Research Article (Araştırma Makalesi)

Late Diagnosed Classical Phenylketonuria Cases and the Causes

Geç Tanı Klasik Fenilketonüri Olgularımız ve Geç Tanı Nedenleri

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Özet

Amaç: Fenilketonüri, yenidoğan tarama programı kapsamında erken tanı ve tedavisiyle başarılı sonuçları olan metabolik bir hastalıktır. Yenidoğan tarama programı kapsamı dışında tanı alan vakalar "geç tanı" olarak kabul edilmekte ve tedavisiz geçen süreç sonunda geri dönüşümsüz gelişim geriliği ve zihinsel gerilik oluşmaktadır.

Gereç ve Yöntemler: 15/09/2018-15/12/2019 tarihleri arasında Pediatrik Metabolizma polikliniğinde geç tanı klasik fenilketonüri olgularımızı ve geç tanı nedenlerini retrospektif olarak inceledik.

Bulgular: On beş ay gibi kısa bir süreçte Çocuk Metabolizma Polikliniğimizde, 6 geç tanı klasik fenilketonüri vakamız oldu. Hastalarımız 3-35 yaş aralığında olup, en sık başvuru şikayetleri otizm spektrum bozukluğu, epilepsi, nöromotor gelişim geriliği, nörokognitif gerilik idi. Hastalarımızın tümünde kan fenilalanin düzeyi 1200 µmol/L (normal aralık 60-120 µmol/L) üzerinde idi ve klasik fenilketonüri tanısı aldılar.
Bir hasta yenidoğan tarama programı kapsamında eksik kan örneği olması nedeni ile tanı geç tanı almıştı. Beş hasta ise yenidoğan tarama programının yaygın uygulanmasından önce doğmuş ve kan örneği alınmamıştı. Hastaların birinde doğduğu ülkede yenidoğan tarama programı yoktu ve kan örneği alınmamıştı.

Sonuç: Akraba evliliği oranının yüksek olduğu Türkiye'de, fenilketonüri hastaları her yaşta farklı kliniklerle karşımıza çıkabilmektedir. Ülkemizde yenidoğan tarama programının başlangıcından önce doğan çocuklar ve erişkinlerde, tedavisi başarılı bu metabolik hastalığı unutmamalıyız.

Anahtar kelimeler: Fenilalanin, Fenilketonüri, Maternal Fenilketonüri Sendromu, Metabolik hastalık

Abstract

Objective: Phenylketonuria is a congenital metabolic disease which can be successfully treated if it is diagnosed in the early period with the neonatal screening program. Cases diagnosed apart from the neonatal screening program are considered as "late diagnosis" and irreversible developmental delay and intellectual disability occurs at the end of the untreated process.

Material and Methods: Between 15/09/2018-15/12/2019, we examined our late diagnosed classical phenylketonuria cases in the Pediatric Metabolism Outpatient Clinic and causes of late diagnosis, retrospectively.

Results: We had six late diagnosed classical phenylketonuria cases in our Pediatric Metabolism Outpatient Clinic in a period of 15 months. The age of our patients were between 3 and 35 years, and the most common complaints were autism spectrum disorder, epilepsy, neuromotor developmental retardation and neurocognitive retardation. All of our patients had a blood phenylalanine level above 1200 µmol/L (normal range 60-120 µmol/L) and they were diagnosed with classic phenylketonuria.
One of our patients had a delay in the diagnosis due to missing blood sample within the newborn screening program. Since four of our patients were born before the neonatal screening program was started, no blood sample was taken. One of our patients did not have a neonatal screening program in their country, and no blood sample was taken.

Conclusion: In Turkey, where the rate of consanguineous marriage is high, patients with phenylketonuria can present with different clinics for all ages. This congenital metabolic disease which can be treated should not be forgotten in children born before the neonatal screening program and also in adults in our country.

Keywords: Phenylalanine, Phenylketonuria, Maternal Phenylketonuria Syndrome, Metabolic disease

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INTRODUCTION

Phenylketonuria (PKU) is an autosomal recessive congenital disorder of phenylalanine metabolism characterized by a mutation in the phenylalanine hydroxylase (PAH) gene (1). Phenylalanine hydroxylase is the enzyme that converts phenylalanine to tyrosine and whose cofactor is tetrahydrobiopterin (BH4). As a result of this enzyme deficiency, blood Phenylalanine (Phe) concentration increases.

The prevalence of phenylketonuria varies widely around the world, in Europe the prevalence is about one case per 10000 live births (1). The incidence of these diseases is higher in Turkey, where the rate of consanguineous marriage is high.

The normal range of blood Phe concentration is 60-120 µmol/L. According to the blood Phe level at the time of diagnosis, PKU can be classified as classical PKU (Phe >1200 µmol/L), mild PKU (Phe 600-1200 µmol/L) and mild hyperphenylalaninemia (HPA) (120-600 µmol/L) (1).

Untreated phenylketonuria patients may have eczematous rash, fair hair and eye color, autism, seizures, motor deficits and progressive intellectual impairment. Behavioral disorders, psychiatric symptoms and developmental problems become more severe as the patient grows (1). Today, PKU is screened within the scope of newborn screening program in many countries of the world. Normal neurocognitive development can be achieved in these patients with early diagnosis and treatment. Dietary restriction of phenylalanine continues to be the mainstay of treatment. However, phenylketonuria disease is an active research area, and new treatment options are emerging that may reduce the burden of the difficult and restrictive diet on patients and their families (2). In our country, the national neonatal screening program for PKU started in 1983. Since 2006, the national neonatal screening program has been applied more widely. Hence, adolescents and adults born before this date were not included the screening program. Therefore, we can see untreated patients with different clinical findings at different ages. Currently, within the scope of the screening program blood samples are taken from babies twice one at the time of discharge from the hospital and the other one week later.

We aimed to draw attention to this disease by examining the admission ages and clinical findings of our late diagnosed PKU cases, which were diagnosed in a short period of 15 months in our pediatric metabolism outpatient clinic, and the reasons for late diagnosis, and to emphasize that we can encounter these patients at any age.

MATERIALS AND METHODS

This retrospective study was conducted between September 2018 and December 2019 in Pediatric Metabolism outpatient clinic of a university-affiliated hospital in Istanbul. Patients who were diagnosed as PKU lately and apart from neonatal screening program, constituted the study population. The demographic and clinical data of the patients were obtained from the patient files, while the laboratory data were obtained from the automation system. At the time of diagnosis, if the blood Phe level was >1200 µmol/L it was classified as classical PKU.

Statistical Analysis

Statistical analysis were performed using SPSS 25.0 for Windows and Microsoft Excel 2019. Numerical variables were given as mean, standard deviation, minimum and maximum.

The written informed consents were taken from the patients and/or their legal caregivers. The study was performed with adherence to the Helsinki Protocol and approval was obtained from the Clinical Research Ethics Committee of Prof. Dr. Cemil Taşçıoğlu City Hospital with protocol number: 48670771-514.10-2020.

RESULTS

Our first case was 3 years old girl and had complaints of inability to walk and speak. The patient, who just started to sit with support, had light hair and eye color, no eye contact, and meaningless laughs. She also had stereotypical movements and dystonic movements in the hands. The patient had truncal hypotonicity, spasticity in the lower extremities, and deep tendon reflexes were detected brisk. Although the birth weight of our patient is not known exactly, it was told by the family that she was born prematurely and there was no history of postnatal hospitalization. Her motor retardation was investigated previously, and cranial magnetic resonance imaging was found to be normal at that time. In the family history; there was a consanguineous marriage between her parents, sister was diagnosed with epilepsy, and her brother was healthy.

In the metabolic investigations of the patient, the blood phenylalanine level was 1309 µmol/L (normal range

60-120 µmol/L), tyrosine level was 47 µmol/L (normal range 22-108 µmol/L), and Phe/Tyr was 27.6 (normal range <1.2). According to these results, the patient was diagnosed with classical PKU and special nutritional therapy was initiated. Approximately 6 months after the nutritional treatment, the patient started to sit with support and then stepped with help.

On the postnatal second day, the screening blood was taken within the scope of the newborn screening program before discharge. But the second screening blood was not given because the family moved to another city.

Family screening was performed by examining the blood Phe level in the mother, father and siblings of our patient. Her sister, who was 18.5 years old, had a diagnosis of epilepsy and her birth history was unknown. Her seizures started at the age of 1.5 years and she was able to walk at the age of 5 years old. She went to school, but could not learn to read and write and dropped out, she was able to take care of herself. The patient's blood Phe level was 1493 µmol/L, blood Tyr level was 39 µmol/L, Phe/Tyr 38.1, and she was diagnosed with classic PKU like her sister. As a treatment, nutritional therapy was initiated first, but due to her non-compliance with nutrition other treatment options were tried, she could not also comply with the treatment. Since the patient was born before 2006, she was not screened for PKU within the scope of the neonatal screening program.

Our third case was a 5-year-old girl who was referred to our outpatient clinic with epilepsy and neuromotor retardation. The patient had dysmorphic facial appearance (forehead, hypertelorism, flattened nasal root, thin upper lip, flat philtrum) and microcephaly. The patient had a delay in the neuromotor developmental stages, she was able to sit at the age of 1.5 years and walk at the age of 2 years. The patient had only 2 meaningful words, understood and followed what was said, and was receiving special education.

Our patient was born on term with 2750 g, and ventricular septal defect (VSD, peri membranous outlet) was detected in the neonatal period. Seizures started when she was 6 months old and she was diagnosed with epilepsy. The seizures were under control with antiepileptic treatment. The patient's blood Phe level was found to be 122 µmol/L and she was followed up for hyperphenylalaninemia. Microcephaly, dysmorphic findings, growth retardation, and congenital heart disease were part of a condition in our patient. The mother of our patient had three abortions, her school life was bad, she was able to learn to read and write, but she could not attend school. After family screening, blood Phe level of a 35-year-old mother was 1567 µmol/L, blood Tyr level was 35 µmol/L, and Phe/Tyr was 44.7 and the mother was diagnosed with classical PKU and her daughter with maternal phenylketonuria syndrome. When the mother was born, there was no neonatal screening for PKU and the mother had not been screened.

Our fourth case was a 5-year-old daughter of an immigrant family with consanguineous marriage, was brought to our emergency department due to seizure. There was no problem in birth and postpartum history, the seizures started when the patient was 6 months old. The patient had agitation, shouting, no eye contact, could not perceive commands, could sit with support, and could not walk or speak. The patient had truncal hypotonicity and spasticity in the lower extremities, and deep tendon reflexes were brisk. The patient's seizures were continuing despite receiving antiepileptic therapy. Her blood Phe level was found as 1212 µmol/L, blood Tyr level was 37 µmol/L, Phe/Tyr 37.2, and she had the diagnosis of classical PKU. After the nutritional therapy was initiated, the patient's agitation and seizures decreased significantly. It was learned that no blood was taken within the scope of the screening program in the country where the patient was born.

Our fifth case was a 15-year-old male and was followed up with a diagnosis of autism from the age of three. The patient had agitation and stereotypical movements, and his developmental stages were delayed. The patient begun to walk at the age of 6, had no eye contact, could not perceive what was being said, and his speech was not understandable. He did not benefit from special education. There was no consanguinity between the parents, but there were those with mental retardation in their cousins. The patient's blood Phe level was 1470 µmol/L, blood Tyr level was 44 µmol/L, Phe/Tyr was 32.8 and was diagnosed as classical PKU. Nutritional therapy was started for the patient, but he could not adapt. No blood sample was taken from the patient as part of the neonatal screening program.

Our sixth case was a 16-year-old male with a diagnosis of autism and epilepsy. The patient, whose seizures started when he was 10 months old, had eye contact, he had always reached his neurological development stages lately, he could partially understand what was said, but could not speak, and had stereotypical movements. He partly benefited from special education. There was a

first-degree cousin marriage between the parents. The patient's blood Phe level was 1320 µmol/L, blood Tyr level was 51 µmol/L, and Phe/Tyr was 25.8. After diagnosing as classical PKU, nutritional therapy was initiated. Although he was diagnosed late, he had a good compliance with nutritional therapy, his autistic findings and seizures improved partially after treatment. It was learned that no blood sample was taken from the patient as part of the neonatal screening program.

The characteristics of the patients (age, gender, consanguineous marriage, clinical findings, blood Phe level, late diagnosing reasons) are given in **Table 1** and **Table 2**.

DISCUSSION

The prevalence of PKU varies widely worldwide; its incidence in Europe is between 1:3000-1:30000, and it is reported as 1:10000 on average (1,3). The incidence is higher than average in Turkey and is about 1/4500. The high rate of consanguineous marriages in our country is the main factor contributing to this high incidence (4).

According to the blood Phe level, it is classified as; classical PKU (>1200 µmol/L), mild PKU (600-1200 µmol/L) and mild hyperphenylalaninemia (120-600 µmol/L). However, recently it has been described Phe level between 360-600 µmol/L as the gray zone, and there are opinions and studies indicating that these cases should be treated (5).

Today, thanks to neonatal screening programs in many countries, PKU patients are diagnosed early and treated. Normal neurocognitive development can be achieved in these patients with early diagnosis and treatment. Although rare, clinical symptoms of classical PKU without treatment can be encountered in children and adolescents, the inevitable end of these patients is developmental delay and intellectual disability. In addition, various behavioral disorders such as microcephaly, convulsions, ataxia, autistic symptoms, self-mutilation, aggression and psychosis can be observed in these patients (1,6) In mild types of PKU, intelligence development may be close to normal, however, mild school problems and learning difficulties, mild behavioral disorders and

Table 1. Patients' age at diagnosis, current age, gender and consanguineous marriage rates

Case	Age at diagnosis (year)	Current age (years)	Gender	Consanguineous
1	3 years	4.5 years	F	+
2	18.5 years	20 years	F	+
3	35 years	37.5 years	F	-
4	5 years	7 years	F	+
5	15 years	16.5 years	M	-
6	16 years	17 years	M	+
Mean±SD (min-max)	15.4±11.4 years (3-35)	17.0±11.7 years (4.5-37.5)		

SD: Standard deviation, Min: Minimum, Max: Maximum, F: Female, M: Male

Table 2. Characteristics, clinical findings, blood Phe levels, late diagnosing reasons of the patients

Case	Clinical findings	Blood Phe levels	Cause of late diagnosis
1	Neuromotor developmental delay, speech retardation	1309 µmol/L	Missing blood sample during screening
2	Epilepsy, neurocognitive retardation	1493 µmol/L	Not screened for PKU
3	Neurocognitive retardation	1352 µmol/L	Not screened for PKU
4	Epilepsy, neuromotor developmental delay	1212 µmol/L	No screening program in the country of birth
5	Hyperactivity, stereotypical movements, mental retardation, speech retardation	1471 µmol/L	Not screened for PKU
6	Hyperactivity, stereotypical movements, mental retardation, speech retardation	1320 µmol/L	Not screened for PKU

PKU: Phenylketonuria, Phe: Phenylalanine

poor social communication can be observed (1). In our cases, there were those who continued their lives with a near-normal intelligence level and had children, as well as those who had a much more severe clinic.

Children with PKU may be misdiagnosed as attention deficit hyperactivity disorder or autism spectrum disorder (7). Two of our patients were also diagnosed as autism, one of them had a good compliance with nutritional therapy and his autistic findings improved partly. In children presenting with autism symptoms, learning or speech problems, the possibility of PKU and other metabolic diseases should be considered, and PKU should be tested unless newborn screening results are available.

Yalaz et al. reported mental retardation, autistic features, microcephaly, tremor and motor retardation in a series of 146 patients with PKU, treated at different ages. In these series, none of the children treated after 12 months were normal mentally. It was concluded that intelligence depends on the beginning age of treatment and family consistency; additional complications may also develop in case of insufficient response to treatment (8).

These differences in cerebral problems caused by high blood Phe concentrations also vary with age, because the clinical picture of PKU which is sub optimally treated progresses with age. Although it is known that high blood Phe concentrations in childhood, mainly affect intellectual functions, it appears to result in behavioral problems and executive dysfunction in adolescence. In adulthood, it seems to be associated with neurological, psychological, mood and behavioral problems and deficiencies in social skills (9–11). It was emphasized that more researches should be done at both genetic and functional levels to understand cerebral reactions to high blood Phe concentrations in PKU patients, including those related to aging (12).

Newborn screening programs for PKU, has been launched in 1983 in Turkey as a pilot project in one central location. National newborn screening coverage rate was 4.7% in 1987, it reached to 86.3% in 2006 and 95% in 2008 (13). Four of our patients who were lately diagnosed as PKU, were born before the neonatal screening program began, and one of our patients came from a country where a neonatal screening program was not available. For this reason, PKU should be kept in mind in suspected cases who were born before the neonatal screening program started or if they come from a country where a neonatal screening program is not available.

Maternal high blood Phe concentrations during pregnancy are teratogenic and can cause growth retardation, microcephaly, significant developmental delays and birth defects in babies of women with poorly controlled PKU during pregnancy. Women of childbearing age with all forms of PKU, including variants such as mild hyperphenylalaninemia, should seek counseling on adverse fetal effects risks, as appropriate, before conception. The best results occur if the maternal blood Phe concentration is strictly controlled before conception and continues throughout pregnancy (14). In our study, it was thought that the findings of the child of the 3rd case diagnosed with HPA could not be explained by HPA alone. When the mother was scanned and diagnosed with PKU, it was seen that the clinical findings of the patient might be due to the high Phe level in the intrauterine period. It was stated that follow-up of these patients in an experienced PKU treatment center is recommended for genetic counseling and nutritional evaluation (15).

There are some limitations of our study. Firstly, we could not perform PAH gene analysis for all patients due to the lack of study in our hospital and the incompatibility of families. Also, for the same reasons, we could not perform cranial imaging in all patients.

CONCLUSION

PKU is a metabolic disease with successful results with early diagnosis and treatment within the scope of neonatal screening program. If the treatment is initiated in the early period, normal neurocognitive development can be achieved and these patients are reintegrated into the society. In our country where the rate of consanguineous marriage is high, PKU patients can appear in different clinics at all ages. This metabolic disease whose treatment is successful should especially be kept in mind for children and adults born before the beginning of the neonatal screening program in our country.

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