

Co-existence of Phenylketonuria (PKU) and beta-Thalassemia Major in a 16 Years Old Girl: A Case Report

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Abstract

While thalassemia major (TM) used to be a prevalent genetic disease in the past, however, Phenylketonuria (PKU) is quite rare in spite of consanguinity marriage rate of about 40% in the region. Preventive efforts for TM started >20 years ago but neonatal screening for PKU started since 2007. This is the first report of co-existence of thalassemia and PKU in Middle East and in consideration of the prevalence of each genes, this chance association is a very unusual event. We report a case of having PKU and TM.

Key words: Hemoglobin, Phenylketonuria, Thalassemia

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Purpose

Thalassemia is the most common monogenic defect around the world occur in the countries of Mediterranean origin, areas of north and west of Africa, the Middle East, Indian Subcontinent and in southeast Asia (1,2). The most prevalence of β gene thalassemia is found in north of Iran and Mediterranean regions (10%), and with less prevalence has been reported in Esfahan (8%), south of Iran (8-10%) and 4-8% in other regions of the country (3).

The "beta gene" cluster and "alpha gene" cluster located on the chromosome 11 (p15) and chromosome 16, respectively (4). The disease is inherited in an autosomal recessive method (5). Controlling and eradication programs have been started in Iran from 1990 and have been running in all parts of the country from 1996 (5).

Phenylketonuria (PKU) is a genetic metabolic disorder (6). PKU is an inborn error of metabolism that most commonly stems from mutations in the phenylalanine hydroxylase gene that is found on chromosome 12 at the locus 12q24.1 (7,8). Untreated patients typically develop a characteristic clinical picture that may include mental retardation, seizures, growth retardation, hyperreflexia, eczematous dermatitis, and hypopigmentation (7). It is transmitted as an autosomal recessive

disorder with considerable variety in incidence among different ethnic populations and the prevalence of the disease is increased by consanguineous marriages.

The incidence of PKU is one in 13,500 to 19,000 births (9). Whereas, the prevalence of the disease is anticipated 1 in 6000 births in Iran. It is less common in the Afro-American population with an incidence of about 1 in 50,000 based on newborn screening data from the state of Maryland (10). Preventive efforts for PKU started since 2007 in Iran.

While thalassemia major (TM) used to be a prevalent genetic disease in the past, however, PKU is quite rare in spite of consanguinity marriage rate of about 40% in the region. This is the first report of co-existence of thalassemia and PKU in Middle East and in consideration of the prevalence of each gene, this chance association is a very unusual event. We report a case of having PKU and TM.

Case report

A 16 year- old girl with TM (HbF: 62%), receives regular monthly blood transfusions since 15 months of age. Head circumference was 48 cm. She had diabetes mellitus, hypersplenism (span of spleen: 151 mm), severe thrombocytopenia and delay in development and investigated for PKU as she

had blue eyes and blond hairs. She was severely mentally retarded when was diagnosed as classic PKU case.

Patient did not use diet and iron chelators regularly because of mental retardation. mean of serum ferritin was 5000 ng/ml since 3 years ago. The patient was under supervision of pediatric neurologist. In requested tests by pediatric neurologist serum level of phenylalanine was 52.1 mg/dl.

Because Phenylketonuria (PKU) screening program has been done from 5 years ago in the country, this patient had referred with symptoms of seizures and mental retardation. She was the first child of an apparently not related marriage with negative family history of both diseases. Both diagnoses were confirmed by molecular analysis. The family has a normal child after prenatal diagnosis for both diseases. The family has a normal child after prenatal diagnosis for both diseases.



Conclusion

PKU first described by Folling in 1934 (8). Phenylketonuria (PKU) is a disorder of phenylalanine (Phe) metabolism associated with deficient activity of Phe hydroxylase (PAH) or its cofactor, tetrahydrobiopterin, and elevated concentrations of Phe and Phe metabolites (11). There are different clinical and biochemical forms of phenylalanine in the body including:

- A) Classical type of Phenylketonuria (PKU)
- B) Malignant hyper phenylalanine (lack of BH₄ cofactor)
- C) Benign hyper phenylalanine
- D) Transient phenylalanine

Treatment consists of dietary control with restricted intake of phenylalanine through the use of special medical formulas or foods (12). When adequate dietary control is maintained,

children with PKU can be expected to have grossly normal growth and development. (13)

The co-existence of these diseases made very difficult the correct interpretation of clinical symptoms as pallor and irritability in early life. Association of these two diseases has not been reported so far. So that, considering different aspects of this association in a person is required.

Infants with severe beta thalassemia major (TM) are well at birth, because the production of beta globin is not essential during fetal life or the immediate perinatal period (4). Newborn PKU infants are asymptomatic prior to the initiation of feeds containing phenylalanine (eg, breast milk or standard infant formula) (9). Most affected children have normal development measured at 5 years of age (11). If undetected by metabolic screening, the onset of PKU is insidious and may not cause symptoms until early infancy (9).

Gropper and et al., in article entitled "Immune status of children with phenylketonuria" divided PKU children with PKU into one of three groups based on fasting plasma Phe levels. Hematologic and immunologic parameters of the children with PKU were compared between the groups and also compared with published values from age-matched children without PKU (4).

The immune system of the discussed patient is weaker due to association of PKU with thalassemia. It should be noted that some drugs such as trimetoprim sulfamethoxazole, methotrexate, and other antileukemic agents are known to inhibit dihydropteridine reductase enzyme activity and should be used with great caution in patients with BH₄ deficiency (15). Therefore, infections should be seriously prevented in patient and in case of infection; the effect of drug metabolism on enzyme systems should be noted.

Skeletal changes in TM are due largely to the expansion and invasion of erythroid bone marrow, which widen the marrow spaces, attenuate the cortex, and produce osteoporosis. Osteopenia with cortical thinning, increased trabeculation of the spine, and severe osteoporosis with fractures remain serious complications, even in well-transfused and iron-chelated patients (16, 17). In young adults with PKU, approximately 40 percent or more

have a low peak bone mass (18, 19). The etiology remains unclear, although there is some indication that increased phenylalanine concentrations may affect normal bone development (20).

Therefore, the possibility of bone damage in this patient is more than patient with any other disease alone.

In PKU, the subject is microcephal (15), While in thalassemia major, hypertrophy of skull is due to extra modularly erythropoiesis.

In MT typical faces (maxillary hyperplasia, flat nasal bridge, frontal bossing) can be seen (15). Prominent maxilla with widely spaced teeth seen in PKU patients (15).

Growth retardation seen in both disease, but etiology is different. (15)

Cardiac malfunction, including heart failure and fatal arrhythmias, are frequent causes of death in MT, and cardiac dilatation secondary to anemia is nearly universal. Cardiomegaly and left ventricular dysfunction ensue in the untreated child, leading to end-stage cardiomyopathy (4). In transfused patients with TM, cardiac hemosiderosis is the most feared complication (4). Babies born to mothers with PKU and uncontrolled phenylalanine levels may have heart defects or other heart problems (11)

The brain is the main organ affected by hyperphenylalaninemia (15). About 25 % of children have seizures, and more than 50% have electroencephalographic abnormalities (15). Untreated PKU is characterized by severe to profound intellectual disability and autistic-like behaviors. (11). So that, consultation with a neurologist and psychiatrist is very important in this case.

In 1993, 500 TM patients were registered at the clinic of the Boo Ali Sina Hospital, Sari, Mazandaran, Iran. From 1993 to 1996, on average of 50 new cases were added to the cohort annually, whereas from 1995 to 2005 the number of new cases declined to 35 per year. Furthermore, the patients' average age increased (2).

In conclusion, at the relatively low cost of premarital screening and genetic counseling, we have offered at-risk couples the possibility of preventing the birth of at least 600 undesired TM patients. Thus, a great deal of suffering and an unbearable financial burden has been

prevented to patients and their families (2). The diagnosis of PKU is carried out by the Guthrie test. This detects elevated levels of phenylpyruvic acid in the blood during the first week of life. This is done with a needle prick in the heel and the blood is dried on filter paper so that the phenylalanine concentration can be measured. PKU must be detected early so that treatment can start within the first 20 days of life (22). Couples should have genetic tests to see if they are carriers of the recessive gene for PKU. If they are then they should definitely take that into account if they decide to have children (22). Genetic counseling should be offered for all women with PKU before and after conception (11).

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