

Maternal phenylketonuria

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Abstract

Phenylketonuria is a hereditary metabolic disorder inherited in an autosomal recessive pattern. Elevated phenylalanine levels in a pregnant woman with phenylketonuria result in phenylalanine embryopathy. Failure to follow special diets during gestation results in neonatal dysplasia. More favorable outcomes are observed when phenylalanine levels remain within normal ranges prior to conception, or at least when they reach normal levels by the 4th-10th weeks of gestation.

We report the case of a newborn with maternal phenylketonuria.

Keywords

Phenylketonuria, maternal phenylketonuria, microcephaly, psychomotor development.

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Introduction

Phenylketonuria is a hereditary metabolic disorder inherited in an autosomal recessive pattern, and caused by a deficiency of the enzyme phenylalanine hydroxylase [1-3].

Phenylketonuria was first described by A. Fölling (Norway) in 1934. He described this disorder as disturbance of phenylalanine metabolism resulting in mental retardation, and called it *imbecilitas phenylpyruvica*. A year later, L. Penrose called the condition *phenylketonuria* and explained the chemical processes that resulted in mental retardation. In 1951, Woolf and Vulliamy explained that diet limited in phenylalanine helped to avoid neurological alterations. After two more years, Bickel et al. proved this in clinical and biochemical studies [2, 4]. The first cases of maternal phenylketonuria were described by Dent in 1957, and by Mambry in 1963. [2].

Case report

24-year-old woman was pregnant for the first time. She had congenital phenylketonuria. Her condition at the beginning of pregnancy was good. At 11 weeks of pregnancy, she was consulted by a geneticist, who was informed about her congenital disease. She was examined for chromosomal anomalies; the examination showed moderate risk of trisomy of chromosome 21, and low risk of trisomy of chromosome 18. There was no recommendations to follow special diets or to measure phenylalanine levels in blood.

At 34 weeks of pregnancy, she was admitted for inpatient treatment due to generalized weakness at Clinic of Obstetrics and Gynecology. The evaluation of clinical and ultrasound examination data revealed fetal hypotrophy and oligohydroamnion. Upon improvement of the condition, she was discharged home several days later.

At 37 weeks of pregnancy, labor started, and the patient arrived at Clinic of Obstetrics and Gynecology where she delivered a male newborn: weight 2,380 g, length 43 cm, head circumference 30 cm and chest circumference 33 cm. The amniotic fluid contained meconium. Apgar score: 9-9. According to the gestation age, the body mass was below 5 percentiles. The neonate was dysplastic – small head circumference, small mandible, and low position of the ears.

Laboratory testing was conducted, yielding normal results of glycemia, total blood count, and CRP levels. IgM tests for cytomegaly, toxoplasmosis, and herpes infection were negative. Screening samples of metabolic genetic blood testing revealed no phenylketonuria.

The neonate was examined by a pediatric cardiologist, and underwent 2D cardiac ultrasonography; patent foramen ovale was diagnosed, and monitoring due to secondary defect of the atrial septum was recommended. Genetic examination of the neonate revealed maternal phenylketonuria. Repeated genetic blood testing at the age of four weeks was recommended due to possible congenital phenylketonuria, and the woman during the next pregnancy was prescribed strict phenylalanine-limited diet three months before conception and throughout the gestation period.

Ultrasonography of the brain and abdominal organs did not show any pathological changes.

The neonate's condition remained stable and satisfactory throughout the inpatient stay. The activity of the internal organs was compensated for.

Physiological reflexes were obtained, and muscle tone was sufficient. The newborn was kept in his bed and fed with breast milk obtained from the mother by using a pump. The child's weight was increasing. At the age of six days, the neonate was discharged home; his condition was satisfactory, and his weight was 2,297 g.

Discussion

Neonatal screening for congenital phenylketonuria was introduced in 1960 [2], and in Lithuania – in Vilnius Center of Human Genetics (CHG) – in 1975. All Lithuanian neonates are screened, and blood samples are taken in inpatient settings on the 2nd-5th day of life (not earlier than 48 hours after the first feeding). The samples are taken from the heel and are dried on a special Schleicher & Schuell 903 test card. Phenylalanine concentration at CHG is tested by applying immunofluorescence.

In Lithuania, congenital phenylketonuria is diagnosed in 1 out of 10,000 neonates, which amounts to 3-4 cases per year. In Europe, the respective rate is 1 out of 10,000-15,000 newborns [3], in the USA 1 out of 13,500-19,000, and in the black American population 1 out of 50,000 neonates [3].

Phenylalanine is one of the principal irreplaceable components of proteins, and is obtained with food. It is broken down in liver, by the enzyme phenylalanine hydroxylase. This enzyme is deficient in patients with phenylketonuria. Without treatment, phenylalanine and its metabolites start accumulating in the body. This results in disturbed psychomotor development of the child. Such children have light hair, blue eyes, and a specific "mouse" smell.

It is highly important to start the treatment immediately after phenylketonuria is diagnosed – not later than by the age of one month. Phenylalanine levels are regulated by applying a special diet limited in phenylalanine-rich products. Neonates and infants are given special amino acid mixtures; later on, a special diet is applied, containing protein-free products [5].

Blood levels of phenylalanine are calculated with respect to age, body mass, and tolerance to this substance. After the prescription of the diet, the schedule for phenylalanine concentration measurement should be the following: at the age of up to 1 year, every week; at the age of 1-12 years, 2 times per month; and at the age of > 12 years, monthly [5].

Elevated blood phenylalanine levels in pregnant women with phenylketonuria result in phenylalanine embryopathy.

According to the recommendations of the National Institutes of Health, blood phenylalanine levels in women before pregnancy should be below 360 $\mu\text{mol/l}$, while the normal levels during gestation are 120-360 $\mu\text{mol/l}$. Blood phenylalanine levels should be measured 1-2 times per week, and the diet should be adjusted accordingly [5]. Placenta is capable of concentrating phenylalanine, and therefore the concentration of this substance in fetal blood may be by 70-80% higher than that in maternal blood. Phenylalanine and its metabolites have a teratogenic effect on the fetus [2, 3, 5], and cause neonatal dysplasia. A review of scientific literature revealed two surveys on pregnancy outcomes in women with congenital phenylketonuria, and clinical signs of maternal phenylketonuria in their neonates (**Tab. 1**) [6, 7].

The outcomes were better when blood phenylalanine levels remained normal before conception, or at least reached normal levels before the 4th-10th week of gestation – this reduced the risk of microcephaly or congenital heart defects [2, 5, 7]. If the women reached the recommended blood phenylalanine levels before pregnancy or at least before the 8th-10th week of pregnancy, the risk of microcephaly dropped by 16.1%, the risk of psychomotor development disorders by up to 26.2%, the risk of hypotrophy by up to 6.5%, and the risk of heart defects by up to 6.6%. However, even good disease control did not ensure any significant difference in the likelihood of miscarriage [7].

Conclusion

Woman with phenylketonuria should be strongly encouraged to receive family planning

and preconception counseling. She should keep to a strict diet during pregnancy, and should check blood phenylalanine levels up to twice a week. To reduce the risk of phenylalanine embryopathy, blood phenylalanine levels should be within the norm, or at least should reach the norm by the 10th week of gestation.

Declaration of interest

The Authors declare that there is no conflict of interest.

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Table 1. Data from studies on pregnancy outcomes in women with untreated phenylketonuria.

Authors	Sample size	Miscarriages	Psychomotor development disorder	Microcephaly	Hypotrophy	Congenital heart defects
Lenke RR, Levy HL 1980	155 women 524 pregnancies	24%	92%	73%	40%	12%
Prick BW, Hop WCJ, Duvekot JJ 2012	98 women 196 pregnancies	13.1%	46.9%	46.2%	19.2%	6.6%