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Case Report

Hypophosphatemia in pregnancy: A case report

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Abstract

Autosomal hypophosphatemic rickets though a rare genetic disorder can lead to significant discomfort to the patient resulting in clinical deterioration and a poor quality of life. We describe a case of a 33-year-old woman G2P1001 at 6 weeks of gestation with complaints of myalgia and bony pains. Keeping her history of bony pains and fractures in mind, she was further evaluated. On evaluation, she was found to have low levels of phosphates 0.99 mg/dl (2.40-4.40) and high levels of fibroblast growth factor 23 (FGF 23) 231.70pg/ml (23.20-95.40). These biochemical parameters were suggestive of hypophosphatemic rickets and further on gene sequencing she was found to have autosomal dominant hypophosphatemic rickets (HR). During her follow-up visits, her checkup and antenatal investigations were normal. Pregnancy acts as a stressor and patients with asymptomatic ADHR may present during pregnancy for the first time with the symptoms of HR. So, a high index of suspicion is required for patients reporting musculoskeletal pains in pregnancy. Early diagnosis can help the mother have a better pregnancy experience. Phosphate and vitamin D supplementation during pregnancy can help these women reduce musculoskeletal pain symptoms. Unfortunately, this patient had a spontaneous abortion in the second trimester. The overall prevalence of ADHR is less than 1 per 1,00,000 live births. Data in pregnancy with ADHR is also minimal due to the condition's rarity. Hence, more and more studies are required in pregnancy with this disease to come to any conclusion and to find any association of ADHR with pregnancy outcomes. Genetic counselling and the need for testing in newborns if symptomatic is also an essential factor to remember when coming across such antenatal patients.

Keywords: *Rickets; Hypophosphatemia; Fibroblast Growth Factor Gene 23.*

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Introduction:

Autosomal dominant hypophosphatemic rickets (ADHR) is a rare genetic disorder caused by missense mutation at the cleavage site in the fibroblast growth factor gene 23 (FGF23)[1-3]. ADHR is more commonly seen in females than males. Depending on the age of onset ADHR is further classified as early and late-onset ADHR caused due to mutation at R 179 and R176 respectively[4]. Early onset ADHR manifests during childhood as poor growth, failure to thrive, deformity in lower extremities, bone pain, delayed walking, short stature, and dental deformities. Spontaneous resolution of this variant by adolescents has been reported [5-10]. On the other hand, late-onset ADHR manifests during adult life as bone pains, muscle weakness, and peudofractures[4]. Hypophosphatemia, phosphaturia, inappropriately low or normal levels of 1,25(OH)2D3, and increased alkaline phosphatase levels are the biochemical manifestations of ADHR. There is no clear-cut evidence of any adverse effect of hypophosphatemic rickets on ongoing pregnancy. However, pregnancy may act as a trigger for the manifestation of symptoms in previously asymptomatic women. Iron deficiency anemia in pregnancy is also one of the known triggers for clinical manifestation of this condition[11-12]. Hence female patients with ADHR or with a family history of ADHR are kept under supervision throughout pregnancy as the symptoms might worsen during pregnancy. On the other hand, women with bone pains, muscle weakness, or pseudo-fractures presenting for the first time in pregnancy should be meticulously evaluated for the condition. However, since the disease is rare, a high index of suspicion is required.

Case summary:

We describe a case of a 33-year-old pregnant female with one live issue, who presented to the outpatient department (OPD) at 6 weeks of pregnancy for an antenatal check-up and having complaints of myalgia and bone pains. In her history, she had similar episodes of bone and muscle pains at the age of 12 years which were managed symptomatically with a routine painkiller. At the age of 17 years, she had an intertrochanteric fracture of the femur which was fixed with intramedullary nails [Fig.1]. The patient was asymptomatic thereafter and she had a full-term lower segment caesarean section of a healthy girl child 3.2 kg three years before the index pregnancy. This caesarean section was done because of the history of femur fracture and intramedullary nails [Fig 1] in situ. There was no other significant past history. There was no family history of such muscle pain, bone pains, or fractures in the family. On examination, general physical, systemic and obstetrics examination was found to be normal. On the lower limb examination, there was slight valgus deformity. The patient was managed symptomatically with routine analgesics but there was no improvement in her symptoms. Her routine antenatal investigations and dating ultrasound were normal. With this background history, the patient was further evaluated for persistent muscle and bone pains in collaboration with the medicine and endocrinology department. The patient was diagnosed to have pseudo fractures on imaging [Fig 2]. On further evaluation, she was found to have low levels of phosphates 0.99 mg/dl (2.40-4.40). Her fibroblast growth factor 23 (FGF 23) was high i.e., 231.70pg/ml (23.20-95.40), and her serum vitamin D,25 Hydroxy level was normal at 96.86 nmol/L (75.00-250.00). The biochemical parameters were suggestive of hypophosphatemic rickets. On next-generation sequencing (NGS) a pathogenic variant (p. Arg176Gln) causative of the autosomal dominant hypophosphatemic rickets (OMIM#193100) phenotype was detected. She was then commenced on oral phosphate and vitamin D supplements along with analgesics. The patient was counselled regarding the nature of disease, its inheritance and the worsening of symptoms due to pregnancy as the pregnancy acts as a trigger. Ultrasound at 11 weeks and dual screening was done and found to be normal. The patient was sent for genetic counselling. Chorionic villus sampling was done at 12 weeks as advised by the genetic counsellor which was found to be normal. However, the patient had a spontaneous abortion at 16 weeks. The post-abortal period was uneventful. After reaching a diagnosis of ADHR in our patient, she told us that her daughter also had delayed walking. She was also evaluated for hypophosphatemia.

Her Fibroblast growth factor 23 (FGF 23) (42.92pg/ml), phosphorus (4.60mg/dl) and vit. D levels (83.41 nmol/L) were normal. There was no significant family history in other members, so they refused to test, and hence, other family members were not evaluated for the same condition.

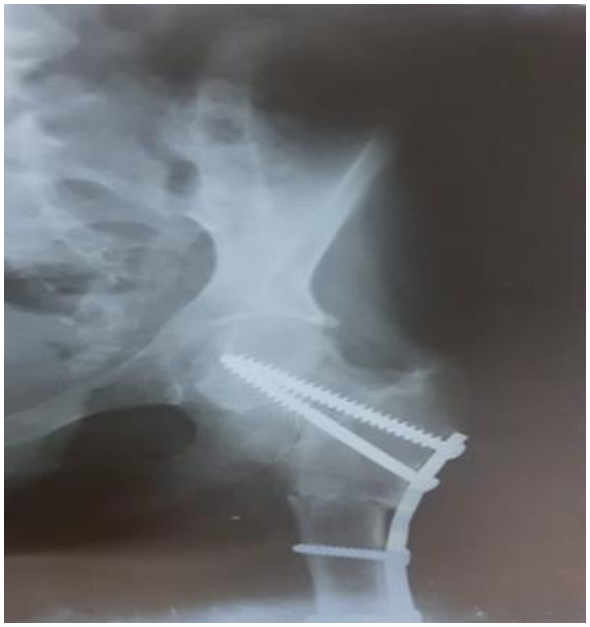

Figure 1: Intramedullary nails and femur fracture

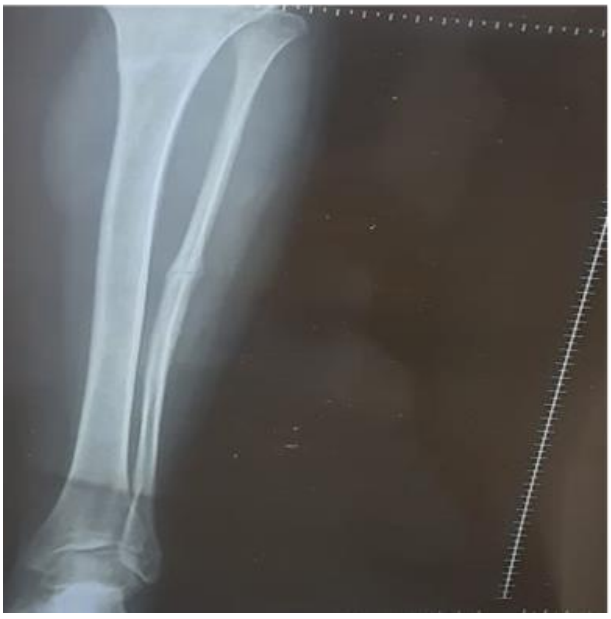

Figure 2: Showing psuedofracture

Discussion:

Autosomal hypophosphatemic rickets though a rare genetic disorder can lead to significant discomfort to the patients with resultant deteriorating clinical state and poor quality of life. Late-onset ADHR or sometimes asymptomatic ADHR can manifest for the first time during the pregnancy. Mild symptoms like muscle pains can often be ignored by the patient or the clinician especially when the symptoms respond to routine symptomatic management. But sometimes these symptoms can be severe and lead to fractures complicating the pregnancy, increasing the incidence of operative interventions. If the clinician is not suspicious these conditions can be missed as in the present case where the patient was not evaluated for hypophosphatemia at 12 years when she presented with muscle and bone pains. The evaluation and diagnosis were again missing at 17 years of age when she had an inter-trochanteric fracture of the femur. Iron deficiency anemia is also known to unmask the features of hypophosphatemic rickets (HR) hence screening pregnant women and treating for iron deficiency helps in relieving symptoms of HR[11-12]. There are no studies to suggest a relationship between ADHR with increased chances of spontaneous abortion in these patients, hence the abortion in the index case cannot be attributed to HR. However, these women can be at increased risk of operative deliveries because of bone deformities (in cases of early-onset unresolved HR) or fracture /pseudo-fractures in the pelvic bones. Hence women who are known cases of HR should receive multidisciplinary care in centres equipped for high-risk deliveries. Treatment of ADHR involves the correction of abnormalities that are caused by raised FGF -23 levels. Supplementation with calcitriol and phosphate will cause resolution of symptoms. However, this treatment can sometimes lead to nephrolithiasis and secondary hyperparathyroidism which is a risk factor for the development of arterial hypertension which can further complicate ongoing pregnancy. Caution is to be taken in women who are already hypertensive and become pregnant.[13]Autosomal dominant hypophosphatemic rickets confers chances of transfer to the baby. Genetic counseling for these patients before conception is a must. Even after the delivery, the infant should be subjected to genetic testing especially when physical manifestations of disease are present.

Conclusion:

Symptoms of ADHR can be manifested for the first time in pregnancy because pregnancy acts as a stressor. Hence, antenatal women with bone or musculoskeletal pain should be evaluated for hypophosphatemia and iron deficiency. Genetic counseling can be done as the risk of inheritance to the baby exists. Adequate treatment can help women to have a comfortable antenatal period and improve their outcomes.

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