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Inborn Errors of Metabolism in Iran: First Report from Iran Metabolic Registry

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Abstract

Background: Inborn errors of metabolism (IEMs) comprise over 1,000 disorders. Wide geographical and racial variations in the global birth prevalence and their inheritance patterns have been reported by epidemiological studies.
Methods: Iran's Metabolic Registry was launched in March 2017. All patients diagnosed with IEM registered in the Iran Metabolic Registry from 2017 to July 2022 were included in this study.
Results: During the five years, 1,233 patients were recorded in the database. Due to missing data, 320 patients were excluded from the study. Of the 913 registered patients, 402 were female, and 511 were male. The median age of registered patients was 10.3 years (one week to 48.3 years). The most prevalent group of IEMs was amino acid disorders, with 596 (66.6%) patients. The mortality rate of the patients was 36.5%.
Conclusions: This study represents the first report from the IEM registry. A comprehensive registry of IEMs for collecting patient data will help clinicians with more accurate diagnoses of the disorders, monitoring, and follow-up. Furthermore, by estimating the burden of IEMs, the healthcare system and government could accurately assess the medication and equipment needed.

Keywords: Inborn Errors Metabolism, Inborn Errors, Errors Metabolism, Registry, Iran

1. Background

Inborn errors of metabolism (IEMs) consist of a considerable group of genetic or inherited disorders due to defects in enzyme activity, proteins, or transporter molecules involved in the metabolic pathway (1). They comprise many disorders, with over 1,000, including over 600 identified in recent years (2, 3). The symptoms mostly occur during the neonatal period or infancy but can also occur in adulthood (1). Clinical decompensation is heterogeneous and can be presented in a wide range, from non-specific conditions such as vomiting, diarrhea, or dehydration to neurological and cardiac manifestations during the newborn period, like a seizure or cardiomyopathy (2, 4).

As known, IEMs occur at varying rates worldwide. The birth prevalence of all IEMs is estimated to be 50.9 in 100,000 live births globally (4). While some IEMs, such as phenylketonuria (PKU), have been included in newborn screening tests using well-established diagnostic methods, rarer disorders often require a high level of clinical assessment with relatively novel diagnostic procedures (5). Most disorders are treatable if detected early; however, without early diagnosis, they can cause fatality or serious complications such as developmental retardation (6). Information on the incidence/prevalence

of the disorders is critical for developing a national policy for the management and care of patients. However, the exact incidence and prevalence of IEMs in Iran are unclear due to the lack of a unified national registry. On the other hand, newborn screening in Iran is limited to certain regions and has been launched in recent years.

To recognize the frequency and pattern of the different IEMs, improve the knowledge of the healthcare system, and enhance the research area about inherited metabolic disorders, Iran's Metabolic Registry was launched in March 2017 as an initiative of the Growth and Development Research Center of Tehran University of Medical Sciences, which is part of Iran's Ministry of Health and Medical Education. This study is the first dataset report to be published. Despite the significant prevalence of IEMs in nations with a substantial number of consanguineous marriages, such as Iran (7) and Arab countries (8), limited research has examined the incidence, type, and distribution of inherited metabolic disorders in Iran. This report presents the demographic information and trend of IEMs in registered cases.

2. Objectives

We aimed to improve the national registry and facilitate an exchange between medical specialists and medical centers involved in diagnosing and treating inherited metabolic disorders. Also, the report can provide an overview of IEMs in Iran.

3. Methods

3.1. Registry Database

The Iran Metabolic Registry was launched with the assistance of the Ministry of Health and Medical Education in the Growth and Development Research Center of Tehran University of Medical Sciences in 2017. The computerized database software system was designed according to the asp.net/mvc/angular language service. The Owin method was used for the system's security, and Stimulsoft was utilized for reporting datasets. The SQL server set up a backup of the database information. To attain countrywide coverage and the largest feasible number of patients, all medical universities or pediatrics departments were invited to register newly diagnosed IEMs. Some centers responded, and this report was conducted in collaboration with 30 medical universities in Iran, which were involved in treating and registering patients with IEMs. This project has been approved with the ethical code IR.TUMS.VCR.REC.1397.359 in Tehran University of Medical Sciences.

3.2. Data Collection

All patients with diagnosed IEMs registered in the Iran Metabolic Registry from 2017 to July 2022 were included in the study. Patients were diagnosed according to neonatal screening or expert requests in symptomatic patients. Since the Growth and Development Research Center is a referral center for inherited metabolic disorders, most high-risk patients are referred to the center. Furthermore, the center started newborn screening as part of a national pilot program in 2017. SSIEM-ICD11 classification was used for the disorder's categorization. Patients' information was divided into six: Patient characteristics (demographic data, birth certificate, phone number), family history (consanguinity, history of IEMs, or related death), clinical presentations, laboratory and pre-clinical tests, diagnosis, and treatment. The patients with missing information were excluded.

3.3. Statistical Analysis

Microsoft Excel was used for basic descriptive statistical analysis.

4. Results

4.1. Frequency and Distribution of Inborn Errors of Metabolism

During the five years, 102,449 newborns were screened in the metabolic laboratory of the Growth and Development Research Center. Based on the screening results, the symptoms of clinically suspected children, and genetic tests, 26 patients were diagnosed. In other ways, about 3,000 high-risk patients were referred to the center. Finally, 1,233 patients were recorded in the registry. Records with missing information or inconclusive diagnosis (320 patients) were excluded from the study. Of the 913 registered patients, 402 were female, and 511 were male. Also, 584 (64%) patients were alive, and 329 (36%) were recorded as dead patients. The median age of registered patients was 10.3 years (one week to 48.3 years). Forty-four percent (405 patients) were born to consanguineous parents, and 30% (270) were first-cousin relations. The most common racial/ethnic group in the dataset was Azari (32%), Kurdish (27%), and Fars (25%).

In the database, 57 disorders were recorded based on the SSIEM-ICD11 classification. The amino acid and peptide metabolism disorders were the most common,

with 596 (66.6%) cases. Among them, PKU (n = 323, 36.4% of registered disorders), tyrosinemia (n = 127, 14.2%), and organic acidemia (n = 111, 12.2%) were the most frequent disorders. The most common clinical manifestations of the patients were seizures, lethargy, vomiting, and hypotonia. Other manifestations were poor feeding and feeding intolerance, cyanosis, growth impairment, and fever.

Disorders of carbohydrate metabolism (n = 201, 22.4%) and lysosomal disorders (n = 70, 7.8%) were reported as other prevalent diseases. The common recorded clinical manifestations were hepatomegaly, abdominal distension, jaundice, diarrhea, fever, hypoglycemia, weight loss, delayed growth, respiratory problems, decreased consciousness level, pneumonia, and lethargy. Four patients were registered with vitamins, cofactors, and metals disorders. The average age of patients was 7.2 years at IEM diagnosis. Different disorders recorded in this database are summarized in Table 1.

Table 1. Number of the Most Frequent Inborn Errors of Metabolism Registered in Iran's Metabolic Registry

Disorders Category	Number of Registered Disorders
Disorders of phenylalanine and tetrahydrobiopterin metabolism	323
Glycogen storage disease	138
Tyrosinemia	127
Organic acidemias	92
Galactosaemia	54
Gaucher disease	37
Methylmalonic acidemia	34
Maple syrup urine disease	20
Mucopolysaccharidoses	19
Propionic acidemia	10
Vitamins, cofactors, and metals	4

5. Discussion

The study represents the first report from the IEM registry in Iran. In Iran's Metabolic Registry, 894 inpatients and outpatients were registered from 2017 to July 2022. Due to the limited number of medical universities involved in the registration system and the lack of comprehensive newborn screening in regions of Iran, the number of patients most likely does not reflect the prevalence and burden of IEMs in Iran. However, due to a shortage of exact information about the prevalence of metabolic disorders in our country, the registry can provide an overview of the IEMs frequency in Iran.

In an attempt to detect IEMs in the population, newborn screening or selective screening studies were conducted in countries and regions worldwide. The incidence rate of IEMs is reported differently among countries. In a study from Saudi Arabia, the prevalence of IEMs was reported at 1:591 (3). According to the Austrian IEMs Registry, a rate of 1.8/10000 births was estimated from 1921 to 2021 (9). The prevalence rate in the United States and Northern Europe was around 1:4000 (10, 11). Newborn screening for IEMs was launched in Iran in 2017, and it is implemented in some regions of Iran using the electrospray ionization-tandem mass spectrometry (ESI-MS/MS) technique. As that previous studies have shown a high prevalence of IEMs in the Middle East (12), we assume that the lack of comprehensive screening in Iran may be a reason for the low rate of diagnosed or registered patients in our database. Moreover, limited access to diagnostic techniques in some pediatric medical centers and insufficient information on the importance of patient registration could be another reason. Also, the median age at diagnosis in the study was older than in comparable registries published in recent years. The age range at diagnosis indicates that many patients with IMDs were not diagnosed in the first months or years of life. Delayed detection and treatment increase mortality rate, disability, weak prognosis, and even the birth of a newborn with IMDs to undiagnosed families. Hence, concerning the importance of early patient detection, a national policy for newborn comprehensive screening and registration is fundamental in managing patients.

Our database showed that aminoacidopathies and organic acid disorders accounted for 66.6% of patients. A five-year report from Egyptian children showed that amino acid disorders are relatively common in Egypt (12), and organic acid disorders are frequent in Arab countries and the Middle East (13, 14). Therefore, the disorder rate in our databases is probably similar to other neighboring countries. Also, the study showed that PKU, as an amino acid disorder category, was the most frequent disorder. The result was similar to previous studies reporting PKU as a predominant IEM in the different regions of Iran (15, 16). The global prevalence of PKU was reported at 6.002/100,000 neonates, with the highest prevalence in Turkey at 38.13 and Iran at 21.28/100,000 (17). Other reports have shown that PKU covers over 50% of IEMs in some European countries (18, 19). There have seen developments in the identification of disease

symptoms, and the advancement of diagnostic procedures has considerably contributed to estimating the high prevalence of PKU in our population.

On the other hand, unlike other studies (20, 21), in our database, a few patients were recorded with propionic acidemia (PA) and methylmalonic acidemia (MMA). Unfortunately, despite an extensive search, no information was found about Iran's PA or MMA detection rates. Previous studies reported that the detection rate of the disorders according to screening programs was between 0.09 and 5.05 per 100,000 newborns in the Asia-Pacific region majority of Saudi Arabia (21).

The mortality rate of the patients in our study was high (39%), similar to other literature (9). Recently a review study reported that the global birth prevalence of all-cause IEMs is 50.9 per 100,000 live births. The mortality rate in middle- and low-income countries is over 33% (4). Diverseness in clinical symptoms, overlapping with other diseases with a similar presentation, and shortage of essential lab equipment and special diagnostic techniques may cause undetectable or misdiagnosed patients with IEMs. Finally, due to mentioned limitations, the mortality rate may be underestimated in our study.

The high consanguinity rate is associated with an increased risk of inherited disorders (22). Consanguineous marriage is common in Asia, Africa, and the Middle East (23, 24). In Iran, a high consanguinity rate (30% - 39%) plays an important role in increasing the prevalence of IEMs with an inbreeding coefficient factor of 0.024 (24, 25). The consanguinity rate is high in some regions of Iran, resulting in inheriting a large portion of the genome from a recent common ancestor (22). Bener 2012 stated that the lack of a comprehensive IEM registry makes it difficult to determine the effect of consanguinity on health at the community level (26). In the present study, 44% of offspring were born in consanguineous marriages, and 72% of the consanguineous parents were first cousins with cross-cousins favored. In line with our results, Keyfi et al. 2018 indicated that 63.24% of children with IEMs were offspring of consanguineous parents, and 76% of consanguineous marriages were between first cousins (27). The Movafagh et al. study showed that 38.57% of children with IEMs were born from consanguineous marriages (15). With attention to the strong preference for consanguineous marriage in some regions of Iran, counseling before marriage or prenatal diagnosis is suitable for reducing IEM prevalence in consanguineous couples.

There are several limitations to this report. Some cases did not undergo genetic tests and were detected based on clinical manifestations and laboratory results. Due to the high cost and unavailability of genetic testing, not all patients can perform it. This might be considered a major limitation affecting the diagnosis of different variations of IEMs in Iran. As data collection was retrospective, there was a high proportion of missing data (about 26%) in our report. Also, some patients' diagnostic data were still incomplete. On the other hand, previous study has reported a high rate of missing data. (9). As not all patients with IMDs were included in the registry, the estimation of the incidence rate or prevalence of IMDs in Iran was not possible in the study.

To our knowledge, this is the first study that reports from Iran's Metabolic Registry. The lack of an organized database for patients with IEMs causes many problems for the healthcare system. The healthcare system and the government could accurately assess the medicine and equipment needed and properly manage the facilities via a registry of patients in the registration system. A comprehensive registry of IEMs is effective in ascertaining the special clinical manifestation of each disorder among the Iranian population. It will guide clinicians to better diagnose and follow patients, resulting in early diagnosis and treatment and decreasing the complications imposed by delayed diagnosis on the health system and families. Furthermore, it could be possible to design sufficient interventions to lessen the incidence of these disorders, for example, carrier testing, prenatal testing, prenatal diagnostic testing, or designing a newborn screening program to diagnose these disorders before getting symptomatic.

5.1. Conclusions

The Iranian Registry of IMDs as a national database could be an epidemiological value by reporting the prevalence/ incidence and national distribution of IMDs and an important tool for assessing and caring for patients. The study results could incentivize Iranian medical specialists and the healthcare system to pay more attention to these patients' screening, diagnosis, and registry.

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Footnotes

Authors' Contribution: M.KH and F.A. participated in the study concept and design and manuscript drafting. S.A. revised the manuscript. R.M. and A.R. participated in the designing and acquisition of data. M.D. and A.T. were involved in the analysis and interpretation of data. A.M. and M.KH critically revised the manuscript for important intellectual content. Collaborating authors participated in the diagnosis and registration of patients. All authors read and approved the final manuscript. A.R. was as study supervisor.

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