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Evaluation of patients with phenylketonuria before and after screening in Qazvin Province, Iran

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Original Article

Abstract

BACKGROUND: Phenylketonuria (PKU) is a hereditary metabolic disorder and is inherited as autosomal recessive, so it is more likely to occur in consanguineous marriages. Early diagnosis is made by screening and timely treatment can prevent brain damage.

METHODS: This was a descriptive study including all children identified with PKU in Qazvin Province, Iran, up to march 2017. The required information was obtained through interviews with parents and reviewing of cases. Data were analyzed using SPSS software.

RESULTS: Of the 63 infected patients, 55.5% were residents of Qazvin City and the rest were residents of other cities in the province. Parents of 54.0% of the patients were related. 20.6% of patients had at least one patient with PKU in their family. The mean age that patients were diagnosed before screening was 34 months, and the statistical difference between the two groups was significant (P < 0.001). 52.4% of the patients were girls. The most common reason of referring of the patients before screening was a developmental delay. The prevalence of hyperactivity, seizures, and delay in walking and language were significantly different between the two groups (P <0.001).

CONCLUSION: Early diagnosis and treatment of children with inherited metabolic diseases can prevent brain damage and retardation in them and reduce the financial and psychological burden of treating these children by maintaining their intelligence quotient (IQ).

KEYWORDS: Diagnosis; Phenylketonuria; Developmental Disabilities

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Introduction

Phenylketonuria (PKU) is one of the most common disorders of amino acid metabolism and an important genetic disease. Elevated blood phenylalanine levels lead to irreversible brain damage. With timely diagnosis and treatment, the intelligence quotient (IQ) of these children can be kept within the normal range.[1,2] The incidence of PKU in whites is reported to be 1 in 10,000 live births. The highest incidence in the world was in Iran and neighboring countries and the lowest in Japan and Ashkenazi Jews.[3,4]

Phenotypic variation in patients with PKU indicates molecular heterogeneity of different mutations in the phenylalanine hydroxylase (PAH) gene. More than 500 different pathogenic mutations have been identified in the PAH gene. More than 53 different mutations have been identified in Iranian ethnic groups.[5-7] Based on the studies conducted, the prevalence

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ratio of this complication is one in 8000 in Iran.[8]

High levels of phenylalanine in the blood saturate blood-brain barrier (BBB) transporters, leading to reduced brain uptake of major amino acids such as tyrosine and tryptophan as a result of brain damage. Few adults with PKU have had normal intelligence without any treatment. Magnetic resonance imaging (MRI) and histological brain studies in people with untreated or late-treated PKU have shown some degree of irreversible cortical atrophy.[9,10]

The severity of hyperphenylalaninemia depends on the degree of enzyme deficiency. In complete deficiency of the phenylalanine hydroxylase, the level of phenylalanine in the blood increases to more than 20 mg/dl, which is called the classic form of PKU. If some activity of the phenylalanine hydroxylase enzyme remains, a milder form of the disease develops. In this case, the amount of phenylalanine in the blood is between 6 and 20 mg/dl and it is called hyperphenylalaninemia. At least 2% of cases of hyperphenylalanemia are due to defects in the metabolism of tetrahydrobiopterin and other cofactors and are considered as malignant PKU.[1] For each month of delay in treatment, the IQ of these children is reduced by 4 points, and if the treatment and food restriction are not fulfilled, by the end of the first year, the IQ of these children will be reduced by 50 points. For this reason, specific treatment or formula and restriction of phenylalanine in the diet should be started as soon as possible based on the type of disease.[2] Numerous studies have been performed on cerebral damage and IQ reduction in patients with late-treated PKU.[11,12]

For example, in a study by Morovatdar et al. in Khorasan, Iran to describe the characteristics of patients with PKU, 78.0% of the patients were reported to have a variety of developmental retardations. The best time to control PKU and maintain IQ in these patients is to start treatment and control the diet before the end of the first month of life.[14]

The aim of this study was to evaluate the delay in starting treatment and controlling diet on brain damage in patients with PKU.

This study was performed in Qazvin University of Medical Sciences, Qazvin, Iran with the code IR.QUMS.REC.1396.252, in order to compare the clinical manifestations of children with PKU before and after neonatal screening of this disease.

Methods

This was a descriptive study carried out on 67 patients with PKU identified up to March 2017 who were monitored in the Children Growth Research Center, Research Institute for Prevention of Non-Communicable Diseases, Qazvin University of Medical Sciences. Before the beginning of the PKU screening, these patients were diagnosed based on clinical findings, measurement of the blood phenylalanine level by the high performance liquid chromatography (HPLC) method, measurement of neopterin and urine biopterin, and in malignant cases by genetic testing. With the start of screening in the province in 2012, on the third to fifth day of birth, a blood sample was taken from the newborn on a paper filter to check the level of phenylalanine and was sent to a reference laboratory for testing. If the blood phenylalanine level was 4 mg/dl or higher, the blood phenylalanine level was measured by HPLC and if the phenylalanine level was again higher than 3.4 mg/dl, the patient was referred to the focal point of inherited metabolic diseases for further evaluation.[15]

The required information including location, demographic characteristics, age of diagnosis, family history and history of PKU in the family, and clinical manifestations were obtained through interviews with parents, review of patients' files, and if necessary, telephone calls. Data were analyzed using the chi-square test in SPSS software (version 22, IBM Corporation, Armonk, NY, USA) considering $P < 0.005$ as the

significance level.

Results

A total of 67 patients with PKU were registered in the patient management center. One of the patients who was kept in the Social Welfare Bureau died. One patient whose mother was from Turkey and whose father was Iranian had migrated to another place and the families of the two infected sisters were also unwilling to cooperate and provide information. Both girls had good IQs, one of the girls presented with lameness and was diagnosed with PKU in this family. Out of the 63 patients monitored in this center, 35 (55.5%) lived in Qazvin and the rest lived in other cities of the province. 38 (60.3%) patients were identified before the start of screening and the rest were diagnosed by screening. The mean height, weight, and head circumference of the patients at birth were 49.0 ± 4.4 cm, 3010 ± 1290 g, and 33.67 ± 2.90 cm, respectively. The age range of the patients was from 15 days to 18 years and the mean age was 5.65 ± 8.17 years. 54.0% of the patients' parents had relatives. In 20.6% of the patients, there was at least one infected person in the family. Eight patients had siblings or parents and five patients had relatives with PKU. After diagnosing PKU in a newborn at screening, it was determined that the patient's father and sister, who was in high school, also had PKU. One of the sick boys was the result of a twin pregnancy, but fortunately his sister was not infected.

The mean age of diagnosis of the patients before screening was 33.72 ± 30.81 months. Only one patient was diagnosed at birth because his older brother had PKU. The age of the patients at the time of diagnosis varied from 7 to 120 months and there was a statistically significant difference between the two groups ($P < 0.001$). 32 (50.7%) patients were of preschool age, 16 (25.3%) attended regular school, and 10 (15.8%) attended special school. 5 (7.9%) patients were unable to study. The comparison in terms of education between the two groups showed significant a significant difference ($P < 0.001$).

4.9%, 9.8%, 47.5%, and 37.7% of the patients were in the weight percentages of > 5, 5-25, 25-50, and > 50%, respectively. In terms of height percentiles for age, 3.3, 24.0, 44.3, and 17.0% were in percentages less than 5, 5-25, 25-50, and more than 50, respectively. There was no significant difference between the two groups in terms of height and weight percentiles (Figure 1). 13 (50.0%) patients who were diagnosed through screening and 20 (54.1%) patients who were diagnosed before screening were female and the difference between the two groups was not significant in terms of sexual prevalence.

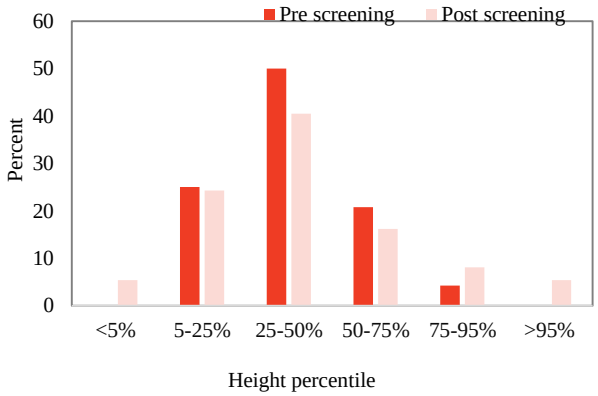

Figure 1. Comparison of height percentiles between the two groups

The most common reason for referring patients to a doctor before screening was delay in sitting, walking, and talking. A number of patients have had skin rash, restlessness, and hyperactivity. There was a significant difference between the incidence of seizures, delay in walking, delay in speaking, and the prevalence of hyperactivity in the two groups ($P < 0.001$). Patients in the two groups did not differ significantly in the incidence of rash (Figure 2). The mean level of phenylalanine in patients at the time of diagnosis was 13.7 ± 7.9 mg/dl.

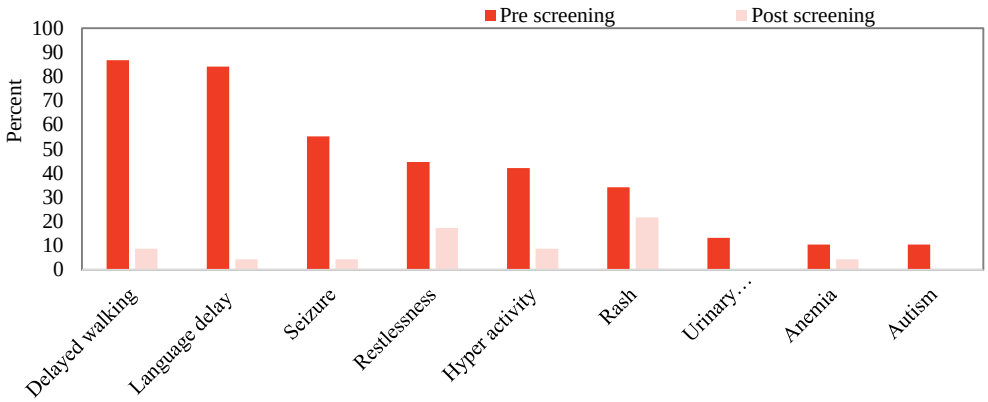

Figure 2. Prevalence of disorders in the two groups before and after phenylketonuria (PKU) screening

Discussion

In the present study, the incidence of seizures, gait delays, speech delays, and the prevalence of hyperactivity in children with PKU who were undiagnosed at birth were significantly higher than those diagnosed by screening timely.

Failure to diagnose and treat inherited metabolic diseases can lead to severe mental retardation, seizures, and developmental delays. Additionally, timely diagnosis and treatment of PKU can maintain the IQ of these children.[16,17] According to the National Phenylketonuria Incidence Screening Program, one case per 8,000 patients is estimated, with a wide range from one case per 3,000 to one case per 60,000 population.[18] PKU is a common inherited metabolic disease and is inherited autosomal recessively, thus increasing the chances of contracting it in consanguineous marriages. 52.4% of our patients were girls and 54.0% of our patients had relatives.

The rate of consanguineous marriages in Iran is reported to be 38.6%.[19] The prevalence of PKU varies by race and geographical location.[13] The mean age of diagnosis of our patients before screening was 34 months. The symptoms of patients diagnosed before PKU screening were delayed walking and talking, seizures, restlessness, hyperactivity, skin rash, and urinary incontinence. Delays in diagnosis and treatment in untreated patients have led to varying degrees of mental retardation in these children. 20.6% of our patients had at least one affected person by PKU in the family. In a study in Mashhad, out of 78 patients with PKU, 49.0% were boys and the mean age of diagnosis was 19 months.

80.0% of the parents were related and in 24.0% of the cases there was a history of preterm delivery. Seizures, mental retardation, gait disturbance, spasticity, and bad smell of urine were observed in 36.0, 60.0, 50.0, 15.0, and 53.0% of the patients, respectively.

Hypopigmentation, autism, hyperactivity, and skin wax were also reported in 14.0, 43.0, 76.0, and 26.0% of the patients. 12.0% of the patients had a family history of PKU. Only 10.0 % of the patients were diagnosed by screening and most patients were diagnosed before screening for clinical signs. The main reasons for referring patients were developmental delay, hypopigmentation of the skin and hair, seizures, bad breath, and hyperactivity, respectively. According to the screening, the incidence rate was one in 17,336 people. 8 families had two patients and one family had 3 patients.[14] This study was different from our study in terms of the mean age of diagnosis, rate of disease in girls, and level of parental kinship. In a study conducted by Eshraghi et al. in Mazandaran, Iran, the mean age of patients diagnosed before screening was 20 months. Parents of 60.0% of the patients

were related to each other. In this report, the age of diagnosis of patients before screening was lower than in our study.[13]

Conclusion

Early diagnosis and treatment of children with inherited metabolic diseases can prevent brain damage and retardation in them and reduce the financial and psychological burden of treating these children by maintaining their IQ. Reducing consanguineous marriages is especially important if there is an affected person in the family.

Conflict of Interests

Authors have no conflict of interests.

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