	16	-	-	-
21	1103	8.2	18	304	56	16	-	-	-

Abbreviations: Leu/isoleu, leucine/isoleucine; Leu:alan, leucine:alanine ratio; Leu:phe, leucine:phenylalanine ratio.





**FIGURE 4** Axial diffusion-weighted MRI of child 1 year with MSUD. There is bilateral symmetrical abnormal restriction involving the globus pallidus and dorsal brain stem. (Case 21 diagnosed by high-risk screening)

**TABLE 4** Other studies showing brain parenchyma involvement in MRI of children with MSUD

Similar studies	Total no. of children	Cortico-spinal Tract	Central portion of centrum semioval	Basal Ganglia	Thalamus	Pons	Mesencephalon	Cerebellum
Patil et al. (2020)	1	1	1	1	1	1	1	1
Chimbili et al. (2020)	1	1	1	1	1	1	1	1
Li et al. (2021)	3	3	1	2	2	2	3	3
Kathait et al. (2018)	1	1	0	1	1	1	1	1
Shah et al. (2018)	1	1	1	1	1	1	1	1
Cheng et al. (2017)	6	5	5	6	4	5	5	5
O'Reilly et al. (2021)	2	2	2	1	2	2	2	2
Jan et al. (2003)	6	6	4	6	5	6	6	5
Jain et al. (2013)	1	1	0	1	1	1	1	1
Cornelius et al. (2014)	1	1	1	1	1	1	1	1
Sener (2007)	1	1	0	1	1	1	1	1
Kilicarslan et al. (2012)	1	1	1	1	1	1	1	1
Ha et al. (2004)	1	1	0	1	1	1	1	1
Indiran and Gunaseelan (2013)	1	1	0	1	1	1	1	1
Hou et al. (2016)	7	5	3	5	4	5	5	5

reported in other studies (Blackburn et al., 2017; Chimbili et al., 2020; Jaradat et al., 2015; Li et al., 2021; O'Reilly et al., 2021; Patil et al., 2020; Yunus et al., 2012).

MRI brain imaging in MSUD patients (especially in classic subtype) has a characteristic hyperintensity particularly DW1 sequence in the first few weeks of life. It

mainly involves the globus pallidus, thalamus, internal capsule, brainstem, and cerebellar white matter, which represent the typical myelinated areas in normal full-term neonates (Li et al., 2021). In our study, all patients with acute onset showed involvement of wide range of brain parenchyma. This was inconsistent with other literatures that discussed the radiological finding of classic subtype of MSUD patients, and reported similar findings, see Table 4. These findings represent demyelination and disrupted water content in the white matter (Li et al., 2021).

The serum leucine/isoleucine at the time of diagnosis was elevated in all cases (mean 2085.5  $\mu\text{mol/L}$ ), and this was lower than the value reported from a study done by Yunus et al who reported the mean in Malaysian MSUD children to be 3037  $\mu\text{mol/L}$  for the classic subtype (Yunus et al., 2012). However, in a study done by (Margutti et al., 2020), the mean plasma leucine level for 11 Brazilian children was 1976  $\mu\text{mol/L}$  (range = 278.9–3252  $\mu\text{mol/L}$ ).

The outcome of children with MSUD (especially the classic subtype) is mainly affected by early diagnosis and long-term control rather than leucine level at time of diagnosis (Margutti et al., 2020; O'Reilly et al., 2021). The MRI abnormalities that was reported in the first month of life were completely resolved by the age of 3 month after specific treatment as reported in many studies (Cheng et al., 2017; Margutti et al., 2020; O'Reilly et al., 2021). These data support the hypothesis that MSUD edema on DWI is intramedullary edema rather than cytotoxic.

Other studies using MR spectroscopy in MSUD children showed significant elevation of the methyl groups of BCAA and BCKA at 0.9–1 ppm; and these abnormalities resolved completely after recovery (Jan et al., 2003; Sato et al., 2014). So, MR spectroscopy can be considered as a specific diagnostic imaging study, which is also effective in follow-up of stable periods.

#### 4.1 | Limitation of the study

The need of more studies with larger population samples are still required to confirm these clinico-radiological observations in order to count on them on diagnosis and follow-up till a local NBS program using MS/MS becomes well established. In addition, the need of specific studies reporting the use of MR spectroscopy at different intervals after MSUD diagnosis and its role as a follow-up tool.

## 5 | CONCLUSION

The unique clinico-radiological features can help in early diagnosis of MSUD children, and thus decreasing the time lag until the confirmatory laboratory results (using

tandem mass spectrometry) become available, which will result in improvement of their outcome.

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### CONFLICT OF INTEREST

The authors have declared that no competing interests exist.

### AUTHOR CONTRIBUTIONS

MMM: conceived and designed the study. MAB: took part in database design, and data collection. RMM: assisted with the study design, data collection, and obtained ethical permission. HSE: undertook biochemical assay and interpretation. MHA: undertook MRI imaging and interpretation. HMA: assisted in the study design, design and interpretation of the statistical analysis, and drafted the initial manuscript. All authors revised and approved the final manuscript.

### ETHICAL APPROVAL

All procedures performed in studies including human participants were as per the ethical standards of the institutional and/or national research committee.

### INFORMED CONSENT

Informed consent was taken from all individual participants/parents included in the study.

### DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ethical restrictions.

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