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Investigation of the Frequency of Congenital Metabolic Disorders in Children Referred to Bu-Ali Hospital in Ardabil During the Years 2016 to 2023

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A B S T R A C T

Introduction: Hereditary metabolic diseases are rare disorders individually, but in countries where family marriages are more common, such as Iran, they have a high prevalence, and in Ardabil Province, due to the fact that family and tribal marriages are more common, the prevalence of these disorders is higher. Since early diagnosis and follow-up treatment of these diseases are important to prevent irreparable damage, and on the other hand, these diseases involve different organs and have different clinical features. If the symptoms are detected, the complications, death, and disability of the disease will be prevented. Therefore, this study was decided to investigate the prevalence of congenital metabolic diseases in Ardabil province during the years 2016 to 2023.

Materials & Methods: In this cross-sectional descriptive study, a total of 195 children (114 boys and 81 girls) aged 1-15 years at Bu-Ali Hospital of Ardabil city were registered with congenital metabolic diseases based on specific biochemical, genetic, and clinical criteria different from those for metabolic syndrome. The data were collected in a checklist and analyzed in SPSS V.21 using descriptive statistical methods in the form of tables, graphs, frequencies, and percentages.

Results: The overall prevalence of congenital metabolic disorders among the studied children was 3.3 per thousand people. The most common types of congenital metabolic disorders in the studied children were phenylketonuria with 62 cases (31.8%) and urea cycle disorders with 26 cases (13.3%).

Conclusion: In this study, more than 20 different types of hereditary metabolic disorders were identified among children, and more than 81% of the children's parents were related.

Keywords: congenital disorders, children, phenylketonuria

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Introduction

Hereditary metabolic diseases are generally rare globally but have a relatively high prevalence in countries such as Iran. Early diagnosis and management of these disorders is critical to prevent irreversible damage and complications later in life. Metabolic diseases affect a number of organs, so early detection before clinical symptoms appear will greatly reduce the risk of serious side effects, disability and death. Additionally, once a metabolic disorder is identified in a family, prenatal diagnosis during pregnancy can be used to prevent the birth of an affected child, providing options for informed reproductive decisions and improved long-term outcomes (1).

Inborn errors of metabolism (IEMs) are a heterogeneous group of rare genetic disorders resulting from defects in specific enzymes or transport proteins that disrupt normal metabolic pathways, resulting in accumulation of toxic metabolites or deficiency of essential compounds (2). Although rare individually, IEMs are found in about 1 in 2,500 live births worldwide and are a major cause of neonatal and childhood morbidity and mortality (3, 4). Clinical presentation is often nonspecific in neonates, but may include metabolic acidosis, neurological deterioration, and developmental delay, emphasising the need for high clinical suspicion (5). Advances in newborn screening using tandem mass spectrometry and genetic testing have revolutionised early diagnosis, allowing presymptomatic treatment with a substantial improvement in outcomes (6, 7). However, the epidemiology and spectrum of IEMs varies according to the regional genetic background, e.g. high rates of consanguinity in Middle Eastern and some Asian populations, and requires population-specific screening panels and therapeutic strategies. Further advances in biochemical and molecular diagnostics, together with multidisciplinary care, are crucial to reduce the disease burden and to maximise quality of life for affected individuals worldwide (8, 9).

Children with congenital metabolic disorders often endure many years of severe complications, including profound intellectual and motor developmental delays. For example, before the advent of newborn screening for phenylketonuria (PKU), individuals suffered devastating consequences that had a very negative impact on their quality of life and imposed a significant burden on their families. But, when identified early through newborn screening programs and placed immediately on a diet low in phenylalanine, children with PKU can grow up to lead healthy, essentially normal lives. Thus, early diagnosis of treatable metabolic diseases can prevent irreversible damage, disability and premature death and improve greatly patient outcome through early intervention and appropriate management (3, 4).

The purpose of the present study was to determine the frequency of congenital metabolic disorders in children referred to Boali Hospital of Ardabil city during the years 2016 to 2023.

Materials and methods

Study Design

This retrospective descriptive cross-sectional study was conducted to investigate the frequency and spectrum of congenital metabolic disorders among children referred to Bu-Ali Hospital during the period from 2016 to 2023.

Setting and Participants

The study population consisted of children younger than 15 years who were diagnosed with congenital metabolic disorders and referred to the pediatric clinic of Bu-Ali Hospital for follow-up and continuation of treatment. Diagnosis of congenital metabolic disorders was established based on clinical manifestations, biochemical investigations, and genetic findings documented in the patients' medical records.

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Children with incomplete medical records or uncertain diagnoses were excluded from the study. Finally, 195 children aged 1–15 years were included in the analysis. Among them, 114 were boys and 81 were girls.

Sample Size

The sample size was estimated using Cochran's formula considering a confidence level of 95%, study power of 80%, expected prevalence (p) of 0.30, and precision (e) of 0.09. Based on the calculation, the required sample size was estimated to be approximately 195 participants.

Measurements & Validity and Reliability

Demographic and Clinical Characteristics Checklist

Data were extracted from patients' medical records using a researcher-developed checklist. The checklist included variables such as age, sex, family history of congenital metabolic disorders, parental consanguinity, developmental status, disease outcome (survival or death), history of abortion in the mother, death of previous children, and type of metabolic disorder.

Diagnostic Evaluation of Congenital Metabolic Disorders

Diagnosis of congenital metabolic disorders was established according to documented clinical manifestations, biochemical laboratory findings, and genetic assessments recorded in the patients' files. Disorders were classified into different categories, including phenylketonuria (PKU), urea cycle disorders, organic acidemias, aminoacidopathies, and other inherited metabolic disorders.

Phenylketonuria was identified as the most common disorder among the studied patients. The diagnostic process was based on standard pediatric metabolic evaluation protocols routinely used in tertiary referral centers. Previous studies have confirmed the validity and reliability of biochemical and genetic diagnostic methods for identifying inherited metabolic disorders, particularly when combined with clinical assessment (2).

Statistical and Data Analysis

The information related to the type of disorder, the outcome of these patients, and other required information was collected by a checklist from the children's medical records, and the data were analyzed using statistical methods in SPSS V.21 in the form of tables, graphs, numbers, and percentages.

Results

A number of 195 children with congenital metabolic disorders between 1 and 15 years of age were examined; of these, 81 (41.5%) were girls and 114 (58.5%) were boys. The average age of the children was 5.1 years with a standard deviation of 3.9 years. There was a family history of the disease in 50 (25.6%) children. In 159 people (81.5%) of the parents, there was a relationship. Development 101: People (51.8%) of normal children and 94 people (48.2%) had developmental delay. 69 people (35.4%) of the children died, and 64.6% of the rest survived. The death of an elder child existed in 16 (8.2%) mothers. There was a history of previous abortion in 50 (25.6%) mothers. The most common types of congenital metabolic disorders in the studied children were phenylketonuria (PKU) with 62 cases (31.8%) and urea cycle with 26 cases (13.3%), respectively (Figure 1). The frequency of PKU in boys with 40 cases was more than girls with 22 cases (Figure 2).

Of all 60,237 hospitalized children during the study years, only symptomatic children were investigated, and of them, 195 people (0.32%) had congenital metabolic disorders, which is about 3.2 per 1000. In terms of the type of disorder, there was a significant difference between the outcome of the disease, the death of an elder child, and the type of development and kinship relationship, but there was no significant

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difference in terms of gender and the history of the disease in the family.

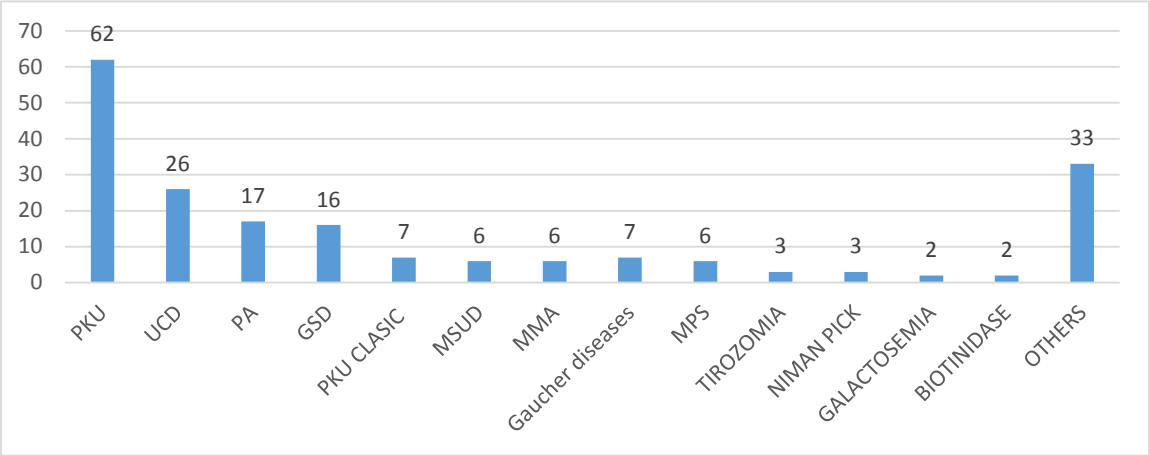
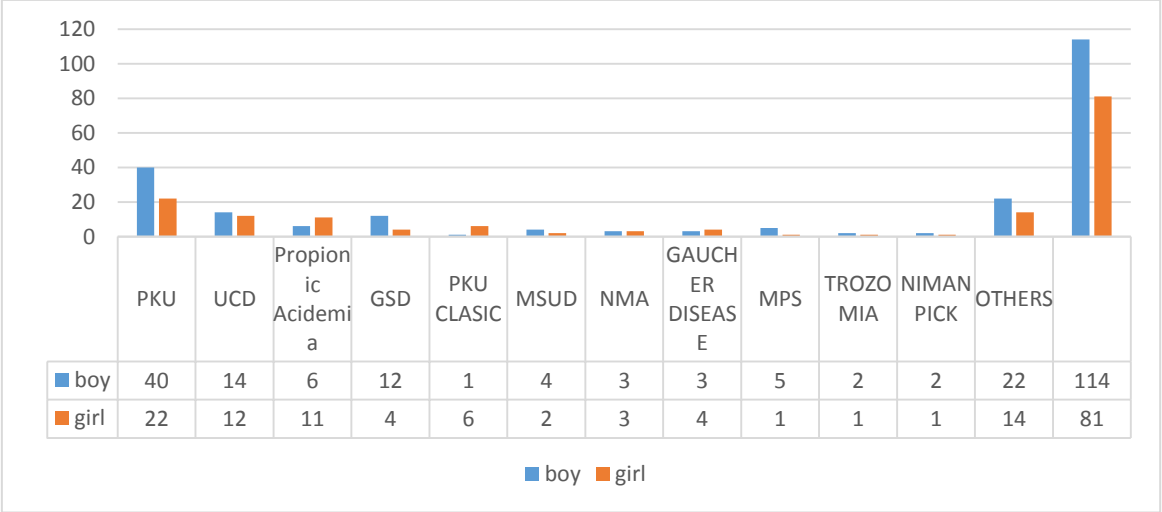


Figure 1. Frequency distribution of types of disorders in the studied samples.



	PKU	UCD	Propionic Acidemia	GSD	PKU CLASIC	MSUD	NMA	GAUCHER DISEASE	MPS	TROZOMIA	NIMAN PICK	OTHERS	
boy	40	14	6	12	1	4	3	3	5	2	2	22	114
girl	22	12	11	4	6	2	3	4	1	1	1	14	81

Figure 2. Frequency distribution of congenital metabolic disorders according to the gender of the studied children.

Discussion

The study found that over a third of the children studied had either died or suffered an irreversible side effect from the disease. The most common hereditary metabolic disorders in this region were phenylketonuria, urea cycle, and propionic acidemia (PA) diseases. In the country, newborn screening has been applied to favism, congenital hypothyroidism, and phenylketonuria. Unfortunately, this program does not cover other more common disorders. In one study, methylmalonic acidemia was found to be one of the common metabolic diseases in China (5).

This research demonstrates marked variation between populations and ethnic groups in the prevalence, natural history, genetic factors, and other characteristics of hereditary metabolic diseases and emphasizes the need for the collection of population-specific data to better understand and manage these diseases. In the present study, 58.5% of suffering children were boys, but there was no statistically significant difference between the two sexes. In this study, 25.6% of the samples had a positive family history of congenital metabolic disorders. In this study we do not screen all the children for IEM to estimate the congenital metabolic (CM) diseases, also due to the single-

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center design, potential referral bias, and methodological issues. So, we cannot estimate the prevalence rate of CM in this study, and this is a limitation.

When we compare the results of our study of inborn errors of metabolism (IEMs) in Ardabil children with the results of the comprehensive review article by Saudubray et al., we find both similarities and unique regional insights. The study shows a high burden of IEMs such as phenylketonuria, urea cycle defects, and propionic acidemia in Iran with high mortality and morbidity rates and limited newborn screening coverage mainly for phenylketonuria, hypothyroidism, and favism. This is in good agreement with the review article's focus on the wide spectrum and genetic heterogeneity of IEMs, the pivotal importance of early diagnosis, and variability in their prevalence among populations. In Iran, the estimated prevalence of IEMs in national neonatal screening studies was approximately 1 in 1000 live births, which is higher than the global average (~50.9 per 100,000), partly due to high rates of consanguinity. As consistent with your findings and the classification of subtypes of IEMs, frequent disorders such as aminoacidopathies, organic acidemias, and fatty acid oxidation defects are often found in Iranian cohorts. Our study provides an uncommon perspective on clinical dilemmas faced in real life with significant mortality (>30%) and developmental delay, and we also demonstrate the lack of a comprehensive screening program in our country in contrast to the more extensive panels used in other parts of the world. Both sources highlight the critical need to expand and regionalize newborn screening, advanced biochemical and genomic diagnostics, and population-specific registries to improve early detection and outcomes in Iran and other populations with high consanguinity. Therefore, your research confirms and complements the general framework of the review, while adding important epidemiological and clinical information in the context of Ardabil (2).

In a study performed in Hong Kong, Belaramani et al. reported on expanded newborn screening for inborn errors of metabolism (IEM) over the course of 7 years, where they screened 125,688 newborns and identified 47 confirmed cases with an overall prevalence of 1 in 2,674. The most common metabolic disorders diagnosed were fatty acid oxidation defects (40%) and amino acid metabolism disorders (38%), with carnitine uptake defects and citrullinemia type II being the most frequent diagnoses. Of note, 78.7% of the affected newborns were asymptomatic at diagnosis, emphasizing the significance of newborn screening for early detection and intervention. Two deaths were reported with methylmalonic acidemia and carnitine palmitoyltransferase II deficiency. In contrast, in our study phenylketonuria, urea cycle disorders, and organic acidemias were the most common IEMs with significant mortality and developmental delay. Both studies emphasize the importance of newborn screening, but differences in disease prevalence and spectrum reflect regional genetic and ethnic diversity. Hong Kong's broader testing and lower mortality show the benefits of a comprehensive strategy that includes second-tier testing to reduce false positives and improve outcomes. Our findings support the expansion of similar newborn screening programs in Ardabil to detect treatable disorders early and reduce disease burden (3).

Our findings demonstrate a high burden of inborn errors of metabolism (IEMs) in Ardabil children, with a predominance of phenylketonuria, organic acidemias (including propionic and methylmalonic acidemia), and urea cycle defects reflecting significant morbidity and mortality and limited newborn screening coverage. Your observations on the spectrum of common IEMs observed are in agreement with the study by Yang et al. from the metabolic registry of Iran. It emphasizes phenylalanine metabolism disorders, organic acidemias, glycogen storage diseases, and lysosomal storage disorders as common in the Ardabil population. Both studies emphasize the effect of

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consanguinity as an important risk factor. Your study therefore provides detailed clinical outcomes and regional prevalence insights. However, the registry report covers a larger sample across multiple regions and years, providing a broader epidemiological picture. Both emphasize the critical need to increase newborn screening and improve early diagnosis to decrease morbidity and mortality among Iran's high-risk populations (4).

Using tandem mass spectrometry, Hao et al. conducted a 19-year study of newborn screening data on 1.17 million infants in Shanghai, China. The study identified 392 newborns with inborn errors of metabolism (IEMs). The overall incidence of IEM was about 1/3,000. The top three common disorders were phenylalanine hydroxylase deficiency (phenylketonuria), methylmalonic acidemia, and primary carnitine deficiency. This large, long-term screening study shows a somewhat lower incidence than the one observed in our study, in which the IEM prevalence seems higher, probably due to factors such as increased consanguinity. In both studies, major IEMs are phenylketonuria and methylmalonic acidemia, although the Chinese study has fatty acid oxidation disorders prominently. The HAO study presents broad genetic mutation profiles, identification of novel variants, and detailed genotype-phenotype correlation that may not be as covered in your clinical study. On the other hand, your study is on clinical outcomes, including mortality and developmental delay, which is a mirror of real-world disease burden in Iran. These studies complement each other by integrating epidemiological, genetic, and clinical viewpoints on IEMs in different populations with distinct genetic backgrounds and healthcare infrastructure, emphasizing the need for tailored newborn screening programs and thorough genetic counseling in both regions (7).

Our finding of inborn errors of metabolism (IEMs) among children in Ardabil is in agreement with the results of the study by Men et al., which was performed in eastern coastal China and showed an overall incidence of IEMs of about 1 in 2,581 newborns. The two studies show that phenylketonuria (PKU) and methylmalonic acidemia (MMA) are among the most common disorders, highlighting that they occur worldwide. However, our study shows the important clinical impact, such as mortality rates of more than 30% and developmental delays, which emphasizes the urgent need for expanded newborn screening and early diagnosis in Ardabil. Conversely, the Chinese study employed complex genetic analysis, identifying specific gene variants associated with these conditions, thereby offering a deeper understanding of genotype-phenotype correlations. Your study found urea cycle disorders to be prominent, while the Chinese cohort also found fatty acid oxidation disorders like short-chain acyl-CoA dehydrogenase deficiency. This might hint at genetic differences by region. Taken together, these studies offer complementary epidemiological, clinical, and genetic insights critical for designing region-specific screening protocols and management strategies to reduce morbidity and mortality of IEMs worldwide (8).

Our study of inborn errors of metabolism (IEMs) in Ardabil children has important similarities with the recent study in Xinjiang Province, northwest China, by Zhu et al. They screened 41,690 newborns by tandem mass spectrometry and followed up with next-generation sequencing for genetics. Both studies identify phenylketonuria (PKU) and methylmalonic acidemia (MMA) as the most frequent IEMs in their populations. However, the incidence rate in Xinjiang was higher (1 in 1,158 births) than estimates from the rest of the world and similar to the high prevalence of the Ardabil cohorts. Our study complements the Chinese data by focusing on clinical outcomes such as mortality and developmental delay that reflect the real-world disease burden. The Chinese study also identified specific pathogenic and hotspot gene mutations in PAH and MMACHC genes, providing molecular

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insights that may be helpful for genetic counseling and precision medicine. Both emphasize the need for improved newborn screening programs together with genetic diagnostics to allow early detection and intervention tailored to local population genetics and epidemiology to reduce morbidity and mortality from IEMs (9).

Limitations and Strengths

One of the major strengths of this study was the assessment of a relatively large number of children with inherited metabolic disorders during a long study period in a referral paediatric centre. In addition, the study provided useful regional epidemiological data about the spectrum and frequency of congenital metabolic disorders in Ardabil province, where consanguineous marriage is highly prevalent. Another major strength was the use of biochemical, clinical and genetic findings to confirm diagnoses, which improved the accuracy of diagnoses. The study also highlighted the large burden of morbidity, developmental delay and mortality associated with these disorders and stressed the importance of newborn screening programmes and early diagnosis.

However, there are also some limitations to consider. First, this was a retrospective study based on medical record review from a single centre, which may limit the generalisability of the findings. Second, not all the newborns or children were systematically screened for inherited metabolic disorders; thus, the true prevalence of congenital metabolic diseases in the region could not be estimated accurately. Third, incomplete documentation in some medical records and possible referral bias could have influenced the results. Finally, not all patients underwent detailed molecular and genetic analyses.

Conclusion

In this study, more than 20 different types of inherited metabolic diseases were identified, and more than 25% of patients had a positive family history of them. Considering the high incidence of consanguineous marriages, which was found to be around 82% in the parents of these patients in this region, it appears that the introduction of newborn screening programs with concomitant prenatal diagnostic testing for couples with a family history of congenital metabolic disorders may help in early diagnosis and early treatment or at least in avoiding severe and irreversible damage to affected individuals. Such approaches may also reduce the length of hospital stay and the financial burden of unnecessary diagnostic procedures, besides better clinical outcomes due to early intervention. Since consanguinity is strongly associated with autosomal recessive disorders, including hereditary metabolic diseases, genetic counseling and public health measures to reduce the incidence and morbidity of these diseases in populations with high rates of consanguineous unions are important.

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CRediT authorship contribution statement

Conceptualization, Methodology: LK, AA, Validation: FA, Formal Analysis, Investigation, Resources, Software, Data Curation, Writing–Original Draft Preparation, Writing–Review & Editing, Visualization, Supervision, Project Administration: LK, FA.

Declaration of Generative AI and AI-assisted technologies in the writing process

We have not used any AI tool in the prepare of this paper.

Conflict of interest

The authors declare no conflicts of interest.

Ethical considerations

This study was approved by the Bioethics Committee at Ardabil Medical University (IR.ARUMS.MEDICINE.REC.1402.131). The informed consent was signed by all parents prior to their participation in the study.

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Data availability statement

Data available on request from the authors.

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