Maple Syrup Urine Disease (MSUD) detected in neurologic disorders Iraqi children

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Background Maple syrup urine disease (MSUD) is a rare inborn error of metabolism, caused by a deficiency in the activity of the branched chain alpha-keto acid dehydrogenase impairing the degradation of the branched chain amino acids (leucine, isoleucine and valine).
Objective To examine the demographic and neurological profile in a case of MSUD.
Patients and Methods A descriptive cross sectional study from 1 February 2014 to 1 February 2016, at Neurological ward and clinic of the Children Welfare teaching Hospital, in Baghdad, Iraq. Plasma specimens of 600 patients, with clinical suspicion of inborn error of metabolism (IEM) because of unexplained neurological deficits, unexplained developmental delay, recurrent coma and/or neuro-degeneration, MSUD were confirmed in 29 patients then clinical data of patients were reported and analyzed statistically.
Results Out of 600 patients visiting the neurological outpatient and ward, clinical and neurological findings were recorded as well as the family history and/or other symptoms suggestive of aminoacidopathy, 35 patients were confirmed their diagnosis as MSUD, 6 patients were excluded because they lost the follow up, therefore only 29 patients were enrolled, most of them (28 patients) were affected by classical MSUD, where only one patient had intermittent type. Considerable delay in diagnosis was noticed, which led to significant neurological abnormalities in most patients and the psychomotor delay was the main clinical presentation.
Conclusion In the absence of newborn screening, MSUD is not uncommon in neurologically disorder patients where MSUD was still diagnosed clinically, but delayed. The importance of clinical awareness and accurate biochemical analysis were the key tools for diagnosis and the necessity for a comprehensive national newborn screening program.
Keywords Maple syrup urine disease, Branched-chain amino acids

Introduction

Maple syrup urine disease (MSUD) is caused by deficiency of the branched-chain alpha-keto acid dehydrogenase enzyme complex characterized by elevated plasma levels of branched-chain amino acids (AAs) and urinary excretion of branched-chain keto acids.[1-4] MSUD is inherited in an autosomal recessive mode, with an incidence of 1 in 185,000.[5] It is more prevalent in populations with a high frequency of consanguinity. The disease was first described in 1954 by Menkes, Hurst and Craig who observed an unusual odor like that of maple syrup in the urine of four infants who died of a progressive neurological disease in the first weeks of life.[6]

Neonatal screening by tandem mass spectrometry (MS/MS), also known as expanded newborn screening, enables diagnosis of MSUD while the patient is still asymptomatic, as well as early treatment onset, two essential factors in improving the clinical course.[7] Before the introduction of expanded newborn screening, the severe form (classical MSUD) was believed to account for 75-80% of cases,[8] but recent data suggest the milder forms of MSUD can account for up to 50% of diagnosed cases.[9]

The Iraqi Newborn Screening Program was implemented in 2010 and does not include screening for MSUD, Furthermore, the laboratory tests required for diagnosis of this condition are also not provided through the governmental lab, and are only available at a few selected private medical laboratories. High rates of consanguineous marriages in Iraq play an important role in increasing expression of autosomal recessive disorders. In Iraq, there are limited data explaining the incidence and clinical presentation of IEM. This study reports our local experience in the field of IEM over the last 2 years.

The objective of this study was to outline the profile of Iraqi patients with MSUD from those attend pediatric neurology and neurodisability clinic so as to contribute to the consolidation of specific public policies for MSUD in the country.

Patients, Materials and Methods

Setting

This is a single center descriptive cross sectional study conducted at the pediatric neurology department and clinic at the Welfare Teaching Hospital, Medical City, Baghdad, for the period from 1 February 2014 to 1 February 2016. A total of 600 patients, who referred to fluorescent high performance liquid chromatography (HPLC) analysis for suspected IEM, were relying mainly on a high index of clinical suspicion warranting confirmatory testing by laboratory analysis of AA, in addition to those already suspected to being MSUD that suggested by tandem mass screening. Most of patients are well known to the neurological service by their Psychomotor delay & behavioral abnormalities who were undiagnosed.

The inclusion criteria included

The ages of all patients enrolled in the study were between 2 months and 15 years with the following criteria:

1. Patients who already well known to neurological clinic with intractable seizures (unclassified with syndrome), unexplained neurological deficits, unexplained developmental delay, recurrent coma,

neurodegeneration, positive family history, unusual urine odour, altered mental status out of proportion of other systemic disorder unusual body or urine odor and hiccup.

2. A significant increase in blood branched chain amino acid (BCAA) levels, on more than one measurement, as determined by a gold-standard method (florescent HPLC-based) BCAA quantitation.

The exclusion criteria included:

1. age: below 2 months and above 15 years.
2. loss of follow up.

Out of 600 patients, 35 patients were found to have an MSUD, and 6 patients are excluded because of loss of follow up.

Clinical data and Study Participants

MSUD patients were thoroughly interviewed, clinically examined and investigated according to the approved standard medical and laboratory work up.

Consanguinity enrolled in the study where it considers a real challenge in our developing country with a high consanguinity rate.

Basic diagnostic investigations

Upon clinical suspicion of an AA disorder, basic metabolic investigations were performed using routine methods for the measurement of serum glucose, electrolyte liver function test (aspartate aminotransferase, alanine aminotransferase), arterial blood gases, ammonia, and lactate.

Ethical approval

All patients and their families were informed about the aim and suspected benefit of the study before obtaining their agreements for participation according to the medical research and ethical regulations, thus an oral consent was taken from all enrolled participants and their families. All the medical research ethics rules and instructions regarding patient's privacy, humanity and security; as well as the medical research, laboratory data and investigation results were strictly considered throughout all the steps of study.

Definitions

Psychomotor retardation or developmental delay; refers to the slow progress in the attainment of developmental milestones this may be caused by either static or progressive encephalopathies.

Intellectual disability; the term intellectual disability is replacing mental retardation, defines as a disability characterized by a significant limitation both intellectual functioning and in adaptive behavior as expressed in conceptual, social, practical and adaptive skills. This disability originates before the age of 18 and manifest with severe problems in the individual's capacity to perform (i.e. impairment), ability to perform (i.e. activity limitation), and opportunity to function (participation restrictions)[12] and in order to get a proper determination of degree of intellectual disability, referred to the psychiatrist's opinion on the 10th floor of Baghdad teaching hospital-medical city and some time to psychology center for research in Baghdad university in Aljadria.

A cousin is a relative with whom a person shares one or more common ancestor, in a general sense, cousins are two or more generations away from any common ancestor

First cousins are the children of two siblings. First cousins have grandparents in common

Distant cousins: second cousin; the children of first cousins (share the great grandparent) while third cousins: grandchildren of two first cousins (share the great great grandparent).

Equipment

The HPLC system consisted of degasser YL 9101, the pump was YL 9110 quaternary pump, and the injection valve Rheodyne was equipped with 20 µl sample loading loop, detector model 1100 Agilent fluorescence

Collection of Samples

Venous blood was collected in heparin-containing tubes. After centrifugation (2000 for 10 min).

Processing of Samples

Add 20 µl from sulfosalicylic acid to deproteinize 200 µl of plasma; mixed on a vortex, incubate at 4°C for 30 min, centrifuged at 3000 g for 15 min remove precipitated protein. The clear supernatants were transferred to polypropylene vials and stored in a refrigerated at −20°C.

Derivatization

To 30 µl of standard solution or plasma add 30 µl from Orthophthaladehyde (OPA) reagent and inject 20 µl on to the column.

Statistical Analysis

Statistical analysis and reporting of obtained data were carried out by descriptive pattern. Data were reported and presented as tables to show the frequency distribution (number and percent (n, %) of variables.

Results

Out of 600 patients with neurological symptoms and /or sign who referred to quantitative AAs by fluorescent HPLC, 29 patients were detected to have MSUD; 28(96.5%) classical type and only one (3.5%) was an intermittent type enrolled in the study that suggested by the significant increase branched chain AA (valin, leucine and isoleucine) and increase leucine to alanine ratio.

Age of the patients at diagnosis are given in Table 1. The main age at diagnosis of MSUD (Table 1) was 2nd year of age.

MSUD were more common in male 72% and the male/female ratio was 2.6 (Table 2).

Family history was negative in 58.6% (Table 3).

Table 1.

Month	No.	%
0	0	0
3–6	2	6.9
7–12	6	20.6
13–24	7	24.1
25–36	3	10.3
37–48	4	13.8
49–60	4	13.8
>60	3	10.3
Total	29	100%

Table 2.

Gender	No.	%
Male	21	79
Female	8	21

Table 3.

	No.	%
Negative	17	59
Positive	12	41

Table 4.

	No.	%
Psychomotor delay without seizure	9	31
Psychomotor delay with seizure	19	66
Recurrent encephalopathy	1	3

Table 5.

	No.	%
Closely related	24	83
Not closely related	2	7
Unrelated	3	10

Clinical Presentation of MSUD patients

Overall, participants show that psychomotor delay represents the main presenting sign (96.5%), with 30% with a seizure while one patient presented with recurrent encephalopathy (3.5%) (Table 4).

The consanguinity among families of our patients shows about 82% as first cousin and 7% as second cousin (Table 5).

Discussion

This is the first study highlighting the clinical and biochemical diagnostic approaches to MSUD in Iraq. Although neonatal screening by MS/MS may enhance early detection of MSUD, HPLC remains the key diagnostic tool for confirmation of all suspected cases, whether clinically symptomatic or initially positive by neonatal screening program. However, in a developing country like Iraq, resources are carefully allocated and testing is targeted based on clinical awareness.

Definitive laboratory diagnosis is crucial in confirming the clinical suspicion of MSUD since its clinical presentation is non-specific and can mimic common conditions such as infections and other IEMs. With the availability of quantitative, plasma AA analysis by fluorescent HPLC, we have started to see an increasing number of children diagnosed MSUD who their parent concerned about their psychomotor delay with or without seizure.

In our case series, MSUD is found to occur predominantly in male gender (72.5%). Most cases are classical type except one case was intermittent type, comparable to a reports from the Malaysia[14] and the Philippines[15] were also the majority is in the classical group. Another noteworthy finding was that parental consanguinity was found in about 90% of cases and it is consider significantly higher in our study and it is coincident with study done in Libya[16] where consanguinity was found in about 87%, in contrast to study from the Malaysia[14] that parental consanguinity was found in 1/3 of cases, as majority of metabolic diseases are autosomal recessive inherited traits occurring frequently in countries with high consanguinity rates,[17] which may suggest possibility of high rate of occurrence of IEM in Arabian world like Iraq although comprehensive published report are not available.

Delayed diagnosis is common in our case series most of them diagnosed at second year. We believe that the delayed diagnosis is contributed by the lack of Newborn screening (NBS) which is considered as effective and important preventive measure, in addition to lack of awareness of IEM among physicians. The problem of delayed diagnosis is compounded by the lack of diagnostic facilities. The awareness and understanding of physicians about MSUD should be heightened through continuous medical education and publicity. Therefore, identification and diagnosis of such disorder remain a real challenge and this agree with study done in other developing countries like Lebanon[18] and Malaysia,[14] whereas it is inconstant with study done in Thailand,[19] this discrepancy related to establishment of neonatal screening, which had been established in Thailand, but it does not in our country.

The psychomotor delay was the main presenting symptom in about 96% from them 65% with seizures while one case (3.5%) experience recurrent encephalopathy, who diagnosed as intermittent MSUD & this in contrast with Thailand study where diagnosed at early infancy (1st 5 mo.) period during work up for neonatal encephalopathy work up,[19] and it might be attributed to attended patients in the present study who survive the initial metabolic crisis typically have neuro developmental delay and learning deficit.[12]

About two third of MSUD patients in present study experienced a seizure (GTCS) while the seizure present in only ¼ of patients in Lebanon study,[18] this difference might be related to dietory regimen adapted by different societies.

Very few parents are able to identify the special burnt sugar smell associated with MSUD, although this was present in almost all patients in our case series, but when repeat the question or smell the urine, we find it is present in most of cases and this is because some of parents, they don't experienced maple syrup odour. There for the smell of patient urine may be considered as part of clinical assessment in suspected patient with metabolic diseases.

Conclusions

1. This study provides useful information for health policy and planning services for future metabolic newborn screening programs, which should include screening for MSUD.
2. Consanguinity had a definite role in the increased frequency of metabolic disease in our population as most of them are autosomal recessive Mendelian inheritance.
3. Late diagnosis, of AA disorders like MSUD was still considered challenging issue.

Recommendations

1. Expanding and extending of tandem mass liquid chromatography-metabolic screen mass spectrometry (LC-MS/MS)

to involve all Iraq with involvement other AA disorder particularly MSUD.
2. Establishment of specific metabolic centers in various universities and research institutes and provided them with advanced metabolic diagnostic equipment.
3. Establishment of Health education program about early detection of metabolic disorder in term of psychomotor delay, urine and sweat odor, positive family history of AA disorders and education about the consanguinity and its role in metabolic disease.

Competing Interests

The authors declare that they have no competing interests.

Authors Contributions

A. K. did the literature research, analysed the data and drafted the manuscript. A. A. were involved in discussion and evaluation of the data and critically revised the manuscript and also participated in the study coordination and helped to draft the manuscript in addition to contributed clinical data. All authors read and approved the final manuscript.

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