Discrepancies in the Phenotypical Classification of Osteogenesis Imperfecta in a Patient with COL1A2 Mutation: A Case Report

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Patient: Male, 3-year-old
Final Diagnosis: Osteogenesis imperfecta
Symptoms: Blue sclerae • brittle bones at birth • short stature
Clinical Procedure: —
Specialty: Genetics • Orthopedics and Traumatology • Pediatrics and Neonatology

Objective: Unusual clinical course
Background: Osteogenesis imperfecta (OI) is a rare genetic disease that results from mutations in type 1 collagen (COL1) or its interacting proteins. Such mutations lead to defects in bone structure, causing brittle bones, short stature, hearing loss, and dental problems, among others. The current classification system arranges OI into types according to a clinical phenotype that includes the severity of the disease and a combination of specific features, such as blue sclerae and dental abnormalities.

Case Report: Here, we present a clinical report of a 3-year-old boy diagnosed with OI in utero who has been followed by our pediatric clinic postnatally. The patient was born with multiple bone fractures, a small head circumference, and blue sclerae and later had a concomitant diagnosis of dentinogenesis imperfecta (DI). Soon after birth, the patient was started on bisphosphonate and calcium/vitamin D treatment. The patient’s OI type was inconclusive due to the dramatic difference between perinatal and postnatal phenotypes, the presence of blue sclerae, and the additional diagnosis of DI. The patient experienced only 1 new bone fracture postnatally, had normal anthropometric measurements except for short stature, and was healthy.

Conclusions: This clinical case is unique owing to the dramatic perinatal and mild postnatal OI phenotypes. This and the unique combination of postnatal features demonstrate that classical OI typing could be inconclusive in atypical disease presentation. This case may demonstrate a new classification possibility outside the current OI nomenclature. However, the potential beneficial role of pharmacological treatment in the clinical outcome of OI cannot be excluded.

Keywords: Collagen Type I, alpha2 Subunit • Dentinogenesis Imperfecta • Osteogenesis Imperfecta

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Background

Osteogenesis imperfecta (OI) is a rare connective tissue genetic disorder caused by inherited and sporadic mutations in type I collagen or proteins that interact with it [1]. Type I collagen is a molecule composed of two $\alpha 1(I)$ chains and one $\alpha 2(I)$ chain. It is hypothesized that in COL1A2 mutations in which glycine is substituted by another amino acid such as alanine, valine, or serine, there is a disruption of the alpha-helix structure, leading to defective binding of interacting proteins resulting in aberrant function [2]. The clinical picture of OI includes bone fragility, decreased bone density, short stature, early loss of hearing, and, in some cases, dentinogenesis imperfecta (DI), a dentin defect [1,3]. The incidence of this disease is estimated to be approximately 1 in 15,000 to 20,000 births [4].

The original classification of the OI was based on a 1979 publication by Sillence et al, who assigned types of the disease into 4 groups based on the inheritance pattern, severity of symptoms, and color of the sclerae [5]. Furthermore, this classification has been expanded to include numerous newly discovered genes responsible for the OI phenotype. Type 1 is the mildest form, resulting from a non-functional COL1 allele, leading to fractures, blue sclerae, hearing loss, minimal bone deformity, and rarely DI [4,6,7]. Type 2 is lethal perinatally. Type 3 presents as a progressive deforming type with numerous fractures, bowed legs, a short trunk, dark blue/grey sclerae, and DI. Type 4 exhibits overlapping symptoms of types 1 and 3 and variable phenotypic features, such as white or grey sclerae, DI, and potentially normal height.

Unfortunately, this classification system can be challenging due to the variety of disease phenotypes and the early interventions that can influence the progression of the disease. An expanded Sillence classification was published in 2004 by Rauch and Glorieux to consider specific mutations in COL1A1 and non-collagen genes and distinct bone histology [6]. In addition to the classical Sillence OI types 1 to 4, this classification captures histologically distinct types 5 and 6, which lack abnormalities in type 1 collagen. Collagen-folding protein abnormalities in the prolyl-3-hydroxylation complex characterize OI types 7 to 9. Additional non-numbered types possess collagen chaperone protein and osteoblast lineage abnormalities, resulting mostly in a severe clinical presentation. An updated OI nomenclature combined with causative genes has been proposed by Dijk and Sillence [7]. This new OI classification attempts to connect OI types according to specific clinical and radiologic characteristics with gene mutations and their loci. The connection between OI genotype and phenotype may also depend on qualitative versus quantitative collagen defects [8]. For instance, OI type 1 is mostly associated with quantitative type 1 collagen defects.

Here, we present the case of a 3-year-old male patient who was diagnosed with OI during fetal development via amniocentesis DNA analysis.

Case Report

Presentation and Diagnosis

The patient was diagnosed with OI in utero by amniocentesis, demonstrating 46XY karyotype and COL1A2 heterozygous mutation c.982G>A (p.G328S) at the 7q21.3 locus. The mutation in COL1A2 was a de novo autosomal dominant mutation, with a lack of mutation in either parent. Genetic testing was performed due to a prenatal ultrasound study that suggested fetal skeletal dysplasia with bowed short and long bones.

The patient was born by Cesarean delivery without complications. The patient's weight at birth was in the 34th percentile (3.3 kg), height was in the 22nd percentile (44 cm), and head circumference was in the 6th percentile (34 cm), indicating asymmetrical fetal growth restriction. He passed the audiology test at birth.

Immediately after birth, multiple fractures were identified. The perinatal skeletal survey exhibited fractures of the upper and lower extremities and the posterior 9th rib in various stages of healing, diffuse osteopenia, gracile-appearing ribs, and bowing deformities of the femoral shaft bilaterally (Figure 1). The patient was discharged from the hospital on postnatal day 5.

At 3 months, the patient had a recorded fracture of the right humerus (Figure 2). Subsequently, there was no evidence of additional fractures. A dual-energy X-ray absorptiometry (DEXA) scan was performed at 8 months and 23 days of age and showed a lumbar spine bone mineral density of 0.253 g/cm². DI was also diagnosed once teething occurred. The patient’s sclerae at birth and thereafter were blue. The image demonstrating the sclerae is shown in Figure 3. Postnatal visits to an orthopedic surgeon failed to determine this patient’s Sillence class of OI, owing to an inconclusive clinical phenotype combination. None of the currently classified OI types have a combination of severe in-utero/perinatal phenotype, mild postnatal/childhood phenotype, and blue sclerae with DI.

Management

On postnatal day 3, the patient was started on intravenous zoledronate infusions (0.025 mg/kg) every 6 months, calcitriol 0.2 μg once daily, and 60 mg/kg elemental calcium 3 times per day. The pediatrician at our clinic followed up with the patient since postnatal day 7. The patient regularly sees a...
Figure 1. **Fifteen views according to a standard skeletal survey.** There was some osteopenia that most notably involved the calvarium with thin calvarial inner and outer table involving the parietal and temporal bones, with some sparing of the frontal and occipital bones. It was difficult to discern fractures in areas of abnormal irregular calvarial ossification. There was a healing left posterior ninth rib fracture; the first through sixth posterior ribs appeared thin and gracile. Metaphyseal irregularities of the right distal radius, ulna, and proximal humerus had some sclerosis and irregularity consistent with healing fractures. Additional lucency at the distal left radius laterally was without significant healing changes at the time of the imaging. There was an irregularity to the proximal left humeral metaphysis with some sclerosis consistent with a healing fracture. There was a bowing deformity of the bilateral femoral shaft with irregular metaphyseal contours, which were ill-defined and had some areas of sclerosis involving the proximal and distal femur bilaterally as well as the proximal tibia (left greater than right).
pediatric orthopedic surgeon for physical examinations and zoledronate infusions.

Follow-Up

The patient, 3 years old at the time of this report, continued the above treatment. The patient’s growth chart from birth to 24 months is shown in Figure 4, demonstrating very short stature. The anthropometric measurements at the most recent wellness examination were as follows: weight, 12.2 kg (40th percentile); height, 84.5 cm (below 5th percentile); and head circumference, 50 cm (50th percentile). According to these values, the patient’s weight and head circumference were tracking within the age-appropriate range; the height was below the expected values. The patient was physically active and demonstrated age-appropriate gross and fine motor development. The patient has not had any recorded fractures since 3 months of age until the present, nor have there been any reports of bone deformities. Short stature and tooth abnormalities are the only pathological characteristics that differentiate this child from his peers. The patient has been healthy and has had no additional health concerns or clinical diagnoses.

Discussion

The current classification of OI is based on the work of Sillence et al, published in 1979. In 2014, Van Dijk and Sillence published a New OI Nomenclature Combined with Causative Genes and a Pre-and Postnatal Severity Grading Scale [7]. This updated OI nomenclature is not much different from the original version regarding OI types 1 to 4, although it includes specific mutation loci in COL1 genes. According to either classification, the intrauterine asymmetric fetal growth and multiple bone fractures perinatally would place our OI patient in the type 3 category. However, the mild bone fragility phenotype throughout early childhood placed this patient in type 1 or type 4. Since OI type 1 is mostly seen with quantitative collagen defects, type 1 was less likely in this patient. It is important to note that Van Dijk and Sillence’s classification does not include any COL1A2 mutations at 7q21.3, the loci where the patient’s amino acid substitution occurred; however, this is because the updated classification is a guidance and not a rule, as hundreds of COL1 mutations are known to cause OI. There is only 1 published OI case with the same mutation in the COL1A2 gene (although maternally inherited); it was classified as OI type 4 [9]. The ClinVar database describes the same collagen mutation (accession No. RCV000763174.3) and multiple associated conditions, including OI types 2, 3, and 4 and Ehlers-Danlos syndrome.

Thus, what we observe here is not a simple mismatch between a genotype and a phenotype, as the genotype and the phenotype cannot be easily matched in this and many other COL1 mutations. For instance, the updated nomenclature by Dijk and Sillence shows that COL1A1 mutations at 17q21.33 and COL1A2 mutations at 7q22.3 loci are seen in OI types 1, 2, 3, and 4 [7]. A specific amino acid substitution, such as Gly to Ser
at the 7q21.3 locus, as in our patient, may play a more critical role in classification than does the mutation’s locus. This information could help exclude a specific class of OI. It is possible that OI type 1 is not observed in patients with c.982G>A at the 7q21.3 locus, as no OI type 1 has been reported with this mutation. Conversely, the lack of reports does not mean that this mutation cannot exist in OI type 1 patients. The blue sclerae were an additional clinical finding in the patient. This sign placed the patient in the OI type 1 category; although, according to Sillence et al (1993), the blue sclerae can also be found in types 3 and 4 postnatally and during infancy but can fade later in life [10]. The patient’s DI diagnosis does not further clarify OI typing, as this phenotype correlates more frequently with type 4 than type 1 but does not exclude the latter [5].

Epidemiological studies show that some clinical phenotypic features can overlap between OI types, as they are based on frequencies, which may not equal 100% for a particular phenotypic characteristic in a specific patient cohort [11,12]. Therefore, the Sillence classification is not a rigid rule. The importance of such a classification is the prognosis and management of the disease. Since current limited pharmacological treatment modalities do not depend on the classification, an inconclusive clinical phenotype will not preclude a patient from receiving treatment for the condition. To estimate disease prognosis, assessing data from known OI cohorts and identifying children and adult patients with the above inconclusive phenotypic characteristics might be useful. Such information should be added to the existing classification system if clinically significant.

Current OI treatment includes early intervention with bisphosphonates, such as pamidronate and alendronate [13,14]. Other treatment modalities include orthopedic management of fractures and scoliosis and limb rodding for straightening large bone bowing without growth impediment [13]. According to the Cochrane review of 14 clinical trials with a total of 819 participants with OI, in which bisphosphonates were used to reduce the incidence of bone fractures, statistical significance was only found in 2 trials [15]. Early interventions, such as high calcium intake, vitamin D supplementation, and regular bisphosphonate injections, could have influenced the classification of our patient’s OI. It is impossible to determine whether the intake of zoledronate, calcium, and vitamin D supplements has influenced the typing of the patient’s OI.
The prognosis of OI depends on the severity of the bone deformities and fractures and ranges from perinatal death in type 2, death before the age of 30 in type 3, to a relatively normal life for patients with type 1 [15]. Furthermore, OI diagnosis is associated with conductive hearing loss, which starts between the second and fourth decades of life in approximately half of cases with COL1A1 and COL1A2 mutations [16]. The prognosis for the patient in this report is good, but regular clinical follow-up is necessary to ensure that appropriate growth and developmental milestones are reached. The patient’s stature will likely remain short compared with that of peers of the same age. Regular audiometry testing should also be performed. Emergency department visits and orthopedic specialist follow-ups might be necessary to ensure bone intactness in cases of accidental injuries. How long bisphosphonate therapy should be continued for maximum benefit in OI patients is currently unknown.

The present case demonstrates the challenges of using the OI classification system and the need for clinically proven treatment protocols, both of which are impeded by the rarity and heterogeneity of the disease’s mutations and phenotypes. Nevertheless, continuous attempts to predict clinical outcomes by comparing specific COL1 mutations to the disease presentations are crucial. Individual case reports, such as this one, provide detailed data that can be used to analyze multiple cases reporting on the same genotype.

Conclusions

OI is a genetic disease with varying clinical course severity and an array of phenotypes. The presence of skeletal dysplasia in utero and multiple bone fractures at birth may not correlate with the clinical progress of the disease as predicted by the current OI classification system. As this classification system is used as a guide rather than a rule, the rare clinical case presented here can be an important reminder of the classification’s flexibility, although it may constitute a class of its own. In addition, treatments such as bisphosphonate therapy can influence the clinical outcomes of such patients, impacting postnatal OI classification.

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References: