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**Original Article**

# Epidemiology of phenylketonuria and its related factors in Kurdistan province during 2012-2014



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## ABSTRACT

**Introduction:** Phenylketonuria (PKU) is caused due to a genetic disorder in amino acid metabolism and, if not detected and treated in a timely manner, results in mental retardation and psychological problems due to toxic effects of phenylalanine increase in the brain. The aim of this study was to investigate epidemiology of PKU in Kurdistan province.

**Methods:** This cross-sectional study was conducted to determine the incidence of PKU for all newborns born in 2012-2014 in Kurdistan province. Data collection was done through medical records of patients. The prevalence and relationship between variables were analyzed using Stata 12 software.

**Results:** The incidence of PKU in the years 2012, 2013 and 2014 was 3.2, 2.3 and 2.9 per 10000 live births, respectively. The prevalence of PKU was higher in males than females and in the city as compared to the villages, though the differences were not significant ($P > 0.05$). Prevalence of PKU between consanguineous and non-consanguineous couples did not have a significant difference ($P = 0.976$). In this study, PKU cases were found to be higher in infants who were the first child of a family (44%).

**Conclusion:** The prevalence of PKU in the Kurdistan province is relatively high and the importance of PKU screening and its consequences should be taken into account in the health education curriculum development.

## Introduction

Phenylketonuria (PKU) is an important genetic disorder caused by an abnormality in the metabolism of amino acids and was first described in 1934 (1, 2). The incidence rate in the general population is 1 per 10,000 live births, but the highest incidence of this disease in the world has been reported in Iran and neighboring countries, with an estimated incidence rate of 1 in 4000 in Turkey and 1 in 3672 in Iran. This disease is an autosomal recessive disorder caused by a mutation in the phenylalanine hydroxylase gene (PAH). The PAH enzyme converts phenylalanine into tyrosine and requires the use of a tetrahydrobopterin cofactor (BH4), molecular oxygen and iron to perform this activity (2, 3). The inactivation of phenylalanine hydroxylase causes chronic hyperphenylalanidemia and increases the level of phenylalanine in blood and fluids, particularly urine and the spinal fluid (CSF) (1, 4). Children with severe PKU have higher concentrations of phenylalanine than 1200 µmol / l, and when the treatment begins with a newborn diet, the blood Phe level is kept close to normal and can be considered to have a normal progression. However, in the absence of treatment, the disease is associated with continuous mental disorders and will lead to more symptoms such as eczema, autism, seizure and motor disorders. Growth problems, irregular behavior patterns, and psychiatric disorders are often manifested when the baby grows up. In the meanwhile, there are effective therapies to prevent symptoms, and all countries should screen the infants for PKU (6, 7). Research has demonstrated that screening programs for newborn babies are significantly successful, and as long as neonatal PKU is detected soon enough in the neonatal age, newborn babies can grow and have a normal lifespan (8-10). In the past few years, recognition of patients with PKU has inactively begun through screening in Iran since the middle of 2012; though a systematic, well-defined, analysis of the status of the patients has never been fully performed. Therefore, it is necessary to identify and report the distribution of PKU and its other epidemiologic features in different provinces of the country in order to take precautionary measures. Since there has been no comprehensive study on the epidemiological pattern and distribution of PKU in Kurdistan province, this study aimed to investigate epidemiology of PKU in neonates of Kurdistan province.

## Methods

This cross-sectional study was conducted to determine the incidence of PKU for all newborns born from 2012 to 2014 in Kurdistan province. Based on the aims and variables of the study, a checklist was designed to collect the information necessary to complete it by examining patients' records. In the patients forms, information on the national PKU screening plan was completed as well. Throughout the National PKU Screening, each newborn infant in the maternity ward must receive advice on the importance of screening tests on 3-5 days of birth for newborns, by maternity care staff. For PKU screening, a neonate heel sampling is performed at the nearest health center of their place of residence. Blood samples were screened on Whatman 903 paper by colorimetry using an ELISA device for the presence of Phenylalanine. If the levels of Phenylalanine are higher than 3.9 mg / dL, the sample is suspected. In the next step, suspicious specimens were sent to the Pathobiology Center where a high-chromatography liquid (HPLC) test was used to confirm the final diagnosis. If HPLC was positively identified, the newborn was considered as a definite case for PKU. All cases of patients with definite diagnosis of PKU were studied in this study. The variables in the checklist included the age at the time of the diagnosis, current age, clinical symptoms of diagnosis, the reason for referring to the physician prior to the diagnosis, the family history of the parents, the patient history in the family and the birthplace of the patient. Information that was not included in the records, was completed with follow-up through phoning parents of the patients. Data analysis was performed using descriptive statistics such as calculation and drawing frequency tables and related ratios. For quantitative variables, such as age, an analysis was a moderate (mean or median) report with standard deviation (or inter-quartile domain). To analyze the inferential data, the goal was to explain the behavior of the statistical population based on the information in the samples. For analytical purposes, Chi-square test was used to determine the relationship between sex, location, and screening of the disease.

## Results

We examined 88339 live births, of which PKU was detected in 25 new cases. The highest incidence of PKU was in 2012 with 3.2 in 10,000 live births and the lowest was for 2014 with 2.9 per 10,000 live births (Table 1). Table 2 describes the prevalence of PKU in Kurdistan province during 2012-2014 based on the place of residence. The results showed that the highest prevalence of PKU was in Sanandaj in 2013, which reached 44.5%, and the lowest frequency (4%) was observed in Saravabad, Bijar, Qorveh, Dehgolan and Divandareh (Table 2). The results of the study showed that the prevalence of PKU was higher in males than females, but no significant difference was observed (P = 0.840). The prevalence of PKU was higher in urban than in rural areas, which was not significant either (P = 0.976). According to our research, the prevalence of PKU in subjects with a family history was less (20%), although there was no significant difference (P = 0.906). The prevalence of PKU in consanguineous couples was not significantly different (P = 0.976) (Table 3). Table 4 shows that the highest prevalence of PKU (44%) is attributed to the first-born children (Table 4). The results of this study reported an incidence of 3.2 in 10,000 live births in 2012 to 2.9 per 10,000 live births in 2014, which is almost above the national average (Table 1).

## Discussion

Many studies have been conducted around the world which have measured the prevalence of PKU in highly heterogeneous ethnic and genetic populations with reports of changes in the incidence of this disease (11). In Asia, the highest distribution rates are found in Iran (16.6 per 100,000), Japan (16.3), and the lowest in the Philippines (0.3 per 100,000) (8, 12, 13). The prevalence in Iran varies in different geographical areas, from 1 in 4,000 to 1 in 10,000 (14). However, due to lack of a large screening system in Iran, the exact level of the disease is unclear, and it has been only in recent years that several studies have been carried out on these patients, reporting a relatively high prevalence of PKU in the population (14). In a large study conducted in Tehran in 1982, the prevalence was reported to be 1.15 per 10,000 (15).

**Table 1**. Incidence of PKU in Kurdistan province in 2012-2014

| Rate of incidence | 2012 (Number in 10000) | 2013 (Number in 10000) | 2014 (Number in 10000) |
|---|---|---|---|
| New cases | 9 (36) | 7 88 (28) | 9 (36) |
| Number of live births | 28053 | 29289 | 30997 |
| Incidence in 100000 | 3.2 | 2.3 | 2.9 |

**Table 2:** Incidence of PKU in Kurdistan province during 2012-2014 by city of residence

| City of residence | 2012 Number (%) | 2013 Number (%) | 2014 Number (%) | Total number | Incidence (Total) |
|---|---|---|---|---|---|
| Sanandaj | 1 (11.1) | 2 (28.5) | 4 (44.5) | 7 (28) | 17 |
| Saghez | 2 (22.2) | 2 (28.5) | 1 (11.1) | 5 (20) | 20 |
| Baneh | 1 (11.1) | 1 (14.3) | 0 (0) | 2 (8) | 3 |
| Marivan | 2 (22.2) | 0 (0) | 1 (11.1) | 3 (12) | 4 |
| Bijar | 1(11.1) | 0 (0) | 0 (0) | 1 (4) | 2 |
| Ghorve | 0 (0) | 0 (0) | 1 (11.1) | 1 (4) | 2 |
| Dehgolan | 1 (11.1) | 0 (0) | 1 (11.1) | 1 (4) | 2 |
| Kamyaran | 1 (11.1) | 0 (0) | 1 (11.1) | 3 (12) | 3 |
| Sarvabad | 0 (0) | 1 (14.3) | 0 (0) | 1 (4) | 1 |
| Dinandare | 0 (0) | 1 (14.3) | 0 (0) | 1 (4) | 7 |
| Total | 9 (36) | 7 (28) | 9 (36) | 25 (100) | 62 |

**Table 3.** Incidence of PKU based on demographic variables

| Variables | | 2012 Number (%) | 2013 Number (%) | 2014 Number (%) | Total number | P-value |
|---|---|---|---|---|---|---|
| Gender | Male | 7 (77.8) | 4 (57) | 8 (89) | 19 (76) | 0.840 |
| | Female | 2 (21.2) | 3 (43) | 1 (11) | 6 (24) | |
| Place of residence | Urban | 8 (89) | 6 (85.7) | 8 (89) | 22 (88) | 0.976 |
| | Rural | 1 (11) | 1 (14.3) | 1 (11) | 3 (12) | |
| Family history | Yes | 2 (22.2) | 1 (14.2) | 2 (22.2) | 5 (20) | 0.906 |
| | No | 7 (78.8) | 6 (85.8) | 7 (78.8) | 20 (80) | |
| Consanguineous marriage | Yes | 3 (33.3) | 2 (28.5) | 2 (22.2) | 7 (28) | 0.871 |
| | No | 6 (67.7) | 5 (71.5) | 7 (77.8) | 18 (72) | |

In European countries, PKU has been reported at variously. The highest prevalence of PKU was observed by Ozalp et al. in Turkey in 1995 to be about 22.2. The prevalence of PKU is 1 per 10,000 in Greece, 1 in 18,000 in Bulgaria, and 1 in 7,000 in Poland, 1 in 7400 in Germany, 1 in 14,000 in Spain, and 1 in 11500 in Italy (16). In other studies, including France and the United Kingdom, 1 in 13500 and 1 in 14300 has been reported respectively. The absence of PKU in these countries could be due to less consanguineous marriages in these areas (11, 17, 18). The incidence rate in the United States and Colombia was 7.8 and 7.5, which was relatively low, and no cases were reported in Australia (4, 11, 17-19). In our study, the prevalence of PKU in males was greater than that of women, which can be attributed to the fact that PKU is an autosomal recessive disorder and the dominance in men is evident. However, in a study by Habib et al. in Fars province (2004-2007), 87091 female and 88143 male newborns were examined, of which 15 girls and 13 boys were diagnosed with PKU. The prevalence was 1.7 in females and 1.5 in every 10,000 males, with a mean prevalence of 1.6 (20). In the present study, the prevalence of PKU in urban areas is higher (88%), which can be due to the lack of screening of patients. Infants in rural areas or smaller cities are usually not screened for genetic and hereditary diseases, and a wider screening system should be used to overcome this problem. In this study, the prevalence of PKU was not significant in consanguineous couples. A study conducted in Lorestan province between 2006 and 2016 found that out of a total of 74 patients, 82% of the parents had a kinship relationship. In the study, it was stated that the primary cause of neonatal PKU was consanguineous marriages. Accordingly, screening tests before marriage, particularly in consanguineous marriages, are necessary (2). The findings of this part of the study are not consistent with the research findings in Lorestan. This suggests that PKU can be attributed to other factors such as inheritance or gender. The findings of this study also showed that PKU is more prevalent in first children of families. This can be due to the lack of referrals of couples to genetic counseling centers for genetic testing before pregnancy. Screening for inherited metabolic diseases is an important program for the prevention of neonatal diseases and it should be noted that many congenital defects are treated successfully with early diagnosis. Therefore, the incidence of the disease in the next pregnancies can be reduced by genetic counseling, as in our study, where the incidence of illness in second children was reduced.

**Table 4.** Prevalence of PKU in Kurdistan province in 2012-2014 based on birth rank

| Birth rank (2012-2014) | Total number |
|---|---|
| 1 | 11 (44) |
| 2 | 8 (32) |
| 3 | 4 (16) |
| 4 and more | 2 (8) |
| Total | 25 |

The screening programs, along with the counseling programs for positive cases or those in the family with a patient, are vital for prevention of the disease. Given the fact that the infected child is at the beginning of the birth, and mental retardation progresses gradually, the condition is noticeable in a few months. Thus there is a possibility of effective intervention. If the child does not receive treatment, he loses his IQ of 4 points for each month, which means he will lose 50 points of his intelligence by the end of his first year. Contrary to what has happened in developed countries, where PKU is timely treated and switched from a symptomatic disease to a genetic trait, it is still treated as phenotypic disease in underdeveloped countries. Generally speaking, all physicians who treat patients with mental retardation or behavioral problems should consider this disease in distinguishing their differentials. Also, lack of sufficient information on the need for timely diagnosis of the disease and the onset of treatment will have irreparable effects on the health of children with PKU. Therefore, parents of affected children should receive appropriate training in this regard.

## Conclusion

The prevalence of PKU in Kurdistan province is roughly high. Hence, young and related couples need to be educated about the importance of PKU screening and its consequences. Therefore, this should be taken into account in the health care delivery system training program. One of the limitations of this study is the lack of accurate information on PKU in recent years.

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## Ethical disclosure

In this study, tests that threatened the health of individuals were not used.

## Author contributions

All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

## Conflict of interest

The authors declare that they have no conflict of interest.

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