UNEXPLAINED FRACTURES IN AN INFANT, A CLUE TO *OSTEOGENESIS IMPERFECTA*

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ABSTRACT Introduction: *Osteogenesis imperfecta* (OI) is an autosomal dominant disorder affecting 6-7/100,000 patients. **Case report:** We describe a term neonate with a supervised pregnancy and fetal ultrasonography at 23 weeks with bone dysplasia suspicion. A physical exam revealed axial hypotonia, increased anterior fontanel with distant cranial sutures, and a small, tapered nose. Skeletal radiography showed hypomineralization and wormian bones of cranial calotte, thin ribs and short and curved femurs. The genetic test revealed a heterozygous variant of p.(Gly328Ser) in exon 19 of the COL1A2 gene of the missense type. By 2 months of age, their parents noticed unexplained left lower limb oedema associated with severe pain and crying, and he was diagnosed with an aligned fracture of the left femur diaphysis. **Discussion:** Several genetic disorders and congenital defect conditions, such as OI, have been associated with bone fragility and fractures that can be misdiagnosed, as child abuse is possible. This case report highlights the importance of valuing an infant's bone fractures, especially if the fracture is unexplained and located in places like long bones of the arms and legs, ribs and small bones of the hands and feet. **Conclusion:** Clinicians should always look for fragile bones and exclude causes such as OI. Never forget to exclude, as well, child abuse as part of differential diagnosis.

KEYWORDS *osteogenesis imperfecta*, unexplained fractures, bones, infant

Introduction

Osteogenesis imperfecta (OI) is an autosomal dominant disorder that affects about 6-7/100,000 patients[1,2]. Low bone mass is OI's main feature, making one fragile and susceptible to deformities and repeated fractures [3].

Several subtypes of OI vary according to clinical features, radiological aspects and responsible genes. The diagnosis of OI is made by identifying a pathogenic variant in the COL1A1 or COL1A2 gene by molecular diagnosis. Mutations in these genes represent the largest proportion of OI cases, accounting for more than 90% of OI causes[4]. There should be clinical suspicion initially when there are some typical findings, namely, fractures with minor trauma or absence of trauma, short stature or shorter stature than expected based on target family stature, blue/grey sclera, dentinogenesis imperfecta (defined as dysplasia of the mesoderm affecting both primary and permanent dentition varying in the colour of teeth from blue to brown[5]), progressive postpubertal hearing loss, ligament laxity or family history of OI2. Craniofacial alterations are characterized by a higher incidence of prominent frontal bosses, anterior and/or posterior open or crossbite, Angle Class III bite and underdevelopment of the midface[6,7]. Usually, these patients have normal values of vitamin D, calcium, phosphorus and alkaline phosphatase (AF), which helps to distinguish OI from other pathologies. There are some cases where there may be an acute elevation of AF in response to a fracture.[2]

The severity of OI varies from perinatal death to skeletal deformities with a limited range of motion to asymptomatic individuals with a mild predisposition to fractures, normal structure and life expectancy equal to the general population [8]. Nevertheless, being a chronic patient with its own particularities, it should be followed from the beginning of life by a multidisci-

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plinary team in order to improve his quality of life.

Case report

We describe a male neonate delivered at 40 weeks and 3 days gestational age. His mother was 20 years old and G1P0. During pregnancy, she had no infections, accidents or trauma. Serologies during pregnancy were normal, and fetal ultrasonography performed at 23 weeks revealed a bilateral suspicion of bone dysplasia with the curved and short femur. The fetal echocardiogram was normal. Labour onset was spontaneous, with amniotic sac rupture 12 hours before delivery. Amniotic fluid was clear. Delivery was made by cesarean section due to bone dysplasia suspicion. The newborn was born hypotonic, without respiratory movements, with a heart rate of 60 bpm. He was ventilated by positive pressure with a mask and T-piece, with a maximum FiO2 of 30%. He gradually recovered with respiratory movements at 3 minutes of life. His APGAR score was 3/7/9. He was transferred to the Neonatology Unit. The baby weighed 3495g (P10-50) and measured 49cm (P10-50) in length and 35cm (P50) in the cephalic perimeter.

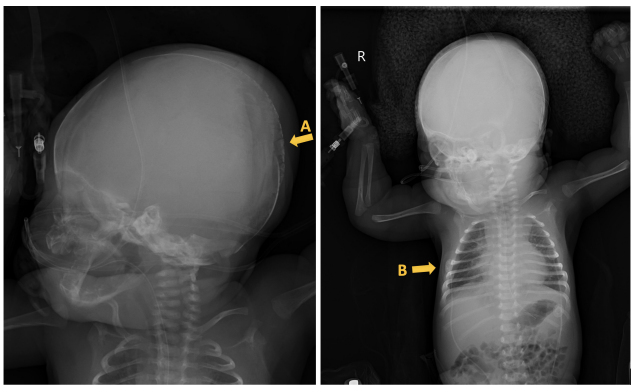
During hospitalization, he required oxygen until the 3rd day of life, and then he spontaneously breathed in room air. Physical examination revealed axial hypotonia and increased anterior fontanel with distant cranial sutures. Scleras were white, and the nose was small and tapered. The remaining physical examination was normal. Skeletal radiography (figures 1 and 2) performed on the first day of life revealed cranial calotte with hypomineralization, wormian bones, thin ribs, and short and curved femurs. Blood tests showed a vitamin D deficit (<20 nmol/L), and he started vitamin D supplementation. Parathyroid hormone, calcium, phosphorus, magnesium and alkaline phosphatase levels were normal. In the suspicion of bone dysplasia, genetic testing was requested. The genetic test revealed a heterozygous variant of p.(Gly328Ser) in exon 19 of the COL1A2 gene, of the missense type, that disrupts the formation of the normal type I collagen triple helix compatible with OI. He was discharged by the 6th day of life, clinically well. The universal newborn hearing screening was normal, with auditory evoked potentials bilaterally present.

There were no occurrences during the neonatal period. By 2 months of age, parents noticed unexplained left lower limb oedema, more evident in the thigh, associated with severe pain and crying and difficulty to comfort. They denied trauma, fever or other symptomatology. He was observed in the pediatric emergency room. His limb x-ray revealed an aligned fracture of the left femur diaphysis (figure 3). Femur fixation was performed with a plaster splint for one month, with resolution. The fracture healed successfully. Around 4 months, he returned to the pediatric emergency room with severe pain and crying. Physical examination was normal, but he started to cry when his mother held him in her arms. A New x-ray revealed a relapsed fracture in the left femur, same location (figure 4). Femur fixation was again performed, with resolution. The infant was followed regularly in orthopaedics, genetics and paediatrics consultation.

Discussion

Several genetic disorders and congenital defect conditions, such as OI, have been associated with bone fragility and fractures that can be misdiagnosed as child abuse. OI is the most common genetic abnormality associated with unexplained fractures in an infant or child.[9]

Figure 1: Cranial calote with hypomineralization and wormian bones (A) and thin ribs (B)



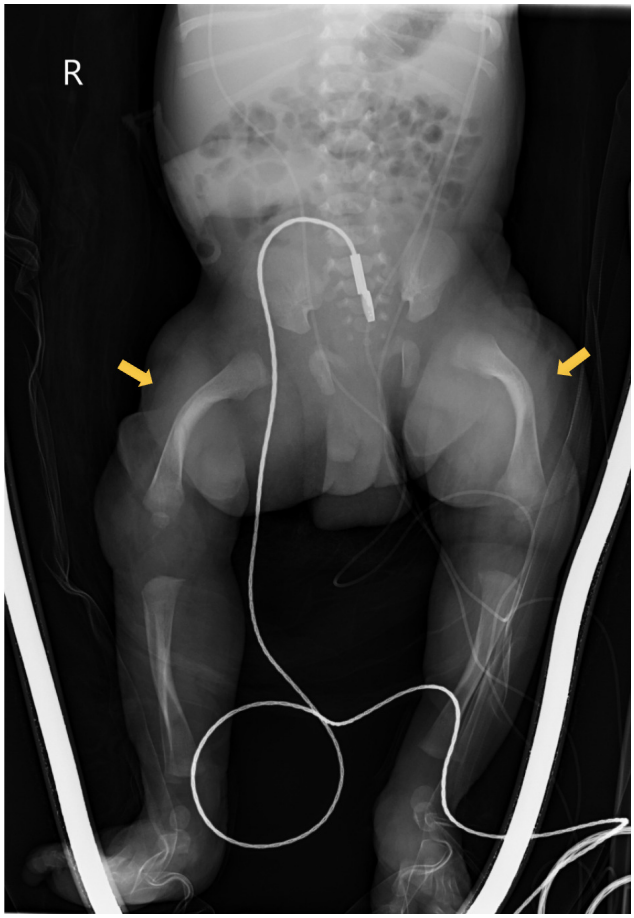
In 1975, Bauze et al.[10] described the clinical, radiological and biochemical features of 42 patients classifying OI into three: mild, moderate and severe, based on the deformity of one or more long bones. Mild had no long bone deformity, moderate had minor long bone deformities, while severe had severe long bone deformities. He argued that long bone deformity was a strong prognostic feature and easily recognizable. In 1979, Sillence et al.[11] grouped the disorder into four: Type I (a dominant inherited mild form of OI, with recurrent fractures and blue sclera), type II (perinatally lethally deforming OI with crumpled femora), type III (progressive deforming OI with normal sclera) and type IV (dominant inherited OI with normal sclera). Type III and IV represent intermediate phenotypes, with type III being the most severe non-lethal form, causing significant bony deformity secondary to multiple fractures, which can be congenital. Over the past few decades, histological and molecular findings have identified additional types (V-XVI).[12-15]

Clinical manifestations of OI include excess or atypical fractures (brittle bones), short stature, scoliosis, basilar skull deformities, which may cause nerve compression or other neurologic symptoms, blue sclerae (especially in types I, II, IX and X of OI), hearing loss, dentinogenesis imperfecta, increased laxity of the ligaments and skin, Wormian bones (small, irregular bones along the cranial sutures) and easy bruising. Infants with moderate to severe OI (types III to IX, XV and XVI) have an increased number and frequency of fractures, mild to moderate bone deformities, kyphoscoliosis and variable short stature. In addition, children may develop ossicular dislocation, stapes fixation, or fracture of the ossicles, resulting in conductive hearing loss.[15]

In OI, biochemical parameters of bone and mineral metabolism are usually normal. Some abnormalities may be noted, such as elevated serum alkaline phosphatase levels, especially in OI type VI hypercalciuria, reflecting the severity of the skeletal disease. Markers of bone formation may be lower such as C-terminal propeptide of type I procollagen, and markers of bone resorption can be higher, such as C-telopeptide of type I collagen. These tests are useful in assessing bone metabolism and excluding other conditions and are typically repeated yearly for ongoing monitoring.[15] In this case report, biochemical parameters were normal, except vitamin D, which was decreased.

In the present case, clinical manifestations and genetic tests were compatible with a moderate to severe form of the disease (probably type III of OI). Therefore, our diagnosis was made not only with prenatal fetal ultrasound that revealed bone dysplasia but also by clinical (repeated fractures), radiological and

Figure 2: Bilateral short and curve femur.



genetic testing. Treatment for OI requires a coordinated multidisciplinary team approach and consists of physical therapy, surgical interventions and medications. In moderate to severe OI, bisphosphonate therapy is helpful. In addition, patients with OI require regular surveillance for potential complications, including hearing loss, worsening of osteoporosis, growth retardation, and bone deformities, so appropriate intervention is initiated as soon as possible. This case report highlights the importance of valuing an infant's bone fractures, especially if the fracture is unexplained and located in places like long bones of the arms and legs, ribs and small bones of the hands and feet.

Conclusion

OI is the most common genetic abnormality associated with unexplained fractures and fragile bones in an infant or child. Clinicians should always look for fragile bones and exclude causes such as OI. Never forget to exclude, as well, child abuse as part of differential diagnosis.

Author's contributions

Joana Moscoso and Mariana Dias: original draft conceptualization and design, manuscript writing. Rita Barreira and Duarte Malveiro: manuscript editing and review. All authors read and approved the final manuscript.

Figure 3: Align fracture of the left femur diaphysis by 2 months age.

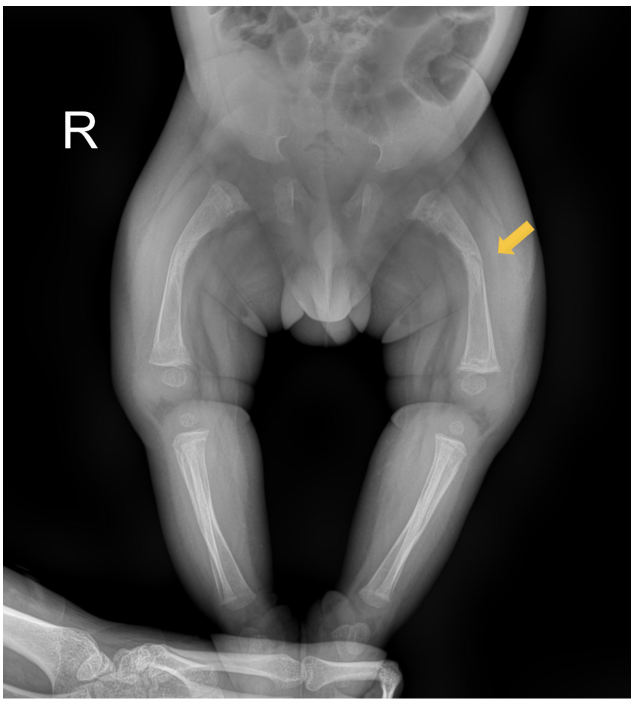
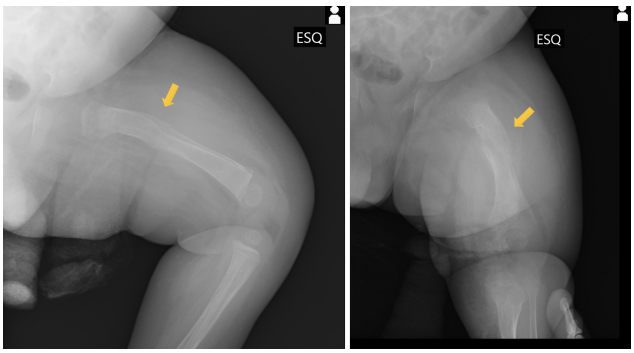


Figure 4: Relapse fracture of the left femur diaphysis by 4 months age.



Conflict of Interest

The authors declare no conflict or competing interests.

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