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Original article

Assessing the phenylketonuria (PKU) neonatal screening program and the incidence rates of PKU in Kerman County, Iran: a health system research

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Abstract

Background: Phenylketonuria (PKU) is a genetic autosomal recessive disorder, which, if not treated on time, can lead to mental retardation and severe developmental delay. The aim of this study was to assess the PKU neonatal screening program in Kerman County, Iran.

Methods: This was a health system research study carried out on all newborns screened for PKU from 2012 to 2018 in Kerman. Data were extracted from the Comprehensive Social Genetics Program forms, genetic records, and the national form for investigation of genetic disease incidence.

Results: Totally, 121,533 newborns were screened. 108,972 (89.7%) were Iranian, and 12,561 (10.3%) were non-Iranian. Screening coverage in the Iranian population was 92.1%. 80.9% of Iranian and 62.8% of non-Iranian newborns were screened from 3 to 5 days of age. Timely screening

of newborns in the Iranian and non-Iranian populations in 2012 was 70.0% and 46.9%, and in 2018, it was 90.2% and 75.1%, respectively. The first visit at the PKU treatment center in 30.7% of Iranian and 33.3% of non-Iranian neonates was before 14 days of age. In the Iranian population residing in Kerman, the incidence rate of PKU was estimated to be 1.35 per 10,000 live births. 62.5% of parents of Iranian and 100% of parents of non-Iranian PKU patients were relatives.

Conclusion: PKU screening coverage in Kerman is relatively acceptable, and most newborns were screened on time. Timely screening of newborns in both populations has increased since the beginning of the program until the time of this study. Interventions are required to improve early diagnosis and start treatment during the first 2 weeks of life. The incidence of PKU in Kerman County is approximately equal to the national average. Due to the fact that most parents of PKU patients are relatives, increasing awareness to prevent consanguineous marriages can be effective in decreasing the incidence of this disease.

Keywords

Phenylketonuria, screening, newborn, incidence, consanguinity, Kerman, Iran.

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Introduction

Phenylketonuria (PKU) is an inherited metabolic disorder caused by a deficiency in the liver enzyme phenylalanine hydroxylase (PAH). PAH converts phenylalanine (Phe) into tyrosine. PAH deficiency leads to increased concentrations of Phe in the blood and brain. PKU is an autosomal recessive disorder in which consanguineous marriages can increase its incidence [1].

Newborns with PKU usually seem healthy at birth. Untreated patients are characterized by mental disability, neurological complications, and developmental delays [1-3]. PKU is diagnosed through screening programs on the first days of birth. Newborn screening helps early diagnosis and timely intervention [4]. Every 4 weeks delay in beginning the treatment leads to about 4 points decrease of the Intelligence Quotient (IQ) score [1].

The prevalence of PKU varies worldwide [1] and is different among races, ethnic groups, and geographical areas [4, 5]. The most important reason for the high incidence of this disease is the high frequency of consanguine marriages in a population [6]. The incidence of PKU has been reported from 1 per 10,000 to 1 per 70,000 live births, worldwide [7].

After thalassemia, PKU is considered the most common autosomal recessive disorder in Iran [8]. 2,500 patients with PKU live in Iran, and 200 neonates with this disease are born annually [9].

The incidence of PKU in various studies in Iran has been reported from 0.66 per 10,000 [10] to 1.91 per 10,000 live births [11].

In 2007, the national neonatal screening program was piloted in Tehran, Mazandaran, and Fars Provinces. In 2012, the neonatal screening program was implemented across the country; and in May 2012, the neonatal screening program for PKU was initiated in Kerman [10].

Due to the severe consequences resulting from the late diagnosis of PKU [11, 12], the process of neonatal screening should be done with proper quality [13]. The prerequisite for the implementation of any health-associated program is a periodic assessment of functional indices related to that program. This assessment can determine the possible causes of failure to achieve the desired goals by knowing the current status, so that the necessary interventions can be performed as early as possible [14]. Therefore, the aim of this study was to assess the situation of the PKU neonatal screening program in Kerman County.

Methods

This study was a health system research, conducted on all Iranian and non-Iranian newborns screened for PKU from 2012 to

2018 in Kerman County, Iran. In this research, the following indices were determined: the percentage of neonates screened, percentage of timely screening, repeated sampling percentage, percent screened in hospitals, percentage of the timely announcement of screening test results, the time of the patients first visit to the PKU treatment center, the PKU incidence rate, and percentage of parents that were family relatives.

Data collection instruments

Screening test data were extracted from the data recorded in the Comprehensive Social Genetics Program forms from the beginning of the neonatal screening program.

Patient information was extracted from genetic records and the national form for investigation of genetic disease incidence. Information about the patient's gender, date of birth, nationality, screening results, and the treatment beginning time, as well as the characteristics of parents, including familial relations, were extracted from these forms.

These forms had been completed based on information asked from the patients' family, and the information available in the patient's records at the genetic counseling and PKU treatment center. The form had been completed by the genetic program experts of the Kerman Health Center and had been confirmed by the genetic program officer of Kerman Province Health Center.

In order to calculate the incidence rate, the number of live births was obtained from the district Registration Office website.

Neonatal screening process

In accordance with the national instructions, after making sure the newborn has taken in some protein, either from breast milk or formula, in the first 3 to 5 days after birth, 5 drops of blood were taken from the newborn heel by a lancet and collected on Whatman® 903 (W-903) filter paper. Then, dried blood spot (DBS) specimens were immediately sent from sampling centers to the special screening laboratory in Kerman. In cases such as prematurity, unsuitable DBS specimens, or physician's order, neonates are recalled and sampling is done again.

Sometimes, because of technical problems or if the neonate had not ingested enough breastmilk before blood sampling, the screening test becomes false-negative. In these conditions, or based on the physicians' discretion, blood sampling and the screening test should be repeated 72 hours after the neonate has been fed with breast or formula milk.

Phe is measured quantitatively by the colorimetric method. If the Phe levels are ≥ 4 mg/dl, this is considered positive, and the infant is recalled and sampling is done again. Then, the DBS specimen is sent to a confirmation diagnosis laboratory for the evaluation of Phe by high-performance liquid chromatography (HPLC). If the Phe levels are ≥ 3.4 mg/dl, the infant is referred to a PKU treatment center for further evaluation by a pediatrician. Neonates considered as definitive cases of PKU are referred for nutritional counseling and treatment to PKU treatment centers. And then, they are routinely visited at health centers for care and follow-up.

Ethics approval

This study was approved by the Ethics Committee of Kerman University of Medical Sciences (Ethics approval number: IR.KMU.REC.1398.553).

Results

During 2012-2018, 121,533 neonates were screened. 108,972 (89.7%) were Iranian and 12,561 (10.3%) were non-Iranian. The total number of Iranian babies born in Kerman during this time was 118,341 Iranian babies, which means 92.1% of them were screened.

88,141 (80.9%) Iranian and 7,884 (62.8%) non-Iranian neonates were screened on time, which is between 3 to 5 days from birth. Early screening had an ascending trend in the Iranian and non-Iranian populations from the beginning of the program (70.0% and 46.9%) until the time of this study (90.2% and 75.1%). The trend of timely screening in the Iranian and non-Iranian populations is shown in **Fig. 1**.

5,931 (5.4%) Iranian and 352 (2.8%) non-Iranian neonates were hospitalized and sampling was done in the hospital.

A total of 12,100 neonates (9.9%) needed resampling. Out of this number, in 414 neonates (3.4%), resampling was done since the samples were unsuitable; and in 11,686 neonates (96.6%), resampling was done because of conditions such

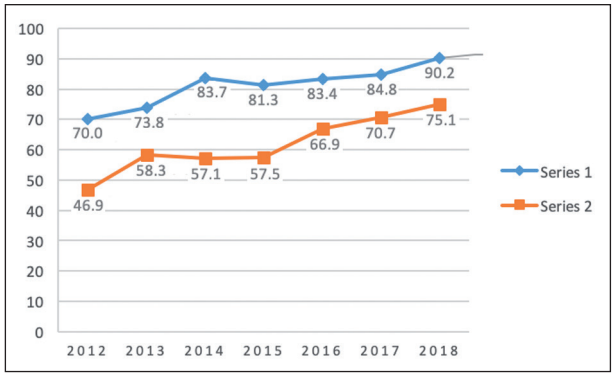

Figure 1. Trend of timely screening in the Iranian (series 1, blue line) and non-Iranian (series 2, orange line) populations from 2012 to 2018 in Kerman.

as dialysis, blood transfusion, blood injection, oral or intravenous feeding with low-protein food, or other medical reasons. Totally, 0.34% of DBS specimens were unsuitable or invalid.

98 (0.09%) Iranian and 19 (0.15%) non-Iranian neonates were positive at the screening. After measuring Phe by the HPLC method, 14 Iranian and 3 non-Iranian neonates were confirmed as positive. One of the Iranian neonates died before being referred to a pediatrician. Eventually, 13 (7 girls and 6 boys) Iranian and 3 (2 girls and 1 boy) non-Iranian neonates were diagnosed as definitive cases of PKU. In addition to the cases identified in screening, 2 patients were false negative (PKU patient with a normal screening result), and 1 patient was identified outside the screening program.

This means, totally, 16 Iranian patients (9 girls and 7 boys) were identified during this period.

In this study, in the Iranian population residing in Kerman, the incidence rate of PKU was estimated to be 1.35 per 10,000 live births. The results of neonate screening among the Iranians and non-Iranians in Kerman are shown in **Tab. 1** and **Tab. 2**.

Positive screening results were reported in 27% of Iranian neonates (**Fig. 2**) and 32% of non-Iranian neonates (**Fig. 3**) at 7 to 9 days of age.

The average age of diagnosis and referral time to the PKU treatment center was 20 days. The first visit at the PKU treatment center in 30.7% of Iranian and 33.3% of non-Iranian neonates was before 14 days of age. In the Iranian population, the first visit to the PKU treatment center in most neonates was before 21 days of age (**Fig. 4**). Treatment was initiated for all patients identified in screening before 28 days of age.

All of the parents of Iranian and non-Iranian patients had been referred to the Genetics Counseling Center. Also, 100% of Iranian and

Table 1. Neonatal screening results and incidence rates for phenylketonuria (PKU) in the Iranian population from 2012 to 2018 in Kerman.

Date	Number of live births	Number of newborns screened (percentage)	Number of newborns screened during the first 3 to 5 days (percentage)	Phe levels (at screening)			Phe levels (at diagnosis confirmation)			Number of patient			Incidence in 10,000 live births
				< 4 mg/dl	4-19.9 mg/dl	≥ 20 mg/dl	< 3.4 mg/dl	3.4-19.9 mg/dl	≥ 20 mg/dl	Identified by screening	False negative	Identified without screening	
2012	15,004	11,144 (74.3)	7,803 (70.0)	11,137	6	1	4	1	2	3	1	1	3.33
2013	15,571	15,699 (100.8)	11,584 (73.8)	15,668	30	1	30	0	1	1	1	0	1.28
2014	16,739	16,491 (98.5)	13,802 (83.7)	16,477	13	1	13	0	1	1	0	0	0.59
2015	17,691	17,236 (97.4)	14,011 (81.3)	17,229	7	0	3	3[b]	1	3	0	0	1.69
2016	18,467	17,068 (92.4)	14,244 (83.4)	17,058	9[a]	1	5	3	1	4	0	0	2.16
2017	18,285	16,376 (89.5)	13,884 (84.8)	16,369	7	0	7	0	0	0	0	0	0
2018	16,584	14,958 (90.2)	12,813 (90.2)	14,936	22	0	21	1	0	1	0	0	0.60
Total	118,341	108,972 (92.1)	88,141 (80.9)	108,874	94[a]	4	83	8[b]	6	13	2	1	1.35

Phe: phenylalanine.
[a] An infant died before performing the diagnosis confirmation test.
[b] An infant died before visiting the PKU treatment center.

Table 2. Neonatal screening results for phenylketonuria (PKU) in the non-Iranian population from 2012 to 2018 in Kerman.

Date	Number of newborns screened (percentage)	Number of newborns screened during the first 3 to 5 days (percentage)	Phe levels (at screening)			Phe levels (at diagnosis confirmation)			Number of patients Identified by screening
			< 4 mg/dl	4-19.9 mg/dl	≥ 20 mg/dl	< 3.4 mg/dl	3.4-19.9 mg/dl	≥ 20 mg/dl	
2012	1,349	634 (46.9)	1,349	0	0	0	0	0	0
2013	1,716	1,002 (58.3)	1,704	12	0	12	0	0	0
2014	1,897	1,084 (57.1)	1,895	2	0	2	0	0	0
2015	1,773	1,020 (57.5)	1,773	0	0	0	0	0	0
2016	1,805	1,209 (66.9)	1,805	0	0	0	0	0	0
2017	1,970	1,394 (70.7)	1,967	3	0	1	2	0	2
2018	2,051	1,541 (75.1)	2,049	2	0	1	1	0	1
Total	12,561	7,884 (62.8)	12,542	19	0	16	3	0	3

Phe: phenylalanine.

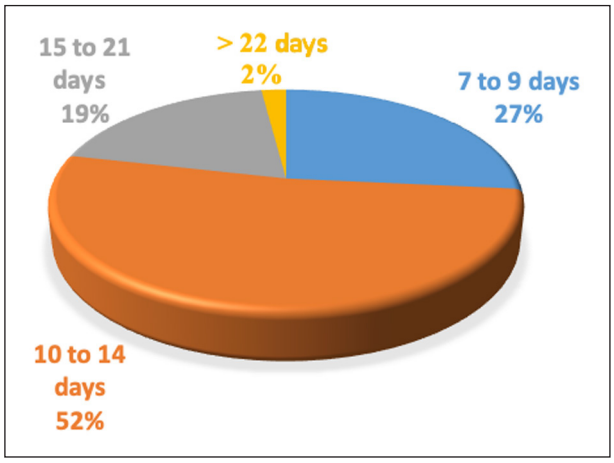

Figure 2. Time of announcing positive screening test results based on the newborns' age in the Iranian population in Kerman.

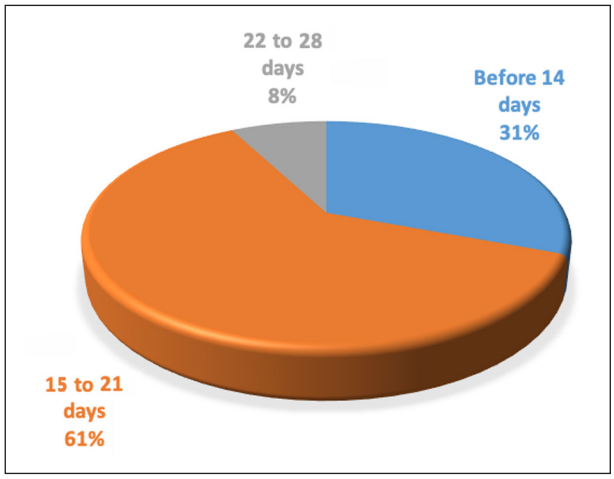

Figure 4. The first visit of Iranian patients identified in the screening program, to the phenylketonuria (PKU) treatment center based on the newborns' age in Kerman.

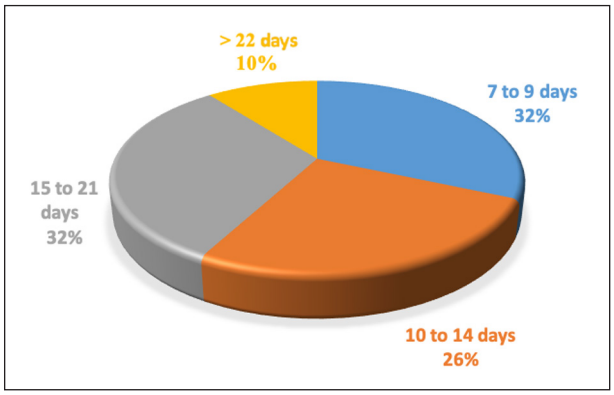

Figure 3. Time of announcing positive screening test results based on the newborns' age in the non-Iranian population in Kerman.

non-Iranian patients and their parents had been referred to health care centers and were under routine care. 62.5% of parents of Iranian and 100% of parents of non-Iranian PKU patients were relatives.

Discussion

This study was performed with the aim of assessing the PKU neonatal screening program and the incidence rates of PKU in Kerman County. According to the results of this study, around 92% of Iranian neonates participated in the PKU screening program. Because the screening program was initiated in 2012, in this year the screening coverage was lower than other years. Based on documents from other counties covered by Kerman University of Medical Sciences, the screening coverage

was above 100% in some counties. A number of newborns born in Kerman had been screened in their area of residence, which can be the reason for the low screening coverage in Kerman and above 100% coverage in other counties. In Southern Khorasan, PKU screening coverage had been reported 100% between 2012 and 2014 [15]. Ganji et al. also reported 100% screening coverage in Chaharmahal and Bakhtiari Province [13]. However, in the study conducted by Mahmoudi et al. in Tehran, 91.4% of neonates had been screened for PKU in 2011 [16], which is consistent with the results of the present study. In studies conducted in Brazil and China, the average screening coverage was reported to be 94.5% and 93.6%, respectively [17, 18]. However, non-Iranian (mainly Afghan) birth numbers were not available, and their screening coverage was not calculated in our study.

In the present study, early screening had an ascending trend in the Iranian and non-Iranian populations from the beginning of the program until the time of this study.

In Iran, in health centers, training sessions on timely screening of infants are held for all pregnant women in the last months of pregnancy, and this probably has had an effect in improving this index.

At the national level, screening coverage also increased from 67% in 2012 to 100.7% in 2014. In the study done by Ganji et al., early sampling had an ascending trend in the study years and had grown from 80% in 2012 to 84.6% in 2015 [13]. In Brazil, the coverage of the screening program increased from 54% in 2001 to 80.2% in 2005 [19], which is in line with the results of this study. Increasing awareness about PKU among parents and referring mothers during pregnancy to healthcare centers have probably contributed to the increased rates of this indicator.

In the present study, most Iranian (80.9%) and non-Iranian (62.8%) newborns had been screened at 3-5 days of birth. The average percent of neonates screened on time in Iran is estimated to be 84%. In the study by Badiee et al. in Torbat Heydarieh, 89% of samples had been taken at the age of 3-5 days [20], which is higher than the present study. In Mexico, the average age of newborns at the time of screening was 18 days, and the range was 3-30 days [5]. Evidence shows that timely screening of newborns in Iran is more frequent than in Mexico. An increase in timely screening is one of the important executive objectives of the PKU screening program.

In this study, 0.34% of the samples sent from the sampling centers and at the proper time were not suitable for laboratory analysis.

The average percentage of unsuitable samples throughout Iran is reported to be 1.31%, so in Kerman it is less than the national average. According to the Genetics Department of the Iranian Ministry of Health, the expected rate of unsuitable specimens in Iran is estimated to be less than 3%.

Sampling should be done based on standards presented by the Clinical and Laboratory Standard Institute (CLSI) and should be performed only by trained personnel [21].

The use of experienced and trained samplers and the fact that the samplers are fixed in most sampling centers and observing all the points of sampling and sending samples based on national instructions can be some of the reasons for the low level of inappropriate samples in Kerman.

In this study, positive screening results were reported in 27% of Iranian neonates and 32% of non-Iranian neonates at 7 to 9 days of age, which is lower than the national average (58.2%). This rate was reported to be 16.6%, 25%, 26%, 36.5%, 78.5%, 84.7%, and 96.4% in Zahedan, Jiroft, Mashhad, Lorestan, Isfahan, Tabriz, and Fars University of Medical Sciences, respectively [22]. Immediate reporting of screening results has a significant impact on the early diagnosis and treatment of patients.

Kerman Province is the largest province of Iran, and 5 universities of medical sciences are located in this province, and samples of all infants born in this province are sent to the laboratory of the center of the province, Kerman city, which faces a volume of tests. Therefore, setting up another laboratory in the South of the province or increasing the capacity (equipment and human resources) in the central laboratory of the province may improve the timely reporting index of tests.

In the present study, the average age of diagnosis and referral time to the PKU treatment center was 20 days. Only 30.7% of Iranian and 33.3% of non-Iranian patients were referred to the PKU treatment center before 2 weeks of age. This rate has been reported in different provinces from 10% to 100%, and the national average was 47.9% [22]. In the study conducted by Zafar Mohtashami et al. in Lorestan Province, the mean age at the time of diagnosis of 20 screened PKU patients was 20 days [23], which is consistent with the results of this study. In France, with the start of the screening program, the age for starting the

special diet for patients changed to less than 14 days [24]. Researchers believe that the best age to start PKU treatment is the first 2 weeks of life [9]. The opinion of Kerman Health Deputy Experts is that factors such as not screening on time, delays in reporting positive screening cases, inadequate sampling, disruption of the program execution process, newborn conditions and diseases, and lack of parental cooperation affect this indicator in Kerman.

In order to improve the index of timely diagnosis and treatment of patients, measures have been taken in Kerman city. For example, in order to better access Afghan refugees, 3 sampling centers have been set up in their habitat. For better access to the villagers, sampling centers have been set up in 5 districts of Kerman city, which are relatively far from the city center. Also, in 2 hospitals in Kerman, a screening center has been set up for a timely sampling of hospitalized infants. The cost of a diagnosis confirmation test and a doctor's visit is free for some low-income families who cannot test their baby because of financial problems.

The implementation of screening programs in Iran has affected the early diagnosis and treatment of this disease [13, 20, 23]. Before starting the newborn screening program, patients were identified with delay, and most of them developed complications. For example, in a study in Ahwaz, performed on patients within the age range of 1-18 years, the age of diagnosis of this disease in 77.7% of cases was over 6 months [25]. In Mazandaran, the mean age of PKU patients at diagnosis was 20 months [26]. Also, in Mexico, the age of diagnosis in the absence of routine screening was 2 years and 8 months [5]. Studies have shown that early detection of patients, while creating beneficial effects for patients and increasing their quality of life, reduces the long-term costs of healthcare [27].

The findings of the present study indicated that, in the early years of the neonates screening program, the screening test result had been reported negative for 2 neonates screened on days 3-5 postnatally.

These infants had a history of hospitalization and, according to national guidelines, resampling should have been performed, but due to the lack of knowledge of parents, resampling was not performed. These children were under the care of a health center, but no attention was paid to the children's developmental delay.

One of these patients had been diagnosed by a pediatrician at the age of 10 months and another at 13 months after showing clinical symptoms and complications of the disease. The parents of these children had visited different physicians because of developmental retardation, but the disease had been diagnosed late and after the incidence of complications.

In Kerman, in order to prevent similar cases, the staff of the sampling center needs to pay special attention to infants who need to be resampled and infants who are not breastfed. Continuous training should be provided to health staff, and the transfer of experienced and trained personnel should be avoided. There should also be annual training sessions for staff and physicians at health centers to diagnose and treat patients who have not been identified in screening.

However, Ganji et al. reported no false-negative cases in Iran in 2015-2016 [13]; and other similar studies did not mention the false-negative cases [11, 15, 20, 28]. The patients who show negative screening tests may get identified by physicians and referred to PKU treatment centers, after a long time. In a study conducted in Mexico, the results showed that, due to an error in the screening test, 4 PKU patients were reported as false-negative [5]. Like the patients mentioned in our study, these patients were identified after the onset of symptoms and started the diet with a delay.

In this study, the incidence rate of PKU in Kerman, Iran, was estimated to be 1.35 per 10,000 live births. Based on the latest screening data from different Medical Sciences Universities of Iran (2014), the national average has been 1.23 per 10,000 live births [22]. This rate was reported to be 0.99 in 10,000 in Southern Khorasan [15], 1.91 in 10,000 in Lorestan [11], 1.6 in 10,000 in Fars [12], and 0.66 in 10,000 in Mazandaran Province [10].

Researchers think the most important reason for the high incidence of this disease in Iran is the high frequency of consanguine marriages [6, 11, 12, 29, 30]. The results of a study showed that 34.4% of marriages in Kerman are consanguine [31]. Consanguineous marriage in Afghan refugees living in Pakistan has been reported to be 55.4% [32]. Marriage with relatives doubles the chance of the incidence of this disorder [15]. However, after the implementation of prevention and control programs and prenatal diagnosis tests, the incidence of PKU has decreased in Iran [22].

In this study, all parents of non-Iranian (Afghan) patients and most parents of Iranian patients had a familial relationship. In studies done in other regions of Iran, including Lorestan [11], Khorasan Province [9], and Mazandaran Province [26], respectively, 82%, 80%, and 60% of PKU patients' parents had a consanguineous marriage. In a study conducted in Southern Khorasan, the parents of all the identified patients were relatives [15].

Other studies have shown that many PKU patients in Arab countries are the result of consanguineous marriage as well [4]. However, the results of a study in Southern Brazil showed, from the 34 PKU patients evaluated, only 2 patients had a history of parental consanguinity [33]; in a study from Thailand, from 15 PKU carrier couples, only one couple were relatives [7], and in Mexico, from the 50 PKU patient families evaluated, the marriage of two PKU patients' parents was related [5]. In a study conducted in Denmark, the frequency of autosomal recessive metabolic disorders was 25.5 times higher among newborns of Pakistani, Turkish, Afghan and Arab origin than among Danes [34]. These results indicate that consanguineous marriages are less common in non-Muslim countries.

Limitation

One of the limitations of this study was that we did not have access to the number of non-Iranian births, and we could not calculate the screening coverage in this group.

Conditions such as dialysis, blood injection, blood transfusion, oral or intravenous feeding with low-protein food and hospitalization were not specified separately in social genetic forms.

Economic, cultural, or other factors might have had an influence on the indicators of the screening program, but their impact was not evaluated in this study.

Conclusion

This study showed that the incidence of PKU in Kerman County is approximately equal to the national average. Also, the screening coverage and the rates for screening on time were similar to the national average. Moreover, the percentage of unsuitable or invalid samples was lower than the national average and acceptable. In Iranian children, the screening percentage on days 3 to 5 of birth was almost close to the national average, but it was lower in non-Iranian children. However, in the Iranian and non-Iranian populations, the percentage of children who got the results of their screening test and started treatment before day 14 of birth was less than the national average. Fortunately, from 2014, no false negatives had been reported. Most parents were relatives, and awareness about this disease among high-risk populations should be increased.

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Declaration of interest

The Authors declare that there is no conflict of interest.

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