Case report

An unusual cause of chronic backache

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A 46-year-old man of mixed race had been followed up for the past 7 years at our Rheumatology clinic. He was labelled as ‘burnt out’ rheumatoid arthritis with secondary osteoarthritis. Methotrexate had been stopped 5 years ago.

His main complaint was chronic lower backache that had been worsening over the past few years. He did not have any symptoms suggestive of an inflammatory arthropathy. His grandfather had similar symptoms. His siblings were all healthy.

Examination revealed a middle-aged male of short stature (1.51 m). Back examination revealed loss of lumbar lordosis, limited extension with fairly preserved forward and lateral flexion. There was no evidence of peripheral arthritis and systemic examination was unremarkable.

Radiographs of his lumbar spine revealed scoliosis, degenerative changes (marginal osteophytes, loss of joint space) and striking calcification of the intervertebral discs (Figure 1). Early degenerative changes of both radio carpal joints and metatarsophalangeal joints were also noted. No peripheral joint space calcification or any changes suggestive of an inflammatory arthropathy were noted.

Laboratory investigation revealed normal renal function, ferritin and serum calcium. A urine sample showed high levels of homogentisic acid (HGA). Tyrosine and phenylalanine metabolites were not detected in the urine.

The presence of intervertebral disc calcification and high urine HGA levels prompted the diagnosis of alkaptonuria (ochronosis).

Discussion

Alkaptonuria (MIM 203500) is a rare autosomal recessive metabolic disorder of tyrosine catabolism characterized by the accumulation of oxidized HGA pigment in connective tissues (ochronosis) and excretion of large amounts of HGA in urine. Homozygous mutations in the HGA oxidase gene (chromosome 3q 21–23) leads to deficiency of the enzyme homogentisate 1,2-dioxygenase (HGO) resulting in this disorder.1 Heterozygotes are carriers of the gene but are otherwise normal. The incidence of this inborn error of metabolism is estimated to be one case in 250 000–1 million live births.2 The Egyptian mummy Harwa (1500 BC) had alkaptonuria.3

HGA oxidizes forming a dark pigmented polymer with collagen. This polymer binds to connective tissue, appearing ‘ochre’ coloured microscopically—hence the term ochronosis. HGA accumulates in connective tissues, such as joints (cartilage), skin, eye, cardiovascular, genitourinary and respiratory systems. Alkaptonuria may go unrecognized until middle age when degenerative joint disease develops.1

Several theories as to the pathogenesis of joint degeneration exist. Accumulation of HGA in joints may act as a chemical irritant, leading to joint inflammation and degeneration. Free radicals may trigger the inflammatory process and hasten degeneration.4

The disease usually begins between the ages of 30 and 40 with chronic lower backache with restricted...
movement. Radiographs may reveal disc calcification with degenerative changes resembling osteoarthritis. Peripheral arthritis involving large joints, such as shoulders, knees, hips develop later. Radiological degenerative changes in peripheral joints appear on an average of 10 years after spinal changes. In some patients, accumulation of HGA as a blue–black pigment in the helix of the ear, nasal concha and sclera may assist in earlier recognition of the disorder. Valvular heart disease (aortic stenosis, mitral stenosis) and development of pigmented renal stones are some of the extra-articular manifestations of this disease.

The differential diagnosis (in terms of rheumatic complaints) includes ankylosing spondylitis, rheumatoid arthritis, haemochromatosis, acromegally, idiopathic chondrocalcinosis and Pott’s disease.

The disorder may be accidentally discovered in childhood—when black discolouration of urine left standing is noted. This is due to the oxidation and polymerization of the HGA at alkaline pH. The diagnosis is confirmed by the presence of high levels of HGA in urine.

There is no effective treatment for this disease. Symptomatic therapy of rheumatic manifestations with non-steroidal anti-inflammatory drugs and physiotherapy is useful. Osteoarthritic joint destruction may necessitate joint replacement. The ideal treatment is HGO enzyme replacement—currently not possible. Studies of vitamin C or E supplementation and protein restriction have been ineffective in reducing HGA production.

Nitisinone (an inhibitor of the tyrosine degradation pathway) together with dietary protein restriction has been shown to lower the urinary excretion of HGA in both mouse and human models. This drug is approved by the Food and Drug Administration for the treatment of tyrosinemia type 1. Further studies are needed to determine the safety and efficacy of this drug in treatment of alkaptonuria.

Conclusion

Ochronosis should be considered as part of the differential diagnosis in middle-aged patients with...
chronic lower backache and intervertebral disc calcification of plain radiographs. High urine HGA levels confirm diagnosis of alkaptonuria.

Conflict of interest: None declared.

References