

Case Report

Sickle Cell Disease with Osteogenesis Imperfecta

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Abstract

A 16 yr old female presented with generalized weakness and easy fatigability since 2 months.

Her medical history included that she had sickle cell disease (ss pattern) on regular treatment. She denied smoking and consumption of alcohol. She had adequate calcium intake and her menstrual history was non-contributory. History of right tibial diaphysal fracture 1 year back followed by refracture at the same site 6 months later.

On examination patient was 146 cm tall & weighed 48 kg. She had pallor, blue-grey sclera, scar mark of previous operation on right leg. Her mother and two maternal aunts also had blue-gray sclera. She had normal dentition and other systems were normal.

Radiological screening showed diffuse osteopenia of all visualized skeleton, biconcave vertebral bodies in lumbar spine, Old healed fracture of right tibial diaphysis with intra-medullary nail in situ, wormian bones seen along the lambdoid suture, old healed fracture with sclerosis noted involving diaphysis of first metatarsal.

Secondary causes of osteoporosis were ruled out. Skeletal involvement in sickle cell disease is usually in the form of avascular necrosis, dactylitis, joint effusions or osteomyelitis however osteoporosis and long bone fractures are not known in sickle cell disease. Owing to high index of suspicion a diagnosis of osteogenesis imperfecta was pursued, since the patient presented at 16 years age with relatively minor symptoms type 1A osteogenesis imperfecta (mildest form) was established. Systemic screening for disease complications included osteopontogram, audiogram and consultation with ophthalmologist and geneticist. Therapy with calcium and vit D was initiated and an in depth discussion regarding bisphosphonates was pursued. Anaemia was corrected with blood transfusion and treatment of sickle cell disease was continued. Family screening was offered.

Fractures particularly adults older than 45 are associated with osteoporosis. This case illustrates the importance of family history, fracture history and clinical correlation when assessing patients with osteoporosis. Mild OI most often presents after infancy and should be considered whenever children or adults have recurrent fractures. Early diagnosis of this disease by family physicians will enable initiation of therapy as well as patients education regarding management of modifiable risk factors linked with osteoporosis (e.g. diet, smoking, alcohol). Genetic counseling and family screening could also be offered.

Osteogenesis imperfecta (OI) a secondary cause of osteoporosis, principally manifests as bone fragility. It is an inherited disorder of connective tissue integrity; it affects up to one in 10,000 persons.¹ Diagnosis of mild OI is challenging due to its variable course and phenotypic expression. Family physicians must maintain a high index of suspicion as, diagnosis along with proper follow up and counseling can prevent many complications of this disorder.

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On examination patient was 146 cm tall and weighed 48 kg. She had pallor, blue-grey sclera (Figure 1), scar mark of previous operation on right leg. Her mother and two maternal aunts also had blue-gray sclera. She had normal dentition and other

systems were normal.

Radiological screening showed diffuse osteopenia of all visualized skeleton, biconcave vertebral bodies in lumbar spine, Old healed fracture of right tibial diaphysis with intra-medullary nail in situ (Figure 2), wormian bones seen along the lambdoid suture, old healed fracture with sclerosis noted involving diaphysis of first metatarsal (Figure 3). These features though characteristic of osteogenesis imperfecta are not pathognomic.

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Discussion

Osteogenesis imperfecta result from mutations in genes

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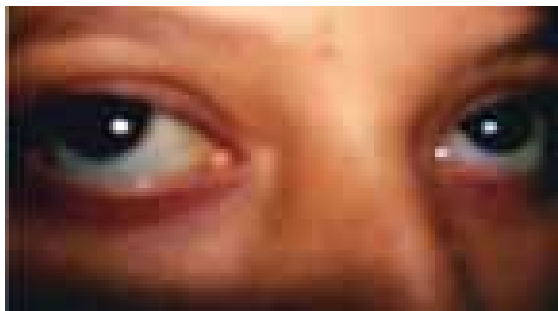


Fig. 1 : Blue-gray sclera in the patient



Fig. 2 : Old healed fracture of right tibial diaphysis with intramedullary nail in situ

encoding for type I collagen. Collagen is the major structural protein in bone ligaments, tendons, skin, sclera and dentin. Mutant expression produces non-functional collagen (severe OI) or insufficient quantities of collagen (mild OI). There are seven subtypes of OI varying in severity, age of presentation and clinical features.

Type IA OI the most prevalent and mildest form and is genetically transmitted in an autosomal-dominant or sporadic-mutation fashion. Children with Type IA OI are five to fifteen times more likely to have fracture than unaffected children and parents are often accused of abuse. Fracture frequency declines after puberty but increase again with inactivity, childbirth and aging. In women with OI the third trimester of pregnancy and the postnatal period of high fracture risk.² Type IA OI does not affect longevity but influences morbidity due to recurrent fractures and related complications.

Other clinical characteristics of type IA OI can include blue-gray sclera and sensorineural hearing loss beginning in early adulthood. Neurologic sequelae result from basilar invagination and cervical spinal cord compression syndromes presenting as paresthesias, peripheral weakness, incontinence, central sleep apnea and upper motor neuron signs.³ Cardiac complications include aortic and mitral valve insufficiency as well as increased aortic root diameter predisposing to dissections.⁴ Restrictive lung disease secondary to spinal deformity and rib fractures can occur.⁵ Nephrolithiasis and vascular fragility can also occur.

In practice, OI is usually diagnosed on the basis of clinical criteria. The presence of fractures together with blue sclerae, dentinogenesis imperfecta, or family history of the disease is usually sufficient to make the diagnosis, although rarely warranted include serum quantification of low levels of type 1 procollagen peptide, bone biopsy demonstrating high osteocyte levels with low bone turnover, direct collagen analysis from fibroblast culture through skin biopsy and confirmation of mutation by DNA extraction for white blood cells. Prenatal



diagnosis is possible as well through isolation of mutation specific DNA polymorphisms. mutations analysis can be defined in most patients by the sequencing of genomic DNA with about 100 polymerase chain reactions (PCRs) to amplify all the exons and exon/intron boundaries of the two large genes (the *COL1A1* and *COL1A2* genes) that are available from specialized laboratories. Because each proband and each family usually has a private mutation, extensive analysis of about 10,000 bases in each of the two genes is required to identify the exact mutation. This may not be practically feasible always, however could be considered if clinical criteria are not met and there is diagnostic dilemma and often testing one individual in the family is enough to know the defect as testing every member doesn't lead to any extra information Recent development in OI therapy are promising. Lifestyle modifications such as use of orthotics and physiotherapy should be considered. Medical management of OI with the exception of bisphosphonates has been largely unsuccessful. Bisphosphonates (antiresorptive agents that inhibit osteoclasts) have been shown to increase bone mass, decrease fracture rates and relieve symptoms of OI patients.⁶ The long-term safety of bisphosphonates in mild OI has not been determined, particularly for women of child-bearing age because the drug is thought to remain in the system for many year after treatment is stopped.

More invasive surgical interventions include intramedullary rod insertion, surgery for basilar invagination and correction of scoliosis.

Conclusion

Fractures particularly adults older than 45 are associated with osteoporosis. This case illustrates the importance of family history, fracture history and clinical correlation when assessing patients with osteoporosis. Mild OI most often presents after infancy and should be considered whenever children or adults have recurrent fractures. Early diagnosis of this disease by family physicians will enable initiation of therapy as well as patients education regarding management of modifiable risk factors linked with osteoporosis (e.g., diet, smoking, alcohol) for many disease detection can prevent the trauma of separation of parents and children when OI is misdiagnosed as child abuse. Genetic counseling and family screening could also be offered.

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