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Original Article

Incidence of Phenylketonuria in Southern Iran

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Abstract

Background: Phenylketonuria is a hereditary, autosomal recessive disorder caused by deficiency of phenylalanine hydroxylase or its cofactor tetrahydrobiopterin. The purpose of the present study was to evaluate the incidence of this disorder in southern Iran.

Methods: All the neonates born between 22/Dec/2004 and 7/Sep/2007 were screened and their blood samples were tested by colorimetric and high performance liquid chromatography methods to obtain a diagnosis of phenylketonuria.

Results: Of the screened newborns (87091 females and 88143 males) 15 female and 13 male neonates were diagnosed definitely as having phenylketonuria.

Conclusion: The incidence of phenylketonuria in girls and boys was 1.7 in 10000 and 1.5 in 10000, respectively (mean: 1.6 in 10000) in southern Iran (Fars province).
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Keywords ● Phenylalanine ● phenylketonuria ● phenylalanine hydroxylase ● tetrahydrobiopterin

Introduction

Phenylalanine is one of the essential aminoacids. Dietary phenylalanine not utilized for protein synthesis is normally degraded by tyrosine pathway to Co_2 and water. Deficiencies of the enzyme phenylalanine hydroxylase or its cofactor cause accumulation of phenylalanine in the body fluids and central nervous system. In affected persons, excessive phenylalanine is metabolized to phenylketones that are excreted in the urine. The central nervous system damages in affected patients are caused by the elevated concentrations of phenylalanine in the brain. Elevated phenylalanine, if not treated in the first days of the life causes irreversible brain damages. Deficiency of phenylalanine hydroxylase causes classic phenylketonuria (PKU) and deficiency of its cofactor tetrahydrobiopterin causes malignant PKU.[1]

Up to now there has not been a large scale, exhaustive study on the incidence of PKU in Iran. Limited scattered studies by others have shown various results.[2-4]

Phenylketonuria is an autosomal recessive disorder and attentive to the high prevalence of relatives marriages in Iran, it is anticipated that this disorder has a high prevalence and incidence in Iran.

Materials and Methods

The present study was performed with the cooperation

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of the Deputy of Health, Shiraz University of Medical Sciences. In our study, all of the newborns in Fars province with a population of 4336878 (6% of Iran's population) from 22/Dec/2004 to 7/Sep/2007 were screened through a mandatory neonatal screening program including galactosemia, Glucose-6 phosphate dehydrogenase deficiency, and PKU. During the days 3 to 5 after birth, heel blood samples were taken on S and S 903 (Schleicher and Schuell 903, Bioscience, Germany) papers by an experienced technician and the samples was sent to a special screening laboratory where the serum phenylalanine were measured quantitatively by the colorimetric method. All newborns with serum phenylalanine levels more than 4 mg/dL were referred to a pediatric endocrinologist. Three mL of venous blood were obtained from these newborns and their sera were sent for re-evaluation by high performance liquid chromatography (HPLC) method. If the serum phenylalanine levels were equal or more than 10 mg/dL, the newborns were diagnosed as having phenylketonuria. In those with serum phenylalanine levels between 7 to 9.9 mg/dL, another blood sample was checked one week later and if the serum phenylalanine levels was equal or more than 7mg/dl, they were diagnosed definitely as having phenylketonuria. The newborns with serum phenylalanine levels between 4 to 6.9 mg/dL were considered healthy and they were only scheduled for visit by a pediatric endocrinologist.[5]

If a newborn was diagnosed as having PKU but in a future visit transient hyperphenylalaninemia was confirmed, she/he would be excluded from our study. If in the repeated visits, we confirmed that the newborns actually had phenylketonuria, they were included in our study.

Results

From 22/12/2004 to 7/9/2007, all the newborns who were born in Fars province (175235 newborns) were screened. Of them, 87091 were female (49.7%) and 88143 were male (50.2%). Blood testing showed that serum phenylalanine levels in 16 female and 14 male newborns were equal or more than 4 mg/dL. They were referred to a pediatric endocrinologist for further evaluation. All of the results were confirmed by HPLC method. In outpatient follow-up, transient hyperphenylalaninemia in one male and one female neonate was confirmed and they were excluded from the study. According to clinical findings in frequent visits, one of the patients suffered from malignant type of phenylketonuria and despite effective reduction of serum phenylalanine level, his symptoms including hypotonia, failure to thrive, and pallor continued. He finally expired at 3 months of age.

Unfortunately we were not able to do special tests including measurement of serum and urine biopterin and neopterin, tetrahydrobiopterin loading test, or do enzyme assay for the patient.

Finally, according to the screening blood test, HPLC method, and future outpatient visits, phenylketonuria was confirmed in 28 newborns (1.6 in 10000, [95% CI: 1.58-1.61]) including 15 female and 13 male newborns. In other words, the incidence of phenylketonuria in female and male newborns was 1.7 in 10000 (95% CI: 1.67-1.72) and 1.5 in 10000 (95% CI: 1.47-1.52), respectively.

There is significant statistical difference in the incidence rate in boys and girls ($P<0.0001$). The incidence of malignant phenylketonuria in patients with PKU was about 3 in 100.

Discussion

The incidence of phenylketonuria is varied in different populations. The lowest incidence is in Finland, less than 1 in 100000,[6] and in Japan, which is 1 in 1200000.[7] Among European countries, the incidence in Ireland and western Scotland is unusually high (one in 4500), which is one of the highest incidences in the world.[8] In Asian countries, in China the incidence rate is one in 18000.[9] In the United States, the incidence rate is from 1 in 19000 to 1 in 13500.[10]

In Iran, there have been limited studies on the incidence of phenylketonuria. In a study performed by Kabiri and Farhud on 8633 newborns born in different hospitals in Tehran, the incidence rate was calculated as 1.1 in 10000.[2] In another study by Golbahar and his colleagues on 1544 children with signs and symptoms of metabolic diseases, the incidence of phenylketonuria was calculated to be one in 3672.[3] In another study in Isfahan, the incidence rate among 1611 mentally retarded institutionalized patients was 20% (36 in 1611).[4]

In our study, the incidence of phenylketonuria in Fars province was 1.6 in 10000, which is similar to the study of Farhud and Kabiri.[2] Other than a proportional similarity with their study, our investigation cannot be compared with any other study. In the study done by Farhud and Kabiri only a small number of newborns (8633) were evaluated which cannot be compared with our study (187734). In the study done in Isfahan, the mentally retarded institu-

tionalized patients were studied, whereas in our study all the newborns were studied. Our study, so far, is the largest study evaluating the incidence of phenylketonuria in Iran.

Conclusion

The incidence rate of phenylketonuria in southern Iran (Fars province) is 1.6 in 10000. Because of ethnic and populace similarities between Fars province and other provinces of Iran, we might extrapolate our results to other regions of the country and estimate that the incidence rate of phenylketonuria in Iran might be about 1.6 in 10000.

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Conflict of Interest: None declared

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