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Maple Syrup Urine Disease: Incidence and Related Factors in Infants 2008-2015, Tehran, Iran

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Abstract

Background: Maple syrup urine disease is an inherited autosomal recessive disorder. Infants with MSUD appear normal at birth. In Iran, no data concerning the incidence of MSUD has ever been reported. The aims of this study were (a) to estimate the incidence of MSUD in Iran (b) to establish a preliminary comparative analysis of clinical presentation and diagnosis. **Materials and Methods:** This retrospective analytical study was conducted between 20 March 2008 and 20 February 2015. We evaluated babies born in Najmiyyeh Hospital and referring to Niloo, Masoud and Saeid laboratories in Tehran, Iran. Blood leucine level was measured. Normal leucine levels in blood samples from healthy infants were less than 4.27 mg/dl. In patients whose blood leucine levels were higher, the experiment was repeated once again. If the result was positive again for the final confirmation of the disease in infants, quantitative measurement of amino acids such as leucine, isoleucine and valine was performed by HPLC (high-performance liquid chromatography). The prevalence of MSUD was determined in newborns. **Results:** Of 200,000 cases, 11 had MSUD. The prevalence was 1:18,180. The mean age of symptom onset was 6±2.8 days. Special diets for MSUD, diet and liver transplantation, diet and blood transfusion and peritoneal dialysis were performed on 9, 1, 1, 1, respectively. **Conclusion:** We should consider the diagnosis of MSUD in infants with poor feeding, lethargy, smell of burnt sugar in the urine and nneurological involvement.**[**GMJ.2015;4(4):164-68**]**

Keywords: Neonatal; Branched Amino Acids; Maple Syrup Urine Disease; Leucine, Isoleucine; Valine

Introduction

Maple syrup urine disease (MSUD) is a rare autosomal recessive disorder related to branched-chain alpha-keto acid dehydrogenase (BCKAD) complex deficiency. It is characterized by increased level of branched-chain amino acids (BCAAs) including leucine, valine and isoleucine and urinary excretion of branched-chain keto acids [1-4]. Leucine is a toxic agent for the central nervous system (CNS) [5]. Incidence of MSUD worldwide is estimated to be about 1:185,000 newborns [6] that is more prevalent in populations with a high frequency of consanguinity [1].

The most common form of MSUD is classic form with neonatal presentation and extremely low enzymatic activity (0–2%) [6].

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By the end of the first week, infants with MSUD become lethargic and develop progressive neurological failure while they are normal at birth. Seizure, cerebral edema, apnea and coma occur in untreated patients and death usually occurs within the first month of life [7,8]. Treatment with a low protein diet supplemented with a branched-chain-free amino acids mixture is a good and successful treatment [8-13]. Peritoneal dialysis or hemodialysis may be needed if this fails. During the maintenance phase, treatment with dietary BCAA restriction is needed [14, 15]. A good alternative is liver transplantation [16, 17].
There are no data concerning the incidence of MSUD in Iran, despite a generalized suspicion among clinicians that it could be more frequent than in other populations.
The aims of this study were (a) to estimate the incidence of MSUD in Iran (b) to establish a preliminary comparative analysis of clinical presentation and diagnosis before and after the introduction of MSUD in the newborn screening program.

Materials and Methods

This retrospective analytical study was conducted between 20 March 2008 and 20 February 2015. Two hundred thousand infants from the health records existing in referral laboratory were selected using census method in Najmiyeh Hospital, Niloo, Masoud and Saeid laboratories in Tehran, Iran. All infants who participated in neonatal screening program in Najmiyeh Hospital and Niloo, Masoud and Saeid laboratories in Tehran, Iran between March 2006 and February 2012 were assessed. The infants were excluded if they did not want to participate in study. Their parents were asked to answer a questionnaire including familial marriage of couples, previous pregnancy history, abortion history, infant gestational age and birth weight.
To measure serum levels of branched amino acids, Nitro-phenyl hydrazine DNA screening test was conducted. We added 2,4-dinitrophenyl hydrazine as reagent to 25mg of alpha-ketoglutaric- acid in 100cc of normal urine composition. We considered forming of yellow or white chalky deposits within ten minutes as positive reaction. We confirmed the results by nuclear magnetic resonance method.

Ethical Considerations
This study was approved in Ethics Committee of Baqiyatallah University of Medical Sciences and Health Services. Individuals were asked to sign an informed consent form before answering the questionnaire. All the terms of Helsinki declaration were considered and the personal information remained anonymous.

Statistical Analysis
Data were analyzed using statistical package for social sciences (SPSS) version 16 (SPSS Inc. Chicago, IL) for windows. Normal distribution variables (approved by one-sample Kolmogorov–Smirnov test) were compared using independent sample t-test between the sub-groups. Fisher's exact test was also used to compare categorical variables in subgroups. A p-value of less than 0.05 was considered statistically significant.

Results

Of total 200,000 infants (50.3% males and 49.7% females), 11 infants (3 males and 8 females) were positive for maple syrup urine disease. The mean age of male and female infants was 4.21± 1.82 and 4.45±1.90, respectively. The average age in both groups showed no significant difference (P= 0.339). Table 1 shows demographic data for MSUD patients. According to this table, mean age of patients in both groups (males and females) showed no significant difference (P=0.137). According to Table 1, the average birth weight in both groups showed no significant difference (P=0.145).
There was no significant difference in the distribution of family history of MSUD (P=0.21). The parents of 9 cases had familial marriage in that 36.3% were from Mashhad, Iran. Distribution of family relationship between the patients had no significant difference (P=0.42). The mean gestational age showed no significant difference in both

groups (P=0.365) (Table1). The most common chief complaints were poor feeding in 72.7% (8 cases), lethargy in 36.3% (4 cases) and the smell of burnt sugar in the urine of 36.3% (4 cases). Figure1 shows the distribution of chief complaints of patients. In one infant (9%), disease was diagnosed randomly and in 10 patients (91%) disease was diagnosed after the onset of symptoms. There was no significant difference in the distribution of disease diagnosis (P=0.08).

According to the various subtypes of MSUD, a total of 8 patients with MSUD (72.7%) were with the classic type of disease. One patient (9%) was with intermediate type. One patient (9%) was with intermittent and 1 patient (9%) with thiamine –responsive subtype. There was no significant difference in the distribution of subtypes (P=0.32).

The mean age at diagnosis was 23.3 ± 2.82 days. The mean age at diagnosis showed no significant difference between both groups (P=0.18). A total of 6 patients (2 males and 4 females) were with neurological involvement. There was no significant difference between the two groups in distribution of neurological involvement (P=0.62). A total of 9 patients (81.8%) were treated with MSUD special diets. One patient of MSUD (9.1%) was treated with diet and blood transfusion, one patient of MSUD (9.1%) underwent liver transplantation. Peritoneal dialysis was performed in one patient (9.1%). In total, 2 patients (18.2%) survived and 9 patients (81.8%) died. There was no significant difference between the two groups (P=0.42).

Table 2 shows serum levels of leucine, isoleucine and valine in the patients based on high-performance liquid chromatography (HPLC). The mean serum levels were significantly different between the two groups (P=0.01).

Discussion

In our study, the prevalence of MSUD was 1:18,180, more common in females than in males. We found that the majority of parents had familial marriage and most of them were from Mashhad, Iran. The most clinical symptoms were poor feeding, lethargy and smell of burnt sugar in the urine. The most patients were treated with MSUD special diets. Mortality rate was 81.8%. In the recent study, most patients were in classic subtype of MSUD. According to TADA *et al*. [18] study, the prevalence of MSUD in Japan was about 1:525980. Simon *et al*. [19] from Germany reported prevalence of MSUD as 1:500000. In all these studies, the prevalence rate was much lower than our study.

In Golbahar *et al*. [20] study, the prevalence of MSUD was more common in females than in males. This finding was similar to our study.

Table 1. Demographic Data for Maple Syrup Urine Disease Patients

	Mean age (day)	Mean birth weight (gram)	Positive family history of MSUD	Positive familial marriage	Gestational age (weeks)
Males(N=3)	7.3 ± 2.1	3230 ± 404	0(0%)	2(66.6%)	39.2 ± 2.1
Females(N=8)	5.6 ± 2.3	3050 ± 379	3(37.5%)	7(87.5%)	37.3 ± 1.8
Total(N=11)	6 ± 2.8	3100 ± 375	3(27.2%)	9(81.8%)	38.3 ± 2.1
P value	0.137	0.277	0.21	0.42	0.365

Table 2: The Mean Serum Levels of Branched Amino Acids

	Leucine	Isoleucine	Valine
Males(N=3)	3107 ± 937µg	583 ± 549µg	578 ± 663µg
Females(N=8)	2983 ± 695µg	373 ± 205µg	473 ± 244µg
Total(N=11)	2984 ± 721µg	478 ± 315µg	525 ± 364µg
P Value	0.30	0.06	0.01

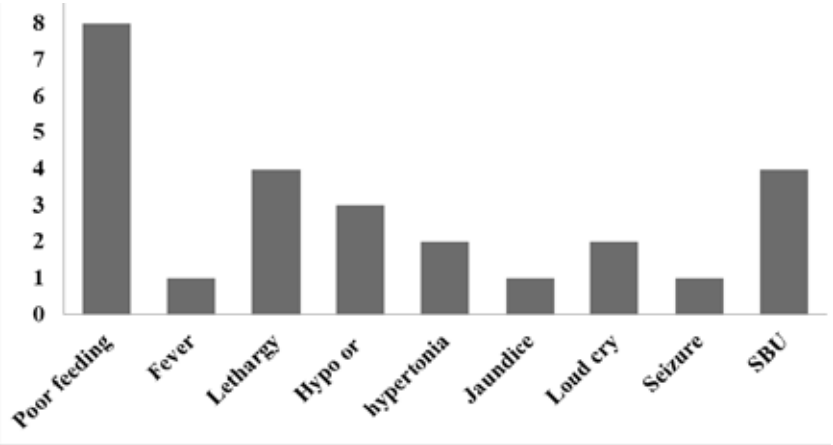

Figure1: Distribution of Chief Complaints of Patients

Herber *et al*. [5] demonstrated that average age at symptoms presentation in Brazilian infants was 4-7 days. This mean in Pangkanon *et al*. [1] study was about 8 days. The average age at symptoms presentation in our study was similar to these studies.

Simon *et al*. [19] concluded that a majority of patients did not have a positive family history of maple syrup urine disease and only there was one abortion through the study of fetal diagnosis of MSUD. In our study, a majority of patients did not have a positive family history of maple syrup urine disease but 3 mothers had a history of uncertain abortions.

In Herber *et al*. [5] study, majority of patients' parents had non-familial marriage. These findings were obtained in other studies [1]; however, in the majority of studies done in Iran, a majority of patients' parents had familial marriage [20]. In the recent study, we found that a majority of patients' parents had familial marriage and most of them were from Mashhad, Iran. It seems that this difference is because of popularity of consanguinity in Iran.Quental *et al*. [21] reported the average age of diagnosis about 15 days while this value in Herber study was 60 days [5]. Our average age of diagnosis was about 20 days. We think that this relatively long time was due to sending tests out of our country, so response time was prolonged.

In the majority of studies, the most clinical symptoms were poor feeding, lethargy and smell of burnt sugar in the urine [1] as we concluded.In many studies, most of the patients were treated by medical therapy[1, 19]. But we treated most of the patients with MSUD diet.

Dau-Ming *et al*. [22] reported that mortality rate in Taiwan among MSUD infants was about 7.7% and also this rate was low in many others studies [18, 21]. Our mortality rate was very higher than these studies.

Pico *et al*. [23] showed that most of patients had classic subtype of MSUD. Our findings confirmed this.In all studies, leucine serum levels in patients were increased. [5, 19]. Leucine serum levels also in our patients were increased.

Herber *et al*. [5] reported that 98.8% of their patients had neurological involvement. In Pangkanon *et al*. [1] study, this rate was 92.3% and in Dau-Ming *et al*. [22] study , 23% of patients were with nneurological involvement. Neurological involvement rate in our study was 54.4%.

Conclusion

We conclude that according to the prevalence of MSUD in Tehran, we should consider the diagnosis of MSUD in infants with poor feeding, lethargy, smell of burnt sugar in the urine and neurological involvement, particular in patients whose parents had familial marriage. Our limitaions in this study included incomplete file data in some cases. Finally, it is recommended to use screening tests for newborns and prenatal diagnostic test to prevent MSUD.

Conflict of Interest

There is no conflict of interest.

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