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Letter to the Editor

BRITTLE BONE DISEASE

E. Qorri[1,*] and P. Daliu[1]

[1]*Dental School, Albanian University, Tirana, Albania*

[*]Correspondence to:
Erda Qorri, MD
Dean Dental School, Albanian University, Tirana, Albany
e-mail: e.qorri@albanianuniversity.edu.al

ABSTRACT

Osteogenesis imperfecta (OI), sometimes called brittle bone disease (BBD), is an inherited genetic illness marked by extreme bone fragility or brittleness. Families can pass on the BBD to their offspring. A mutation in the gene that produces collagen causes it. When type I collagen levels are lowered, bones become brittle and more vulnerable to fractures. BBD types II, III, and IV results from mutations in the COL1A1 and COL1A2 genes. Osteoid synthesis is typically inadequate due to abnormalities such as reduced collagen type I production or aberrant collagen secretion. As a result, both intramembranous, as well as enchondral ossification are impacted. The usual histological features are a large, uneven physics with disordered proliferative and hypertrophy zones and a calcified thinning zone. Other features include sparse spongiosa, bone resorption, and accelerated bone turnover. For the development and evaluation of treatment in people with heritable illnesses, a thorough clinical description containing the knowledge of precise molecular genetic aetiology is the starting point. This article aims to cover the histology, diagnosis, and therapy of three types of BBD to make it easier to assess the situation and suggest fresh alternatives to surgery.

KEYWORDS: *Brittle bone disease, Osteogenesis imperfect, clinical manifestation, bone, resorption, fracture*

INTRODUCTION

Brittle bone disease (BBD), also known as osteogenesis imperfecta (OI), is a genetically inherited condition accompanied by high bone brittleness or fragility. BBD is transmitted via families. It is triggered by a mutation in a gene that makes collagen. Bones become brittle and more prone to fractures when type I collagen levels are reduced. BBD types II, III, and IV are caused by mutations in the COL1A1 and COL1A2 genes. These polymorphisms often alter the sequence of type I collagen subunits, leading to aberrant type I collagen. Although a child can inherit this gene from both parents, most infants with BBD only inherit it from one. The genetic variant can occasionally arise as a fresh mutation (1).

Clinical characteristics are typically used to distinguish between four main categories. Patients with type I have a

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moderate presentation and frequently are of higher average age, while type II is typically fatal during the prenatal period. In children who survive the newborn period, Type III is by far the most severe kind. These individuals have an identifiable phenotype that includes multiple fractures, short height, anomalies of the growth plate, and developing limb and spinal deformities. Type IV patients are those with mild to severe phenotypic who do not fall into one of the abovementioned groups. It is evident that this is a diverse set of illnesses, and some type IV patients exhibit characteristics that contradict the Sillence categorisation (2). A hyperplastic callus is one of these characteristics, and it can develop following fractures or reconstructive surgery. Hyperplastic callus usually manifests as a warm, severe, and firm swelling over the damaged bone, which may imply a differential diagnosis with sarcoma and inflammation. Excessive formation of poorly structured, partially calcified extracellular matrix is visible at the microscopic level. The shape and size of the callouses may stay constant for several years after a phase of fast growth (3).

Other symptoms include dentinogenesis imperfecta, blue sclerae, small height, and adult deafness. Aortic root enlargement and valvular insufficiencies have also been reported. Some milder signs are generalised flexibility, easy bleeding, hernias, and excessive sweating. Clinical signs range from moderate, completely asymptomatic type to most severe variants, which involve infants arriving with crumpled bones, a fragile skull, and lengthy bone fractures inconsistent with life, leading to neonatal mortality (4).

Epidemiology

BBD is thought to occur in about 1 out of every 20,000 births. BBD is thought to be prevalent across the United States at a rate of 20,000–50,000 people; this makes it an orphaned disease, that is, one that only affects 200,000 people or less in the United States (5). According to reports, there are 2.35 to 4.7 cases of type I OI per 100,000 people worldwide. Type II OI is reported to occur between 1 in 40,000 and 1.4 in every 100,000 live births. Even though the prevalence is significantly less frequent than type I, the precise incidence of kinds III and IV OI is unknown. Congenital A (19%), congenital B (31%), tarda A (25%) and tarda B incidence rates were roughly 25% in Shapiro's study (6).

Pathophysiology

A quantitative reduction in the number of structural, normal type I collagen can be brought on by frameshift mutations (which involve a premature termination codon in the afflicted allele). Heterozygous for this syndrome, a patient may produce half as much type I collagen as is typical. PLS3/ AD, COL1A1 and COL1A2 / X-linked mutations are involved. As an alternative, alteration in the form of substitutions or deletion in the polypeptide chain containing a glycine peptide sequence might lead to the formation of collagen that is structurally or quantitatively aberrant or less effective. Whether glycine is substituted at the carboxy-terminal (extreme condition) or amino-terminal (mild version) of the protein molecules determines the phenotypic variation of these abnormalities (7).

Due to the triple helix's starting to cross-link at the carboxy terminus of polypeptide chains, mutations at the carboxy end of the peptide may be more harmful. These patients experience more severe skeletal symptoms than those who have haploinsufficiency abnormalities. Mutations cause haploinsufficiency abnormalities at glycine sites that alter the integrity of collagen strands, a defect frequently found in types II, III, and IV (7). Type II (perinatal) Mutations are COL1A2, AD, CRTAP, AR / COL1A1, PPIB, LEPRE1, and BMP1. In type III (progressively deforming) are AD, COL1A2, AR / COL1A1, CRTAP, PPIB, LEPRE1, FKBP10, SERINF1, SERPINH1, and WNT1. In type IV (moderate) are AD, COL1A2, CRTAP, AR / COL1A1, SP7, FKBP10, WNT1, SERPINF1, and TMEM38B. Calcification of interosseous membrane or hypertrophic callus-type V has mutations found in AD / IFITM5 (8, 9).

Diagnosis

A relatively low stature does not rule out the diagnoses in type I OI because patients frequently have normal statures. Type I OI is not the same as mild OI. People may experience a few or no fractures, typically in the first few years of their lives, or many fractures throughout their lifetimes. Their faces could be triangular. They have complete mobility and no lengthy bone bowing, yet they could have osteoporotic fractures. Most people have blue sclera, although it can also be white or lose its blue tint with age. It is an autosomal dominant feature passed down from parent to child (10).

The apparent lack of relevance of bone density in individuals with OI is highlighted by the fact that bone density can be extremely low even in the lack of fractures and has no link to clinical severity.
In many cases, bone density is typical during the first few months of birth, and their ability to enhance bone mineral density declines as they age. Sometimes the diagnosis is a chance discovery following a fracture. Even in very mild cases, dentinogenesis imperfecta may exist. These people may have early hyperacusis, cardiac problems, and aortic valvular diseases (11, 12).

Patients with type IV are often diagnosed based on their small stature, lengthy bone bending, and spinal fractures. In addition, there could be joint slackness and scoliosis. Patients with this type of OI can typically ambulate; however, they might need assistance when walking. The sclera in these patients is white. Because the clinical symptoms of this kind of OI are not well described in the literature and because different centres use different diagnostic standards, accurate identification is frequently challenging (13). Due to their larger heads and underdeveloped facial bones, these individuals have triangle faces. They also have significant long bone malformations, vertebral injuries, chest abnormalities, and scoliosis. They are also noticeably low in stature. Despite some of them being capable of walking with assistance, they typically use a wheelchair. Ultrasonography can occasionally be used to make difficult prenatal testing. A "popcorn look" is a unique structural modification of the metaphyses and epiphyses of long bones caused by altered growth circular plates. Respiratory problems in severe cases may make survival riskier (14).

Most infants with this type of OI do not survive the prenatal period. The central nervous system's abnormalities or haemorrhages, the ribs' severe brittleness, or pulmonary hypoplasia are all potential causes of death. In addition, the infants have numerous intra-uterine fractures, including injuries to the skull, bony protrusions and vertebra, beaded sternum, and significant long bone deformity. It is typically impossible to differentiate between severe and deadly OI during pregnancy. In really severe circumstances, birth might result in dismemberment. Most cases include autosomal dominant novel mutations. It has been hypothesised that deadly OI may come in various clinical presentations. Despite the severity, some individuals have endured it for a long time (15).

Histopathology

Lamellar on woven bone synthesis is demonstrated as a compel self-assembly system and bone synthesis having followed the normal developmental pattern, but showing factor delay in growth and development caused by missense mutation or insufficient quantities of the collagen matrix, according to explanation in the context of woven to membranous bone growth by mesenchymal and surface osteoblasts, respectively (16). The more extreme the BBD variety, the more persistent the woven bone is and the more immature the morphological pattern is. Once a minimum accumulation for an acceptable framework of woven bone has been achieved, the pattern changes to a structurally firmer lamellar configuration. Lethal perinatal variants are characterised by woven bone alone; gradually deforming variants have varying quantities of woven plus lamellar bone, and lamellar bone progressively develops rudimentary, then partially compressed osteons without achieving full compaction. Lamellar bone is characterised by short, vertically oriented laminae with a mosaic pattern in increasingly deforming forms at various levels of microscopic magnification; polarisation specifies tissue conformational changes and localises lamellar formation beginning. Ultrastructure of bone-forming cells reveals significantly dilated rough endoplasmic reticulum, notable Golgi bodies, disoriented cisternae, swollen scattered tubules and vacuoles, structural indicators of storage disorder/stress responses, and mitochondrial inflammation in cells with significantly dilated rough endoplasmic reticulum indicating cell death (17).

Treatment

After a thorough evaluation by the treating physician, many children with OI start receiving bisphosphonate (BP) medication to reduce osteoclast activity. In this sense, cyclical intravenous BP treatment has emerged as the preferred method for treating children with moderate to severe OI. A relatively recent randomised, placebo-controlled double-blind trial of oral Risedronate in children with OI, which included many children who were more mildly to moderately affected, revealed a significant reduction in fracture risk, expanding the beneficial properties of this medication in children with OI (18). Unfortunately, by the conclusion of the early decades in the past, about two-thirds of patients had passed away. Kyphoscoliosis, pulmonary oedema, and cardio-respiratory insufficiency were the sequelae of skeleton chest wall deformities that typically led to death. It is believed that most patients with OI type III will live into adulthood, given the

current therapeutic choices, particularly BP treatment with cyclic injectable pamidronate started in infancy (19). Studies show that centres of competence treating children with severe OI achieve very low fracture incidence and close to normal development rates in newborns who started receiving cyclic injectable pamidronate by the age of three. The treatment seems to be well accepted, and studies have shown that it raises bone density, lowers the frequency of fractures, and improves vertebral form (20, 21).

The effectiveness of BPs (oral or intravenous) administration on patients affected by BBD is still debatable. A systematic review reported conflicting results since Dwan et al. (22) concluded that studies included in their analysis do not show BPs conclusively improve clinical status (reduce pain; improve growth and functional mobility) in people with OI, whereas Ying et al. (23) reported significant improvement of bone mineral density in patients affected with OI when treated with oral BPs. Finally, Constantino et al. (24) showed that randomised controlled trials did not demonstrate a significant improvement in function and mobility with oral BPs administration. In contrast, non-randomised open-label uncontrolled studies demonstrated that oral and intravenous BPs administration objectively improved function and mobility.

Phenotyping is of paramount importance for diagnosing, classifying, and evaluating OI severity, giving patients and associated families knowledge about the likely progression of the condition and enable doctors to assess the effectiveness of therapy. For developing and evaluating treatment in people with heritable illnesses like OI, a thorough clinical description knowledge and understanding of the precise molecular genetic aetiology is the starting point (25).

CONCLUSION

Although there have been suggestions that there could be different types of OI, the most common description of BBD separates the condition into four categories. These types have names that are numerical, eponymous, or descriptive. Some diseases can be regarded as congenital varieties of OI-like brittle bones. For developing and evaluating treatment in people with heritable illnesses like OI, a thorough clinical description containing the knowledge of precise molecular genetic aetiology is the starting point.

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