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The Epidemiological and Clinical Study of Phenylketonuria (PKU) Patients in Khorasan, North-eastern Iran

Negar Morovatdar[1], Shapour Badiee Aval[2]*, Seyed Mohammad Reza Hosseini Yazdi[3], Farzaneh Norouzi[4], Tahereh Mina[5]

1. Treatment Affairs of Vice Chancellor, Health System Research Committee, Mashhad University of Medical Sciences, Mashhad, Iran
2. Complementary Medicine Research Center, Faculty of Traditional Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
3. Treatment Affairs of Vice Chancellor, Special Diseases Center, Mashhad University of Medical Sciences, Mashhad, Iran
4. Department of Information Technology, Treatment Affairs of Vice Chancellor, Mashhad University of Medical Sciences , Mashhad, Iran
5. Treatment Affairs of Vice Chancellor, Special Diseases Center, Clinical Psychologist, Mashhad University of Medical Sciences, Mashhad, Iran

ABSTRACT

***Background*:** Phenylketonuria (PKU) is an autosomal recessive disease. Early diagnosis could act as an effectual public health intervention in order to prevent neurological impairments. This study aimed to describe the characteristics of PKU patients in the region of Khorasan located in the Northeast of Iran.

***Methods*:** In total, 79 patients were known to be suffering from PKU in Khorasan until September 2013 who were all included in this study. Variables such as the diagnosis age, sibs and parents, cause of referring to the physician and screening or clinical diagnosis were investigated. Descriptive statistics were used for data analysis.

***Results*:** The mean age of diagnosis in the studied subjects was 19 months. Moreover, 80% of the PKU patients had a positive history of consanguineous marriages in their parents. The incidence of new cases identified via screening in 2012-2013 was 57 per 1,000,000 live births. Furthermore, 10% of the patients were identified via screening within the first week of birth.

***Conclusion*:** Nearly all of our patients (90%) had been diagnosed only by the clinical manifestations in the first year of their life without screening within the first days of birth. Regarding the efficacy of early diagnosis and dietary treatment, the enforcement of public health policy through screening is critical to public health preventive interventions.

Key Words: Clinical, Epidemiology, Khorasan, Phenylketonuria

Introduction

Phenylketonuria (PKU) is a metabolic error which is caused by the deficiency of phenylalanine hydroxylase (PAH) enzyme inverting phenylalanine to tyrosin. This enzyme deficiency induces high levels of phenylalanine in the blood (1).

If they do not receive any treatment, most of the patients are likely to experience severe neurological impairments, reduced IQ and mental retardation.

However, it is believed that adequate treatment within the first two weeks of birth could noticeably alter the natural outcome of the disease (2-4).

The early diagnosis of the disease, at least within the first days of birth, is a critical measure. In this regard, neonatal screening has been widely recognized as a fundamental public health intervention in the past fifty years (5).

US Preventive Services Task Force (USPSTF) recommended neonatal screening as an A-category being able to demonstrate a high certainty of benefits (6).

The benefit-cost ratio of PKU screening has been analyzed by several studies many of which confirm numerous benefits for this method (7-9).

The prevalence of PKU ranges from one per 10000-20000 live births depending on the geographical regions across the world.

Depending on the subjects' country and race, the prevalence of the disease is estimated from one per 4000 live births in Northern Ireland to one per 71000 live births in Finland while in European and American countries, the prevalence is as much as one per 10000-20000 live births (10).

* *Corresponding author*: Shapour Badiee Aval, Complementary Medicine Research Center, Faculty of Traditional Medicine, Mashhad University of Medical Sciences, Mashhad, Iran. E-mail: BadieeASH@mums.ac. Ir

Consanguineous marriages are known as one of the significant causes of PKU in these regions (10).

PAH enzyme deficiency induces high levels of phenylalanine in the blood as well as in other body fluids, especially the urine and cerebrospinal fluid (CSF) (11).

Furthermore, Hyperalaninemia is known to give rise to such complications as severe mental retardation, Microcephaly and seizures by causing an imbalance in the central nervous system (12).

Recent studies in Iran have been indicative of a high incidence rate of PKU in the Iranian population estimated as one per 3627 live births (13-17).

In a study conducted from 2000 to 2005 in the region of Fars, the incidence rate of PKU was estimated to be one per 4698 live births (18) while a recent report revealed a prevalence of 1.7 per 10000 live births (18).

On the other hand, the incidence of PKU was reported to be noticeably higher among the mentally retarded who were institutionalized in long-term care facilities (19).

In another study, the prevalence of the disease among the mentally retarded was estimated to be as much as 2.1-5% (20).

As a result, PKU is regarded as one of the major causes of mental retardation in the Iranian population.

PKU is presumed to be more prevalent among the neonates of consanguineous marriages. High incidence of relative marriages is directly associated with a high prevalence of the disease in the population (21, 22).

The most prominent symptom of the disease is mental retardation. In comparison with the control group, PKU patients were found to have a lower IQ, weaker verbal function, impaired attention and underdeveloped motor control skills (23).

The IQ of these patients is usually less than 50. Among other frequent deficiencies caused by PKU are Microcephally, cognitive impairments, neuropsychiatric disorders and psychosocial problems.

Developmental retardation does not occur until several months after birth. Some of the common symptoms of the condition include vomiting, eczema rashes, severe mental retardation, urine odor, seizures and dermal hypopigmentation. Hyperactivity is also a common feature of PKU patients (23, 24).

PKU is an autosomal recessive disease (25) the diagnosis of which is mainly based on hyperalaninemia (26, 27). It is believed that restricting phenylalanine could decrease the levels of this amino acid in the blood preventing neurological impairments.

To the best of our knowledge, the most efficient prognosis of the disease is to control phenylalaninemia which should be done before the end of the first month of birth (28).

This study was designated and approved by Mashhad University of Medical Sciences (911115 confirmed code) aiming to describe the features of PKU patients in the region of Khorasan (the largest province of the Northeastern part of Iran). We investigated the epidemiological, clinical and demographical characteristics of the PKU patients who had been diagnosed via neonatal screening or without it.

Method

This study was conducted on 81 patients who were all known to suffer from PKU in Mashhad city (located in the Northeast of Iran) until October 2013.

The patients' diagnoses were based on the confirmation obtained from the high-performance liquid chromatography (HPLC). All the patients had referred to the Endocrinology Clinic of Ghaem Hospital affiliated with Mashhad University of Medical Sciences. Data were collected from the medical records of the patients and in case any of the subjects lacked sufficient data in their records, we would contact them in order to complete the information.

The information included the diagnosis age, history of consanguineous marriages in parents, history of PKU in other sibling and the clinical manifestations at the time of diagnosis.

The collected data were analyzed by SPSS software V.16 and descriptive statistics were used for data description.

Results

In total, 81 PKU patients were referred to the Endocrinology Clinic of Mashhad University of Medical Sciences until September 2013. Of all the patients, one died and two others lacked adequate data in their medical records**.**

Ultimately, 78 patients were included in the present study. Approximately 49% of the PKU patients who participated in this study were male and the mean diagnosis age of the subjects was 19 months (ranging from 1month to 14 years).

A blood relationship was found in 80% of the subjects' parents. Furthermore, 78% of the patients had a variety of developmental retardations. The history of preterm labor in 24%

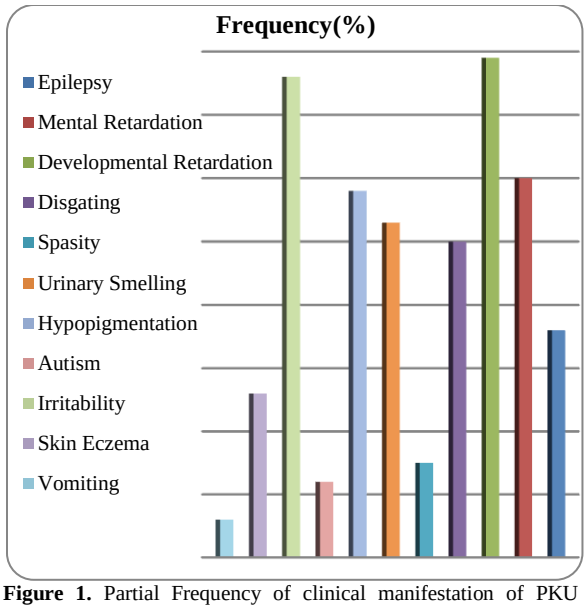

Figure 1. Partial Frequency of clinical manifestation of PKU patients

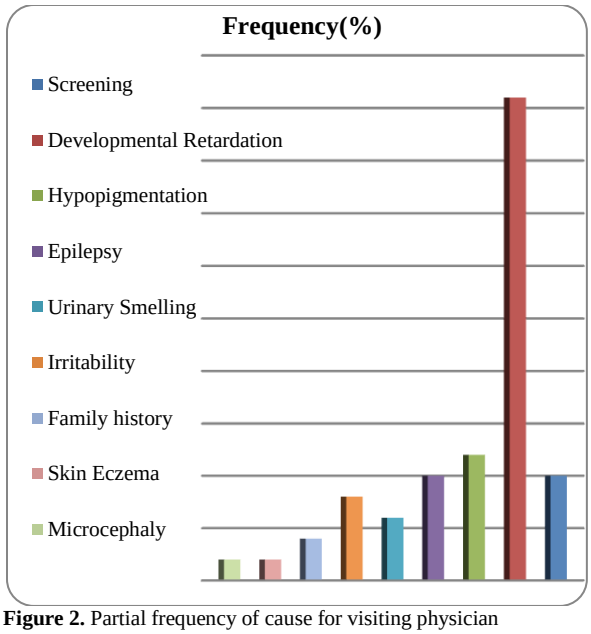

Figure 2. Partial frequency of cause for visiting physician

of the patients was positive. Other clinical manifestations of PKU included a history of seizure in 36% of the cases, mental retardation in 60%, Abnormal gating in 50%, spasticity in 15%, urine odor in 53%, Hypopigmentation in 43%, autism in 14%, hyperactivity in 76% and skin eczema in 26% of the patients (Figure 1).

For another thing, 12% of the patients had a history of PKU in their elder siblings and the medical history of abortion was positive in 21% of the mothers of the PKU patients.

Only 10% (8/78) of the patients had been diagnosed via first-week neonatal screening. The majority of the subjects had been detected by clinical manifestations of PKU. The major reasons for these patients to refer to a physician was symptoms of developmental retardation, dermal and hair Hypopigmentation, seizure, urine odor, hyperactivity, a medical history of the disease, skin eczema and hypoactivity, respectively (Figure2).

According to the findings of this study, early diagnosis of PKU via screening was made in only 4 cases per 69347 live births (one per17336 live births) in 2012 and 2013.

It was also observed that in the studied patients, there were 8 families with two PKU patients and one family with 3 PKU patients.

Discussion

According to the findings of the present study, the early diagnosis of PKU via screening is made in only one case per 17336 live births per year.

As stated in the national neonatal screening program, the incidence rate of PKU is estimated to be one patient per a population of 8000 ranging from one per a population of 3000 to one per a population of 60000 (26).

Since PKU is an autosomal recessive disease, its prevalence will increase along with an increase in the number of familial marriages.

In our study, the mean diagnosis age was 19 months, which is similar to the studies conducted in the countries where PKU screening is not yet included in the routine neonatal screening.

In a study conducted in the region of Mazandaran, the mean diagnosis age was 20 months while it was 32 months as estimated by another study in Mexico. This age range is normally the time for the neurological impairments of the disease to occur. For this reason, screening programs are considered crucial to the public health care (28, 29).

The diagnosis age could decrease with neonatal screening programs resulting in a more efficient prevention and management of the disease.

The main reason behind delayed diagnosis in the Mexican study was reported to be the absence of routine screening programs in the health care system. After 2006, a national routine screening program was included for PKU in Mexico after which the number of early-detected patients noticeably increased (29).

The gender composition of our study was 49% male and 51% female. In a study

conducted in Shiraz, approximately 70% of the patients were male.

Furthermore, we found that the history of PKU in the subjects' family accounted for 12%, which is a finding similar to that of several other studies. It was also observed that 80% of the parents had a blood relationship, which was reported to be 60% and 82% in a number of other studies (27, 28, 30).

The rate of consanguineous marriages in Iran has been estimated to be around 38.6%, 28% of which are recorded as first-degree (18).

Due to the considerable rate of consanguineous marriages in Iran, awareness should be raised regarding screening programs as well as the management of PKU patients as a crucial part of the public health preventive intervention.

In our study, only 10% of the patients had been detected via screening programs. This rate was 8% and 17% in some other studies conducted in developing countries (27-30).

In the countries where PKU is not included in the Newborn Screening (NBS), most of the patients are detected via clinical manifestations of the disease.

Among the mentally retarded individuals who live in long-term care facilities, the prevalence rate of PKU is estimated to be about 2.2% which has been reported to be between 1-3% by a few other studies (17).

Conclusion

According to the national estimation of PKU in Iran as performed by the Ministry of Health, one per a population of 800 is at the risk of the disease. Comparing this figure with our findings, we realize that the prevalence rate is considerably lower in our study than the actual incidence rate.

On the other hand, since familial marriages were shown positive in 80% of our patients, it is essential to pay close attention to the screening programs, especially in case of such marriages.

Since PKU patients appear normal in their early stages of life and mental or other developmental retardations might develop gradually, effective interventions are to be made as to control the occurrence of such disorders.

Without appropriate treatment, the IQ is likely to drop by 4 scores per month as it is explicitly known that it declines to 50 within the last half of the first year of life. Thus, brain disorders caused by PKU could turn into severe problems if the patient does not receive proper treatment in time.

Contrary to developed countries where PKU patients are managed through timely treatment which alters the clinical disease to a genetic specification, in developing countries patients are still being treated by full clinical phenotypes.

Therefore, it is vital for all the physicians who are specialized in managing patients with mental retardations or developmental disorders to pay close attention to PKU in their differential diagnoses.

Since the most efficient prognosis of the disease is made only by the early treatment before the first month of birth, physicians as well as the public are to be made aware of PKU.

Appropriate treatment is known to benefit 90% of the PKU patients via screening along with all their families.

In order to promote the screening programs, the following approaches are recommended: 1) raising awareness in the physicians and families about the benefits of neonatal screening; 2) appropriate sampling within the first 3-5 days of birth; and 3) following up the positive samples of the disease for a specific period of time.

In summary, screening program counseling is of paramount importance for other family members of the old or recent PKU cases in order to prevent repeated cases in the family.

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