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ORIGINAL RESEARCH ARTICLE

Assessment of Demographic, Clinical, and Paraclinical Characteristics of Children with Phenylketonuria in West Azerbaijan Province (2012–2021)

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Abstract

Background Phenylketonuria is among the most common inherited metabolic disorders and, if not diagnosed and treated promptly, can result in severe disability. Since 2006, neonatal screening for Phenylketonuria has been implemented in Iran. This study aimed to investigate the demographic, clinical, and paraclinical characteristics of children with PKU in West Azerbaijan Province.

Methods This descriptive cross-sectional study included all children diagnosed with Phenylketonuria through the national newborn screening program between 2012 and 2021. Data on demographic, paraclinical, anthropometric, and neurological features were collected using a researcher-designed checklist and analyzed with SPSS version 21.

Results Of 130 identified cases, data from 46 children were analyzed. The mean age was 76.6 months, and 56.5% of the participants were female. A family history of Phenylketonuria was reported in 4.3% of cases, while 33.1% were born to consanguineous parents. Good dietary adherence was observed in 69.6% of patients. The mean phenylalanine level was 5.8 ± 4.2 mg/dL, with 41.3% exceeding the normal range. Anemia was present in 17.4% of cases, elevated AST in 15.2%, and ferritin deficiency in 4.3%. No patients exhibited motor or speech delay or seizures.

Conclusion Although the national screening program has facilitated early diagnosis, challenges persist in maintaining optimal phenylalanine levels and ensuring dietary adherence in some patients. Continuous follow-up, family education, and careful monitoring of nutritional and biochemical status are critical to preventing complications.

Keywords Neonatal screening, Nutritional deficiency, Phenylalanine, Phenylketonuria

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1 Introduction

Phenylketonuria (PKU) is one of the most common inherited metabolic disorders, which is transmitted in an autosomal recessive manner, and caused by a deficiency of the enzyme phenylalanine hydroxylase. This enzyme is responsible for converting phenylalanine to tyrosine; its absence or reduced activity results in the accumulation of phenylalanine in the blood, which is further metabolized to toxic compounds such as phenylacetic acid and phenyllactic acid, ultimately leading to severe brain damage.[1,2] The early clinical manifestations of this disease typically appear within the first six months of life and include growth retardation, behavioral problems, and reduced cognitive abilities.[3] Without timely diagnosis and treatment, PKU can result in intellectual disability, neurological disorders, seizures, and impairments in physical growth and cognitive development.[4] Early treatment and strict adherence to a low-phenylalanine diet can prevent irreversible complications. Multiple studies have demonstrated that initiating treatment within the first two weeks of life enables normal growth and development in affected children.[5] Accordingly, newborn screening for PKU is recognized as one of the most successful preventive measures in public health.[6] This program was first introduced in the 1960s through the efforts of Robert Guthrie and was gradually implemented worldwide, including in Iran since 2006.[7,8]

The prevalence of PKU varies globally depending on genetic, ethnic, and cultural factors. The worldwide average prevalence has been reported as approximately one in 23,930 live births; however, substantial variation exists across countries. For instance, the prevalence is about one in 4,500 in Italy and one in 125,000 in Japan.[9] In Iran, the prevalence of PKU has been reported to be higher than the global average, ranging from one in 3,627 to one in 7,000 live births according to different studies.[10] This elevated prevalence may be partly attributed to the relatively high rate of consanguineous marriages in certain regions of the country, which increases the risk of genetic disorders such as PKU.[11,12] These statistics highlight the critical importance of newborn screening and genetic counseling for the effective prevention and management of PKU, particularly in populations with a high prevalence of consanguineous marriages. Furthermore, studies have shown that the benefits of newborn screening programs far outweigh their costs, playing a substantial role in preventing permanent disabilities.[13,14]

Newborn screening is typically performed between the third and fifth day after birth by measuring phenylalanine levels in a blood sample obtained via heel prick. If elevated phenylalanine is detected, confirmatory testing with high-performance liquid chromatography (HPLC) is conducted, and upon confirmation, treatment is initiated promptly.[9] Although phenylalanine is an essential amino acid, its intake must be carefully regulated in patients with PKU to maintain safe serum levels (2–6 mg/dL in children under 12 years).[15] For individuals with PKU, lifelong adherence to a specialized diet is essential. While complete elimination of phenylalanine is not possible, its intake must be tightly controlled to prevent toxic accumulation. The dietary regimen typically excludes major protein sources such as meat, dairy products, eggs, legumes, and nuts. Consequently, patients are at risk of nutritional deficiencies, particularly calcium, vitamin D, and iron, which may predispose them to osteoporosis and other complications.[16]

Given the irreversible consequences of delayed diagnosis, the necessity of newborn screening, the requirement for lifelong dietary management, and the importance of regular paraclinical monitoring, local studies in different regions of Iran are essential. Despite the existence of a national screening program, limited data are available on the epidemiological, clinical, and paraclinical characteristics of PKU patients in West Azerbaijan Province. Therefore, this study was conducted to evaluate the demographic, clinical, and paraclinical features of children with PKU in this province from 2012 to 2021, in order to improve patient identification and enhance the quality of healthcare services provided.

2 Methods

This descriptive cross-sectional study was conducted to evaluate the demographic, clinical, and paraclinical characteristics of children with PKU in West Azerbaijan Province. The study population included all children diagnosed with PKU through the national newborn screening program between 2012 and 2021 who were receiving dietary and therapeutic management. Using a census sampling method, all identified and treated children within this period were considered for inclusion. Data were collected using a researcher-designed checklist developed based on scientific literature and expert opinions in metabolic disorders. Three specialists in pediatrics and genetics confirmed the content validity of the checklist. As the study utilized secondary data extracted from patient medical records, reliability testing of the tool was not required. The checklist included demographic data such as age at diagnosis, age at assessment, sex, parental consanguinity, family history of PKU, and treatment adherence. It also comprised paraclinical data, which encompassed the results of the most recent laboratory tests, including phenylalanine, vitamin D, calcium, phosphorus, hemoglobin, fasting blood sugar (FBS), platelet count, TSH, free T4, urea, creatinine, sodium, potassium, zinc, ferritin, AST, and

ALT. Clinical data were gathered through the assessment of motor and speech development based on CDC developmental growth charts extracted from patient files, as well as the presence of neurological complications such as seizures and irritability. Additionally, anthropometric data were recorded, including height, weight, weight-for-age, height-for-age, body mass index (BMI), and BMI-for-age.

Dietary adherence was assessed using three criteria: (a) parental self-report during follow-up visits, (b) laboratory results of phenylalanine levels, and (c) evaluation by a nutritionist. Patients were classified as having good adherence if they maintained controlled phenylalanine levels in more than 70% of follow-up visits and if parents demonstrated adequate cooperation; otherwise, they were categorized as having poor adherence.

During the study period, a total of 130 children with PKU were identified in the province. Of these, 70 met the initial eligibility criteria. However, due to loss to follow-up or incomplete clinical and laboratory records, complete data were ultimately available for analysis in 46 children. Patients were excluded only if they did not attend follow-up during the study period or had incomplete records.

Data were analyzed using SPSS version 21 (IBM Corp., Armonk, NY, USA). For quantitative variables, descriptive statistics, including the mean and standard deviation, were calculated. For qualitative variables, frequency and percentage were reported. Results were presented in appropriate statistical tables.

3 Results

This study examined the demographic, anthropometric, paraclinical, and neurological characteristics of children with PKU in West Azerbaijan Province between 2012 and early 2021. Among the 130 children identified through the national newborn screening program, 43 (33.1%) had hyperphenylalaninemia, six (4.6%) had non-classical PKU, and one child (0.8%) had died. Of the remaining 80 children on dietary treatment, 10 were excluded due to the absence of routine laboratory requests in those under two years of age, leaving 70 eligible cases. Ultimately, complete clinical, paraclinical, and treatment follow-up data were available for 46 children. Twenty-four children were excluded due to a lack of follow-up during the study period or incomplete documentation.

Parental consanguinity was assessed for all screened cases (n = 130). Consanguineous marriage was documented in 43 children (33.1%), absent in 64, and unrecorded in 23 cases. These figures refer to the total screened cohort and are independent of the final analyzed sample (n = 46). In addition, one child with attention-deficit/hyperactivity disorder (ADHD) and one with mild mental retardation (MR) were identified. No cases of motor or speech developmental delay or seizures were reported.

The mean age of the analyzed patients was 76.6 ± 26.6 months (range: 29–121 months). Of the 46 patients, 26 (56.5%) were female and 20 (43.5%) male. A positive family history of PKU (previous affected sibling) was documented in 2 cases (4.3%). Dietary adherence was categorized as good in 32 children (69.6%) and poor in 14 children (30.4%) (Table 1).

Table 1 Family history of PKU, dietary adherence, and sex distribution of study participants

Variable	Category	Frequency	Percentage
Family history of PKU	Yes	2	4.3
	No	44	95.7
Sex	Female	26	56.5
	Male	20	43.5
Dietary adherence	Good	32	69.6
	Poor	14	30.4

Regarding anthropometric indices, the mean height, weight, and BMI of the patients were 119.64 ± 16.09 cm, 27.17 ±10.50 kg, and 17.8 ± 3.4 kg/m², respectively (Table 2).

Table 2 Anthropometric characteristics of children with PKU

Variable	Mean	SD	Minimum	Maximum
Weight (kg)	27.17	10.50	12.0	50.0
Height (cm)	119.64	16.09	88.0	147.0
BMI (kg/m²)	17.80	3.40	12.9	27.7

The frequency distribution of weight-for-age, height-for-age, and BMI percentiles is presented in Table 3. According to this table, for weight-for-age, the 95th percentile had the highest frequency with 12 patients (26.08%), followed by the 50th percentile with 11 patients (23.91%). The lowest frequency corresponded to the 5th percentile, with no patients. Regarding height-for-age, the highest and lowest frequencies were observed at the 50th percentile with 14 patients (30.43%) and the 5th and 10th percentiles with one patient each (2.17%), respectively. For BMI, the highest frequency was at the 95th percentile with 11 patients (23.91%), and the lowest frequencies were observed at the 5th and 10th percentiles, each with two patients (4.34%).

Table 4 presents the mean and standard deviation of paraclinical parameters in children with PKU included in this study. The mean serum phenylalanine level was 5.8 ± 2.4 mg/dL, with 19 patients (41.30%) exceeding the normal range (> 6 mg/dL). Vitamin D deficiency was observed in two patients (4.35%) as severe deficiency, four patients (8.70%) as insufficient, and 40 patients (86.97%) were within the normal range. Ferritin deficiency was reported in 2 patients (4.35%), anemia in eight patients (17.39%), urea levels above 36 mg/dL in

Table 3 Frequency distribution of weight-for-age, height-for-age, and BMI percentiles in the study population

Percentile	Weight-for-age (n / %)	Height-for-age (n / %)	BMI (n / %)
5th	0 (0%)	1 (2.17%)	2 (4.34%)
10th	1 (2.17%)	1 (2.17%)	2 (4.34%)
25th	6 (13.04%)	8 (17.39%)	7 (15.22%)
50th	11 (23.91%)	14 (30.43%)	11 (23.91%)
75th	9 (19.57%)	6 (13.04%)	5 (10.87%)
85th	4 (8.70%)	3 (6.52%)	3 (6.52%)
90th	3 (6.52%)	5 (10.87%)	5 (10.87%)
95th	12 (26.08%)	8 (17.39%)	11 (23.91%)

14 patients (30.43%), and TSH levels above 4.2 μIU/mL in five patients (10.87%). Elevated liver enzymes were observed in seven children (15.22%) for AST and three children (6.52%) for ALT, which was likely associated with irregular L-carnitine supplementation. Additionally, one case each of zinc deficiency (2.17%) and phosphorus deficiency (2.17%) was documented.

Table 4 Paraclinical parameters of children with PKU

Variable	Normal range	Mean	SD	Minimum	Maximum
Phenylalanine (mg/dL)	2–6	5.8	4.20	0.10	17.0
Vitamin D (ng/mL)	Deficient < 20 Insufficient 20–30 Sufficient 30–100 Toxic > 100	43.61	15.21	6.40	88.0
Calcium (mg/dL)	8.5–10.5	9.94	0.50	8.60	10.9
Phosphorus (mg/dL)	4.5–6.5	5.06	0.62	3.80	7.10
Sodium (mEq/L)	135–145	136.87	3.55	127.0	141.0
Potassium (mEq/L)	3.5–5.5	4.27	0.50	3.10	5.10
Zinc (μg/dL)	65–110	92.33	18.20	48.0	125.0
Fasting blood sugar (mg/dL)	60–100	83.17	8.4	69.0	89.0
TSH (μIU/mL)	0.4–4.2	2.65	1.23	0.52	5.8
Free T4 (ng/dL)	0.8–1.8	1.33	0.30	0.84	2.3
Urea (mg/dL)	11–36	35.62	9.2	19.0	59.0
Creatinine (mg/dL)	0.2–0.8	0.54	0.11	0.40	0.87
AST (U/L)	5–42	39.99	15.60	16.90	82.90
ALT (U/L)	5–40	31.22	9.34	14.70	54.0
Hemoglobin (g/dL)	> 11.5	12.76	1.40	10.0	15.6
Platelets ($\times 10^3/\mu L$)	150–450	284.15	71.15	136.0	452.0
Ferritin (ng/mL)	13–400	44.87	29.91	5.30	143.0

Regarding neurological complications, no cases of seizures were observed among the children. However, four children (8.70%) exhibited irritability (Table 5).

Table 5 Neurological complications (seizures and irritability) in children with PKU

Variable	Category	n	Percentage
Seizures	Yes	0	0
	No	46	100
Irritability	Yes	4	8.70
	No	42	91.30

4 Discussion

PKU is one of the most common inherited metabolic disorders in Iran, which, if not correctly diagnosed and treated, can lead to irreversible neurological damage. In the present study, conducted on 46 children with PKU in West Azerbaijan Province, some findings were consistent with previous national and international reports, while others were different.

In this study, more than half of the patients were female (56.5%), which aligns with the sex distribution reported in similar studies.[17] The mean age of patients at the time of the study was 76.6 months, reflecting continued treatment and follow-up in the years following birth. Among the children identified through newborn screening in West Azerbaijan, 33.07% were born to consanguineous marriages. It is important to note that this statistic refers to the entire screened cohort of 130 children, not just the final analyzed sample (46 children). Therefore, this percentage serves as a regional indicator

of the prevalence of consanguineous marriages among PKU patients in the province, which is considered a significant risk factor for genetic disorders, including PKU.[10,18]

Regarding dietary adherence, approximately 70% of patients demonstrated good compliance. This rate is higher than that reported in some international studies. Nevertheless, 30% of patients exhibited poor adherence, which may lead to elevated phenylalanine levels and subsequent neurological complications.[19] In the present study, 41.30% of patients had phenylalanine levels above the target range, highlighting the need for enhanced parental education and closer monitoring of dietary therapy.[15]

With respect to nutritional indices, the mean BMI of patients was within the normal range. However, a detailed assessment revealed that some patients suffered from micronutrient deficiencies, including vitamin D, ferritin, zinc, and phosphorus deficiencies. These findings are consistent with studies such as Viau et al. in the United States, which demonstrated that PKU patients, despite metabolic control, remain at risk for micronutrient deficiencies.[20]

Among paraclinical parameters, elevated liver enzymes (AST and ALT) were observed in a proportion of patients, which could result from chronic phenylalanine toxicity or nutritional complications. Anemia was present in 17% of children, indicating the importance of regular hematologic monitoring. Additionally, irritability was reported in 8.7% of children, potentially related to elevated phenylalanine levels, although severe neurological complications such as seizures were not observed in this group.

Overall, the findings of this study indicate that, despite the existence of successful screening programs in the province, challenges persist regarding treatment adherence, follow-up testing, and nutritional and metabolic complications. Enhancing family awareness, training healthcare personnel, and providing pre-marital genetic counseling—particularly in consanguineous marriages—can play a crucial role in better prevention and management of PKU.

While this study provides valuable data on the clinical, demographic, and paraclinical characteristics of children with PKU in West Azerbaijan Province, several limitations must be considered when interpreting and generalizing the results. These include a relatively small sample size, reflecting the low regional prevalence of PKU, which may reduce statistical power; the cross-sectional design, which does not allow assessment of temporal changes or the impact of therapeutic interventions; and the lack of control over psychosocial variables, such as parental mental health, literacy, household income, and access to healthcare services, which may influence treatment adherence and clinical outcomes. Finally, the absence of genetic data limits a deeper understanding of phenotypic variability and disease prognosis, given the genetic nature of PKU.

To address these limitations and expand current knowledge of PKU in Iran, future research is recommended, including: long-term cohort studies to assess disease progression and the impact of treatment adherence on cognitive, growth, and quality-of-life outcomes; investigation of correlations between PAH gene mutations and clinical phenotype to inform personalized therapeutic strategies; interventional educational studies to evaluate the effectiveness of programs in improving dietary adherence and reducing phenylalanine levels; comprehensive psychosocial analyses to identify behavioral and social barriers to treatment compliance; and multicenter studies across the country to compare epidemiologic and genetic characteristics of PKU patients, thereby supporting national policy-making in PKU management.

5 Conclusion

Given the significant prevalence of PKU in Iran and West Azerbaijan Province, the continued implementation of widespread newborn screening programs and the enhancement of post-diagnostic care quality are essential. The findings of this study indicate that key factors, including consanguineous marriage, dietary adherence, and nutritional deficiencies, play a critical role in disease management. Therefore, it is recommended that structured educational programs for patients' parents be developed, periodic screening of nutritional and paraclinical status be conducted, and pre-marital genetic counseling—particularly in regions with a high prevalence of consanguineous marriages—be expanded. Additionally, larger prospective studies in other provinces are warranted to provide a more comprehensive understanding of PKU in Iran.

Declarations

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Authors' Contributions

All authors contributed to the initial idea generation, study design, data collection, and manuscript drafting. All authors have read and approved the final version of the manuscript and declare no disagreement over its contents.

Availability of Data and Materials

The data and materials used in this study are available from the corresponding author upon reasonable request.

Conflict of Interest
The authors declare that this study was conducted independently and that there are no conflicts of interest with any organizations or individuals.

Consent for Publication
All authors have read and approved the final manuscript and provided their consent for publication.

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Ethical Considerations
The study was conducted after obtaining ethical approval from the Ethics Committee of Urmia University of Medical Sciences with the Code of Ethics IR.UMSU.REC.1400.115.

Artificial Intelligence Disclosure
No AI-assisted technologies were utilized in any part of this work.

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