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Osteogenesis Imperfecta: One Disease, Two or More Faces: A Case Report

Anjali-Larisha Chhiba[1,2], Firdose Lambey Nakwa[1,2], Kebashni Thandrayen[1,2]

[1]Department of Paediatrics, Chris Hani Baragwanath Academic Hospital, Johannesburg, South Africa
[2]School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa
Email: anjalichhiba@gmail.com

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Abstract

Being such a rare condition in paediatrics, osteogenesis imperfecta (OI) is not a diagnosis which is made often. It is however, a diagnosis necessitating early diagnosis and timeous and effective management to improve morbidity and increase the quality of life for our patients. We report two cases of osteogenesis imperfecta in this case report to highlight the different phenotypic presentations. Both of these patients are unique in their presentations and each case highlights the importance of a high clinical index of suspicion by the practitioner in making the diagnosis of osteogenesis imperfecta. The first case is a patient who was diagnosed with osteogenesis imperfecta on day one of life. She had disproportionate short stature, blue sclera, a small chest and bowing of her lower limbs with swellings and tenderness over both of her femurs. A babygram radiograph revealed multiple fractures, with the presence of callus formation at some fracture sites suggesting intrauterine fractures. The second case is a patient who had normal anthropometry and was well at birth. She was subsequently diagnosed at two weeks of age when she presented to the Chris Hani Baragwanath Academic Hospital with an *E. coli* meningitis and she was suspected to have a right clavicular fracture and possibly rib fractures as she had pain on palpation over these areas. She was noted to have no blue sclera. Subsequent X-rays confirmed a right clavicular fracture as well as left and right rib fractures at different stages of healing. A lateral skull radiograph revealed Wormian bones. With no available genetic testing in South Africa, both diagnoses were made clinically. Both of our patients were started on zoledronic acid at three months of age and were followed up by the Metabolic Unit at the Chis Hani Baragwanath Academic Hospital. This case report of two patients highlights the characteristics important in diagnosing and treating this uncommon condition with varying phenotypical presentations, thus ensuring that the diagnosis is not missed or misdiagnosed: one disorder, two different faces.

Keywords

Paediatrics, Osteogenesis Imperfecta, Case Report, Fractures, South Africa

1. Introduction

Osteogenesis imperfecta is a rare genetic disorder with a global incidence of one per 20,000 live births [1]. Interestingly, the proportion of *de novo* mutations, which is 35% - 60%, is lower than that of other musculoskeletal disorders [1]. While the incidence is unknown, research shows that Type III osteogenesis imperfecta occurs in the indigenous black population of South Africa, with a minimum population frequency of 0.6 per 100,000 [2]. In a study by Oduah *et al*., which was based at the Chris Hani Baragwanath Academic Hospital, it was found that 48.7% of the patients presenting to the Metabolic Bone clinic had type III osteogenesis imperfecta; with the next most prevalent being type IV, comprising 29.5% of the patients in this study [3]. Type III osteogenesis imperfecta is referred to as "progressively deforming" which emphasises its severity. The pattern of inheritance of type III osteogenesis imperfecta is either autosomal recessive or autosomal dominant, with the former being more prevalent in South Africa [2].

There are 18 gene-based types of osteogenesis imperfecta [4]. With genetic testing not being readily available for routine analysis, especially in our state hospitals, we rely greatly on clinical and radiological features to characterize the type of osteogenesis imperfecta. Identification of specific genes would further assist in accurately classifying osteogenesis imperfecta according to type, which is important in prognostication. As a broad clinical and radiological classification, the Sillence phenotypic classification classifies Type I osteogenesis imperfecta as mild, type II as severe and perinatally lethal, type III as severely deforming and type IV as moderately deforming [4].

Dominant mutations in the COL1A1 (collagen type 1 alpha-1 chain) and COL1A2 (collagen type 1 alpha-2 chain) gene encompass the majority of osteogenesis imperfecta cases [5]. It has been found that these genes are involved in 90% of cases of osteogenesis imperfecta [6]. These mutations result in a decreased production or abnormal synthesis of collagen. There are however, 17 other genes involved in collagen synthesis or osteoblast formation which are also implicated in osteogenesis imperfecta [7].

Mutations of a variety of genes result in Type III osteogenesis imperfecta, with mutations in the FKBP10 gene being reported in South Africa [2]. In the study by Vorster *et al*., 45% of patients with osteogenesis imperfecta Type III had mutations in the FKBP10 gene [2]. The study emphasized the necessity of genetic testing for families of patients with osteogenesis imperfecta as this could assist with carrier detection, antenatal diagnosis and preimplantation genetic diagnosis. However, Zhytnik *et al*. demonstrated that 85.29% of osteogenesis imperfecta

Type III patients in their study had de novo mutations [1].

This case report describes two interesting cases of patients with differing forms of osteogenesis imperfecta. Informed consent was obtained for both patients. The objective of this case report is to bring awareness to osteogenesis imperfecta and the importance of early diagnosis and referral to decrease morbidity and ensure prompt management and support.

2. Case Report

Case 1 was a baby girl born at Chris Hani Baragwanath Academic Hospital via spontaneous vaginal delivery. She was born premature at 34 weeks gestation with a birthweight of 1185 g, a length of 34 cm and a head circumference of 24 cm. All of her growth parameters plotted below −2 standard deviations on gestation-appropriate growth charts. She had an upper to lower segment ratio of 1.3:1 indicating disproportionate short stature. Clinically, she had a soft skull with mild sutural diastasis and was noted to have blue sclera. She had a small chest with mild subcostal recessions but clinically normal breath sounds auscultated bilaterally. Her cardiovascular examination was normal, as were her abdominal, genitourinary and neurological examinations. There was no increased laxity of her ligaments or skin. On mild palpation of the long bones, there were swellings and tenderness felt over both her femurs with bowing of her lower limbs. There were no other skeletal abnormalities noted of the upper limbs and she had no scoliosis. Her respiratory distress settled on nasal prong oxygen.

A clinical diagnosis of skeletal dysplasia was made and she was admitted to the neonatal unit for further workup and management. A babygram radiograph revealed six fractures involving her right clavicle, humerus, femur and tibia and her left ulnar and femur (**Figure 1**). The presence of callus formation at some of the fracture sites suggested intrauterine fractures. Her bones appeared to be osteopenic. There was no family history of any skeletal dysplasias. Blood investigations were unremarkable and her congenital pneumonia resolved within four days after treatment with intravenous antibiotics. Cranial ultrasound at two weeks of age was normal and ruled out hydrocephalus at this stage. She grew well in the ward to a discharge weight of two kilograms and by this time her mother had gained confidence in handling her and was comfortable to take her home.

Case 2 was a baby born at term with a birth weight of 2670 g and a length of 49 cm which plotted appropriately for gestational age. There was no family history of any medical conditions or comorbidities. There were no obvious skeletalfeatures recognized at birth and a paediatric review was not requested as she was well at delivery and required no hospital admission. Thereafter, at two weeks of age, she presented to Chris Hani Baragwanath Academic Hospital and was diagnosed with an *E. coli* meningitis. She was noted to have blue sclera and she appeared to be in pain on handling during the admission. The pain was particularly over her right clavicle and rib cage. Radiographs evidenced fractures of the right clavicle and right and left ribs at different stages of healing (**Figure 2**). A

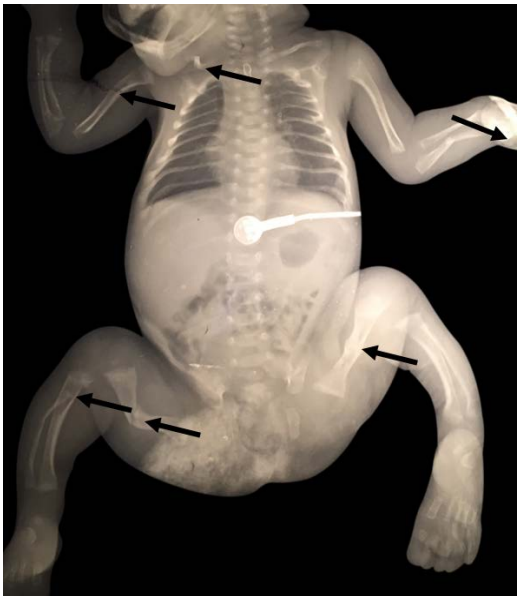

Figure 1. Is a babygram of the patient from Case 1 showing six fractures as denoted by the arrows.

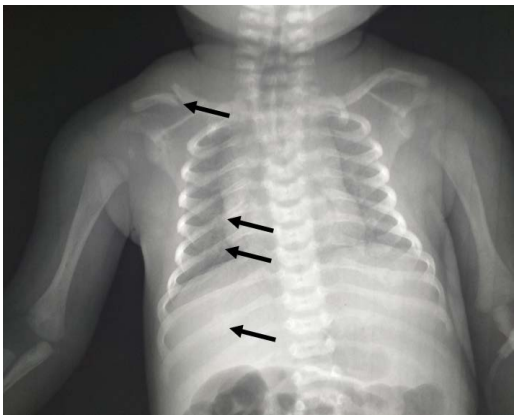

Figure 2. Shows the right clavicular and rib fractures (as demonstrated by the arrows) found in the patient for Case 2. These fractures were noted to be in different stages of healing. The bones also appear oste.

lateral skull radiograph revealed Wormian bones (**Figure 3**).

The severe type of osteogenesis imperfecta (Case 1) presented at birth with clinical features of OI, fractures and deformities whilst the possible moderate type (Case 2) with blue sclera had presented at two weeks of age at a tertiary institution with an underlying meningitis, and with the experience of the paediatricians and bone specialists was diagnosed at this stage with OI. If the child was not admitted, she would have possibly been a delayed diagnosis as the pain or crying may have been attributed to other causes such as colic and the fractures could have been missed.

Case 1 was admitted for a lower respiratory tract infection two weeks after

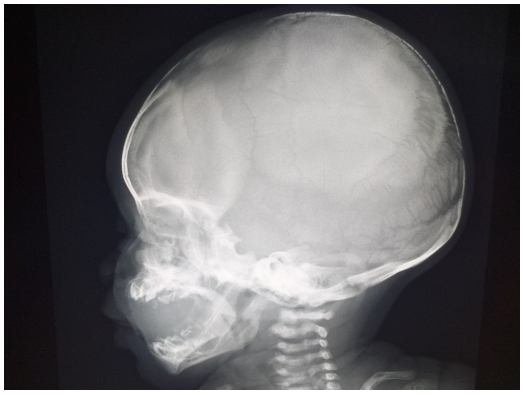

Figure 3. Clearly demonstrates the presence of Wormian bones on this lateral skull Xray of the patient in Case 2.

discharge and unfortunately deteriorated and demised in the paediatric ward. Case 2 is doing well. She follows up with the Paediatric Metabolic Bone clinic and receives bisphosphonates.

3. Discussion

In South Africa, the diagnosis of OI is largely a clinical and radiological diagnosis together with the history of fragility fractures. Case 1 was diagnosed as Type III osteogenesis imperfecta which is associated with long term survival, despite the multiple in utero fractures, multiple long bone and rib fractures at birth and limb deformities [8]. Case 2 was diagnosed as a possible Type IV osteogenesis imperfecta, a comparatively less severe form of osteogenesis imperfecta with a later diagnosis. Radiologically, fractures in various stages of healing were noted, as well as Wormian bones on skull Xray. Short stature with blue sclera also pointed to the diagnosis of Type IV osteogenesis imperfecta.

Clinical and radiographic features, family history and natural history classifies osteogenesis imperfecta into four main types [9]. This is broadened to 18 types with the addition of genetic assessment and the identification of the specific genes involved [9]. Importantly to note is that clinical and radiological features overlap across the various types. Classic non-deforming osteogenesis imperfecta (type I OI), is characterized by normal stature and blue sclera [9]. Fractures in this group of patients usually first occur with walking and falling, with a few to several fractures per year which subsequently decrease in frequency after puberty [9]. A subset of osteogenesis type I is dentinogenesis imperfecta (OI type IB) when there is premature wearing down of the teeth [9].

Perinatally lethal osteogenesis imperfecta (type II OI) is apparent at birth with dark blue sclera, extremely fragile connective tissue, a large soft skull and short and bowed extremities [9]. Affected infants occasionally demise in utero, with majority demising in the immediate perinatal period – 80% within the first week of life, usually resulting from pulmonary insufficiency related to small thoraces, rib fractures or flail chests with unstable ribs [9].

Progressively deforming osteogenesis imperfecta (type III OI) is apparent at birth with fractures in the neonatal period and blue sclera [9]. Patients have short stature and because of severe bone fragility and marked bone deformity, they require assistance for mobilizing and usually require a wheelchair [9]. Patients may develop dentinogenesis imperfecta and some patients have a relative macrocephaly and barrel chest deformity [9]. Basilar impression can occur and progress to brain stem compression, obstructive hydrocephalus and syringomyelia [9]. Commonly variable osteogenesis imperfecta (type IV OI) is characterized by mild short stature, dentinogenesis imperfecta and blue sclera in the neonatal period which change to grey later on [9]. Hearing loss my occur in adulthood and in some patients basilar impression can occur [9].

Of note, blue sclera are also present in other conditions such as Ehler-Danlos, Russel-Silver, Marshall-Smith, Loeys-Dietz and De Barsy syndromes, as well as in some patients with iron deficiency [7]. Wormian bones can be present in the normal paediatric population as well as conditions such as hypophosphatasia, hydrocephalus, congenital hypothyroidism and Down Syndrome [7]. Various other conditions increase the risk of fractures and these also need to be considered as differential diagnoses. These include metabolic bone disease of prematurity, idiopathic juvenile osteoporosis or monogenetic osteoporosis, Ehlers-Danlos syndrome, hypophosphatasia, hereditary hyperphosphatasia, osteoporosis-pseudoglioma and vitamin D and/or calcium deficiency rickets [7]. This shows the importance of a holistic assessment of patients when making a clinical diagnosis.

It is also important to consider other syndromes which may resemble osteogenesis imperfecta. Cole-Carpenter Syndrome patients have brittle bones with craniosynostosis and ocular proptosis [10]. Bruck syndrome is a disorder with brittle bones and congenital joint contractures [10]. Osteoporosis pseudoglioma syndrome patients have mild to moderate osteogenesis imperfecta and blindness due to secondary glaucoma [10]. Other conditions with brittle bones have associated redundant callus formation, mineralization defects or rhizomelia [10]. This highlights the importance of genetic testing to confirm a diagnosis of osteogenesis imperfecta and rule out other conditions with similar clinical findings.

Radiological evidence of fractures helps with diagnosis of osteogenesis imperfecta. Typical radiographic features include Wormian bones on lateral skull radiographs, which are small supernumerary bones found between the sutures and fontanelles of the skull [7]. They are suggestive of osteogenesis imperfecta and are occasionally evident in type I, III and IV [9]. Other radiological features include fractures at various stages of healing and spinal compression fractures or "codfish vertebrae" which are more commonly seen in adult patients [9]. Protrusio acetabuli, whereby the acetabulum bulges into the pelvic cavity, is occasionally seen in patients with type IV osteogenesis imperfecta [9]. Thin cortices of the extremity bones occurs in types I, III and IV versus the severely deformed, broad, crumpled and bent femurs found in patients with type II osteogenesis imperfecta [9]. Small beaded ribs are pathognomonic of type II, versus thin ribs being observed in patients with type III osteogenesis imperfecta [9].

In terms of laboratory findings, vitamin D, calcium, phosphorous and alkaline phosphatase are typically normal with an occasional raise in alkaline phosphatase post fractures [9]. Markers of bone resorption (C-telopeptide of type 1 collagen) may be higher and markers of bone formation (C-terminal propeptide of type 1 procollagen) may be lower in patients with osteogenesis imperfecta, especially in severely affected patients [11].

Prompt diagnosis of osteogenesis imperfecta is important to prevent further complications. Management of this condition is multidisciplinary and involves paediatricians, endocrinologists, geneticists, orthopaedic surgeons, dentists, social workers, psychologists, physiotherapists and occupational therapists. The aim is to improve and maximize function and thus outcomes [8]. The mainstay of treatment for osteogenesis imperfecta is bisphosphonates, which has been shown to decrease bone turnover, bone pain, improve bone mineral density and reduce fracture rates [12].

Besides fractures, chronic pain (irrespective of the type of osteogenesis imperfecta) even without fractures is a major cause of morbidity in patients with osteogenesis imperfecta. The pathophysiology of this chronic pain is unclear but it is speculated that inflammatory cytokines, such as prostaglandins and thromboxanes, may contribute to bone turnover and result in pain [12]. The pain may subsequently result in delayed motor development. This highlights the importance of treatment in decreasing morbidity and maximizing functional capabilities. Bisphosphonates is important in pain control in patients with osteogenesis imperfecta.

Both of our patients were started on zoledronic acid at three months of age. Studies have shown that zoledronic acid has a longer biological half-life (thus allowing for longer dosing intervals) and can also be given more rapidly as a half hour infusion [8]. Comparing with pamidronate, zoledronic acid has a similar response in terms of reported quality of life and bone density [8]. A study by Garganta, *et al*. showed an acute reduction of pain and improved daily functioning in patients with chronic cyclic treatment of a half hour infusion of zoledronic acid at 6 monthly intervals [12]. Pain improved immediately after the infusion and analgesia lasted for several weeks and subsequently waned [12]. It was demonstrated that pain and functional levels return to pre-treatment levels by the subsequent infusion [12].

An important modality in treatment along with bisphosphonates is orthopaedic interventions such as intramedullary telescopic rods which significantly improve patient mobility [8]. Important to consider here is the timing of bisphosphonate therapy after intramedullary rod insertion as callus formation at the osteotomy site needs to occur [8]. It has been shown that bisphosphonate therapy delays the healing of osteotomy sites after intramedullary rod insertion [13]. A study by Anam *et al*. showed that delayed osteotomy healing was significantly lower with a bisphosphonate infusion-free interval of four months post osteotomy and with a change in surgical method, an osteotome was used instead of an oscillating power saw [13]. Unfortunately, they were unable to identify the effects of each contribut-

ing factor individually [13]. The same approach of temporarily stopping bisphosphonates applies when patients sustain a fracture to allow for healing. Orthopaedic management is also required for the treatment of scoliosis [8].

An often overlooked, yet extremely important, aspect in the management of children with osteogenesis imperfecta is the psychological care of our patients and their families. Osteogenesis imperfecta can be an overwhelming experience for patients and their families. It is important to consider the psychosocial implications at various developmental stages of childhood and adolescence [8]. For Case 1, who was diagnosed on day one of life, the diagnosis came as a surprise for her mother, who had never heard of such a condition before. She was scared to even handle her baby initially as she cried from pain with minimal movements, despite analgesia. Over time, she gained confidence as she became more comfortable with handling her.

An article by Stephen *et al*. highlights the psychosocial challenges of osteogenesis imperfecta Type III in South Africa [14]. Parents had initial feelings of shock, depression and anxiety as they now had a child with a physical disability [14]. These feelings then progressed to helplessness, loneliness and stress with unexpected financial implications [14]. Adequate emotional and psychological support greatly improves parents' feelings and their outlook on the condition osteogenesis imperfecta. Parents then become more involved with the realization of the importance of providing support for their children. There are available support groups for patients with osteogenesis imperfecta and their families in South Africa which offer emotional as well as financial support where possible.

Children affected with osteogenesis imperfecta also need to deal with physical and emotional barriers that come with the diagnosis [14]. The use of adaptive devices allow for full independence which in turn benefits patients psychologically [14]. The physical barriers that children with osteogenesis imperfecta face at school which limit mobility also need to be addressed [14]. As this is an evolving condition with differing implications throughout a child's life, great care and consideration needs to be taken at every step of the way.

4. Conclusion

This case report aimed to highlight the importance of consideration and early diagnosis of this rare yet prevalent condition. Timeous and effective management, in addition to the importance of a holistic approach, in order to decrease morbidity and increase the quality of life for our patients with osteogenesis imperfecta is mandatory.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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