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Case Report

Bowing of the Lower Limbs in a Newborn with Maternal Hypoparathyroidism: A Case Report

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Abstract

Introduction: Skeletal deformities cause difficulties in diagnosis and lead to uncertainty. Bowing of the lower limbs include a heterogeneous and large group of conditions, which might seriously affect body function or could even lead to neonatal death. Maternal diseases, such as hypoparathyroidism, with the potential to affect the bone metabolism of the unborn child are often not taken into consideration.

Case presentation: We report on a 36-year-old pregnant woman suffering from postsurgical hypoparathyroidism. The course of pregnancy was uneventful until the third trimester. The woman was under regular endocrinological control, receiving oral calcium and vitamin D supplementation. At 30 weeks of gestation bowing of the long bones of the lower extremity, a femur and tibia length below the 5th centile and a poor fetal growth were detected. On suspicion of skeletal dysplasia amniocentesis was performed. Molecular genetics sequencing filtering for skeletal dysplasia, including COL1A1/A2 genes was uneventful. Besides low birth weight and bowing of the lower limbs a clinically completely unimpaired child was born at term. Laboratory findings showed a highly elevated parathyroid hormone (161 ng/l in the cord blood) indicating neonatal hyperparathyroidism. Detailed analysis revealed maternal calcium levels below the reference range of 2.15-2.55 mmol/l during pregnancy.

Discussion: We present a case of fetal compensatory hyperparathyroidism with intrauterine hypocalcemia causing bowing of the lower limbs in a newborn. The case demonstrates, that the management of pregnant women with hypoparathyroidism is challenging. Further therapeutic options like recombinant human parathyroid hormone must be evaluated.

Keywords: Hypocalcemia; Maternal hypoparathyroidism; Neonatal hyperparathyroidism; Bowing of the lower limbs; Recombinant parathyroid hormone

Introduction

When fetal skeletal abnormalities are detected prenatally a rapid diagnostic workup must be performed to narrow down the differential diagnoses, to counsel parents and, if necessary, to decide on the course of pregnancy in case of lethal outcome. Bent and shortened bones may belong to the group of skeletal dysplasias including more than 400 disorders [1]. Prenatal ultrasound, postnatal examination, radiography and genetic analysis are the basic elements of diagnosis [2]. Maternal hypoparathyroidism can affect fetal bone metabolism and mimic skeletal dysplasia. Hypoparathyroidism in pregnant women is rare, but may lead to disturbed calcium homeostasis in mother and child [3]. Genetic, endocrinological and metabolic investigations in mother and child are required for differentiation.

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Case Presentation

We report on a 36-year-old woman, gravida 1, para 0 who had been suffering from symptomatic postsurgical hypoparathyroidism for one year at the onset of pregnancy. She was treated with up to 1.5 µg oral calcitriol daily, 1600 units cholecalciferol and calcium and was under regular endocrinological monitoring. There was a limitation of oral calcium intake of 1500 mg daily due to increased urinary calcium excretion and the risk of nephrocalcinosis. Under the therapy, the woman was asymptomatic without paresthesia or muscle cramps. The mother admitted nicotine consumption of about 10 cigarettes per day.

Until the third trimester, the pregnancy was uneventful. There were no unusual findings in the first trimester screening, the 20-week scan was not performed. At 30 weeks of gestation, the outpatient gynecologist noticed a shortened and curved femur on fetal ultrasound. The patient was referred to our fetomaternal division for further diagnostics. Fetal growth restriction was noted with an estimated fetal weight below the 3rd centile without any further signs of placental insufficiency. The femur and the tibia measured 49.1 mm (<5th centile) and 41.1 mm (<5th centile) in contrast to the fetal head and abdomen which were both measured on the 19th centile. The femur length to abdominal circumference ratio was normal measuring 0.19 (>0.16). There was a bowing of the femur bilaterally. Intrauterine fractures could not be ruled out with certainty due to irregularities along the distal long bones of the lower extremity. On suspicion of skeletal dysplasia amniocentesis was performed at 30+6 weeks of gestation. Genetic analysis revealed a normal female karyotype without chromosomal aberrations. In particular, molecular

genetic sequencing filtering for skeletal dysplasia, including COL1A1/A2 was uneventful (TruSightTM One Panel Expanded, Illumina + NextSeq, Illumina). Differentially, maternal hypoparathyroidism causing fetal hypocalcemia was considered to cause the abnormalities.

Primary cesarean section was planned at term. After prelabor rupture of membranes at 37+1 weeks a vital, small for gestational age female neonate was born by cesarean section in breech presentation and admitted to the neonatal intensive care unit for further investigation. The girl showed a nonproblematic adaptation with an Apgar score of 9-10-10. The birth weight was 2310 g (<10th centile), the length 46 cm (<10th centile) and the head circumference 32.5 cm (15th centile). On physical examination bowing of the lower limbs were noticeable, the legs crossing at rest (Figure 1). Besides no abnormal findings were apparent. In particular, the hands and feet, as well as the upper extremity, appeared completely normal and there was no evidence of blue sclera, joint laxity, or facial dysmorphic feature. The performed X-ray showed bilateral shortening and bowing of the proximal femur and varus deformity of the distal tibia and fibula bilaterally (Figure 2). Mineralisation, cortical bone and epiphyses were age appropriate. Likewise, sonographically all tubular bones showed continuous cortical bone without evidence of fractures. Laboratory findings revealed a highly elevated parathyroid hormone (161 ng/l) in the cord blood and in the venous blood sampling in the child on the second day of life (148 ng/l). Serum calcium, phosphate and alkaline phosphatase were within the normal range. Electrolytes and blood sugar were initially measured daily and were within the norm. Clinically, the girl was in good general condition without tetanic events.

Further screening of malformations was performed: The cranial and abdominal sonographies were normal. In the echocardiography a small atrial septal defect was discovered. Hip ultrasound demonstrated a Graf type IIa (physiological immaturity).

As the mother decided against breastfeeding, the girl received formula feeding and substitution of 800 units of vitamin D daily. The weight course in the first days of life was adequate. We discharged the family after six days and saw the patient again in our pediatric endocrinology outpatient clinic. The parathyroid hormone was still slightly elevated at 96 ng/l after two weeks, but declining to normal after 2 months. Serum calcium, phosphate and alkaline phosphatase were within the normal range. However, urinary calcium and phosphate excretion were low, so additional calcium supplementation with oral calcium gluconate 10% (0.25 mmol/kg/day) was started.

In conclusion, besides the dystrophy and bowing of the lower limbs, we saw a clinically completely unimpaired child.

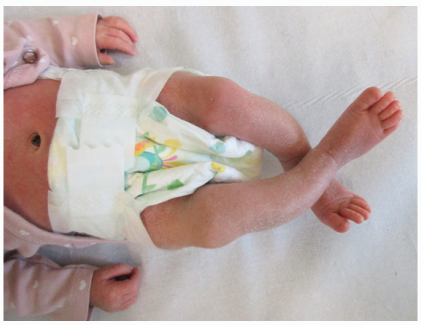

Figure 1: Bowing of the lower limbs.

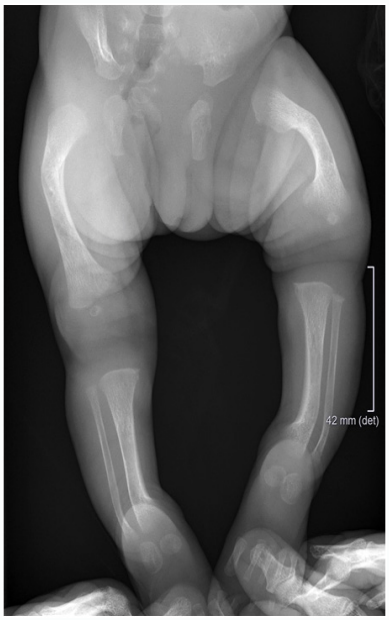

Figure 2: X-ray of the lower limbs showing bowing of femora and tibia bilaterally.

Laboratory findings in the newborn clearly indicated neonatal hyperparathyroidism. Evaluating the mother´s calcium levels hypocalcemia persisted largely during pregnancy (Figure 3), despite repeated adjustment of medication. Two-thirds of the time, the values were below the reference range of 2.15 - 2.55 mmol/l. The lowest value of 1.79 mmol/l was observed in the first trimester. In combination with the postnatal clinical, radiologic and laboratory findings, as well as the intrauterine genetic workup, we hypothesize fetal compensatory hyperparathyroidism with intrauterine hypocalcemia causing the bowing of the lower limbs.

Discussion

Maternal hypoparathyroidism is a rare disorder. Due to adaptive mechanisms mineral blood levels of the fetus are higher than the maternal concentrations in order to mineralize the skeleton before birth. It is assumed that the placenta provides the fetus with sufficient minerals, even if the mother's blood levels are low. Thus, only severe maternal hypocalcemia would cause fetal hypocalcemia [4]. Usually, fetal parathyroid hormone levels are suppressed and maternal parathyroid hormone does not cross the placenta [4]. Still chronic maternal hypocalcemia may lead to hyperplasia of the infant's parathyroid gland and hyperparathyroidism [5,6]. The fetal response

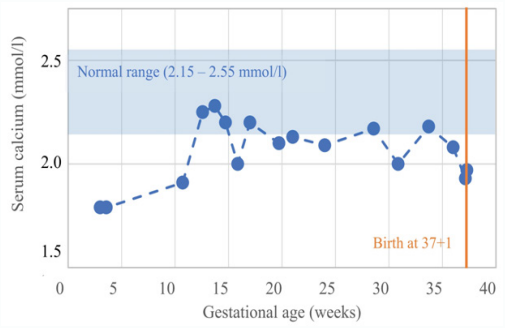

Figure 3: Maternal serum calcium during pregnancy.

involves increasing skeletal resorption causing demineralization. The clinical manifestation in the newborn is highly variable: completely asymptomatic children have been described as well as children with severe skeletal deformities, multiple fractures, respiratory distress and even neonatal death [7-9]. In our case, fetal hyperparathyroidism resulted in extensive bowing of the lower limbs. The birth measurements fulfilled the definition of small for gestational age, which also has been reported in maternal hypoparathyroidism [10].

The evaluation of skeletal abnormalities in a fetus or newborn is challenging. Considering the highly suspicious fetal bone ultrasound findings prenatally a skeletal dysplasia seemed quite likely in our case. Most common among live births are osteogenesis imperfecta, achondroplasia and thanatophoric dysplasia. Bone fragility is the characteristic feature of osteogenesis imperfecta leading to bone deformities. In case of genetic disease, children often show further features such as dysmorphic facies in addition to skeletal abnormalities [2,11]. We had no evidence of further malformations or dysmorphic features. Nevertheless, an amniocentesis was performed, because a severe genetic disease should not be overlooked. Lethal diagnoses must be considered as well as more benign and potentially reversible conditions. Fortunately, detailed genetic analysis showed no evidence of skeletal dysplasia in our case.

Based on the maternal history, maternal metabolic disease was equally discussed at initial presentation. The mother reliably attended the regular endocrinological appointments, medication was modified and adjusted several times, but the low calcium levels may have been underestimated. Additionally, it was not possible to achieve lasting adequate serum calcium levels and further increase of the oral intake was not tolerable, without the risk of provoking secondary complications in the mother.

There is not only a substantial impact on the unborn child, hypocalcemia also carries the risk of obstetric complications such as miscarriages and preterm labor [10]. Achieving normocalcemia is important for both mother and child. The current recommendation in pregnant women with hypoparathyroidism is limited to oral calcium supplementation and administration of vitamin D analogues [12]. However, in our case, this strategy failed to achieve adequate serum calcium levels. Early in pregnancy, the breasts and the placenta begin to secrete parathyroid hormone-related protein. Though parathyroid hormone-related protein is believed to reduce calcium supplementation and calcitriol needs, this is not always observed [13]. Treatment with the hormone itself has received more and more attention in recent years [14]. Ilany et al. [15] reported treatment of a pregnant woman, suffering from hypoparathyroidism, by continuous subcutaneous infusion of recombinant human parathyroid hormone. They were not able to reduce the infusion rate during the course of pregnancy as would have been expected from rising parathyroid hormone-related protein levels. This is currently the only report on the use of recombinant parathyroid hormone in a pregnant woman as its safety in pregnancy has not yet been evaluated.

Normalization of parathyroid hormone and serum calcium in the newborn within the first months of life has been described, as well as healing of the existing bony lesions: Alikasifoglu et al. [8] presented a newborn with multiple fractures whose parathyroid hormone levels were high for 4 months postnatally, the bones showing signs of recovery within 5 weeks. There are cases of laboratory normalization at the age of 4 weeks and even at the age of 12 days [9,16]. Sann et al. [17] reported secondary deficiency of vitamin D due to congenital hyperparathyroidism sustaining parathyroid stimulation. To prevent vitamin D deficiency in our case we prescribed 800 units daily - twice the amount of vitamin D supplementation recommended for healthy children.

There is only limited data and follow-up is rarely described. Nevertheless, given the triggering mechanism is no longer present postnatally with adequate nutritional electrolyte intake, laboratory normalization and clinical improvement can be expected. Improvement of bowing of the lower limbs before the onset of walking is desirable to avoid secondary orthopedic complications. For further pregnancies, even greater efforts should be made to keep calcium levels into the normal range and other treatment options may need to be considered.

Conclusion

Hypoparathyroidism in pregnant women is rare, but the effect of maternal hypocalcemia on the unborn child should not be underestimated. Detection of bowing of the lower limbs has serious consequences. Unlike a genetic disease, in maternal hypoparathyroidism there might be a chance to avoid such skeletal deformities and we assume that they are reversible. The maternal calcium levels necessary for prevention are not known. Optimal therapeutic management for pregnant women should be determined. Therefore treatment options like recombinant human parathyroid hormone should also be considered and further studies performed.

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Consent

Parental consent to publish was obtained, as well as permissions for the use and publication of the radiograph and photograph.

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