CASE REPORT

Bone and joint involvement in Fabry disease

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Fabry disease (FD) is an X-linked lysosomal storage disorder caused by deficient activity of the enzyme α-galactosidase A. Although the disease has progressive effects on most organ systems in the body, data is limited regarding skeletal involvement in this rare disorder. We describe four family-related patients, three men and one premenopausal female, sharing a classic phenotype of FD. Dual-energy X-ray was performed in all cases and osteoporosis or osteopenia were found in all patients and osteoporotic fractures in one. One patient also showed both neuropathic joint disease and osteonecrosis. Several mechanisms that may explain osteoporosis and osteoarthropathy in the setting of FD are emphasized.

Fabry disease (FD) is an X-linked lysosomal storage disorder resulting from a deficiency of the enzyme alpha-galactosidase A (α-gal A). The lack of α-gal A causes an intracellular accumulation of globotriaosylceramide (Gb3) in various cell types. FD is characterized clinically by chronic pain and acroparesthesia, gastrointestinal disturbances, angiokeratomas, progressive renal impairment, cardiomyopathy, and ischaemic stroke (1, 2). Although the classical form of FD is known to be a multisystemic disorder with an expanding clinical spectrum, data are limited regarding skeletal involvement. We report on osteoporosis, neuropathic arthropathy, and osteonecrosis in four related patients sharing a classic phenotype of FD.

Family study

Three men (P1, P2, P4) and one female (P3) were family-related adult subjects showing a severe classic phenotype of FD (Figure 1). Some disease manifestations such as acroparesthesias, angiokeratomas, and hypohidrosis occurred early, before the age of 10, whereas kidney, cardiac, and central nervous system complications developed later in life. The missense mutation D266E in exon 5 of the α-Gal A gene has been identified in all four patients. Clinical, biochemical, and bone mineral density (BMD) data for the four patients are summarized in Table 1.

Case 1

A 45-year-old male (P1, Figure 1) suffered painful acroparesthesias and hypohidrosis from the age of 8 years. Physical examination showed several angiokeratomas in the pelvic area and widespread telangiectasia. Ophthalmological examination revealed typical ‘cornea verticillata’. Brain magnetic resonance imaging (MRI) showed bilateral ischaemic lesions in the pulvinar region. Cardiac MRI showed concentric left ventricular hypertrophy. Low leucocyte specific activity of α-Gal A confirmed the diagnosis of FD. Cardiac MRI also revealed uncomplicated vertebral fractures with a reduction in height of the T5, T6, and T7 vertebra (Figure 2A). Dual X-ray absorptiometry (DXA) revealed osteoporosis (Table 1). Enzyme replacement therapy (ERT) was initiated in association with bisphosphonate, calcium, and vitamin D supplementation. The patient received 60 mg of methylprednisolone as premedication therapy before agalsidase alpha infusion (0.2 mg/kg) because of an allergic reaction. Two years after the initiation of treatment, DXA showed an unchanged BMD with a T score at lumbar spine and femoral neck of −3 and −2.8 s.d., respectively.

Case 2

A 44-year-old FD male (P2, Figure 1) was treated with biweekly 0.2 mg/kg agalsidase alpha infusion. Severe
organ failure due to FD had led to combined heart and kidney transplantation. The immunosuppression protocol included steroids, mycophenolate mofetil, and cyclosporin A. Mild neuropathic pain was treated previously with carbamazepine. Nineteen months after organ transplantation, physical examination disclosed bilateral limb lympho-oedema. The right ankle was warm and swollen. The subtalar and midtarsal joints showed marked but painless instability. The tarsometatarsal joints were deformed with dorsal prominence and plantar protrusion. The patient complained of limb distal sensory loss with no patellar and Achilles reflexes at examination. The ankle synovial fluid was haemorrhagic without bacterial infection or crystals. Right-ankle X-ray revealed soft-tissue swelling and bone demineralization, with subluxation and collapse of the talus, and fracture of the calcaneus (Figure 2B). A computed tomography (CT) scan showed osteolysis with ill-defined bone margins of the distal part of the tibia and confirmed destruction of the talus and the calcaneus. MRI of the right foot (Figure 2C) revealed osteonecrosis of the posterior part of the calcaneus and of the cuneiform bone. DXA showed a T score at lumbar spine and femoral neck of \(-3.3\) and \(-2.7\) s.d., respectively (Table 1). The diagnosis of neuropathic ankle arthropathy associated with osteonecrosis of feet bones and osteoporosis was retained.

Case 3

A 42-year-old premenopausal female (P3, Figure 1) was regularly followed in a nephrology department for FD. Clinical manifestations of FD began in childhood and included angiokeratomas and neuropathic pain episode lasting hours to days and treated with carbamazepine. In adulthood, concentric left ventricular hypertrophy, mitral insufficiency, and progressive renal impairment developed. End-stage renal disease (ESRD) required dialysis despite initiation of ERT 1 year earlier. A kidney transplantation was performed 2 years later. A 22-month post-transplantation physical examination was unremarkable except for angiokeratomas over the pelvic area. Treatment included biweekly agalsidase alpha infusion (0.2 mg/kg), low-dose steroids,
mycophenolate mofetil, cyclosporin A, and carbamazepine. Systematic BMD assessment by DXA showed mild osteopaenia with a T score of –1.2 s.d. at both lumbar spine and femoral neck (Table 1).

Case 4

A 38-year-old male (P4, Figure 1) was regularly followed for FD. The diagnosis was suspected at the age of 5 on the association of painful acroparesthasias, hypohidrosis, chronic abdominal pain, and angiokeratomas. ESRD led the patient to chronic haemodialysis. A first kidney transplantation was performed. Because of chronic graft rejection, the patient went back to dialysis 13 years later and a second transplantation was performed. Six years after transplantation, physical examination was unremarkable except for a low body mass index (BMI) of 18.9. Treatment included biweekly agalsidase beta infusion (1 mg/kg), sirolimus, mycophenolate mofetil, carbamazepine, clopidogrel, and losartan. BMD assessment by DXA showed osteoporosis with a T score at both lumbar spine and femoral of –2.5 s.d. (Table 1).

Discussion

We report on various skeletal manifestations in four young family-related patients suffering a severe classic phenotype of FD including osteoporosis, neuropathic joint disease, and osteonecrosis.

The specificity of the FD rheumatic features should be addressed. In fact, solid organ transplantation, chronic renal failure, and steroid therapy might all explain the reduced BMD that was observed in our patients. Despite these confounding factors, two recent studies have highlighted the risk of reduced BMD and osteoporosis in hemizygous men with FD (3, 4). Of interest, several mechanisms could explain the secondary osteoporosis in the setting of FD, such as malabsorption, which could account for the decreased intestinal vitamin D absorption (5) and low 25-hydroxyvitamin D [25(OH)D] blood level as shown in patient 1. Moreover, a low BMI (<20), a well-known risk factor for osteoporosis (6), was found in patients 1, 2, and 4. In addition, three patients were treated with carbamazepine, which may also alter bone metabolism (7).

Our four patients exhibited a severe classic phenotype of FD associated with the D266E mutation. Genotype–phenotype correlations are complex in FD because the same mutation can lead to both classic and atypical disease within the same family. Although there is no clear-cut relationship between gene mutations and organ involvement, the genotype may be associated with reduced lumbar spine BMD (4). Our observations are consistent with the hypothesis that FD is associated with an increased risk of osteoporosis. On practical grounds, screening and conventional therapy for osteoporosis prevention should be discussed in patients with the classic phenotype of FD.

Osteonecrosis and pathological fractures are well-known disabling aspects of Gaucher disease, another glycosphingolipid storage disease (8), but are not considered a usual complication of FD. However, Gb3 accumulates in almost all tissues, including bones (9), and endothelial Gb3 load may cause both avascular necrosis and decreased osteoblastic activity.

Neuropathic joint disease is a chronic form of arthropathy associated with reduced sensory innervation of the joints. Neuropathic arthropathy can occur in various neurological disorders although causes other than diabetes are rare (10). FD neuropathy predominantly affects small nerve fibres. The nerve damage may be caused by diffusion and accumulation of Gb3 in the axons and dorsal root ganglia (11). FD neuropathy is a highly painful disorder, in contrast to the usually painless features of neuropathic arthropathy. However, acute pain is an early and transient feature of FD. In our patient severe osteoarthropathy could be ascribed to FD-specific neuropathy.

In conclusion, the emerging ERT and the hope for increased life expectancy (12) have led to increased awareness of unusual FD-related complications. Our report emphasizes the diversity of bone and joint involvement associated with this rare, but now treatable, disorder.
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References