A discussion of the contribution of complex genetics to the aeteology of osteoporosis based on a clinical case

Janarthanan Sathananthan
House Surgeon
Auckland City Hospital

Janar is a graduate of the University of Auckland Medical School currently working as a first year house surgeon at Auckland City Hospital. He has research interests in cardiovascular and general medicine and wrote this case study as a Trainee Intern.

CASE

Mr AM is a 29 year old Fijian-Indian male who presented to the endocrinology clinic after a low trauma fracture to the neck of his left femur earlier in the year. The injury was sustained after he fell to the ground while carrying a chair and he has no previous history of fractures. The patient was screened for symptoms suggestive of a secondary cause of osteoporosis such as Cushings, hyperprolactinemia, hyperthyroidism, hypogonadism, chronic malabsorptive conditions, alcohol excess, and other chronic diseases, all of which were negative.

The patient is normally fit and well with no significant past history, and no regular medications. He works as a store salesman, and is a non-smoker with minimal alcohol intake (two standard drinks per week).

Mr AM's brother also recently had a low trauma fall without sustaining a fracture and a DEXA scan showed decreased bone density at the spine. However Mr AM could not recall the exact T-score of his brother's scan. There is no family history of fractures.

Physical examination was normal other than a slightly low BMI of 19.9.

Investigations:

1) 25 hydroxy vitamin D: 37nmol/L (Normal range: 50-150)

2) Normal liver function tests, thyroid function tests, B12/folate, serum cortisol, full blood count, antinuclear antibodies, gliaden/gluten sensitivity, neutrophil cytoplasmic antibodies, iron studies, testosterone, LH, FSH, HIV antibodies, calcium, crp, albumin, creatinine and rheumatoid latex test.

3) DEXA scan: T score: spine -2.4 and right hip -2.6

Problem list:

1) 'Idiopathic' osteoporosis

2) Vitamin D insufficiency

Summary:

Mr AM is a 29 year old Fijian-Indian man who sustained a left hip fracture following low trauma. He has no previous fractures, no family history of fractures and his general health has been good. His DEXA scan confirms osteoporosis. He is lean (BMI: 19.9) and is Vitamin D insufficient with a level of 37nmol/L. This may contribute to his osteoporosis by increasing parathyroid hormone bone turnover which can lead to a low grade loss of bone density. However these low levels are commonly seen in patients of Indian ethnicity and are unlikely to be the primary cause of his osteoporosis. A complete screen of possible secondary causes of osteoporosis was negative. Therefore the diagnosis of 'idiopathic' osteoporosis was made, with a possible genetic component considering Mr AM's brother's low bone density.

DISCUSSION

Osteoporosis is a disease characterized by low bone mineral density (BMD) and micro-architectural deterioration of bone tissue. This subsequently leads to an increase in bone fragility and increases fracture risk, particularly of the spine, hip and wrist.[1] Osteoporosis is mainly a disease of the elderly and is generally a multifactorial disease process due to a number of risk factors such as ethnicity, gender, age, glucocorticoid therapy, low body mass index, Vitamin D deficiency, environmental factors and coexisting diseases. It has also been shown that a positive family history is also an important risk factor in the pathogenesis of osteoporosis.[2,3] Considering Mr AM's young age at the time of diagnosis and the lack of any other significant risk factors, the cause of his osteoporosis is likely to have a genetic component, especially considering his brother's low BMD.

Research in the genetics of osteoporosis has focused mainly on two separate areas: (1) genetic factors associated with peak BMD and rate of loss of BMD, and (2) family history of fractures. These two variables have shown to be independent risk factors of osteoporosis. Two separate studies in women have demonstrated a heritability of wrist fractures of approximately 25 per cent and 54 per cent. In both studies this was independent of patient BMD. This demonstrates that identifying genes which affect BMD does not necessarily correlate to a family history of fractures.[4] In this case study there is no family history of fractures, therefore it is probable that Mr AM's genetic risk factor is related to BMD.

Genetic factors in osteoporosis are believed to be polygenic in nature and are influenced by the polymorphisms of certain genes.[2] The effect of these genetic factors in the pathogenesis of osteoporosis is still unclear.[4] Research has mainly focused on female osteoporosis and a large number of genes have been identified which may affect BMD and thus increase risk of fracture. Certain genes have been identified which may contribute more specifically to male osteoporosis: Lipoprotein receptor related protein 5 (LRP5) Vitamin D Receptor Gene (VDR), Collagen Type I Alpha I gene (COL1A1), Insulin growth factor I (IGF-1), Estrogen receptor, Androgen receptor and Aromatase genes.

LRP5 is a receptor that functions as a co-receptor for canonical Wnt signaling, which plays a role in osteoblast and chondrocyte differentiation. Several studies have shown that LRP5 is related to BMD and/or osteoporosis fracture. Subtle polyporphisms of the LRP5 gene have been shown to regulate BMD. In addition a strong association has been seen between LRP5 and male osteoporosis.[4]

VDR is a specific hormone receptor that is responsible for the action of the bioactive form of Vitamin D, 1,25-(OH)2D3. Studies have demonstrated correlations between VDR and male osteoporosis particularly relating to peak bone mass, bone size, skeletal growth, fracture risk and intestinal calcium absorption.[3,4]

COL1A1 encodes Collagen type 1, a major structural protein of bone which has clear implications for osteoporosis. Mutations in this gene cause the syndrome of osteogenesis imperfecta. Polymorphisms of the COL1A1 gene have been associated with osteoporosis in both men and women. In addition to BMD, COL1A1 has also been associated as a marker of bone fragility. However there is limited research regarding the relationship of COL1A1 with male osteoporosis.[3,4]

IGF-1 may be a significant genetic factor in male osteoporosis. Low IGF-1 levels have been demonstrated in idiopathic osteoporosis in men. Studies have shown that certain allelic configuration of the IGF-1 gene (CAn dinucleotide repeat polymorphism) is associated with lower BMD. In addition this polymorphism also appears to be gender specific affecting mainly male patients.[3]

Oestrogen deficiency is a risk factor in both male and female osteoporosis. Oestrogen receptor, androgen receptor and aromatase genes all have an effect on sex steroid metabolism which ultimately affects BMD. Case studies have shown that mutations in any of these genes can lead to male osteoporosis.[3]

Current research has demonstrated that the genetics of osteoporosis is mainly mediated by a number of genes and their polymorphic variants which contribute collectively to both BMD and skeletal integrity. Some case studies have demonstrated that single gene defects can contribute to osteoporosis. For example, mutations in aromatase and estrogen receptor genes have been shown to result in osteoporosis. However these cases are rare and also tend to have a strong family history, usually inherited as an autosomal dominant trait.[3,4] Considering his lack of a positive family history it is unlikely Mr AM's osteoporosis is due to a single gene defect. The most plausible causative explanation of his osteoporosis is probably due to multiple genetic variants, which may possibly include some of the genes discussed above. Therefore it is not possible to definitively determine the genetic cause of Mr AM's osteoporosis.

Mr AM was placed on long term alendronate treatment and calciferol tablets, with clinic review every two years. Alendronate is a potent bisphosphonate that is an inhibitor of osteoclast-mediated bone resorption. It is most commonly used for the treatment and prevention of osteoporosis. Research has shown that alendronate significantly increases BMD and reduces the incidence of osteoporotic fractures in post-menopausal women and patients with glucocorticoid induced osteoporosis.[5] While it is a proven therapy in women, there have only been a few large controlled trials analysing the effectiveness of alendronate therapy in male osteoporosis. This is an important issue to address as this is Mr AM's primary treatment.

While research in men is limited compared to women, large trials have been conducted that demonstrate alendronate significantly increases BMD and decreases the incidence of osteoporotic fractures. One double-blinded trial compared alendronate versus placebo in 241 men with osteopororsis over a two-year period. Men who had alendronate had a mean increase in BMD of 7.1±0.3 per cent at the lumbar spine, 2.5±0.4 per cent at the femoral neck, and 2.0±0.2 per cent for the total body. Men who took alendronate had a significantly higher BMD in all areas compared to placebo ($P<0.001$).[5] In this particular trial all patients were given calcium and vitamin D supplements. A recent study comparing the effect of alendronate with and without cholecalciferol showed that patients who took cholecalciferol and alendronate reduced the relative risk of vitamin D deficiency by 91 per cent.[6] This has clear implications for Mr AM. His investigations revealed a slightly low vitamin D level, and based on the above trial he will benefit from Vitamin D supplements in combination with his alendronate therapy.

In addition it has also been demonstrated that the magnitude of benefit in BMD in men, is also similar to that seen in post-menopausal women after two years of therapy. The reduction in the incidence of vertebral fractures is also similar between men and women on alendronate therapy.[7] The benefit of alendronate in patients who have long-term therapy has not been discussed. Mr AH is a young man and it is likely he will need to remain on alendronate for a minimum of 5 years. The long term ramifications and benefits of such prolonged alendronate therapy in men have not been discussed as there are currently no major trials which address this issue.

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