A woman with brittle bones and blue sclerae

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A 46-year-old perimenopausal woman with severe osteoporosis and blue sclerae presents with a suspected second rib fracture. Should her current medication of a bisphosphonate be revised?

Case scenario

Tanya is 46 years old and attends her GP because she thinks she has fractured a rib during a coughing fit. She has fractured a rib once before. She has known osteoporosis. This was diagnosed three years ago; she was not perimenopausal at the time and was commenced on a low-dose oral contraceptive pill and has had annual bisphosphonate infusions since. There is no family history of osteoporosis and all investigations have shown no reversible cause. She is noted to have blue sclerae, which she says have been lifelong. Her current T-score is -3.0.

- What investigations should be arranged for this patient given her unusually early and severe osteoporosis?
- Blue sclerae are an unusual feature. Combined with early osteoporosis, does this fit into any specific category of osteogenesis imperfecta?
- What is the likelihood this patient's condition is hereditary, and what investigations should be suggested for her teenage children (a boy and a girl)?
- Should Tanya's medical management be changed?

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Figure. The distinctive blue coloured sclera associated with osteogenesis imperfecta.
Image courtesy of Dr Ana Miguel Quintas, Santa Maria University Hospital, Lisbon.

Commentary

This case presents some interesting challenges, including the diagnosis of osteogenesis imperfecta (OI) and the management of severe osteoporosis in a premenopausal woman in this context.

Initial clinical assessment

Differential diagnoses of T-score < -3.0 in a premenopausal woman

Tanya's bone mineral density (BMD) measurement demonstrates she has reduced BMD equating to a T-score of -3.0. The original WHO definition of osteoporosis (T-score less than or equal to -2.5) applies to postmenopausal women. In premenopausal women, the Z-score (age-matched comparison) should be used, and a value of less than -2 at the lumbar spine or femur indicates a BMD value below normal for the age and sex of the individual. Low BMD in a young person may reflect a poor acquisition of peak bone mass (determined by genetics, lifestyle and hormonal factors). Therefore, it is important to consider additional features such as a history of fragility fractures (as in Tanya's case) to diagnose osteoporosis in a premenopausal woman.

It is also important to distinguish osteomalacia from osteoporosis as both can cause reduced bone density. Osteomalacia is due to decreased mineralisation of bone. Diagnosis is based on clinical features such as bone pain, proximal muscle weakness, fracture, difficulty walking, muscle spasms or cramps and laboratory abnormalities including low serum 25-hydroxyvitamin D (below 25 nmol/L), low to low–normal serum calcium and phosphate levels, and high parathyroid hormone and alkaline phosphatase levels. In contrast, patients with osteoporosis do not have the clinical symptoms described above.

Tanya should also be screened for secondary causes of osteoporosis as more than half of premenopausal women with osteoporosis have a secondary cause, with the remainder having idiopathic osteoporosis.

Investigations

To exclude osteomalacia and common secondary causes of osteoporosis, the following initial investigations should be

TABLE. OSTEOGENESIS IMPERFECTA CLASSIFICATION ACCORDING TO THE INTERNATIONAL SKELETAL DYSPLASIA SOCIETY[1]

OI type	Inheritance	Sclera	Additional clinical features	Dentinogenesis imperfecta	X-ray features
Nondeforming (type I)	AD	Blue–grey	Fractures Progressive hearing loss with onset in second to fourth decade Minimal bone deformity Normal stature	Rare	Fractures
Perinatal lethal (type II)	AD, AR	Blue–grey	Extreme bone fragility with many fractures in utero, often detected by prenatal ultrasound, small for gestational age, limb deformities, perinatally lethal	Not applicable	Multiple fractures with crumpled appearance, beaded ribs, long bone deformity, limited calvarial mineralisation, osteopenia, short thoracic cage
Progressively deforming (type III)	AD, AR	Blue or grey	Short stature, severe bone fragility with hundreds of fractures, progressive deformities, severe scoliosis, adolescent onset hearing loss, usually non-ambulatory, posterior fossa compression syndromes due to basilar impression	Common	Osteopenia, multiple fractures, long bone deformity, thin ribs, skull shows multiple Wormian bones
Moderate (type IV)	AD, AR	White	Less severe than type III Usually ambulatory Moderate bone fragility, moderate to severe deformity of the long bones and spinal column, moderately short stature, adult onset hearing loss	Common	Intermediate appearance between OI types I and III
Calcification in interosseous membranes (type V)	AD	White	Restricted pronation and supination and radial head dislocation/subluxation due to calcification of interosseous forearm membrane Moderate to severe bone fragility	Absent	Hyperplastic callus (massive callus with swelling and pain) after fractures or surgical interventions

Abbreviations: AD = autosomal dominant; AR = autosomal recessive; OI = osteogenesis imperfecta.

performed:

- biochemistry (electrolyte profile, renal and hepatic functions)
- thyroid hormone function tests
- 25-hydroxyvitamin D level measurement
- parathyroid hormone level measurement
- full blood count.

Further testing would be guided by the clinical presentation. Given Tanya's blue sclerae, the diagnosis of OI should be considered in her case.

Blue sclerae and osteogenesis imperfecta

Tanya's clinical constellation of low BMD, fragility fractures and blue sclerae is suggestive of OI, a disorder of connective tissues characterised by increased bone fragility and usually caused by mutations in collagen genes. Features of the five different clinical subtypes are summarised in the Table.[1]

Type I or 'classic nondeforming OI with blue sclerae' is the mildest and also most common type of OI and has an incidence in Australia of 3.5 in 100,000.[1] This type is characterised by blue–grey sclerae, which helps to distinguish it from the other types of OI (Figure). The discolouration is quite striking, and should not be mistaken for the slightly blue–grey hue that is common in the general population, especially in children. Patients typically experience multiple minimal trauma fractures during childhood and adolescence. Fractures first occur when an infant begins to walk (and fall), and then may occur at a rate of several per year before decreasing in frequency after puberty, perhaps due to patients reaching peak bone mass. Fracture frequency may increase again in postmenopausal women and in men beyond the fifth decade. Fractures usually heal normally with no resulting deformity.

Additional features of type 1 OI may include hearing loss (with onset in the teenage years to young adulthood), easy bruising and joint hypermobility. Some people with OI type I also have translucent teeth that chip easily (dentinogenesis imperfecta). Tanya should be assessed for these clinical features and, as hearing loss may be subclinical, should be referred for audiology testing.

Genetic testing

Most cases of OI have an autosomal dominant pattern of inheritance, so Tanya should be asked whether there is any family history of OI, recurrent fracture or blue sclerae. Even if there is no family history, given the high clinical suspicion in Tanya and the implications for her children if she does have OI (up to a 50% chance of inheriting the condition, both sexes affected equally), she should be referred to a clinical genetics service for genetic counselling and consideration of genetic testing to confirm the diagnosis. Of note, the age of onset and number of fractures can vary considerably even in the same family.

OI can be caused by mutations in any of 17 genes, with mutations in the genes for collagen type 1 (*COL1A1* and *COL1A2*) accounting for most cases.[2] Although genetic testing can detect most known mutations, negative studies do not exclude the diagnosis as there may be more genes involved in OI than currently known. If Tanya's children are affected, they should have appropriate antenatal counselling when starting their own families because of the risk of passing OI on to their offspring.

Medical management

The immediate clinical priority in this case is to confirm whether Tanya has fractured her rib. A chest x-ray with rib views may demonstrate the fracture but if no fracture is evident then a nuclear medicine bone scan should be performed. Given the severity of her osteoporosis, it would be appropriate to arrange a thoracolumbar spine x-ray to screen for vertebral fractures, which may be asymptomatic.

As this is a complex case of OI associated with osteoporosis in a young person who continues to fracture despite appropriate therapy, Tanya should be referred to an endocrinologist for ongoing management.

The goal of Tanya's management should be to reduce future fractures. Although the bisphosphonates, the monoclonal RANKL antibody denosumab and the recombinant human parathyroid hormone fragment teriparatide have been shown to decrease the risk of fracture in postmenopausal women and men with osteoporosis, the evidence for their use in adults with OI is less clear. There have been several studies of bisphosphonate use in adults with OI, including two prospective randomised controlled trials. Although there is evidence for a significant increase in spine and hip BMD, both a Cochrane review and a meta-analysis of placebo-controlled trials did not find definitive evidence for fracture risk reduction.[3,4]

Tanya has received three annual infusions of zoledronic acid yet continues to sustain fractures. Although this may reflect the lack of efficacy of bisphosphonates in OI, it is important to exclude additional factors that may be contributing to bone fragility. In addition to a comprehensive history and examination, Tanya should be screened for diabetes, multiple myeloma, coeliac disease, vitamin D deficiency, systemic inflammation and thyroid, parathyroid, gonadal, hepatic, electrolyte and renal dysfunctions, and her vitamin D and calcium status optimised (25-OH vitamin D level greater than 60 to 70 nmol/L and total daily calcium intake of 1000 to 1300 mg).

The treatment option of teriparatide (off label use) should be considered, given its efficacy in postmenopausal osteoporosis and the severity of Tanya's osteoporosis, although there is no evidence for teriparatide and fracture risk reduction in adults with OI. According to the current Australian PBS criteria for teriparatide, if Tanya's rib fracture were confirmed, she would qualify for teriparatide as this represents a second minimal trauma fracture after at least 12 months of antiresorptive therapy and she has a T-score of less than -3.0 SD. Teriparatide is an anabolic agent that increases BMD and reduces vertebral and nonvertebral fractures in postmenopausal osteoporosis.[5] A randomised, placebo-controlled trial in 79 adults with OI (predominantly type 1) found that in comparison with placebo, teriparatide significantly increased lumbar spine and hip BMD and increased bone turnover markers but did not reduce the incidence of self-reported fractures.[6] Further studies are needed to clarify whether teriparatide is more efficacious than bisphosphonates (antiresorptive agents) in patients with OI.

Conclusion

OI is a rare, hereditary connective tissue disorder. The diagnosis should be suspected based on clinical signs with confirmatory genetic testing, including cascade testing in family members. The optimal management for adults with OI who continue to fracture remains a challenge as the currently available treatments do not target the primary collagen defect and there is no conclusive evidence for fracture risk reduction in adults with the condition. MT

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COMPETING INTERESTS: None.