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Pregnancy in patient with X-linked hypophosphatemic rickets – management and outcome

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Summary

Introduction: X-linked hypophosphatemia (XLH) is a genetically determined disorder inherited as a dominant trait associated with mutation within the *PHEX* gene. Phenotypic presentation of XLH ranges from isolated hypophosphatemia to severe lower-extremity bowing. *Case Report:* Preterm hypotrophic infant was born to a mother with a history of XLH, arterial hypertension, and aortic valve insufficiency. The course of pregnancy was complicated by severe symmetric intrauterine growth restriction (IUGR), abnormal umbilical artery flow, and fetal heart rate decelerations during the non-stress test. *Discussion:* Occurrence of IUGR was most probably due to severe maternal disorders, as no data suggesting association between XLH in mother and symmetric IUGR is available. XLH, treatment side effects, and secondary hyperparathyroidism may manifest by variety of medical conditions including nephrocalcinosis, hypertension or heart disease. Proper management of pregnancy in this group of patients requires appropriate preconception counseling and multidisciplinary approach during pregnancy and after delivery.

Key words: Familial hypophosphatemic rickets; Fetal growth retardation; Hypertension; Pregnancy; Rickets.

Introduction

X-linked hypophosphatemia (XLH) or hypophosphatemic rickets is a genetically determined disorder with the incidence of 1 in 20,000 live births [1]. XLH is inherited as a dominant trait linked to chromosome X associated with a mutation within the *PHEX* gene located in the short arm of chromosome in the p22.1-p22.2 region [1]. Rickets was identified as early as the 17th century, when its symptoms were described by David Whistler. The first documented medical report on rickets resistant to treatment with vitamin D was published by Albricht *et al*. in 1937 [2]. The background of XLH is associated with improper absorption of phosphates in proximal renal tubules, leading to phosphaturia (>20 mmol/day) and hypophosphatemia. In addition, the disorder is characterized by impaired transformation of 25-(OH)D_3 to 1,25-$(OH)_2D_3$ [3]. Serum level of fibroblast growth factor 23 (FGF23) in patients with XLH is two to three times higher than in healthy subjects [4]. The disease usually manifests at an age of about one year but first symptoms may occur in adolescent patients. Clinical symptoms of the disease vary from isolated hypophosphatemia to multiple skeletal deformations [1, 3]. Low height of patients is not associated with growth hormone deficiencies although impaired secretion of this hormone was reported [5, 6]. The treatment is symptomatic as it involves phosphate supplementation and administration of active vitamin D metabolites. Treatment complications may include hypercalciuria, hypercalcemia, hyperparathyroidism, and nephrolithiasis, which may in turn lead to renal insufficiency [1].

Case Report

A primiparous patient reported to the Outpatient Clinic for Gestational Pathologies at the 9th week of gestation. Physical examination revealed short stature (143 cm) and discrete features of valgus deformity. Medical history included X-linked hypophosphatemic rickets, 12 years of arterial hypertension, and aortic valve insufficiency. Observation and treatment in the Outpatient Clinic for Metabolic Disorders began when she was one-years-old. Alphacalcidol administration was continued until the age of 19 years. No history of tetanic seizures was reported. There were no cases of short stature in patient's family history. Genetic testing among family members was not performed. Hypertension treatment in the preconception period included metoprolol 2×25 mg and L-methyldopa 5×250 mg. Self-assessed blood pressure parameters were appropriate reaching maximum values of 140/80 mm Hg.

The second outpatient visit occurred at the 14th week of gestation. Self-assessed blood pressure parameters were normal. Ultrasound checkup revealed gestational age consistent with the time of last menstruation. Normal renal function parameters were observed in follow-up investigations. Of note were low phosphorus serum level of 1.72 mg/dL with a normal range of 2.5-5.5 mg/dL.

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During the subsequent outpatient visit held at the 18th week of gestation, metoprolol was discontinued due to low self-assessed blood pressure values. Fetal echocardiography and ultrasound performed at the 21st week of gestation revealed dimensions appropriate for 20th week of gestation and bilateral uterine arteries notching along with delta wave within the umbilical artery. Correlated fetal biometrics via ultrasound scan performed at week 26.5 corresponded to week 24. Due to the diagnosis of symmetric fetal growth failure and persistent notching in uterine arteries, patient was admitted to the Department of Pathology of Pregnancy. Correlated fetal biometrics via ultrasound scan performed at week 27.4 corresponded to week 24.3. Progressive symmetric fetal growth retardation was observed in subsequent ultrasonographic examinations.

Diabetic diet was initiated during hospitalization because of gestational diabetes mellitus diagnosed due to abnormal oral glucose tolerance test results. Self-assessed blood glucose levels during hospitalization were normal. Antihypertensive treatment was modified as blood pressure results increased. On the 30th day of hospitalization, the non-stress test (NST) revealed decelerations, although the ultrasound Doppler examination of both the umbilical and middle cerebral arterial flows remained within a normal range.

During the 34th week of gestation, NST decelerations occurred together with abnormal umbilical artery flow and severe symmetric growth retardation with fetal measurements characteristic for six-weeks younger pregnancy. An oxytocin challenge test (OCT) confirmed fetal distress and a cesarean section was performed at the 34th gestational week. A healthy female was born, weighing 1,570 grams and 44 cm long. Neonatal status was assessed as good, with Apgar scores of 8-8-9 for the 1st, 3rd, and 5th minute, respectively. The newborn had normal muscle tone, normal respiratory function with 60% saturation, and a heart rate above 100/min. When NeoPuff ventilation was initiated at 2nd minute followed by nCPAP, saturation increased to 90%. At minute 10, the neonate was transferred to the Department of Neonatal Pathology with 95% saturation. Surfactant was administered at the 4th hour postpartum. Dobutamine infusion was initiated due to low blood pressure parameters. The neonatal cardiac ECHO scan on the 5th day was unreliable. Transparietal ultrasound revealed grade I intraventricular hemorrhage and increased echogenicity around lateral cranial chambers in the parieto-occipital region. Due to metabolic disease burden, genetic testing was performed but no congenital hypophosphatemia was detected. On the 33rd day after delivery, the child was discharged in good general condition, with a body weight of 2,070 grams and a length of 48 cm. There were no maternal complications during the postpartum period. Abdominal ultrasound performed in puerperium revealed no signs of nephrolithiasis.

Discussion

The occurrence of symmetric fetal growth retardation is mainly due to severe maternal disorders, fetal infections, genetic disorders or congenital defects. No data suggesting a relationship between maternal disease and symmetric reduction in intrauterine fetal growth were observed when searching for correlations between X-linked hypophosphatemic rickets and symmetric fetal growth failure. In the available literature, neonates of XLH mothers were born with normal body length but with growth inhibition occurring during the first two to three years of life [7]. A noteworthy observation was made in the study conducted by Kruse *et al.* in 1998 concerning the results of early treatment of children with XLH: they observed features of intrauterine growth inhibition due to unknown reasons in two out of eight in-term neonates [8]. It is suspected that XLH patients treated with oral phosphates supplementation vitamin D analogs are at higher risk of nephrolithiasis and secondary hyperparathyroidism which is the risk factor for developing arterial hypertension [9-11]. Chronic arterial hypertension is one of the causes of fetal growth failure [12]. Therefore, it is likely that chronic arterial hypertension in pregnancy might have been responsible for the symmetric fetal growth failure. In the reported case, the patient gave birth to a small for gestational age child, but without further complications.

Management of patients with XLH during pregnancy requires a multidisciplinary approach at every stage, beginning with the preconception period. As in case of every hereditary disorder, patients with XLH may benefit from genetic counseling in order to better understand their condition, probability of transmission to offspring and importance of early screening in newborns as there is a wide range of phenotypic spectrum of the disease [1, 13].

Due to various possible complications including nephrolithiasis, electrolyte imbalance, hypertension or even acquired heart defects (e.g. ventricular hypertrophy), patients should be treated and managed accordingly to presented non-communicable diseases [10, 11]. Monitoring of renal function and cardiovascular system is necessary before, during, and after pregnancy in this population. In the reported case, the mother presented with a cardiac defect of aortic valve insufficiency, which might have affected the development of the fetus. Physiologic changes during pregnancy influence hemodynamics of patients with valvular heart disease, therefore cardiology consultation as part of preconception counseling is advised [14]. Not only does structural heart disease require regular monitoring during pregnancy, but also indicates choosing appropriate mode of delivery and selection of adequate anesthesia [14]. Moreover, replacement of drugs contraindicated during pregnancy is one of the key purposes of preconception appointments. In the reported case patient had been treated for hypertension since the age of 14 year. During the preconception period as well as at the beginning of pregnancy L-methyldopa (FDA pregnancy class B) and metoprolol (FDA pregnancy class C) were administered. Beta-blockers are usually recommended as safe for use in pregnancy. However, there are reports in the literature demonstrating the harmful effects of atenolol on the fetus [12]. The FDA classifies atenolol as pregnancy class D due to the associated risk of premature birth, neonatal hypoglycemia, and bradycardia, as well as low birth weight. No increased risk of low birth weight was observed in neonates born from mothers who were treated with metoprolol during pregnancy [12].

Last but not least, obstetric care of XLH patients should include frequent monitoring of the fetus by means of cardiotocography and ultrasound together with blood flow assessment. In the reported case, bilateral flow abnormalities in the uterine arteries were observed as early as at the 21st week of gestation. The notching effect is associated with numerous gestational complications, such as preeclampsia, as well as intrauterine fetal growth failure [15].

Proper family planning for patients with XLH combines all aforementioned elements and leads to optimal supervision over maternal and fetal welfare. Chronic maternal hypertension caused by secondary hyperparathyroidism with the early onset appears to be the probable cause of hypotrophy in the infant of the patient with XLH.

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