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Inborn Errors of Metabolism Referrals- Shahid Sadoughi Hospital: A Cross- Sectional Study

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ABSTRACT

Background: Inborn Errors of Metabolism (IEMs) are a group of heterogeneous disorders resulting from absent or decreased metabolic pathway activity. They are typically rare, but are more common in consanguineous population.

Methods: In this cross sectional study, all children with symptoms suspicious for IEMs who referred to Shahid Sadoughi Hospital in Yazd during a 5-year period (2013-2018) were investigated for metabolic diseases. The diagnoses were further confirmed by clinical symptoms and biochemical analysis. IEMs type, age of diagnosis, family history and disease outcome were recorded.

Results: In this study, 39 symptomatic children with a median age of 48 months were diagnosed with different types of metabolic diseases. About 64.1% of the patients were born from consanguineous marriage. The patients' mean age at the time of diagnosis was 25.3 ± 5.1 months. The most frequent disorders were organic acidemias which were found in 12 patients (30.8%), lysosomal storage disorders which were found in 8 patients (20.5%), and amino acid disorders excluding phenylketonuria which was found in 8 patients (20.5%). Most of the patients (60%) were diagnosed before the age of 6 months. Mortality from metabolic disorders was 5 (12.8%). The rest of the patients (22 cases, 56.4 %) had developmental delay.

Conclusion: It was found that the prevalence of inherited metabolic disorders was higher in countries with a high prevalence of consanguineous marriage, such as Iran. More extensive newborn screening is needed for ensuring early diagnosis of these patients given that delay in diagnosis of this disorder may be associated with high morbidity and mortality.

Introduction

Inborn Errors of Metabolism (IEMs) are a group of genetic biochemical diseases leading to defective of enzyme function in the metabolic pathway. The clinical symptoms of these diseases are complex and often result in death or development of complications and disability. Many infants with IEMs may seem normal at birth, but neurological manifestations start to appear in childhood few months later. Early diagnosis and treatment are very important to improve quality of life and clinical outcomes of the sufferers. Although each disorder is individually rare, but collectively they occur in 1 in 800 to 2500 live births.[1] As consanguineous marriages are a common tradition in our country, the incidence of these disorders would be very high in this population.[2] In a study done by Aghamaleki et al., from 2005 to 2015, it was found that the prevalence of hereditary metabolic disorders was 150 cases per 100,000 live births.[3] Thus, it is expected that the prevalence of these disorders be higher in Iran compared with other countries such as Australia (15.7/100,000 live birth), Italy (27/100,000), and Canada (1:2500).[4-6] To the best of our knowledge, there is limited data on the true incidence of IEMs that lead to difficulties in planning and providing appropriate clinical services for the patients. Therefore, this study aimed to determine the prevalence of metabolic disease and its consequences in patients referred to Shahid Sadoughi Hospital in Yazd, Iran.

Materials and Methods

In this cross-sectional study, all patients with suspected hereditary metabolic diseases who were referred to Shahid Sadoughi Hospital in Yazd during a 5-year period (2013-2018) were included. After obtaining written informed consent from their parents, information such as the patient's age, sex, consanguineous marriage, first-degree family history of metabolic disease, and clinical signs was recorded. Appropriate biochemical tests were requested for the patients suspected of IEMs according to clinical examination. Laboratory investigations such as baseline biochemical investigations, plasma acylcarnitine profile, blood and urine amino acid levels, enzyme assay, and urine organic acid profiles were performed. Metabolic disorders were diagnosed based on clinical problem as well as laboratory and genetic findings. After diagnosis, information about the type of metabolic disease, the age of diagnosis, and the occurrence of complications were also recorded. Patients were followed up during the study period in terms of complications, disease course, and mortality.

Statistical analysis: The obtained data were assessed by SPSS software version 19. Chi-square test was run for the comparison of nonparametric variables. The level of statistical significance was set at $P < 0.05$.

Results

In this study, 39 children with diagnosis of metabolic disease were included. The patients were selected among those referred to Shahid Sadoughi Hospital in Yazd, Iran. The patients' mean age at diagnosis was 25.3 ± 5.1 months. Nearly half of them (17 cases) (43.6%) were from Yazd province. Median age was 4 years (ranging from 15 days to 6 years). Sixteen were male and twenty three were female. About two-thirds (64.1%) of the patients were born to consanguineous parents. Positive family history of metabolic disorders was found in 7 cases (17.9%). The most common inherited metabolic disorder was organic acid disorders with a frequency of 12 children (30.8%) followed by lysosomal storage disorders (20.5%), and amino acid disorders (20.5%). Methyl malonic acidemia was the most common organic academia with frequency of 6 children followed by 2 cases of Isovaleric aciduria (Table 1). The patients were divided into three categories of under 6 months, 6-12 months, and 1-6 years.

Table 1. Types of Inherited Metabolic Disorders

Type of disorder		Number
Amino acid metabolism	Urea cycle defect (UCD)	1
	Lysinic protein intolerance (LPI)	1
	Tyrosinemia type I	2
	Tyrosinemia type III	1
	Maple syrup urine disease (MSUD)	2
	Glutathione synthetase deficiency	1
Organic aciduria	Glutaric aciduria type 1	1
	Metylmalonic acidemia	6
	3-Hydroxy-3-methylglutaryl-CoA lyase deficiency	1
	Isovaleric academia (IVA)	2
	Biotinidase deficiency	1
	Ethylmalonic aciduria	1
Fatty acid oxidation disorder	Carnitine palmitoyltransferase- 1A deficiency	3
	Glutaric aciduria type II	1
Lysosomal storage disorders	Niemann-Pick diseases Type B	4
	Gaucher's disease Type1	2
	GM1 Gangliosidosis	1
	I-cell disease	1
Disorders of carbohydrate metabolism	Glycogen storage diseases 1a (GSD1a)	2
	Galactosemia	2
Bone disorders	Hyperphosphatasia	1
Other disorders	Gluconeogenesis defect (Fructose-1,6-bisphosphatase deficiency)	2

There were 21 cases in age class 1 (60%), 6 cases in age class 2 (17.1%), and 8 cases in age class 3 (22.9%). Most disorders were diagnosed at the age under 6 months (Table 2). After diagnosis, 11 (28.2%) patients were treated, 22 patients (56. 4 %) were diagnosed with complications, and 5 (12.8%) of them died due to complications.

Discussion

The available information regarding the incidence of metabolic disorders is mainly from studies conducted in developed countries. However, very few studies were conducted in Iran. In this country, due to high incidence of consanguineous marriages, some rare metabolic disorders are relatively common. In some areas, IEMs prevalence exceeds 50% of all marriages because of social, cultural, and religious background. In the current study, consanguinity was positive in 25 patients (64.1%), reflecting a high consanguinity rate. This finding was in line with those conducted in Egypt, Lebanon, and in Saudi Arabia.[7-9] In a study by Karam et al., in Lebanon on 294 patients with 27 different metabolism defects, it was found that 60% of patients were born from consanguineous parents.[8] Lowest rates were reported in China (1.6%)[10] and Iraq (9.9%).[11] In Shafeghati's study, eighty-two percent of participants were close relatives, mostly first cousins.[12]

Table 2. Age at Diagnosis for the Inherited Metabolic Disorders

IEMs	Age at diagnosis		
	< 6 months	6-12 months	> 12 months
Amino acid metabolism	4	1	3
Organic acid metabolism	7	3	2
Fatty acid metabolism	2	0	2
Lysosomal storage disorders	2	5	1
Disorders of carbohydrate metabolism	2	2	0
Bone disorders	0	0	1
Other disorders	0	1	1

There are several studies that highlighted the high incidence of inherited metabolic disorders in the Middle East and Northern Africa (MENA) from high consanguinity marriages (25-70%).[13]

In this study, most disorders (60%) were diagnosed by the age of 6 month. Similar results were seen in a study by AlObaidy.[14] This may be due to many factors, including the ease of diagnosis, the presence of diagnostic laboratories and specialist centers or specialist practitioners for investigation and treatment although death occurs before a diagnosis in some cases of IEMs.[15]

Organic acidemia (OA) was the most common type in our study, detected in 30.8% of diagnosed cases, followed by lysosomal storage disorders (20.5%), and amino acid disorders (20.5%).

In Sherazi et al.'s study[16], it was found that 88 patients had IEMs, and OA (46.5%) was the most common disorder. They found that the most common OA in the population was Methyl Malonic acidemia (MMA) and this was in accordance with our study. In a selective study in Iran, it was reported that organic acidemias were also the most common and affected 42% of the patients, followed by disorder of galactose metabolism (30%).[17] On the other hand, another study in Iran revealed that the incidence of organic academia was 42% and formed the first major type of IEMs.[18] Other studies also showed that OA was quite common in India.[19,20] Turkey[21] and North Carolina, as reported by Frazier et al.[22] In McKusick's study, organic acidurias were found to be the most common form (42%), followed by aminoacidopathies and lysosomal storage diseases (16.8% each).[12] This was in agreement with the findings of current study.

In contrast, a study done in Egypt by Khalaf et al.,[23] reported Amino acid disorder (AA) as the most common disorder. In addition, Selim et al.,[24] and Han et al.,[25] studied 3070 children suspected with IEMs in China and diagnosed 212 cases with IEMs, including 92 amino acidurias and 107 organic acidurias.

Golbahar et al., studied 1044 symptomatic children. They also showed high incidence of phenylketonuria, tyrosinaemias, and maple syrup urine disease in the south-west of Iran.[2] Alijanpour et al., reported 65 patients with 19 different types of IEMs during 10-year-follow up from 2005-2015. Phenylketonuria (PKU), methyl malonic acidemia, maple syrup urine disease, and galactosemia were the most prevalent inherited metabolic disorders, respectively.[3] This could be explained by the fact that PKU, the most frequent IEMs, was left undetected in our patient group.

According to Cheema et al.' study, the most frequent metabolic disorders were glycogen storage disorders, gaucher disease, and galactosemia as compared to other IEMs.[26]

Regarding OA disorders, MMA was the most common type in our study, detected in 5/12 of diagnosed cases. MMA is the most common organic acidemias in many studies regardless of the geographical/ethnic background of the studies population.[7,9,27-30]

A study conducted by Niu et al., in Taiwan during 2000-2009 revealed maple syrup urine disease (MSUD), MMA, and GA-1 as the commonest organic acidurias.[31] In our study, the second most common OAs were Isovaleric aciduria and 3-hydroxy-3-methylglutaryl-CoA lyase deficiency, which were found in 2 out of 12 cases.

In contrast with previous reports, there was only one patient with MSUD, a disorder which is reported to be the most common in Lebanon and Egypt.[8,32]

These discrepancies in incidence of IEMs across different countries may be due to differences in the characteristics of the studied population (race and the rate of consanguinity), screening criteria selection, diagnostic facilities, and sample size.

Conclusion

We found that IEMs disorders were not rare diseases in consanguineous marriages, which is a common tradition in our country. Organic acidemia was the commonest IEMs diagnosed.

The delay in diagnosis of IEMs leads to high morbidity and mortality, so early diagnosis and early treatment of the disease, before the onset of symptoms, can prevent or, at least, reduce the complications. So, most frequent disorders should be considered for screening.

Conflict of Interests

Authors have no conflict of interests.

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