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OSTEOGENESIS IMPERFECTA INVOLVING A MOTHER AND HER TWO DAUGHTERS WITH A REVIEW OF LITERATURE.

Short title: **Osteogenesis imperfecta in siblings**

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ABSTRACT

In children, fractures following minimal trauma is the most prevalent sign and a hallmark of osteogenesis imperfecta (OI). Long bones, particularly in the lower limbs, are frequent fracture sites in children with OI. The diagnosis is based mainly on history, physical findings and radiographic features. In this report familial clustering, the clinical and epidemiological characteristics of two female siblings (including their mother) with OI are described while the newer classification, the differential diagnosis and the aims of therapy are also emphasized.

Key words: Collagen disorders, dentinogenesis imperfecta, familial clustering, osteogenesis imperfecta.

INTRODUCTION

Osteogenesis Imperfecta (OI) (also called Brittle Bone Disease) is a heterogeneous inherited metabolic bone disorder characterized by short stature, long bone deformity, and susceptibility to fracture from mild or inconsequential trauma due to reduced strength and increased brittleness of the bones [1]. It is a generalized disorder of connective tissue and the most common genetic cause of primary osteoporosis in childhood [2]. It has been proposed that OI be defined as a syndrome of congenital brittle bones secondary to mutation in the genes codifying for pro-collagen genes (COL1A1 and COL1A2) [3]. Majority of cases (approximately 90%) are due to genetic mutations involving the two genes, collagen type 1, alpha 1 (COL1A1) on chromosome 17q21 and collagen type 1, alpha 2 (COL1A2) on chromosome 7q22.1 [4,5]. Most of the mutations that cause OI type 1 occur in COL1A1 gene. Many of the other rare forms of OI are due to defects in protein involved in cross-linking, hydroxylation, and mineralization of type I collagen [2]. Type 1 collagen is a major

protein constituent of bone, dentin, skin, sclera, blood vessels and heart valves and plays a major role in the pathogenesis of OI. Essentially, there are two molecular mechanisms resulting in OI caused by collagen mutation [6]. The first mechanism is through chain exclusion in which the mutant chain is not incorporated into collagen triple helix, resulting in the milder OI type 1 because the abnormal microfibril is unable to incorporate into the triple helix and is thus degraded, leaving the remaining allele to produce less structurally intact collagen triple helix. The second mechanism is through chain non-exclusion in which abnormal collagen chain results in a defective helix (a qualitative defect). The resultant dominant negative effect manifests as more severe OI types II, III and IV. Worldwide, the incidence of OI is one in 20,000 live births and the prevalence is six to seven per 100,000 [7] and its frequency appear similar in all ethnic and racial groups. Some familial recurrences of OI are due to parental mosaicism for dominant collagen mutation [2]. Classical OI (Sillence types I-IV) are inherited as autosomal dominant disorder, so also is OI type V [2]. The diagnosis of OI is established by clinical criteria and confirmed by genotyping of COL1A1 and/or COL1A2 or other pertinent genes. However, failure to detect a genetic mutation does not necessarily rule out OI [8]. Diagnosing the various genes is challenging due to variability in clinical manifestations and the high degree of overlap in phenotypes. In literature, the variable clinical manifestation has been linked to factors such as epigenetics, modifiers and environmental influences [9].

Regarding the aetiopathogenesis of OI collagen, fibres are usually oriented in a preferential direction with hydroxyapatite crystals located in the ground substance within these fibres. The hydroxyapatite crystals provide mechanical rigidity and strength to the bone whereas the fibres provide resilience. Individuals with OI have either less or poorer (or both) quality type I collagen fibres than unaffected people, causing their bones to deform or fracture (or both) [10]. The Sillence classification of 1979, divides OI into four types (I-IV) based on clinical and radiographic findings [11]. However, this classification has two major drawbacks which are the overlapping nature among different types and the difficulty in using it for prognosis based on the type. Therefore, caution is advised in the use of the numeric classification of OI and the severity must always be assessed in each individual case. In 2014, this classification was revised with introduction of OI type V, characterized by interosseous ossification with propensity to develop hyperplastic callus [12]. However, this new classification system still retains the Sillence classification for defects associated with mutations in type 1 collagen genes. Genomic tests can be done with collagen analysis from fibroblast.

Among the oral manifestations of OI, dentinogenesis imperfecta (DGI) is the most prominent [13]. According to Shield's classification, there are three types; DGI type 1

(DGI-1), a syndromic form, always occurs in association with OI while DGI types II and III, non-syndromic forms, are not associated with OI [14,15]. The morbidity and mortality of OI involve the cardiopulmonary system. Recurrent pneumonias and declining pulmonary function occur in childhood and a chronic lung disease (cor pulmonale) may be seen in adults. Neurologic complications include basilar invagination, brainstem compression, hydrocephalus and syringohydromyelia. Apart from these complications, OI is a potentially incapacitating clinical condition, interfering negatively with quality of life (QoL).

The purpose of this report is to raise awareness among clinicians of this rare clinical entity, the familial clustering nature and psychosocial impact. Additionally, to review the literature to highlight its differential diagnosis as well as challenges in diagnosis and management.

Case presentation

Case 1: A 5-year-old girl, born at term, to non-consanguineous parents, presented to our hospital with a history of poor growth noticed from the age of 2 years and recurrent fracture of the arms. First episode of fracture of left arm was 3 years ago while the child was being massaged at home. Second episode was one year ago following a fall while attempting to walk. Mother noticed poor growth since the age of 2 years, being markedly smaller than other children younger than her. She can neither stand nor walk, making it impossible for her to enroll in school. She has no hearing difficulty.

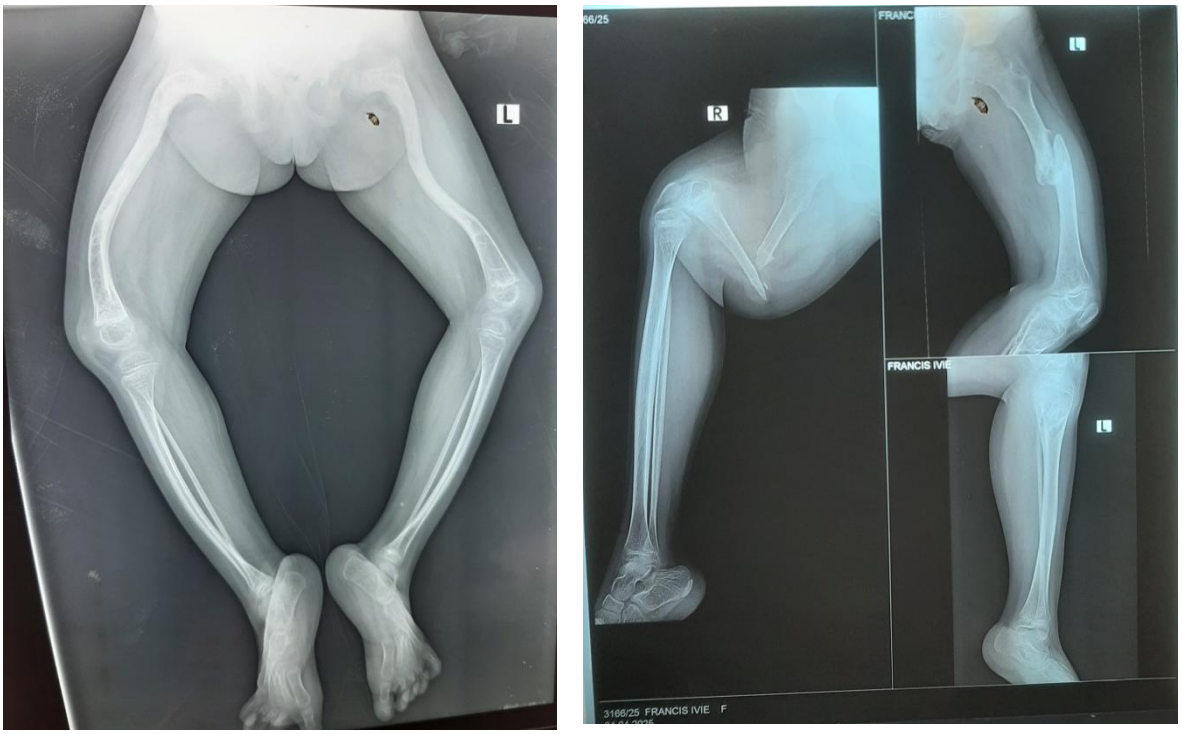
Physical examination revealed small-for-age stature, triangular facie and skull deformity. The auxological findings include length 75.0cm (< 3rd percentile, using OI specific growth chart), weight 9.5kg (< 3rd percentile), BMI 16.9kg/m^2 (75th percentile) occipitofrontal circumference 47.cm, Arm length 9.5cm, Forearm length 12.5cm, Chest circumference 43.5cm. Her vital signs were within normal limits. Additional findings include pectus carinatum, dentinogenesis imperfect, skeletal deformities of the long bones. Abdominal examination revealed hepatomegaly. Cutaneous signs of physical abuse were absent. The radiographic findings include thickening of the diploid space of the left parietal bone, defective modeling and shortening of both humeri, generalized osteopaenia with thinning of the ribs, defective modeling of the femur bilaterally with bowing of the femur and tibia bilaterally.

Case 2: A 9-year-old girl, born at term, to non-consanguineous parents, presented with fracture of the femur 6 months ago and inability to walk since then. This is the second episode of fracture in this patient. The fracture occurred following a fall having been pushed by another child. She did not fall from a height. The first episode of fracture was 6 years ago at the age of 3 years. The fracture occurred when she attempted to walk and fell. She has no hearing

impairment. On examination, her weight was 15kg (< 3rd percentile), length was 90cm (< 3rd percentile) and BMI 18.5kg/m^2 (75th percentile). She had deformity and shortening of right lower limb. Part of the broken femur was protruding posteriorly covered only by a scar. She also has dentinogenesis imperfecta. There are no bruises at the site of fracture. The patient has stopped schooling because of progressive deformity and fractures of the lower limbs.

The family/social history was remarkable. The mother of the two siblings also has a positive history of fracture of left femur following a fall while walking after the rain at the age of 10 years. The mother (a petty trader) has no formal education, and she does not know her age. The father has primary school education, and he is a carpenter. However, he abandoned the children and their mother because of their clinical condition. The patients' medical care is being sponsored by a kind-hearted man. On physical examination of the mother, it was noted that she has short stature (height 145cm) and weighed 40kg. She has skull deformity (like that of case 1) and dentine dysplasia. Having clinically made a diagnosis of OI, the patients commenced on vitamin D supplementation 400units daily because it is known that serum 25-hydroxy-vitamin D is often low, because of immobility and ultimately, insufficient exposure to sunlight. The orthopaedic surgeon and physiotherapist were invited to form a multidisciplinary healthcare team.

Figure 1: Case 1 shows deformities of femur and tibia



Case 1 shows long bone deformities **Case 2 shows fracture of femur**

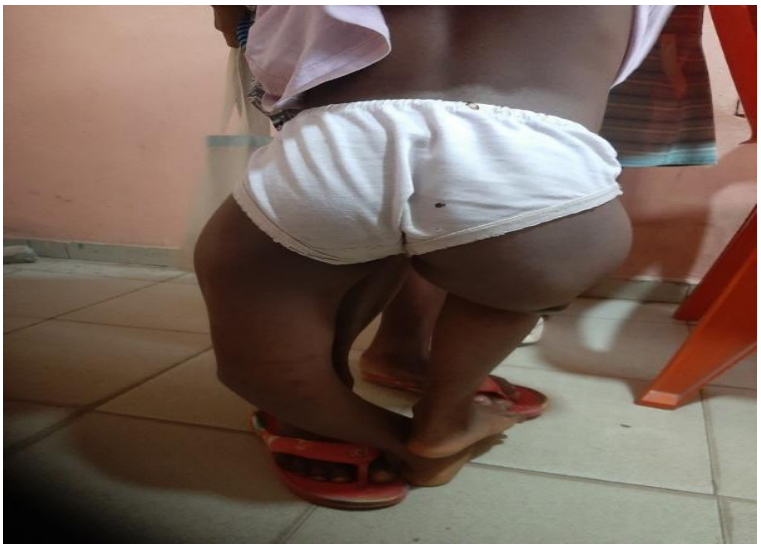


Figure 2 shows deformities of low limbs in case 2.

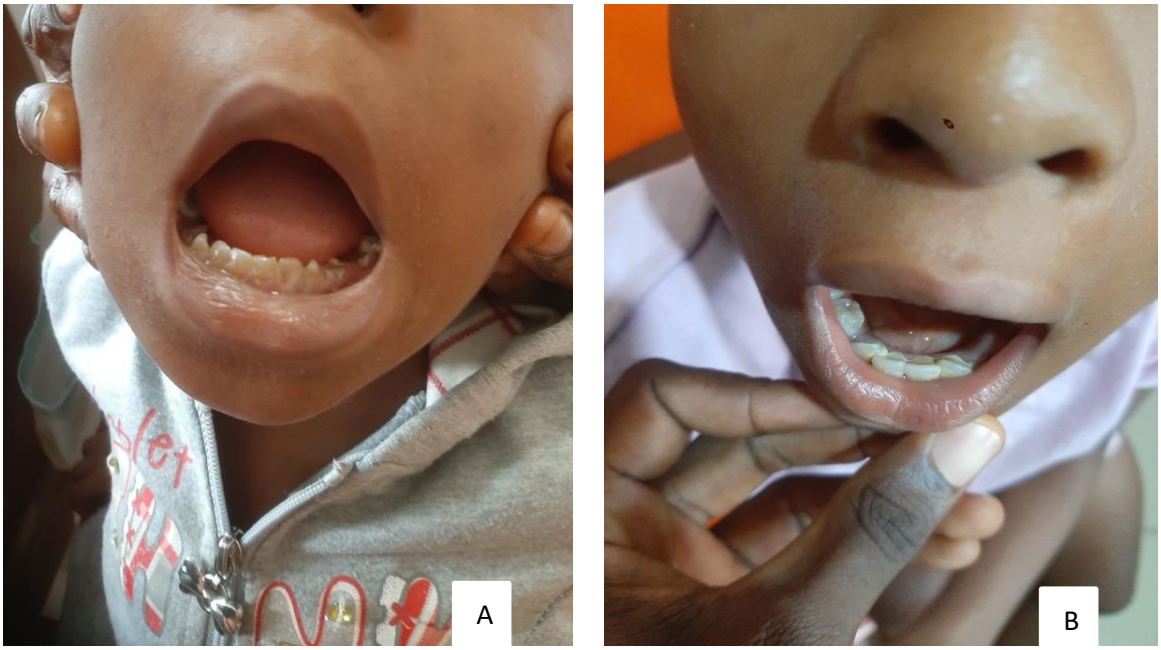


Figure 3a: shows dentine abnormalities: A: Case 1 **B: Case 2**

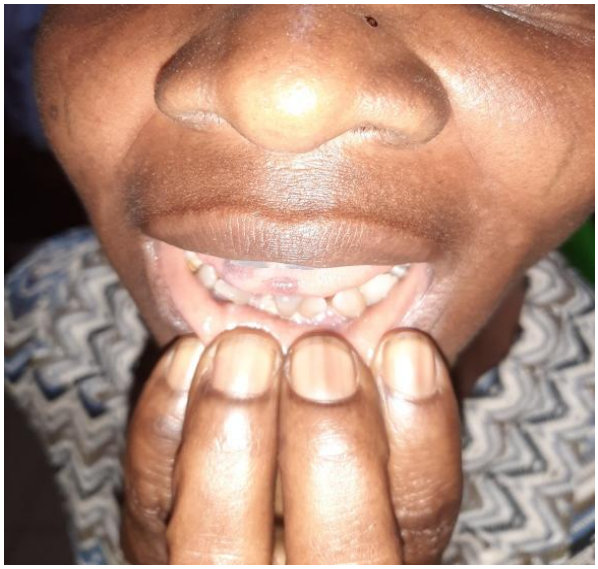


Figure 3b: shows dentine abnormalities: C: Mother

Table 1: Summary of investigation results for cases 1 and 2.

Laboratory parameters	Case 1	Case 2	Reference intervals
Serum calcium	7.6mg/dl	7.9mg/dl	8.0 - 10.5
Serum organic phosphate	3.5mg/dl	4.0mg/dl	4.0 - 7.5mg/dl
Alkaline phosphatase	105iu/L	102iu/L	≤ 270
Serum urea	10mg/dl	9.6mg/dl	10.0 - 50.0
Serum sodium	139mmol/L	140mmol/L	135 – 145
Serum potassium	4.9mmol/L	4.5mmol/L	3.5 - 5.5
Serum bicarbonate	19.0mmol/L	20.0mmol/L	20 – 30
Serum chloride	100.0mmol/L	102.0mmol/L	99 – 107
Serum creatinine	0.4mg/dl	0.3mg/dl	0.6 - 1.4
Aspartate aminotransfarse	56iu/L	48iu/L	≤ 40
Alanine aminotransferase	28iu/L	26iu/L	≤ 40
Total bilirubin	0.7mg/dl	0.5mg/dl	0.2 - 1.2
Conjugated bilirubin	0.3mg/dl	0.3mg/dl	0.2 - 0.6
Non-conjugated bilirubin	0.4mg/dl	0.2mg/dl	0.1 - 0.2
Total protein	6.7g/dl	7.0g/dl	6.0 - 8.2
Serum albumin	3.8.g/dl	4.0g/dl	3.3 - 5.1
Serum globulin	2.8g/dl	3.0g/dl	2.0 - 3.2
Packed cell volume	37.0%	40.0%	33 – 50

DISCUSSION/LITERATURE REVIEW

In this report, the diagnosis of OI was based on history of repeated fractures secondary to mild trauma, positive history of pathologic fractures in a first degree relative (mother), physical examination findings (severe short stature, dentinogenesis imperfect) and radiographic findings of lower limb fractures, long bone deformities as well as generalized osteopaenia. In summary, the known triad of OI (namely, fracture from minor trauma, long bone curvature deformity and growth deficiency) were present in the two siblings. The hallmark of OI in children is fractured due to minimal trauma and this history was positive in the two siblings including their mother, further reinforcing the diagnosis. Lack of adequate laboratory facility prevented performing both the collagen biopsy test and the DNA test which are thought to detect nearly 90% of all type 1 collagen mutations [16].

It is noteworthy that the first case sustained fracture of the upper limb rather than the lower limb which typically is involved in fractures. In addition, the two siblings presented here exhibited clinical features in keeping with Sillence OI type III, which is characterized by severe short stature, progressive skeletal deformities, recurrent pathologic fractures with minimal trauma, scoliosis, triangular-shaped face, basilar skull deformities, dentinogenesis imperfecta as well as thinning of the ribs. Applying the flowchart for clinical diagnosis of OI suggested by the Indonesian Paediatric Association Clinical Practice Guideline on OI, it further supported the diagnosis of OI type III in the two siblings presented here [17]. The possibility that the index cases are OI type III is further reinforced by the report of a study in South Africa regarding its relative prevalence in Blacks. In that report, a study involving children from South Africa and Zimbabwe showed that OI type III is relatively common in an indigenous Black population [18]. The results of a study in South Africa showed that among indigenous black population of South Africa, the minimum population frequency of OI type III was 6 per 100,000 [19].

In addition to these characteristics, the mother also has a positive history of pathological fracture at the age of 10 years, indicating familial clustering. Physical examination of the mother showed dentine dysplasia, skull deformity and triangular-shaped face similar to that of the observed in Case 1, suggesting that the mother also has OI, probably of a lesser severity than that of her offspring. In this regard, most likely OI type 1 (the most common subtype of OI) or type IV (intermediate severity). Thus, illustrating the heterogeneous nature of OI. This finding is supported by a recent report by Cruz-Centeno et al [20] in Puerto Rico in which a mother and her two children (a male and a female) had OI. In the present report, the mother and her two daughters are affected. It has been documented that majority (approximately 90%) of cases of

type 1 collagen mutation involve autosomal dominant mode of inheritance [4,5]. There is no history of consanguinity in parents. The father did not have similar history or physical features. In a comprehensive review article, the authors stated that the differential diagnosis of OI is largely determined by the age of presentation and clinical severity [7].

In that review, the stated common differential diagnosis of OI includes osteopaenia of prematurity, hypophosphataemia, idiopathic juvenile osteoporosis and non-accidental injury. The two siblings (index cases) were full term deliveries, making osteopaenia of prematurity unlikely.

In hypophosphataemia, serum phosphate is low while alkaline phosphatase is elevated. In the two siblings, these biochemical parameters were within normal limits, and the typical radiographic features (flaying, splaying, cupping) of rickets were absent, making hypophosphataemia less likely. Idiopathic juvenile osteoporosis (IJO) presents in previously healthy prepubertal children (usually 2 to 3 years before puberty) and resolves spontaneously over 2 to 5 years [21].

This disorder (IJO) is not inherited, therefore familial clustering is not expected. Non-accidental injury may be distinguished by metaphyseal, rib and skull fractures. Such pattern of fracture was absent in the two siblings presented and there was no history suggestive of non-accidental injury. Bruises which are typical of non-accidental injury were absent on examination of the skin of these two siblings. Also, multiple injuries and fractures at various stages of healing were absent. The risk of non-accidental injury is inversely related to age, with majority of the victims being below two years of age [22].

In contrast, the index cases were aged 5 and 9 years, respectively. These findings further make non-accidental injury less likely. Further details are shown in Table 2 [23] and it outlines the key features of the common differential diagnosis.

Table 2: Common differential diagnosis of osteogenesis imperfect

Clinical condition	Clinical features
Non-accidental injury	May be distinguished by metaphyseal, rib and skull fractures and presence of bruises.
Rickets	Distinguished by typical radiographic features of fraying, splaying cupping at metaphysis. Widening of the wrist and ankle.

Infantile Hypophosphatasia	Presents with a low alkaline phosphatase levels and spurs extending from sides of the knee and elbow joints. Presence of excessive excretion of phosphorylethanolamine in urine.
Campomelic dwarfism (compomelic dysplasia)	Congenital bowing and angulation of long bone may be mistaken for OI but fractures are not common. They have peculiar facial anomalies (flat face, long philtrum, micrognathia). Survival beyond the newborn period is rare.
Achondroplasia	Rhizomelia and enlarged head, radiographs sufficient to differentiate
Idiophatic juvenile Osteoporosis	The disorder is characterized by its prepubertal onset (2 to 3 years before puberty) and resolve spontaneously after puberty.

Adapted from Phonela et al [23]

In the present report, dentine abnormalities were observed in both the mother and her two daughters. The results of a study by Sillence et al [11] indicated that dentinogenesis imperfecta (DGI) was present in 50% of cases of OI, making it a relatively common finding in patients with OI. Similarly, in a study in Vietnam involving 68 children aged 3 to 17 years with OI, 47.1% of them had DGI [24]. The two siblings (females) had dentinogenesis imperfecta; a clinical feature which has been reported to be more common in girls than boys [25]. The results of a study by Yamaguti et al [26], showed that dentinogenesis imperfecta is a common finding in OI and that its frequency is higher in patients with COL1A2 than in those with COL1A1 mutation. In this context, is it possible that the index cases have COL1A2 instead of COL1A1 mutation? Sillence et al [11] observed that DGI is more common in OI type III than other subtypes. Similarly, Andersson et al [27] reported a higher prevalence (86%) of DGI among children and adolescents with OI type III. In this context, the results of the two studies increased the possibility that the two siblings reported here may have OI type III. This view is further supported by literature in which it was stated that abnormal dentition has been observed in 80% of children less than 10 years of age with OI type III [20]. The two siblings presented here are below 10 years of age. Additionally, it is documented in literature that OI type III is an autosomal-dominant trait due to point or frame-shift mutations in COL1A1(Gly154Arg, Gly844Ser) and COL1A2 (Gly526Cys) [20]. Appropriate dental care can lead to improved control of oral disease, function and esthetics in DGI.

There exists a wide variation in clinical characteristics of different types of OI, among people with the same type of OI, and within members of the same family with a particular type of OI. In the present report, the mother did not have any repeat episode of fracture since

the first at the age of 10 years, illustrating the variability in severity. However, she has dentine dysplasia, triangular-shaped face, skull deformity, and short stature resembling those present in younger child (Case1). In sum, these features suggest that the mother has undiagnosed OI but does not have deformity of long bones and reoccurrence of fractures noted in her two daughters. This variation in clinical findings is in keeping with what has been documented in literature which stated that the mutation will usually be identical in a given family but its expression (i.e., the degree of severity and the number of fractures) may differ among members [16]. This characteristic points to the importance of molecular diagnosis which is useful for counseling on prognosis, recurrence, and heritability as well as for variable response to drugs [11]. In the index cases, there was no molecular diagnosis because of lack of laboratory facility for that purpose in the health facility where we practice. Some of the clinical features present in the index cases and their scientific bases are worthy of note. The triangular facial shape is due to overdevelopment of the head and underdevelopment of the face bones [28]. The brittle teeth (dentinogenesis imperfecta) is one of the most important oral findings in type III OI and inherited in an autosomal dominant fashion. Dentinogenesis imperfecta (DGI) is characterized by presence of opalescent yellow brown-coloured brittle teeth and can affect both primary and secondary dentition as illustrated in the index cases. The enamel may be normal in thickness but gets dislodged easily because of smooth dentinoenamel junction, exposing the softer dentin [29]. Genetic analyses have found two subgroups of DGI namely, DGI type 1, syndromic form which is associated with OI and DGI type II, non-syndromic form that is not associated with OI [30,31]. The progressive deformities of long bones result from frequent fractures of long bones, tension of muscles on soft bones, and the disruption of growth plates. Children with OI type III have severe short stature and as adults are shorter than 102cm [28]. The increased curvature of the long bones leads to increase in maximum stresses within the bone shaft. Such increase in stresses attributed to bone deformities in OI might contribute to occurrence of bone fractures. The altered structure of the growth plates gives a popcorn-like appearance to the metaphyses and epiphyses. In Case 1, pectus carinatum was present but absent in case 2, illustrating variability in manifestation of OI in a given family. The total serum calcium was slightly reduced in both siblings presented here. Vitamin D and calcium are vital components of skeleton, and their deficiency can worsen the osteopaenia caused by OI. Therefore, vitamin D supplementation at maintenance dose of 400units daily was prescribed for the patients. In individuals with OI, outdoor activity decreases due to limited mobility and the resultant insufficient exposure to sunlight may contribute to vitamin D deficiency.

Regarding gender, the two siblings presented here are females. Although in literature, it is stated that there is no significant gender difference in incidence of OI, many cases reported from Nigeria, Akiola et al [32] in Lagos and Ogundare et al [33] in Ado Ekiti were all females. So also, was the case reported by Bastos et al [34] in Angola. In consonance, the results of a study in Iran involving 23 children showed that 69.1% were females and the rest were males [25]. In a nation-wide data analysis in Taiwan involving 319 patients with validated OI, 52% were females [35]. Even in the context of subtypes of OI, Aglan et al [36] in Egypt observed that among 24 children with OI type III, 66.7% were females while the rest were males. All pointing towards slight female preponderance.

Consistent with the results of the study by Lund et al [37], the two siblings and their mother had short stature. In that study, it was emphasized that the frequency and severity of growth retardation were more in patients with OI types III and IV. Typically, by the age of 2 to 3 years the growth retardation becomes obvious with stature below the third centile [38]. The two siblings being reported here have stature less than third percentile. However, the patients' mother was unable to state the age at which growth failure was noticed in her children as she was more concerned with the fractures. The poor linear growth and short stature in patients with OI has been linked to skeletal abnormalities such as lower limb bowing and extremity fractures, scoliosis, vertebral compression and growth plate disintegration ("pop-corn epiphyses" typical of severe OI) [3]. In that report, it was stated that short stature is the hallmark of moderate and severe OI. In addition, defective osteoblastic/bone matrix feedback on growth hormone-IGF 1 axis has been suggested as a mechanism for the short stature observed in OI types III and IV [37,39].

Apart from the classification suggested in 1979 by Sillence [11], newer classification of osteogenesis imperfecta by the International Nomenclature Group for Constitutional Disorders ICHG of the Skeleton (INCDS) (and preferred by Orthopaedic Surgeons) proposed that OI syndromes be classified into five different groups based on phenotype alone. Consequently, five clinical types of OI are generally recognizable with routine diagnostic methods, namely history, clinical examination and radiographs.

The division of OI according to the INCDS classification uses Roman nomenclature for identification and uses Arabic nomenclature to indicate phenotypes [12] and this is outlined in Table 3 (INCDS classification).

Table 3: The International Nomenclature Group for Constitutional Disorders ICHG of the Skeleton (INCDS).

New OI classification/OI type	Phenotype
1/I	Mild non-deforming
2/II	Severe, seen as perinatal and lethal forms
3/III, VI, VIII, IX, X, Bruck syndrome Type 1	Moderately severe, progressive deforming
4/IV, IV, VII, XI, XII, XIII	Moderate
5/V, osteoporosis-pseudoglioma syndrome, Idiopathic juvenile osteoporosis, Bruck syndrome Type 1 and Type 2	Presence of moderate calcification of interosseous membranes.

OI = Osteogenesis imperfect. Adapted from [12]

Healthcare issues in OI type III include the need to prevent fracture cycles, the need to develop strategies to cope with short stature, fatigue and the family's need for emotional support. It is equally important to address difficulties with social integration, participation in leisure activities and maintaining stamina [28]. In hospitals, non-invasive blood pressure cuff should be positioned carefully, but in some patients intra-arterial catheter is needed.

An important but often overlooked aspect of management of children with OI is the psychological care of the patients and their families. In Case 1, she has never walked at the age of 5 years and has never been enrolled in school. Although Case 2 was able to walk initially but lost the capacity by the age of 9 years and as a consequence, dropped out of school. Thus, illustrating the psychosocial problems of OI on the sufferers as well as its adverse effects on quality of life. The parents were deeply sad because of the physical disability of their children. This feeling progressed to helplessness and depression. A similar finding was reported in South Africa by Stephen et al [40]. With the financial support provided by a kind-hearted individual who is now sponsoring the healthcare of the two siblings the mother expressed some happiness. Childhood OI imposes a huge financial and psychological burden on the sufferers and their families as illustrated in the present report. The parents of the two siblings not only must perform their daily duties, roles and obligations but also meet the specific needs arising from their children's clinical conditions. This causes serious disruption of the family dynamics [41]. In the index cases the mother is the prime caregiver having been abandoned by their father. The potential effect on the mother is physical and psychological exhaustion due to accumulation of functions at home [42]. As a result, this mother can develop health problems and can be considered a "hidden patient" even if she did not

have OI. One of the strategies to assess the impact of the child's disease on the caregiver is by performing an assessment of the quality of life (QoL). Such assessment of QoL is based on the following aspects: subjectivity, multidimensionality and the presence of positive (i.e., mobility) and negative (i.e., pain, dimensions) [43].

Treatment of OI poses a serious challenge because the available treatment modalities do not target the underlying collagen defect. Modes of therapy vary depending on severity of the disease, degree of impairment, and age of the individual. The goals of pharmacological therapy include reducing associated pain and risk of reoccurrence of fractures as well as accelerating growth, improving bone metabolic indicators, bone histomorphometry, bone mineral density, improving mobility and independence [44-46]. Other therapeutic modalities in OI include physical therapy, rehabilitation and orthopaedic surgery. All these modalities of treatment are aimed at improving the quality of life of both the child and their primary caregivers. It must be emphasized that the chances of achieving these goals depend heavily on a well-coordinated multidisciplinary approach.

CONCLUSION

The heterogeneous nature of clinical manifestations of OI presents serious challenges in diagnosis and management, particularly in resource-poor countries, highlighting the need for increased awareness among clinicians. Some clinical features such history of fracture of long bones with minimal trauma, positive family history and physical findings such as dentinogenesis imperfecta and blue sclera, where present, may aid diagnosis. In general, diagnosis depends heavily on clinical features and radiographic findings. In low- and middle-income countries conventional radiography is a key to identifying the hallmark features OI such as generalized osteopaenia or osteoporosis, long bone deformities and multiple fractures.

Multidisciplinary approach is indispensible for successful management. In this context, the team of specialists should include paediatricians, geneticists, endocrinologists, orthopaedic surgeons, physiotherapists, and nutritionists to handle the various needs of the patient.

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