Maple syrup urine disease: Clinical presentation and diagnosis at Children Welfare Teaching Hospital, Iraq

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Abstract

***Background**:* Maple syrup urine disease (MSUD) is a rare inborn error of metabolism of branched-chain amino acids valine, leucine and isoleucine. It is characterized by neurodevelopmental disorders, encephalopathy, and a maple syrup odour in the urine.

***Objectives**:* To describe the clinical profile and presentations of MSUD at Children Welfare Teaching Hospital, Iraq.

Method: A descriptive retrospective cross-sectional study included patients with MSUD who were registered at Children Welfare Teaching Hospital in Iraq from February 2014 to November 2020. Patients were reviewed regarding their clinical, laboratory and socio-demographic history.

***Results**:* Forty patients who registered as MSUD were included in the study. Of them 19 were male and 21 were female. The median age of the first manifestation was 5.5 months, while the median age of the first diagnosis was 12 months. Parental consanguinity was seen in 87.5% of cases. Hypotonia, seizures and poor response were the common presenting symptoms of MSUD, while spasticity, global developmental delay, intellectual disability and speech delay were the common complications. Due to early diagnosis and dietary restrictions, cognitive function was normal in only two patients. Serum branched-chain amino acids (BCAA) especially serum leucine level, was reported high among all cases at the time of diagnosis.

***Conclusions**:* Hypotonia, seizures and poor response were the common presenting symptoms of MSUD, while spasticity, global developmental delay, intellectual disability and speech delay were the common complications.

(Key words: Maple syrup urine disease, Leucine, Newborn screening, Seizures, Tandem mass spectrometry).

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Introduction

Maple syrup urine disease (MSUD) is an autosomal recessive inborn error of metabolism caused by a defect in the activity of branched-chain α-keto acid dehydrogenase complex (BCKADH)[1]. Impaired BCKADH results in a high concentration of branched chain amino acids (BCAA) that accumulate in the affected patients who are on an unrestricted diet or during episodes of catabolism[2]. Accumulation of BCAA interferes with the function of the immune system, skeletal muscles and central nervous system[3]. Isoleucine and its metabolite, α-ketoisocaproic acid exert direct and indirect neurotoxic effects, through tissue swelling and impaired glutamate homeostasis, that lead to reduced synthesis of neurotransmitters dopamine and serotonin[3-6]. Maple syrup urine odour is caused by a metabolite of isoleucine[1]. Clinical presentation ranges from intermittent symptoms of irritability, hypotonia and poor feeding to acute life-threatening symptoms like opisthotonos, critical cerebral oedema, and central respiratory failure[7].

MSUD has five distinct clinical phenotypes, namely classic (severe), intermittent, intermediate (mild), thiamine-responsive, and E3 deficient. The classic and E3-deficient phenotypes usually present during the early neonatal period while the other phenotypes may present at any age during childhood, especially during episodes of catabolism and acute illness[8].

The *classic phenotype* is the most common (75% of cases) and the most severe form of MSUD, with residual enzyme activity ranging from 0 to 2%[9]. Within the first 48 hours of life, the newborn typically develops ketonuria and encephalopathy in the form of lethargy, poor feeding, and dystonia[10]. Then, by the age of four days, neurological abnormalities like irritability, seizure, apnoea and cerebral oedema develop.

The *intermittent type* of MSUD is the second common type with higher residual enzyme activity than the classic type. During any intercurrent illness or other catabolic states or increased protein intake, affected patients are at increased risk of ketoacidosis and signs of neurotoxicity like seizures, ataxia, lethargy, and coma.

The *intermediate type* is rare with residual enzyme activity between 3-30% of normal.

Thiamine responsive phenotype is also rare with a clinical presentation similar to the intermediate one. Metabolic control is achieved through both dietary restriction and thiamine supplementation.

E3-deficient phenotype involves a wide range of mitochondrial reactions, affected patients presenting with a wide spectrum of manifestations, ranging from early-onset encephalopathy and acidosis to isolated liver disease in adulthood. These patients usually have biochemical abnormalities related to mitochondrial dysfunction like the elevation of serum lactate, alanine, and α-ketoglutarate[8].

The diagnosis of MSUD is established by the measurement of plasma amino acid concentrations that demonstrate elevated levels of BCAA (leucine, isoleucine, and valine) and alloisoleucine. MSUD genetic panel can be included in diagnostic work-up for confirming the diagnosis whenever possible. Newborn screening can detect the classic type of MSUD using tandem mass spectrometry (MS/MS), also called expanded newborn screening[11]. However, it cannot detect milder or other variant forms of MSUD.

In the acute phase, aggressive therapy is needed to reduce the serum leucine level through a high rate of glucose infusion to stimulate insulin secretion that suppresses protein catabolism. Peritoneal dialysis or haemodialysis is an alternative if the above treatment fails. Maintenance therapy consists of BCAA-free diet or formula and thiamine supplementation. However, liver transplantation is a definitive treatment. With early diagnosis and treatment of MSUD, intellectual disability can be prevented with good clinical outcomes[2]. This can be achieved by dietary restriction throughout life and aggressive management of acute metabolic decompensation.

Objectives

To describe the clinical profile and presentations of MSUD at the Children Welfare Teaching Hospital, Iraq, so as to stress the importance of including MSUD within the newborn screening programmes in Iraq.

Method

This is a descriptive retrospective cross-sectional study carried out at the neuro-metabolic department in Children Welfare Teaching Hospital, Iraq from February 2014 to November 2020. Patients who fulfilled the criteria for the diagnosis of MSUD were included in the study. They were diagnosed by MS/MS and confirmed by high-performance liquid chromatography (HPLC) to be cases of MSUD. The total number of patients collected and included in the study was 40 (19 male and 21 female).

The serum amino acids HPLC was done in a private laboratory in Baghdad, Iraq. MS/MS was done in a private laboratory outside Iraq, taking 2-3 weeks from the time of taking the sample to getting the results. The data were collected either from patients' hospital records, phone calls, or direct interviews during follow-up visits. The collected data include the following: socio-demographic characteristics, family history, consanguinity, age of clinical manifestation and age at diagnosis, gastrointestinal tract and central nervous system symptoms at presentation. Laboratory results for liver function tests, serum ammonia, MS/MS and serum amino acids were also included.

Ethical issues: The study was approved by the Medical Research Ethics Committee of the University of Mosul College of Medicine, Mosul, Iraq (No. UOM/COM/MREC/21-21 (12) on 11.11.2021. Written informed consent was obtained from caregivers of all patients included in the study.

Statistical analysis: The data of MSUD patients were analysed by Statistical Package for Social Sciences (SPSS) version 23. Data description are expressed as frequency, percentage, median, mean and standard deviation (SD).

Results

During the period from February 2014 to November 2020, 40 patients were registered as MSUD confirmed by laboratory tests.

Table 1 displays the clinical and demographic characteristics of the 40 patients.

Figure 1 shows the age of first manifestation.

Table 1: ***Clinical and demographic characteristics of patients (n=40)***

Variable	Result
Gender: n (%)	
Male	19 (47.5)
Female	21 (52.5)
Median age at the first manifestation	5.5 months
Age range of the first manifestation (shown in Figure 1)	1 month to 9 years
Birth to <6 months: *n (%)*	20 (50.0)
≥ 6months to <1year: *n (%)*	11 (27.5)
≥1year to <2 years: *n (%)*	06 (15.0)
≥ 2 years: *n (%)*	03 (07.5)
Median age at the first diagnosis	12 months
Age range at diagnosis	1 month to 15 years
Birth to <6 months: *n (%)*	11 (27.5)
≥ 6months to <1year: *n (%)*	06 (15.0)
≥1year to <2 years: *n (%)*	11 (27.5)
≥ 2 years: *n (%)*	12 (30.0)
Interval between age of first manifestation and age at first diagnosis: Mean ± SD	9.5 ± 10.5 months
Interval range	0-40 months
Clinical phenotype: n (%)	
Classic	38 (95.0)
Intermittent	02 (05.0)
Intermediate	0 (0)
Thiamine responsive	0 (0)
E3-deficient	0 (0)
Consanguinity: n (%)	
Yes	35 (87.5)
No	05 (12.5)
History of affected siblings: n (%)	
Yes	14 (35.0)
No	26 (65.0)
Maternal history of recurrent abortion: n (%)	
Yes	21 (52.5)
No	19 (47.5)
Outcomes at the time of the study: n (%)	
Alive	27 (67.5)
Lost to follow up	08 (20.0)
Died	05 (12.5)

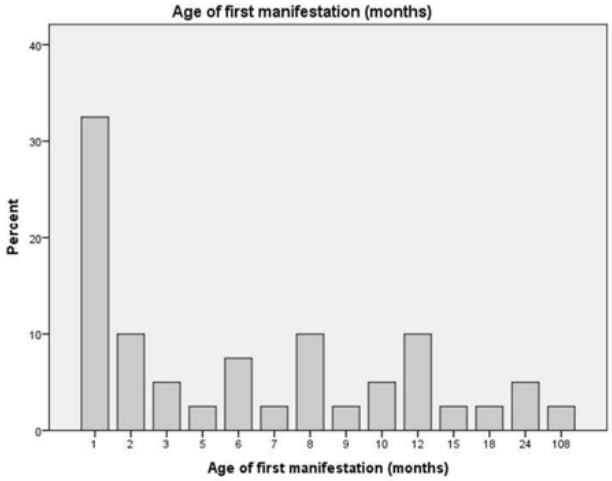

Figure 1: ***Age of first manifestation***

Figure 2 demonstrates the presenting symptoms of the 40 patients at first admission. Hypotonia and seizures were the two most common presenting symptoms, while a bad odour of urine was reported in 55% of cases.

Neurological complications that developed in our cohort on follow-up are shown in Table 2 and Figure 3 with their frequencies and percentages. Spasticity and global developmental delay were reported commonly in our cases (95% & 92.5% respectively) followed by intellectual disability and speech delay.

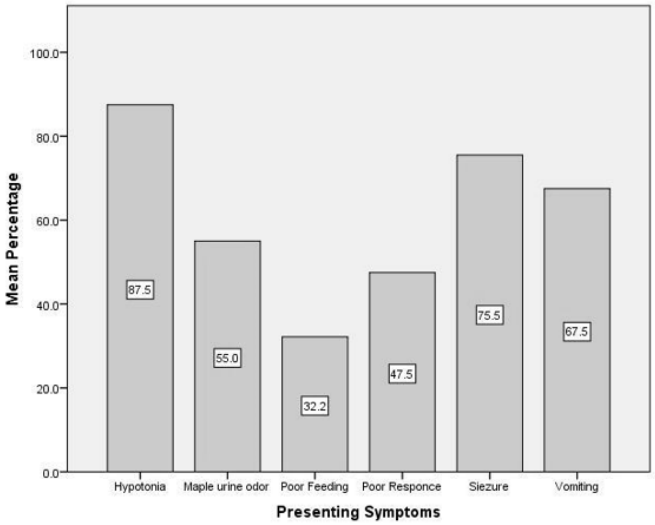

Figure 2: ***Presenting symptoms at the first admission***

Table 2: ***Neurological complications among patients with maple syrup urine disease***

Neurological complications	Frequency	%
Spasticity	38	95
Global developmental delay	37	92.5
Intellectual disability	36	90
Speech delay	32	80
Behavioural abnormalities	25	62.5
Epilepsy	23	57.5
Ataxia	09	22.5
Nystagmus	05	12.5
Normal	02	5

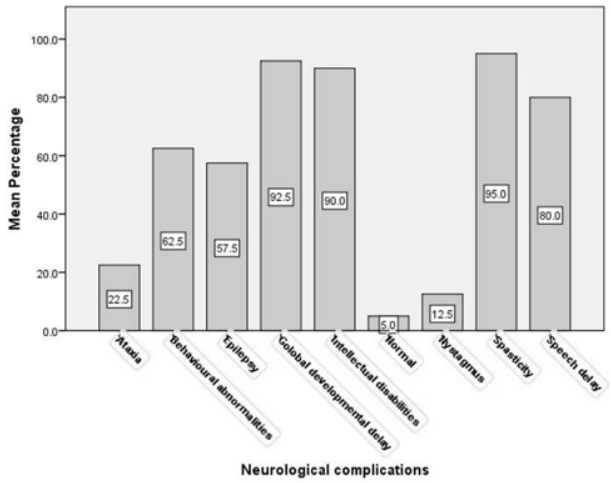

Figure 3: ***Neurological complications***

Table 3 demonstrates the laboratory findings at the time of presentation. Very high levels of serum amino acids valine, leucine and isoleucine were reported in all patients in the study. Liver enzymes like alanine transaminase and aspartate transaminase were also reported high (double normal range) in 12 (30%) and 14 (35%) of cases respectively.

Table 3: ***Laboratory findings and workup at the time of diagnosis***

Laboratory results at diagnosis	Mean (SD)	Results with above normal range values for age - n (%)
Liver function tests		
Alanine transaminase level: IU/L	47.0 (54.5)	12 (30)
Aspartate transaminase level: IU/L	48.2 (44.0)	14 (35)
Serum ammonia level: µg/dl	61.68 (20.5)	04 (10)
MS/MS valine level: µmol/L	667.2 (214.56)	40 (100)
MS/MS leucine level: µmol/L	2061.6 (1470.7)	40 (100)
Serum amino acid – Valine: µmol/L	658.8 (279.7)	40 (100)
Serum amino acid – Isoleucine: µmol/L	695.7 (461.1)	40 (100)
Serum amino acid – Leucine: µmol/L	986.4 (593.8)	40 (100)
Serum amino acid – Alanine: µmol/L	86.7 (42.3)	0 (0)

MS/MS: tandem mass spectrometry,

Discussion

Worldwide incidence of MSUD is 1 case per 185,000 live births[12]. MSUD is characterized by developmental delay, neurological disorders, feeding problems, encephalopathy and a maple syrup odour of urine. MSUD is an autosomal recessive disease. So, there is no male to female difference as we found in our study. A higher incidence is reported in countries with a high rate of consanguineous marriage[13]. Iraq is such a country. In our study, consanguinity was reported in 87.5% of cases. Thus, the incidence is expected to be high. Nevertheless, MSUD is not a part of the newborn screening programme in Iraq.

Some cases in our cohort were diagnosed early by a selective screening test due to either positive family history of MSUD or a history of unexplained encephalopathy and early neonatal death in siblings. Due to the lack of the newborn screening test for MSUD in Iraq, there was a delay in diagnosis of around 9.5 months after the onset of symptoms. This delay in diagnosis was also reported in countries that lack MSUD in their newborn screening programme[11,14]. Delaying diagnosis and thus delaying appropriate dietary restrictions was associated with the appearance of serious neurological complications among our cohort, particularly global developmental delay which was seen in 95% of our patients. The same finding was reported by Herber S, *et al*[11] in 2015 in Brazil. Early diagnosis and initiation of BCAA-free formula before the onset of symptoms are associated with the best outcomes[15]. Therefore, MSUD should be included in the newborn screening programme in Iraq.

Cognitive dysfunction is thought to be related to the plasma level of leucine[2]. In our cohort only two patients had their cognitive function near normal and they were diagnosed early due to positive previous family history, so they were kept on a BCAA-restricted diet immediately after birth. A study on a group of patients with the classic type of MSUD found that during the first six years of life plasma level of leucine concentration is indirectly correlated with intelligence quotient (IQ) scores[2,7].

Among our cohort, hypotonia, seizures and poor response were the common presenting symptoms of MSUD at the time of first admission[16,17]. However, these symptoms are also common presenting symptoms in many other illnesses during the neonatal period like sepsis, hypoglycaemia, meningitis etc. Therefore, there should be a high index of suspicion by any paediatrician, especially in countries where MSUD is not a part of the newborn screening programme. This study highlights the challenges faced by a paediatrician for early detection of MSUD in newborn babies. Thus, negative septic screen in any newborn with unexplained hypotonia, seizures, poor response, and family history of early neonatal death mandate serum essay for BCAAs. Interestingly, we reported a high rate of history of recurrent abortion among mothers of our patients. This was also reported by Dahpy MA, *et al*[17] in Egypt 2021. On the other hand, high levels of all BCAA were reported among all our cohort at the time of diagnosis especially leucine levels, with a mean value of 2061.6 µmol/L. A leucine level of more than 1000 µmol/L is assumed critical and may produce brain damage and death[2,18]. In this study, the elevation of liver enzymes (ALT and AST) at presentation was a distinct laboratory finding, suggesting associated liver damage during metabolic decompensation.

The limitation of this study is that it is an analysis of a retrospective medical records with limited information recorded, However, this is the largest

study conducted on MSUD patients in our locality. Further studies countrywide are recommended.

MSUD, although a rare inborn error of metabolism, is a critical neuro-metabolic illness that has tragic complications with increased morbidity and mortality if not detected and managed early. MSUD should be included in the differential diagnosis of any sick neonate or child who presented with recurrent unexplained encephalopathy. Being not a part of the newborn screening programme, the diagnosis of MSUD is delayed in Iraq. Consanguineous marriage is high in our locality. Consequently, the incidence of this disease is also expected to be high. Therefore, a nationwide newborn screening program should be expanded to include MSUD.

Conclusions

Hypotonia, seizures and poor response were the common presenting symptoms of MSUD. Spasticity and global developmental delay were reported in over 92% of the study population.

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