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The Matriclinous Ossein- Osteogenesis Imperfecta

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Abstract

Osteogenesis imperfecta is a frequently discerned, congenital disorder of connective tissue matrix associated with attenuation of bone cortex. Osteogenesis imperfecta is comprised of a heterogeneous coterie of congenital disorders with autosomal mode of genetic transmission demonstrating anomalous synthesis or processing of type I collagen within connective tissue and bones. Osteogenesis imperfecta affects bone mass and bone constitution with emergence of fragile bones. Osteogenesis imperfecta (OI) is also denominated as "brittle bone" disease". Osteogenesis imperfecta, a genetic connective tissue disorder characteristically displays decimated bone density with enhanced susceptibility of bone fractures. Osteogenesis imperfecta is composed of diverse categories denominated as autosomal dominant type I, type IV and type V whereas the exceptional type II, type III and type VI to type XI delineate an autosomal recessive mode of disease transmission.

1. Disease Characteristics

The exceptional osteogenesis imperfecta demonstrates a disease incidence of one in 15000 to 20000 live births. Classification of osteogenesis imperfecta pertains to phenotypic characteristics and mode of disease inheritance [1,2].

Type I and type II variants are frequently discerned, in contrast to type III and type IV.

Osteogenesis imperfecta displays an equivalent gender distribution. Racial and ethnic diversity is absent. Lifespan of incriminated individual is contingent to manifested subtype [1,2]. Osteogenesis imperfecta may be accompanied by complications such as hyperplastic callus, osteogenic sarcoma, basilar invagination, or malignant hyperthermia [1,2].

2. Disease Pathogenesis

Type I collagen appears as a major constituent of cutaneous soft tissue, dentin, sclera, ligaments, and blood vessels. Osteogenesis imperfecta depicts deranged synthesis of type I collagen which is a predominant extracellular matrix protein of

soft tissues. Bone deficiency of type I collagen is accompanied by osteoporosis along with enhanced possibility of fractures [1,2].

Majority (90%) of subjects demonstrate a genetic defect with quantitative and qualitative anomalies arising within type I collagen molecule. Osteogenesis imperfecta can be transmitted as an autosomal dominant, autosomal recessive or a disorder associated with spontaneous chromosomal mutation [2,3].

Autosomal dominant transmission occurs due to direct defect within type I collagen whereas autosomal recessive disease inheritance arises due to non-collagenous proteins which induce post translational modifications or triple helix formation within the collagen molecule.

Type I collagen molecule may demonstrate frameshift mutations, errors in substitution or deletion of glycine peptide residue within the polypeptide chain or mutations of glycine residue [2,3].

Majority (>90%) of instances of exceptional, genetic, osteogenesis imperfecta emerge on account of preponderant genomic mutations of COL1A1 and COL1A2 genes along with diverse mutations which encode alpha2 (α2) and alpha2 (α2) polypeptide chains of the protein [3,4].

Contingent to subtype, disease inheritance can be autosomal dominant (>95%), autosomal recessive (<10%) or a sporadic mutation. Osteogenesis imperfecta is categorized pertinent to mode of inheritance and associated genetic mutations as

- type I or non-deforming subtype wherein the autosomal dominant variety is associated with mutations of COL1A1 and COL1A2 genes and X-linked variant demonstrates PLS3 gene [3,4].

- type II or perinatal subtype depicts mutations of COL1A1, COL1A2, CRTAP, LEPRE1, PPIB and BMP1 genes] [3,4]. •type III or progressively deforming subtype delineates mutations of COL1A1, COL1A2, CRTAP, LEPRE1, PPIB, FKBP10, SERPINH1, SERINF1 and WNT1 genes [3,4].

- type IV or moderate subtype exhibits mutations within COL1A1, COL1A2, CRTAP, FKBP10, SP7, SERPINF1, WNT1, TMEM38B genes.

- type V or calcification of interosseous membrane or hypertrophic callus is an autosomal dominant condition with mutation of IFITM5 gene. Genetic mutations occurring within autosomal recessive subtypes of osteogenesis imperfecta exceptionally engender type VI, type VII, type VIII, type IX, type X and type XI variants in around < 5% subjects [3,4].

3. Clinical Elucidation

Clinical symptoms are extremely variable and pertain to disease subtype and genetic profile. Osteoporosis and fragile bones are pathognomonic of osteogenesis imperfecta along with frequent appearance of fractures, blue sclera, brittle teeth,

and deafness. Congenital cataracts may accompany diverse clinical manifestations. Several minor or major fractures, especially of lower limbs or around knee joint along with fragmentation of growth plate may ensue during childhood. Additionally, short stature, valvular insufficiency, aortic root dilation, generalized connective tissue laxity, apparent bruising, hernia, and excess sweating is observed [4,5].

Emergence of osteogenesis imperfecta varies from asymptomatic disease or a mild clinical form with absence of bone deformity, normal skeletal stature and minimal fractures or a fatal disease occurring within the perinatal period. Clinical manifestations of severe instances incompatible with survival incriminating infants with occurrence of crumpled ribs, fragile cranium and fracture of long bones with consequent perinatal mortality may ensue [4,5].

Hypertrophic callus may appear within healing fracture. Bone deformities associated with fractures are protrusio acetabuli, proximal varus or anterolateral bowing of femur, tibia, cubitus varus and deformities of proximal forearm. “Elfin facies” and “helmet head” appearance may be exemplified [4,5].

Contemporary classification of osteogenesis imperfecta pertains to phenotypic features and mode of disease inheritance and is comprised of eight categories denominated as type I or mild disease, type II or lethal perinatal disease, type III or progressive, deforming disease whereas the infrequent type IV to type VIII are varying in severity.

Osteogenesis imperfecta is subdivided pertaining to diverse clinical manifestations as

- osteoporosis with significant bone fragility, attenuation of bone cortex and symptoms due to deranged collagen [5,6].
- blue sclera arising due to translucent sclera and visibility of choroid
- dentinogenesis imperfecta with miniature, misshapen, yellowish teeth with dentin deficiency [5,6]. •impaired hearing with sensi-neural defect and impeded sound conduction due to abnormal bones of middle ear [5,6].

Additionally, laxity of ligaments, joint hypermobility, short stature, and tendency for easy bruising is observed. ~Autosomal dominant type I depicts a reduction of normally configured collagen by nearly half (50%). Generalized osteoporosis, fragile bones, decreased bone maturity, blue sclera, conductive deafness and mild physical stunting is observed. Subtype Ia demonstrates normal teeth whereas subtype Ib or Ic exhibit dentinogenesis imperfecta [6,7].

Type I appears due to acquired chromosomal mutation and enunciates normal lifespan with enhanced possibility of fractures during childhood which recede with puberty [6,7].

~Autosomal recessive type II arises due to spontaneous chromosomal mutations and demonstrates extreme bone fragility as observed in “accordion femur”, delayed ossification of skull, blue sclera, and perinatal mortality. Type II is uniformly fatal due to extreme bone fragility, multiple intrauterine fractures, and triple helix configuration of collagen type I molecule [6,7].

~Autosomal recessive or autosomal dominant transmission of type III represents infants with blue sclera converted into a normal hue in adolescence. Moderate to severe bone fragility, coxa Vara, multiple fractures, and significant deformities of long

bones with deranged ambulation are exhibited. Preliminary scoliosis, triangular facies, frontal bossing, basilar invagination, and growth retardation with extreme stunting is observed [6,7].

~Autosomal dominant type IV is a heterogeneous group of disorders delineating normal sclera, moderate to severe bone fragility, deformed vertebral column or long bones, short stature and moderate to severely stunted growth. Subtype IVa represents normal teeth whereas subtype IVb manifests dentinogenetic imperfecta [6,7].

~Autosomal dominant type V is a moderately severe variant which exemplifies mutation within the gene encoding interferon-induced transmembrane protein-5 (IFITM5). Clinically, normal sclera, absence of dental features, hypertrophic callus, calcification of interosseous membrane, especially of the forearm with secondary dislocation of radius and radio-dense zone adjoining long bone physis are observed.

Morphologically, mesh-like lamellar bone is exhibited [7,8].

~Type VI depicts chromosomal mutation of SERPINF1 gene. Moderate to severe skeletal manifestations, normal sclera and absence of dental features are delineated. Characteristic histology depicts lamellar bone with a “fish scale” pattern upon examination with polarized light [7,8].

~Autosomal recessive type VII is moderate to severe disease associated with rhizomelia and coxa vara [6,7].
~Autosomal recessive type VIII is a severe, lethal disease depicting rhizomelia [6,7].
~Autosomal recessive type IX simulates type VII and type VIII and lacks the manifestation of rhizomelia [6,7].
~Autosomal recessive type X depicts defective SERPINH1 gene and type XI demonstrates defective FKBP10 gene [6,7].

Type X displays severe bone dysplasia, dentinogenesis imperfecta, transient skin bullae, blue sclera, pyloric stenosis and renal calculi [7].

Type XI is accompanied by bone dysplasia, ligamentous laxity, scoliosis, and platyspondyly. Sclera are normal and dental disease is absent [8].

4. Histological Elucidation

On gross examination, cartilaginous nodules are discerned due to fragmentation of growth plate [7,8].

Decreased synthesis of type I collagen or secretion of abnormal collagen induces insufficient production of osteoid [7,8].

Upon microscopy, typically endochondral and intramembranous ossification is deranged along with thin, poorly organized bone trabeculae and collagen matrix, minimal primary and secondary spongiosa, abundant osteoblasts and osteoclasts, enhanced bone modulation, broad, irregular bone physis and disorganized zones of bone hypertrophy or proliferation along with emergence of attenuated, calcified osseous zones [7,8].

Moderately severe variants delineate crowding of osteocytes within trabeculae of thin lamellar bone. Variants with severe disease are devoid of organized, trabecular pattern of bone. Amalgamated osteocytes appear within the bone on account of decimated synthesis of collagen. Enlarged foci of woven bone are observed [7,8].

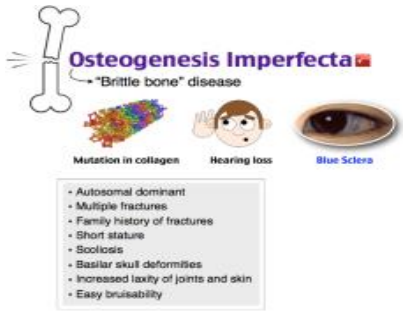

FIG. 1. **Osteogenesis Imperfecta Exhibiting Diverse and Preponderant Symptoms [11].**

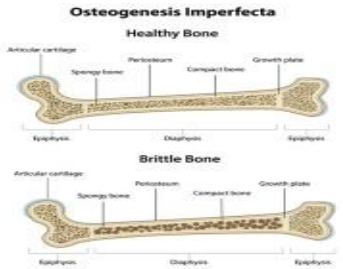

FIG. ss2. **Osteogenesis Imperfecta Exemplifying Brittle Bones Confined to the Diaphysis Circumscribed by the Growth Plate [12].**

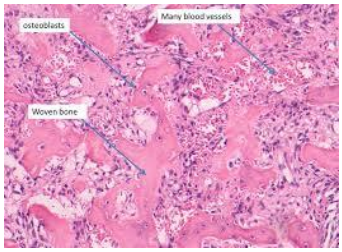

FIG. 3. **Osteogenesis Imperfecta Depicting Brittle Woven Bones Rimmed with Peripheral Osteoblasts and Several Vascular Articulations [13].**

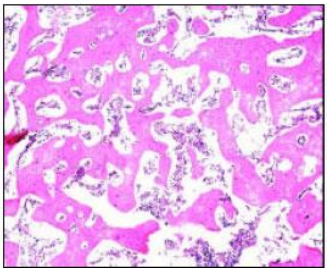

FIG. 4. **Osteogenesis Imperfecta Exhibiting Brittle, Woven Bones with Abnormal Collagen and Prominent vascularity [14].**

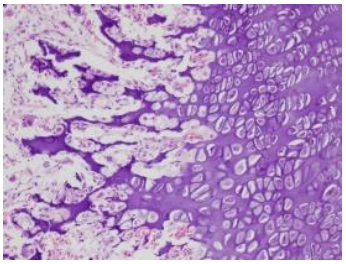

FIG. 5. **Osteogenesis Imperfecta Enunciating Strips of Brittle, Cancellous Bone Admixed with Abnormal Collagen [11].**

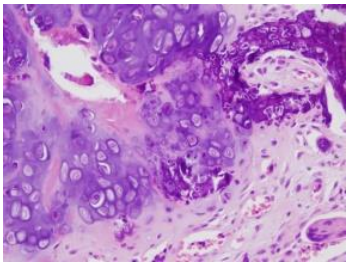

FIG. 6. **Osteogenesis Imperfecta Exemplifying Brittle, Spongy Bone Intermingled with Foci Of Abnormal Collagen [11].**

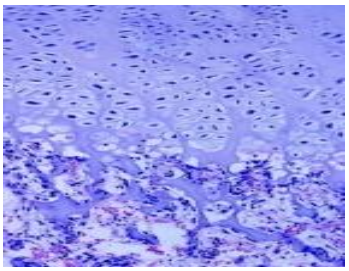

FIG. 7. **Osteogenesis Imperfecta Delineating Brittle, Woven Bone Commingled with Significant Quantities of Abnormal collagen [15].**

5. Differential Diagnosis

Osteogenesis imperfecta requires a segregation from conditions such as congenital hypophosphatasia, achondroplasia, pyknodysostosis, diffuse osteopenia occurring with preliminary leukaemia, idiopathic juvenile osteoporosis and child abuse or battered child syndrome [8,9].

Radiographic demarcation is necessitated from possible physical abuse or non-accidental injury, osteopenia of prematurity, osteomalacia, juvenile osteoporosis, hypophosphatasia, rickets and Menkes syndrome or kinky hair syndrome [8,9].

6. Investigative Assay

Non-accidental bone trauma requires exclusion in individuals with multiple fractures. Bone mineral density, especially of lumbar vertebra, biochemical parameters related to bone metabolism and features on plain radiography aid the distinction [9,10].

Plain radiograph of head, neck and vertebral column are preferred as an initial examination and demonstrate basilar invagination, Wormian bones, kyphoscoliosis, vertebral compression fractures, codfish vertebrae or platyspondyly [9,10]. Radiograph of thoracic cavity depicts pectum excavatum or carinatum and accordion ribs. Radiograph of pelvic cavity delineates protrusio acetabuli or coxa vara [9,10].

Plain radiographs of generalized skeleton depict severe osteoporosis, deformed, excessively tubular bones, attenuation of bone cortex and configuration of hyperplastic callus. Additionally, foci of "popcorn calcification" are observed wherein bone metaphysis and epiphyses exemplify numerous scalloped, radiolucent zones with a sclerotic periphery [9,10].

Pseudo-arthrosis may appear upon the site of healing fractures. Nodules of cartilage arise at the growth plate simulating a bag of popcorn. Significant swelling of distal femur may ensue [9,10].

Cyclical therapy with bisphosphonates induces bone sclerosis along lines of recovery [9,10].

Prenatal ultrasonography may be advantageously adopted in discerning type II (perinatal) and type III variants of osteogenesis imperfecta. Sonography depicts decimated ossification of the calvarium with consequent visualization of foetal brain. Skull may be deformed or compressed with the transducer with possible occurrence of fractures. Long bones appear shortened or angulated along with multiple bone fractures. Ribs may depict a beaded appearance. Polyhydramnios may be observed [9,10].

Computerized tomography demonstrates Wormian bones, basilar invagination, otosclerosis and fracture of long bones. Upon magnetic resonance imaging (MRI), extent of basilar invagination can be evaluated [9,10].

Biochemical evaluation displays a mildly elevated serum alkaline phosphatase (ALP). Culture of fibroblasts may be utilized to analyse type I collagen, especially in instances with ambiguous disease representation [9,10].

Cogent tissue sampling is optimal for analysis of collagen. Iliac crest biopsy demonstrates decimated magnitude of bone cortex, volume of cancellous bone and enhanced bone remodelling [9,10].

7. Therapeutic Options

Prognostic outcome of osteogenesis imperfecta is variable and contingent to diverse subtypes. Disease outcome can be uniformly lethal in type II or display a minimally reduced life span in type I. Non-lethal subtypes may be managed with surgical alleviation of deformities and prevention of fractures [9,10].

Appropriate therapy of osteogenesis imperfecta is contingent to age, disease severity and functional status of implicated individual. Mild disease can be managed with subtle restriction of physical activity, prohibiting contact sports and appropriate treatment of fractures [10]. Moderate to severe disease necessitates rehabilitation and pertinent orthopaedic manoeuvres. Associated acute fractures and scoliosis require treatment [9,10].

Osteotomy with intramedullary rods may be adopted to relive severe bowing of long bones. Disease variants with severe clinical symptoms necessitate insertion of intramedullary rods along with osteotomy to correct significant bowing of long bones [9,10]. Intramedullary rods are recommended for treating repetitive fracture of long bones occurring in children. Diverse categories of telescopic and non-telescopic rods or surgical nails are employed in various surgical methodologies and assessment of bone magnitude or prospective bone growth. Additionally, bisphosphonates or growth hormone can be employed to treat osteogenesis imperfecta [9,10].

Bisphosphonates are beneficial in decimating possible fractures, enhancing bone mineral density and meliorating ambulation as the molecules decrease osteoclastic resorption of bone in children.

Prognosis is inferior with appearance of preliminary fractures. Age of long bone fracture is a superior prognostic indicator. Significant indicators of survival are location and severity of fracture and general radiographic appearance of the skeleton [9,10].

REFERENCES

1. Subramanian S, Viswanathan VK. Osteogenesis Imperfecta. Treasure Island, Florida: Stat Pearls International, USA; 2021.
2. Nicol L, Morar P, Wang Y, et al. Alterations in non-type I collagen biomarkers in osteogenesis imperfecta. Bone. 2019;120:70-04.
3. Valadares ER, Carneiro TB, Santos PM, et al. What is new in genetics and osteogenesis imperfecta classification? J Pediatr. 2014;90(6):536-41.
4. Nagamani SCS. Growth characteristics in individuals with osteogenesis imperfecta in North America: results from a multicentre study. Genet Med. 2019;21(2):275-83.
5. Hoyer-Kuhn H, Netzer C, Semler O. Osteogenesis imperfecta: pathophysiology and treatment. Wien Med Wochenschr. 2015;165(13-14):278-84.
6. Trejo P, Rauch F. Osteogenesis imperfecta in children and adolescents-new developments in diagnosis and treatment. Osteoporos Int. 2016;27(12):3427-37.
7. Van Dijk FS, Sillence DO. Osteogenesis imperfecta: clinical diagnosis, nomenclature and severity assessment. Am J Med Genet A. 2014;164(6):1470-81.
8. Renaud A, Aucourt J, Weill J. Radiographic features of osteogenesis imperfecta. Insights Imaging 2013;4(4):417-29.
9. Montpetit K, Palomo T, Glorieux FH. Multidisciplinary Treatment of Severe Osteogenesis Imperfecta: Functional Outcomes at Skeletal Maturity. Arch Phys Med Rehabil. 2015;96(10):1834-9.
10. Lin TY, Yang CY, Liu SC. Corrective osteotomy with retrograde Fassier-Duval nail in an osteogenesis imperfecta patient with bilateral genu valgum: A case report. Medicine (Baltimore). 2017;96(47):e8459.
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