Original Article

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Clinical Characteristics of Pediatric Patients with Inborn Errors of Metabolism Admitted to Namazi Hospital, a Tertiary Referral Center in Shiraz, Southern Iran

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Abstract
Background: Inborn errors of metabolism (IEMs) are rare genetic disorders that usually cause disease by blocking a metabolic pathway. Delayed diagnosis often occurs due to nonspecific symptoms. This study assesses the demographic and clinical characteristics of pediatric patients with IEMs admitted to Namazi hospital, a referral center in southern Iran.
Methods: All 1-month-old to 18-year-old patients who were admitted to the pediatric ward at Namazi hospital, a referral center in southern Iran, and diagnosed with IEMs were enrolled. Patients with incomplete information were excluded. Comprehensive demographic and clinical data, including age, sex, parental consanguinity, family history of IEM, presenting symptoms, number of hospitalizations, age of onset, and diagnosis of the disease, were collected. All the data were entered into SPSS version 22 and analyzed.
Results: Two hundred patients, 53.5% male and 46.5% female, were enrolled in the study. The predominant clinical symptoms observed were lethargy and vomiting. The most prevalent IEMs were aminoacidopathies, organic acidemia, and mitochondrial disease. Consanguinity was found in 57.5% of patients, while a family history of metabolic diseases was observed in 16.5%. A statistically significant association was identified between consanguinity and the type of disease.
Conclusion: The clinical symptoms of IEMs are nonspecific and may be misdiagnosed as other diseases, such as septicemia. We should always keep IEMs in mind to detect the disease earlier and prevent significant morbidities and mortality through appropriate and timely treatment. Due to the prevalence of family marriages in Iran, we should also consider metabolic screening.
Keywords: Inborn errors of metabolism, Children, Pediatric, Metabolic disease

Introduction

Inborn errors of metabolism (IEMs) are genetic disorders known since 1902, causing diseases through the accumulation of toxic substrates, deficiency of certain products, or diversion to alternative pathways (1). The estimated incidence is 1:2500 individuals (2). These disorders can manifest with a variety of symptoms, including neurologic manifestations (seizure, developmental delay, and hypotonia), hepatic involvement (cholestatic jaundice, liver failure, and hepatomegaly with hypoglycemia), cardiac complications (cardiomyopathy), facial features, hydrops fetalis, and characteristic urine odor (3). Delayed diagnosis and treatment of IEMs lead to irreparable consequences and even death (4). Consanguinity is often associated with these autosomal

recessive genetic disorders (5), and given the high rate of consanguineous marriages in Iran, the country has a higher prevalence of metabolic diseases (6,7). There is no exact assessment of the IEM incidence rate in Iran, and further studies are required to address this issue and develop strategies for early detection and prevention. Tandem mass spectrometry is a reliable method for newborn screening of metabolic disease soon after birth (4), and prenatal screening is another method (7).

In this cross-sectional descriptive study, we aim to evaluate the demographic characteristics and clinical presentations of patients diagnosed with metabolic diseases admitted to the pediatric ward at Namazi hospital between 2017 and 2021. By recognizing the clinical manifestation and looking for metabolic diseases at an

early stage, we can improve these patients' prognosis and quality of life.

Materials and Methods

This descriptive cross-sectional study was conducted from 2017 to 2021 on patients with metabolic diseases admitted to Namazi hospital, a referral endocrine center in southwest Iran. All pediatric patients, aged one month to 18 years, who were admitted to the hospital with the diagnosis of metabolic diseases were enrolled in the study. Some patients had previously known they had metabolic diseases, while others were diagnosed based on the current clinical and laboratory data. Diagnostic methods for metabolic diseases encompass various techniques, including tandem mass spectrometry (MS/MS) analysis of serum amino acid profiles, urine organic acid testing, serum acylcarnitine profile, genetic testing, especially for mitochondrial disorders, and enzyme assays for metabolic diseases such as mucopolysaccharidosis (MPS). Patients with incomplete clinical records were excluded from the study. Demographic information, including age, sex, parents' consanguinity, marriage, and family history, was obtained. Clinical and laboratory data such as signs and symptoms, laboratory data, hospital course, drugs, age on onset, diagnosis, and admission were recorded and entered into SPSS software version 22. We used frequency, percentage, and median for descriptive data. Group comparisons were performed using the chi-square, Fischer's exact, Man-Whitney, Kruskal-Wallis, and one-way ANOVA tests. A P value less than 0.05 was considered statistically significant.

Results

This study enrolled 200 patients with metabolic diseases from one month to 18 years old. Patients were divided into eight groups based on the type of metabolic disease. Tyrosinemia and maple syrup urine disease were the most frequent aminoacidopathies (51.8% and 16.1%, respectively). Among patients with glycogen storage disease (GSD), 55.5% had GSD type 1, and 11.8% had Pompe disease. Organic acidemia included methylmalonic acidemia (MMA) (29.1%), propionic acidemia (16.4%), and glutaric acidemia (10.9%). Half the patients with fatty acid oxidation disorder had short-chain acyl-CoA dehydrogenase (SCAD), and 25% had medium-chain acyl-coenzyme A dehydrogenase (MCAD). According to clinical and laboratory studies, 25 (12.5%) patients were admitted with metabolic diseases, but a specific diagnosis was not obtained as a definite diagnosis is time-consuming and requires the patient's follow-up. Demographic and clinical characteristics based on the type of diseases are shown in Table 1. The lowest median

Table 1. Demographic and clinical characteristics of patients admitted with IEM

Type of the disease	Number (%) Male (%) Female (%)	Consanguinity Number (%)	Family history Number (%)	The median age on admission (month)	The median age of diagnosis (month)	The median age of onset of the disease (month)	The median number of hospitalizations
Aminoacidopathy	56 (28%) 29 (51.7%) 27 (48.2%)	32 (57.1%)	7 (12.5%)	8	6.5	6	1
Organic acidemia	55 (27.5%) 34 (61.8%) 21 (38.1%)	34 (61.8%)	12 (21.8%)	26	20	18	2
Mitochondrial disorder	26 (13%) 17 (65.3%) 9 (34.6%)	14 (53.8%)	8 (30.7%)	9	6.5	6	2
Glycogen storage disease	18 (9%) 7 (38.8%) 11 (61.1%)	14 (77.7%)	1 (5.5%)	20	11	10.5	2.5
Galactosemia	14 (7%) 6 (42.8%) 8 (57.1%)	2 (14.3%)	1 (50%)	5.5	4	4	2
Fatty acid oxidation disorder	4 (2%) 2 (50%) 2 (50%)	4 (100%)	1 (25%)	50	20	19	1
Mucopolysaccharidosis	2 (1%) 2 (100%) 0 (0%)	0	1 (50%)	52	45	45	1
Unspecified	25 (12.5%) 10 (40%) 15 (60%)	15 (60%)	2 (8%)	15		8	2
Total	200 (100%) 107 (53.5%) 93 (46.5%)	115 (57.5%)	33 (16.5%)	14.5	8	8	

age of onset belonged to galactosemia, while the highest was associated with mucopolysaccharidosis. Patients with GSD had the highest number of hospitalizations. Consanguinity was seen in 115 (57.5%) patients, and 33 (16.5%) had a history of metabolic diseases in their family. There was a statistically significant relationship between family marriage and type of metabolic disease (P value = 0.007).

There was a statistically significant relationship between the onset age of symptoms and the age of diagnosis ($P = 0.001$). Among the patients, 94 (47%) had just one hospital admission, and the others had two or more. Patients with GSD and mitochondrial diseases had more hospital admissions. There was a significant relationship between the number of hospitalizations and the type of disease ($P = 0.006$). The difference between males and females was not statistically significant in this study.

The most common clinical sign was weakness and lethargy (38%). Other common central nervous system manifestations were decreased level of consciousness, seizure, and delayed development (11%, 11%, and 10.5%, respectively). Nausea and vomiting were the most common gastrointestinal presentations (31%). Other symptoms are shown in Table 2. Fever, a significant cause of hospitalization, was found in 39 (19.5%).

Metabolic acidosis was found in 63 (31.5%) of participants.

Discussion

The diverse spectrum of IEMs, nonspecific clinical manifestations, complexity, difficulty, and time-consuming nature of diagnosis, and lack of integrated approach concerning IEMs usually lead to delayed diagnosis and inappropriate treatment. Consequently, there are significant implications on the morbidity, mortality, and overall well-being of affected individuals and their families, as well as the health care system. By gathering comprehensive information about these patients, implementing screening programs, facilitating early diagnosis, providing timely treatment, and offering continuous support to patients and their families, we can mitigate the long-term, irreversible complications associated with IEMs. In this study, we collected the data of pediatric patients with metabolic disorders to contribute to these efforts.

IEM often presents with nonspecific symptoms like vomiting, lethargy, hypotonia, poor feeding, seizure, coma, ataxia, and even organ failure (8). There is also an association between IEM and autism spectrum disorders (9). The main clinical symptoms observed in this study were lethargy and vomiting. Neurologic symptoms such as decreased level of consciousness, seizure, and developmental delay are frequently observed in patients with IEMs (10). It is crucial to consider the possibility of IEMs in patients presenting with neurological symptoms

Table 2. Clinical manifestation of patients admitted with inborn error of metabolism

Clinical signs and symptoms	Number (%)
Central nervous system	
Weakness and lethargy	76 (38%)
Decreased level of consciousness	22 (11%)
Seizure	22 (11%)
Delayed development	21(10.5%)
Hypotonia	12 (6%)
Irritability	8 (4%)
Microcephaly	2 (1%)
Ataxia	2 (1%)
Vertigo	1 (0.5%)
Gastrointestinal	
Nausea and vomiting	62 (31%)
Hepatomegaly	30 (15%)
Diarrhea	16 (8%)
Splenomegaly	16 (8%)
Abdominal distension or ascites	12 (6%)
Jaundice	8 (4%)
Biliary stenosis	4 (2%)
Cirrhosis	4 (2%)
Constipation	3 (1.5%)
Respiratory	
Tachypnea	13 (6.5%)
Upper respiratory symptoms	13 (6.5%)
Respiratory distress	8 (4%)
Cardiac	
Cardiomyopathy	2 (1%)
Cyanosis	2 (1%)
Cardiorespiratory arrest	1 (0.5%)
Others	
Fever	39 (19.5%)
Skin lesions	5 (2.5%)
Skeletal disorders	2 (1%)
Clitoromegaly	1 (0.5%)
Lymphadenopathy	1 (0.5%)

without a definite cause.

In our referral center, aminoacidopathies and organic acidemia were the more prevalent IEMs. However, a study conducted in northeastern Iran reported a higher frequency of MMA and propionic acidemia (6). Another survey conducted in Tehran also showed a higher incidence of propionic acidemia and methylmalonic academia (11). Hadj-Taieb et al demonstrated a high prevalence of aminoacidopathies (57.3%) and organic academia (42.7%) in Tunisia (12). In Spain, the highest incidence was observed for hyperphenylalaninemia and MCAD (13).

Consanguinity marriage, observed in 57.5% of parents in our study, has been identified as a contributing factor to the occurrence of IEMs. In Iran, the overall rate of family marriage is estimated to be 38.6% (14). A significant association was seen between consanguinity and the type of metabolic disease. The incidence of IEM was higher among children born to parents with family marriage (5). In our study, all patients with fatty acid oxidation defects and 77.7% of patients with GSD were born in consanguineous marriages. The rates for other types of IEM are presented in Table 1. In a survey conducted in Oman, the rate of consanguinity among parents of pediatric patients with IEMs was 95%, including all patients with fatty acid oxidation defects and 96% of patients with GSD (15). In Bahrain, the rate of family marriage was estimated to be 11.4% (16). Another study in Bahrain reported consanguinity marriage in 84% of patients with IEMs (17).

In addition, a family history of previous affected children was observed in some patients with IEMs. In our study, the prevalence of family history of IEMs was 16.5%. However, higher rates were reported in a study in Libya (63.5%) and Saudi Arabia (57.2%) (18,19). It is important to note that screening older siblings of affected patients is crucial as they may be at risk of developing the same disease (20).

Patients with IEMs often require repeated hospital admissions. Among the patients in our center, 53% had more than one hospital admission, and those diagnosed with GSD had the highest rate of hospitalization. The other patients who had one hospital admission may require admission in the following years through follow-ups. Frequent hospitalization of these patients has significant economic implications for the healthcare system and society. Khneisser et al estimated at least one hospital admission in the first five years for early-detected IEM and at least three times for late-detected patients. They concluded that screening programs are economically beneficial despite IEM being a rare disease (21).

Limitations
The diagnosis of IEMs usually needs more time, and specific laboratory data preparation can be time-consuming. The follow-up of patients is essential for specific diagnosis in the unspecified diagnosis groups in our study. The participants in this study consisted of patients admitted to hospitals. Many IEM patients, such as those with Phenylketonuria (PKU), are diagnosed in early screening in Iran and usually do not need hospital admission. This study had no outpatient data.

Conclusion
Given the nonspecific clinical manifestations of IEMs and the wide range of diseases that may be considered in the differential diagnosis, it is essential to always consider the possibility of IEMs. Screening programs and early detection play a crucial role in ensuring timely and appropriate treatment, which can help prevent irreversible complications and long-term sequelae associated with these conditions. By maintaining a high index of suspicion for IEM and implementing effective screening strategies, we can improve outcomes and minimize the potential long-term impacts on patients' health.

Authors' Contribution
Conceptualization: Homa Ilkhanipoor, Naser Honar, Hossein Moravej, Ali Nazemosadat, Hamide Barzegar.
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Writing–review & editing: Homa Ilkhanipoor, Naser Honar, Hossein Moravej, Hamide Barzegar.

Competing Interests
The authors declare no conflict of interest.

Ethical Approval
The Medical Ethics Committee of Shiraz University of Medical Sciences approved the study protocol (ethics code: IR.SUMS.MED. REC.1400.023).

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