

Received: 2020.06.15

Accepted: 2020.08.21

Available online: 2020.09.11

Published: 2020.10.20

Femur Fracture in a Premature Infant: An Unusual Association of Sickle Cell Disease with Osteogenesis Imperfecta

Authors' Contribution:

Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABDEF **Giselle Gozum**
ABDEF **Michelle Bogdan**
ABDEF **Revathy Sundaram**
ABDE **Jolanta Kulpa**
ADEF **Pramod Narula**
ABDEF **Levon Agdere**

Department of Pediatrics, NewYork Presbyterian-Brooklyn Methodist Hospital,
Brooklyn, NY, U.S.A.

Corresponding Author: Levon Agdere, e-mail: lea9004@nyp.org

Conflict of interest: None declared

Patient: Female, 1-year-old
Final Diagnosis: Sickle cell anaemia
Symptoms: Fracture
Medication: —
Clinical Procedure: —
Specialty: Hematology • Pediatrics and Neonatology

Objective: Rare co-existence of disease or pathology

Background: Bone health is influenced by multiple factors, including genetic disorders such as osteogenesis imperfecta (OI) and sickle cell disease (SCD). OI is a genetic disorder caused by mutations in genes that encode type 1 collagen. Type 1 collagen synthesizes bones, skin, and other connective tissues. Defective synthesis can lead to brittle bones and other abnormalities. Patients with OI present with spontaneous fractures. SCD is an autosomal-recessive disorder resulting in a major hemolytic anemia. The formation of sickle hemoglobin results in increased blood viscosity and sickling of red blood cells, which causes painful vaso-occlusive crisis in bones and joints, acute chest syndrome, and stroke.

Case Report: We present the case of an infant with a dual diagnosis of OI and SCD. The patient was born at 26 6/7 weeks gestational age to a mother who had sickle trait. The infant was admitted to the Neonatal Intensive Care Unit for prematurity and respiratory distress with a clinical course that was complicated by other comorbidities. Newborn screening revealed a diagnosis of SCD-SS type. At 83 days of life, the infant presented with swelling and tenderness of the left leg. Imaging revealed a non-displaced fracture of the femoral shaft. The patient was evaluated for OI and genetic testing confirmed the diagnosis of OI type 1.

Conclusions: An association between SCD and OI is rare. The impact of these 2 major diagnoses on clinical features and outcome as well as challenges to care remains to be seen.

MeSH Keywords: Anemia, Sickle Cell • Fractures, Bone • Neonatology • Osteogenesis Imperfecta • Pediatrics

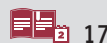
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Background

Osteogenesis imperfecta (OI) is a genetic disorder with either recessive or dominant inheritance. It is caused by mutations in genes that encode type 1 collagen. These genes include *COL1A1*, *COL1A2*, *CRTAP*, and *P3H*, with *COL1A1* and *COL1A2* being the most common. Type 1 collagen is known to synthesize bone, skin, and other connective tissues, and when collagen synthesis is defective, it can lead to brittle bones and various abnormalities [1–3]. The incidence of OI is 6 to 7 per 100 000, and at least 8 different subtypes of the disease are known. Types 1 and 4 have a mild-moderate phenotype [4]. Types 2 and 3 are the most severe forms [5,6].

The most common presentation of OI is spontaneous fracture in a patient with no history of trauma [3]. Other clinical features include blue sclera, sensorineural hearing loss, dentinogenesis imperfecta, and short stature. Severe OI also can cause neurological, respiratory, and cardiac complications [7–9].

Sickle cell disease (SCD) is an autosomal-recessive genetic disorder. The substitution of valine for glutamic acid in the sixth position of the beta globin chain leads to the formation of sickle hemoglobin and results in a major hemolytic anemia. There are several different phenotypes of SCD. The most common and more severe are hemoglobin SS disease (SS), hemoglobin SC disease (SC), and hemoglobin SB 0 (Beta Zero) thalassemia (S beta-thalassemia). The less common and less severe phenotypes are hemoglobin SD, hemoglobin SE, and hemoglobin SO.

Increased blood viscosity and sickling of red blood cells lead to complications such as painful vaso-occlusive crisis, dactylitis, acute chest syndrome, avascular necrosis, priapism, and strokes. Splenic dysfunction contributes to impaired immunity, placing patients at risk of developing overwhelming sepsis. Patients with SCD are placed on prophylactic penicillin for the first 5 years of life to prevent infections. Research is ongoing on ways to reduce morbidity and mortality. The discovery of new medications to address pain and other complications has improved the quality of life for many patients with SCD. Stem cell transplants and gene therapy offer hope for cure. Many patients with SCD, however, face a lifetime of pain and the psychological toll of chronic illness [10,11].

We present the case of an infant with dual diagnoses of OI and SCD. A review of the literature shows 1 case report about a patient diagnosed with both conditions [12]. The case presented here was reviewed and acknowledged by the NewYork Presbyterian-Brooklyn Methodist Hospital Institutional Review Board.

Case Report

The patient was born at 26 6/7 weeks gestational age via normal spontaneous vaginal delivery to a 40-year-old G3P1011 mother who had a history of sickle trait. The infant was admitted to the Neonatal Intensive Care Unit (NICU) for prematurity. Her NICU course was complicated by respiratory distress syndrome, chronic lung disease, suspected sepsis with metabolic acidosis, anemia, suspected necrotizing enterocolitis, and cow's milk protein allergy. Newborn screening done on Day 10 of life revealed a diagnosis of SCD. A repeat hemoglobin electrophoresis at 5 months of age confirmed SCD-SS type.

At 83 days of life, the infant was noted to be irritable. Examination revealed swelling of the left thigh with tenderness and minimal active movement. The affected limb was held abducted and flexed. An X-ray of the extremities revealed a non-displaced fracture of the left femoral shaft with periosteal reaction (Figure 1). An orthopedist was consulted and a splint was placed. Imaging of the limb 10 days later showed a healing fracture (Figure 2). Upon further work-up, calcium, phosphorus, and vitamin D levels were all normal. Four days before, an alkaline phosphatase level was 599 units/L and its peak was 699 units/L at 2 weeks of life. Calcium and phosphorus levels were normal throughout the infant's NICU stay. An endocrinologist was consulted and recommended adding 400 units of vitamin D supplementation to the regimen. Further examination of the infant revealed bluish sclera, which was confirmed by an ophthalmologist. The patient then was evaluated for OI. Genetic testing confirmed the diagnosis of OI type 1.

At 18 months of age, the patient was in the 13th percentile for length and below the third percentile for weight. She has not had any further fractures. She was hospitalized for 2 sickle cell pain crises, at 1 year and 16 months of age. Both times, she presented with irritability and inability to bear weight on her right lower extremity. Imaging performed during the admissions did not reveal new fractures.

Discussion

This is a rare example of 2 unrelated major genetic disorders coexisting in the same patient. Currently there is only 1 such case reported in the literature [12]. A number of factors potentially influenced our patient's bone health, based on the diagnoses and treatment during her NICU stay. One previous study looked at how caffeine given to patients in the NICU is associated with osteopenia of prematurity. During pregnancy, about 80% of bone mineralization occurs during the third trimester. Therefore, premature infants are born with decreased bone mineral content compared with full-term infants as well as decreased bone mineral density (BMD). Prematurity was

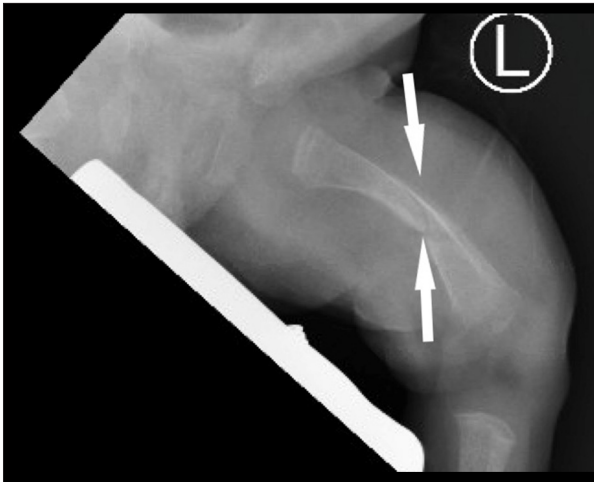


Figure 1. Radiograph of the fracture.

already a risk factor predisposing our patient to fractures. In another study, 335 infants with a gestational age of <31 weeks and birth weight of <1500 g were assessed who were given caffeine during NICU stays to treat apnea of prematurity. Chest X-rays showed that 51% of the infants had osteopenia of prematurity and 8% had fractures [13]. Our patient was treated with caffeine from birth until Day 62 of life, which may have increased her risk of femoral fracture on Day 83 of life.

Our patient was diagnosed with OI type 1, which is a milder form of the disease. Treatment consists of prevention of fractures by maintaining bone strength and BMD. Low 25(OH) vitamin D and BMD have been described in children with either OI or SCD. Multiple hospitalizations and impaired mobility due to pain also can contribute to decreased BMD, thus possibly increasing the rate of fractures [11].

Patients with SCD are prone to chronic bone complications, such as vaso-occlusive crises, avascular necrosis, and osteomyelitis. Vitamin D is important for maintaining bone mineralization and patients with SCD often become vitamin D-deficient. Two previous studies looked at the effect of vitamin D supplementation on patients with SCD. The first study compared a group of patients with SCD who received vitamin D3 supplementation with a group that received placebo for 6 weeks. At the end of the study, the group that received vitamin D supplementation had significantly higher serum vitamin D levels and fewer days during which they experienced pain compared with the placebo group [11,14]. A similar study was conducted in patients with SCD to investigate the effects of vitamin D supplementation in the treatment and placebo groups. The participants in both groups were treated for 6 weeks and then were followed for another 6 months. The result was fewer pain days and better physical function in the treatment group as vitamin D levels rose compared with the placebo group [15]. Given the history of SCD, it appears that it would be beneficial

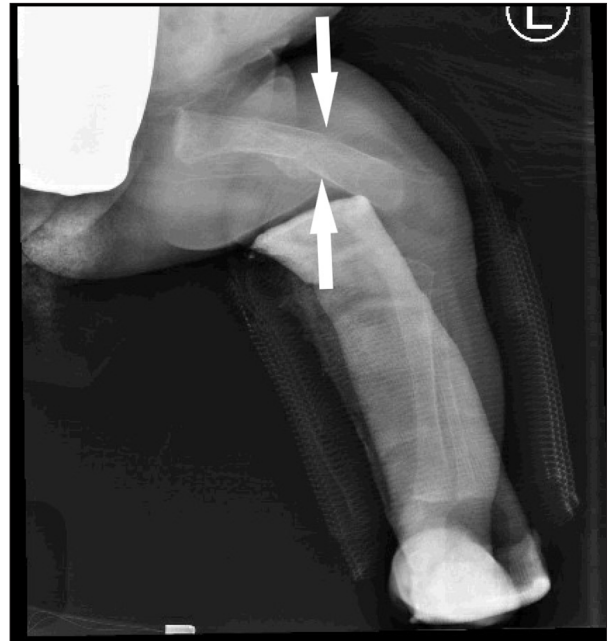


Figure 2. Follow-up radiograph of the fracture 10 days later.

to prescribe vitamin D supplementation for patients with it to help them maintain bone health and possibly decrease their risk of fractures.

A shared feature in both SCD and OI is short stature. In patients with SCD, vasculopathy, transfusional iron overload, and end-organ failure can lead to endocrinopathies, such as thyroid dysfunction, poor growth, and pubertal delay. In a study of 52 patients with SCD, height, weight, vitamin D level, maturity, and growth hormone (GH) levels were monitored over 6 months. Of the patients, 48 had at least 1 endocrine variation. Vitamin D deficiency was seen in 84% and 3% had GH deficiency. Specifically, patients with the HbSS genotype had lower levels of insulin-like growth factor (IGF)-1 than those with the HbSC genotype of SCD [16]. Short stature can be caused by nutritional deficiencies, the hypermetabolic state in SCD, and decreased synthesis of IGF-1 and GH. GH replacement therapy would be beneficial in patients diagnosed concurrently with concurrent SCD and OI who have short stature.

Fortunately, our patient is clinically well. She has not sustained any new fractures since discharge. Her physical examination is normal except for blue sclera. Her height is in the 13th percentile and her weight is below the third percentile. She is on folic acid, prophylactic penicillin, and vitamin D supplementation. She had her first admission for an SCD-related pain crisis at age 1 year and a pain crisis admission at 16 months. During both hospitalizations, no fractures were found and the patient improved with fluids and nonsteroidal anti-inflammatory drugs. She has been referred to a comprehensive center for OI at a tertiary care hospital.

Graff et al. studied growth patterns in 117 patients aged 2 to 18 with OI type 1. Data from healthy children, including height, weight, and body mass index (BMI), were used as a reference. This was a retrospective study that analyzed height measurements, except in those with comorbidities, on bisphosphonates, or who had vertebral compression fractures or surgical intervention for prior bone trauma. The authors found that children aged 2 to 3 years with OI were slightly shorter than children without OI (SD -1.2). Between ages 4 to 7 years, children with OI catch up to their peers (SD -0.5). In adolescents and young adults, growth slows down (SD -2.7). Overall body weight and BMI were similar in children with and without OI [17].

Our patient's height is at the 13th percentile and her weight is below the third percentile. More research is needed on predicting height in patients with OI.

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Conclusions

We report a rare case of concomitant SCD and OI in a premature infant who sustained a fracture in the NICU. Premature infants are at a higher risk for decreased BMD. Other comorbidities, such as the use of caffeine in apnea of prematurity, add to this risk. Multiple therapeutic interventions are put in place in the NICU, such as monitoring calcium and phosphorus and supplementation with vitamin D, to optimize bone health and mitigate complications from decreased BMD. Despite that, fractures still occur.

This case report emphasizes the importance of a thorough physical examination and a high index of suspicion to determine the factors that contribute to fracture in a premature infant. The overlap of symptoms may present challenges to diagnosis and care. Aggressive management of bone health, vitamin D levels, and attention to nutrition and exercise will help. The possibility of cure for both disorders with stem cell transplant or gene therapy offers hope and impetus for future research and clinical trials.