



# Osteogenesis Imperfecta: Multidisciplinary and Goal-Centered Care

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## Abstract

We describe a case of osteogenesis imperfecta (OI) in a late preterm female of 35-week gestation. The mother did have a history of substance abuse, poor prenatal care, and hypertension. On the day of delivery, an ultrasound revealed skeletal dysplasia and breech with nonreassuring fetal tracing, leading to an emergency cesarean. The clinical exam was concerning for OI, and postnatal care was focused on optimizing respiratory status and minimizing pain and discomfort during routine care. Genetics, endocrine, orthopaedics, and palliative care were all involved to diagnose and educate the family. Support and education were needed for bedside staff to minimize angst at performing routine care, given the high risk of fractures. While initially stable on minimal oxygen, once the diagnosis of type III OI was made, a progressively deforming condition with respiratory status decompensation, the family wished to minimize suffering, limited aggressive medical care, and focused on comfort. The infant eventually died from respiratory failure in the neonatal intensive care unit. We present this case to demonstrate the need for an interdisciplinary team approach to support both family and staff in cases of OI.

## Keywords

- ▶ osteogenesis imperfecta
- ▶ prematurity
- ▶ goals of care
- ▶ multidisciplinary care

## Background

Osteogenesis imperfecta (OI) is a group of disorders caused by defects in bone formation, which can cause osteopenia or fractures following minimal or no trauma. The fractures usually occur in long bones but can also occur in the ribs and skull.<sup>1</sup> OI has a prevalence of approximately 6 per 100,000. OI is autosomal dominant; however, 60% of cases are caused by a de novo mutation. Patients with OI have a 50% chance of propagating the disease. If OI is caused by de novo mutation, recurrence in future pregnancies is less than 1%.<sup>2</sup>

Ninety percent of OI cases are caused by mutations in either collagen type 1  $\alpha$  1 (COL1A1) or type 1  $\alpha$  2 (COL1A2). Mutation in these genes causes type I procollagen to be underproduced or produced abnormally. Type I procollagen is a component of bone that provides structural stability, so bones fracture easily if type I procollagen forms improperly. Improper formation can also cause short stature, hearing loss, abnormal teeth, and blue sclerae.<sup>3</sup>

The clinical diagnosis of OI is by the presence of the following features:

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- Fractures after minimal or no trauma.
- Short stature.
- Blue sclerae.
- Dentinogenesis imperfecta (discolored and translucent teeth).
- Progressive postpubertal hearing loss.
- Connective tissue anomalies.
- Family history of OI.

There are multiple types of OI:

- OI type I, classic nondeforming with blue sclerae: mild bone fragility, blue sclerae, and hearing loss.
- OI type II, perinatally lethal OI: most severe form, long bone deformities, and fractures, respiratory failure perinatally.
- OI type III, progressively deforming OI: severe bone fragility, very short stature, blue sclerae, progressive bone deformities, and dentinogenesis imperfecta.
- OI type IV, common variable OI with normal sclerae: short stature, mild-to-moderate-bone deformity, hearing loss, and dentinogenesis imperfecta.

There are also types V, VI, and VII, which are similar to type IV but are not associated with mutations in the COL1A1 and COL1A2 genes and are instead identified by bone histology.<sup>4</sup>

Here, we report on a case of a baby born to a mother with poor prenatal care and born prematurely with skeletal dysplasia concerning for OI. Given the lack of prenatal counseling, extensive postnatal education and counseling are needed. An interdisciplinary team providing patient-centered care with the involvement of parents, bedside staff, neonatology, genetics, endocrine, orthopaedics, and palliative care was essential to ensure adequate care while minimizing pain and suffering.

## Case Report

A 39-year-old gravida 4, para 2 woman presented and was admitted to delivering hospital at 35-week gestation with abdominal and arm pain. Pregnancy was known at 3-week gestation, at which time she was also diagnosed with gestational hypertension and started on amlodipine. No further prenatal care was done until presentation at 35-week gestation.

At presentation, she was hypertensive with a blood pressure of 145/82, and she was given Apresoline. Her group B streptococcus surveillance culture was positive, but the rest of her prenatal laboratory test results were unremarkable. She was given methamphetamine on the day of admission. An ultrasound on admission showed a breech female fetus with long bones less than 26 weeks and femur with angulation at 25 weeks 3 days, concerning for skeletal dysplasia. The fetus was also noted to have category II heart tones. Given the nonreassuring fetal heart tones and skeletal dysplasia, the patient was delivered via emergent cesarean section (C-section). Vancomycin was given more than 4 hours prior to delivery for group B streptococcus prophylaxis. The patient was delivered vertex with clear fluid and underwent 30 sec-

ond delayed cord clamping. Apgar score was 6 and 7 at 1 and 5 minutes, respectively. The patient required continuous positive airway pressure (CPAP) for poor respiratory effort in the delivery room. Physical exam revealed foreshortened limbs with obvious areas of deformities concerning for skeletal dysplasia.

After delivery for respiratory distress, the patient was admitted to an outside hospital neonatal intensive care unit (NICU), and skeletal dysplasia workup was initiated. The patient was symmetrically small for gestational age with birth weight 0.818 kg (< 3rd percentile), length 31 cm (< 3rd percentile), and head circumference of 24.5 cm (< 3rd percentile). Despite decent prenatal dating of 35 weeks, the Ballard exam was consistent with 28 weeks, likely limited due to skeletal dysplasia. A complete exam showed dysmorphisms with brachycephaly, widely separated suture in the posterior aspect of the skull, triangular-shaped face, prominent forehead, blue and gray sclera, malar flattening, pointed chin, shortened and bowed extremities.

The patient remained at a referral hospital NICU for 12 days. She was on CPAP for 2 days for poor respiratory efforts and high-flow nasal cannula (HFNC) at 2 L per minute (LPM). The fraction of inspired oxygen (FiO<sub>2</sub>) was 0.21 throughout. She was briefly on caffeine for apnea of prematurity, but it was discontinued prior to transfer. Initially, she was nil per os and supported through total parental nutrition, but she was eventually transitioned to full enteral feeds through gavage and oral intake. She was started on vitamin D supplements for risk of osteopenia of prematurity and iron supplements for risk of anemia of prematurity. She completed a course of phototherapy for indirect hyperbilirubinemia. She received 3 days of ampicillin and gentamicin, which were discontinued after negative blood cultures. Screening laboratories for toxoplasmosis, rubella, cytomegalovirus, herpes simplex, and HIV were sent due to her small for gestational age status but were all negative. Urine and meconium drug screens were negative despite disclosed maternal substance use.

A skeletal survey shortly after birth showed bowing deformities of bilateral femurs, tibia, and fibula and several rib and clavicle deformities. Lab tests on day of life 2 were notable for calcium (Ca) 8.4 mg/dL, phosphorous (P) 3.9 mg/dL, parathyroid hormone 58.9 pg/mL, and vitamin D 40 ng/mL.

On day 12 of life, the patient was transferred to our hospital for further workup of skeletal anomalies. On admission, she was noted to have decreased hematocrit of 22.4% liter of cells per liter of blood and elevated alkaline phosphatase of 400 IU/L. Her electrolytes were normalized to Ca 10.4 mg/dL and P 6.4 mg/dL. She was on HFNC 2 LPM, FiO<sub>2</sub> 0.21 with capillary blood gas showing appropriate ventilation.

Repeat skeletal survey showed innumerable bilateral fractures throughout the entire skeletal system. Cranial ultrasound showed a left germinal matrix hemorrhage and a focus of increased echogenicity in the right parietal occipital white matter that could represent a separate focus of hemorrhage or white matter injury.

Given the concerning skeletal findings, genetics was consulted for further workup. Microarray from the referral

hospital revealed a copy number variant 396 kb gain of 9q21.11 that was of unknown clinical significance. The initial skeletal dysplasia panel was negative. However, that did not test for OI, so comprehensive molecular testing, including sequencing and deletion/duplication for OI was sent. Endocrinology was consulted for bisphosphonate therapy given high concern for OI, and the patient was started on pamidronate. Orthopaedics was consulted due to multiple fractures and recommended supportive care. Pain was controlled with acetaminophen and morphine as needed. Additionally, all routine care was performed with two nurses to allow for very gentle movements of the infant. Diaper changes and vital sign checks that required movement of limbs were limited to only as needed and/or weekly.

The patient's full gene sequencing and deletion duplication analysis of collagen type 1 identified a pathogenic variant in the COL1A2 gene. Given the findings and the patient's clinical picture, she was presumptively diagnosed with COL1A2-related type III OI.

Given the potential lethality of presumptive diagnosis, palliative care was consulted to support parents and discuss goals of care while awaiting the final diagnosis. The family was counseled extensively by the NICU and genetic teams about what the presumed diagnoses entailed. Initially, given the minimal respiratory support the infant was on and the ability to reach full enteral feeds, the family desired full medical support with no limitations on the escalation of care with the hope that comprehensive medical intervention would result in improved clinical outcomes.

On day of life 30, the patient had decreased respiratory effort. Chest X-ray showed bilateral airspace disease. Patient's respiratory support was increased to CPAP, and she was started on amoxicillin and clavulanate for concern of pneumonia. At 6 weeks of life, the patient started having multiple prolonged apneic events associated with bradycardia and desaturations. Due to her presumptive diagnosis of OI type III, the family was counseled on the severity of her illness. The likelihood of death, no matter the level of medical intervention, was reviewed with the family. Also discussed was the extent of pain, as evidenced by the increasing need for opiate pain medication and vital sign changes with care, directly related to OI that could at best only be managed or controlled, but never "cured." Parents were concerned that in the event of cardiopulmonary arrest, resuscitative measures such as intubation and chest compressions could cause further fracture and pain without affecting the clinical condition resulting in the cardiopulmonary arrest. Consequently, the family made a very brave and loving decision to limit the escalation of aggressive medical therapies, including no intubation or cardiac compressions or support. The medical care plan was then reoriented with a focus on comfort. The patient ultimately died from respiratory failure.

## Discussion

Our patient was transferred due to multiple skeletal anomalies concerning for OI. Her genetic testing showed a pathogenic variant in the COL1A2 gene. Additionally, her clinical

features (severe bone fragility, short stature, blue sclerae, bone deformities, and dentinogenesis imperfecta) led to a presumptive diagnosis of type III OI. Unfortunately, OI type III is the second most severe form of OI and the most severe viable form because type II (the most severe form) usually results in intrauterine or perinatal death.<sup>1</sup>

Given the presumptive diagnosis of OI, bedside care in the NICU was very critical. Physical therapy, occupational therapy, nursing, and respiratory care were coordinated to minimize pain and discomfort while still supporting a premature infant with respiratory insufficiency. Emotional support to the extended team members was needed given concerns with hurting patient while providing full medical support as even nonaccidental trauma can lead to pain and fractures in OI.<sup>5</sup> Palliative care services were key in not only supporting the family, but also supporting the staff as patient's respiratory distress escalated and heightened concern cares were adding to patient suffering. Care team members' comfort and alliance with care goals should be routinely assessed to provide a shared vision.

Our patient was delivered by emergent C-section. The common belief was that C-section was preferred over the vaginal delivery for OI because there is less birth trauma. As a result, it was recommended that when OI is diagnosed prenatally, patients should be scheduled for cesarean delivery. However, recent studies have not shown any significant decrease in the fracture rate between vaginal delivery versus C-section.<sup>6</sup> These results are confounded by patients like ours that are diagnosed late in pregnancy, resulting in emergent cesarean section with numerous fractures.

OI, unfortunately, does not have a cure, and current management is supportive. Our patient did not have a family history, and up to 60% of cases are caused by de novo mutation. This poor prognosis coupled with the possibility of heredity makes discussion regarding advanced care planning and palliative care consultation imperative.

OI is commonly associated with both prematurity and osteopenia. However, osteopenia is also associated with prematurity alone. Currently, there are limited studies on the degree to which OI compounds osteopenia related to prematurity.

One therapy that we trialed on our patient was intravenous bisphosphonate. It is theorized that since bisphosphonates effectively reduce bone resorption in osteoporosis, they can also reduce bone resorption in OI, resulting in increased bone density and decreased fractures. Studies so far have shown that intravenous bisphosphonate therapy results in increased bone mineralization; however, they have not shown a decrease in fracture rates. Additionally, these studies were not compared with placebo.<sup>7-11</sup> Given the unclear benefit of bisphosphonates, it is not always clear cut if they should be started at birth as they can also be associated with adverse effects including elevated body temperature, hypocalcemia, lymphopenia, osteonecrosis of the jaw, and pain in the head, abdomen, bone, and muscle.

In summary, our patient with multiple skeletal fractures was diagnosed with OI type III. She was delivered by cesarean section and treated with intravenous bisphosphonate. She,

unfortunately, died as do many of the patients with OI type III. This disease is rare and has extremely high mortality and morbidity rate without many clear guidelines so more research or expert consensus would be beneficial in gaining a better understanding of the disease and establishing guidelines for management as well as facilitating counseling of families.

#### Conflict of Interest

None declared.

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