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Infantile presentation of osteoporosis-pseudoglioma syndrome: A Case Report

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Abstract

Osteoporosis-pseudoglioma syndrome (OPPG) is a rare disorder characterized by severe osteoporosis and vision impairment, due to mutations in the low-density lipoprotein receptor-related protein 5 (LRP5) gene. This autosomal recessive disorder is characterized by fractures, bone fragility, and pseudoglioma with blindness in infancy. Herein, we present a rare case of OPPG syndrome in an infant who, at 80 days of life (DOL), exhibited multiple fractures without any ophthalmic findings at the time of presentation. This is relatively earlier presentation of the symptoms as fractures are more commonly seen after two years of life.

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Introduction

Osteoporosis-pseudoglioma syndrome is a disorder caused by a mutation in the LRP5 (LDL receptor protein receptor 5) gene, located on chromosome 11q13.4 (1). Osteoporosis leads to bone deformities and fractures. With a typical history of minimal trauma, the time of onset and severity of the osteoporosis is highly variable (2). As the osteopaenic process stabilizes with age, prophylaxis and specialist care for fractures and deformities are essential to prevent incapacitating long-term problems. Intravenous bisphosphonate therapy may prevent fractures, leading to skeletal deformity (3). The function of LRP5 in eye development is complex; however, many studies suggest that it is essential for the normal regression of embryonic vasculature in the eye. Other minor features of OPPG include musculoskeletal problems like short stature, hypotonia, ligament laxity, intellectual impairment, and cardiac anomalies. We present a case of an infant, diagnosed as OPPG, who had unusual multiple fractures initially diagnosed with metabolic bone disease on screening, who had unusual multiple fractures despite treatment.

Case presentation

A very preterm neonate (28+5 weeks GA), extremely low birth weight of 730 g (Small for gestational age), born by preterm vaginal delivery with a significant antenatal history of preeclampsia in the mother and absent end diastolic flow on antenatal Doppler developed perinatal depression requiring bag and mask ventilation for one minute. The baby had respiratory distress syndrome and was on oxygen support for three days. Intravenous fluid was tapered and stopped by day 2, and Ryle's tube feeds were introduced gradually. Routine preterm screenings were done, which showed grade 2 intraventricular hemorrhage on the ultrasonography skull on day of life 3 (DOL-3), which was resolved on subsequent scans. Zone 2 stage 3 retinopathy of prematurity was noted on ophthalmic evaluation and metabolic bone disease workup was positive on DOL-28 with a vitamin D value of 4.3 ng/ml, calcium was 8.0 mg/dl, and phosphorus was 3 mg/dl, for which supplements were increased to therapeutic doses. The baby was gradually shifted to oral bondla feeds and had adequate weight gain. On DOL-80, painful, restricted motion of the left upper limb and right lower limb was noticed, for which an infantogram was done. The infantogram showed marked osteopenia and multiple fractures detected in the upper limb: right humerus mid-shaft, right proximal ulna, left distal end radius and right tibia fracture (Figures 1 and 2). Repeat vitamin D and calcium levels were done, which were in the normal range (Table 1). In view of multiple fractures and dysmorphism (proptosis, low-set ears, triangular facies, pointed chin), a clinical exome was sent suspecting skeletal dysplasia. The exome detected LRP5 mutation s/o OPPG. A detailed ophthalmic evaluation was done to screen for vision, and retinal pathologies, but the ophthalmic examination was normal. Supplements were continued and fractures were treated conservatively with casts. On follow-up, the baby was doing well and had good weight gain. Although fractures were healed, there was a mild left arm deformity post-healing (Figure 3). The plan is to start bisphosphonates, and conduct close IQ, developmental, and ophthalmic assessments for early detection and intervention.

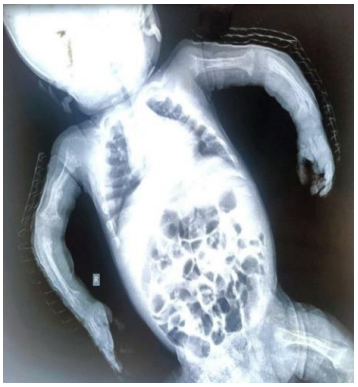

Figure 1. Osteopenia and multiple fractures detected in the upper limb: right humerus mid-shaft, right proximal ulna, left distal end radius

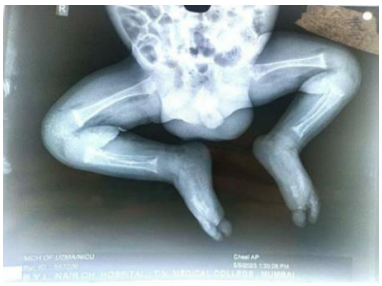

Figure 2. Fracture at right tibia

Table 1. Showing trends of calcium and Vitamin D during initial screening and post-treatment

Parameter	DOL-22	DOL -81	Normal ranges
Calcium	8	9.1	9 to 11mg%
Phosphorus	3.0	3.45	2.5 to 5mg/dl
ALP	947	3537	110 to 410 U/L
Vitamin D	4.8	38.7	30-100 ng/ml
TFT	WNL	-	-
PTH	28	-	15-57pg/ml

Figure 3. Persistent left arm deformity post healing

Discussion

Osteoporosis-pseudoglioma syndrome due to mutations in LRP5 gene. LRP5 is a co-receptor of the Wnt signaling pathway and is situated in the osteoblast membrane between two other receptors, Frizzled 4 and Kremen. The Wnt pathway is involved in cell proliferation, adhesion, migration, and other activities. The binding of Frizzled 4 and LRP5 to Wnt stabilizes beta-catenin and activates bone formation (4,5). LRP5 regulates bone mineral density and is important for maintaining skeletal homeostasis; therefore, this disease presents with osteoporosis. Primary osteoporosis is seen in children with a heterozygous variant of LRP5 mutation (6). OPPG is characterized by osteoporosis and eye abnormalities that lead to vision loss. Ophthalmic findings vary from phthisis bulbi to less severe vitreoretinal findings, such as persistent hyperplasia of the primary vitreous (PHPV), congenital retinal folds, and exudative retinopathy. Fractures are more commonly seen after two years of life (7). Eye examination, coupled with bone phenotype and research of *LRP5* mutation, are key points for diagnosing OPPG. It is an autosomal recessive condition each parent carries one copy of the mutated gene, and is asymptomatic for the condition; however, some carriers may have decreased bone mineral density. Bisphosphonates allow fracture prevention, improvement in bone mineral density, and enhanced mobility in children with OPPG (8). For children and adolescents diagnosed with OPPG who do not respond to other conventional therapies, short courses of teriparatide therapy may be helpful (9). New drugs favoring osteoblast function and osteoclast inhibition are potential candidates in the treatment of OPPG (10).

Conclusion

The clinician should differentiate OPPG from osteogenesis imperfecta and child abuse. This case portrays a rare presentation of OPPG syndrome, as the child presented with multiple fractures in infancy itself, the disease process was exaggerated due to the underlying metabolic bone disease, and the child did not have any ophthalmic findings which are generally diagnosed in infancy. The child is currently appropriate for corrected gestational age and follows objects. Close ophthalmic follow-up has been advised.

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Ethical statement

The authors certify that they have obtained all appropriate patients' parent consent.

Conflicts of interest

There are no conflicts of interest.

Author contributions

All the authors have read and approved the final version of the manuscript and agree to be accountable for the content presented.

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