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A metabolic cause of spinal deformity

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Abstract

A 38-year–old man presented to our clinic with a 6-year history of chronic low back pain. Physical examination showed limited spine mobility; radiographs of the spine demonstrated narrowed disk spaces and calcifications. Lumbar spine magnetic resonance imaging showed Modic type II signal intensity changes in the bone marrow consistent with chronic disk degeneration. The finding of a massively elevated excretion of homogentisic acid (HGA) in the patient's urine confirmed the suspicion that the complaints were due to underlying alkaptonuria. Alkaptonuria (ochronosis) is an uncommon cause of backache and results from mutations in homogentisate 1,2-dioxygenase, an enzyme involved in tyrosine catabolism. Homogentisic acid accumulates in the plasma of the affected individuals, and HGA polymers deposit in connective tissues where they cause cartilage degeneration. So far, there is no proven treatment; but preclinical and phase I data with nitisinone, an inhibitor of HGA formation, are promising. Currently, the effects of nitisinone on joint mobility are being evaluated in a randomized trial. Clinicians involved in the care of musculoskeletal problems should be aware of this rare disorder, particularly because the correct diagnosis may have therapeutic implications.

1. Introduction

Alkaptonuria is a rare autosomal recessive metabolic disorder of tyrosine catabolism in which homogentisic acid (HGA) accumulates as an intermediary metabolite because of deficient activity of HGA 1,2-dioxygenase (HGO) [1]. Alkaptonuria was the first disorder of humans suggested to be in conformity with the principles of mendelian inheritance [2,3]. More than 60 different mutations in the HGO gene have been described until now. The incidence is estimated at between 1 in 250 000 and 1 000 000 live births [4]. The HGO deficiency results in the accumulation of HGA throughout the human body. HGA oxidizes and forms a darkly pigmented colored polymer with collagen. The binding of the polymer to connective tissue, and bone is ochre microscopically; alkaptonuria is therefore also called *ochronosis*.

Ochronotic pigment is deposited in the large joints and the spine, typically in the lumbosacral region. The pigment is considered to accelerate age-associated degenerative processes of the cartilage [5]. In the spinal column, alkaptonuria especially affects the intervertebral disks, where it causes narrowing of intervertebral spaces and ultimately the formation of bony bridges between vertebral bodies [6,7].

The aim of this communication is to present the case of a 38-year–old man who presented with back pain due to spinal involvement of alkaptonuria and to discuss nitisinone as a novel therapeutic option that may become available soon.

2. Case report

A 38-year–old white man presented to our clinic with a 6-year history of intermittent lumbar pain. The pain was exacerbated upon initiation of spinal movements and flexion of the spinal column. Physical activity did not aggravate these symptoms. There was no indication of an inflammatory spondyloarthropathy in his medical history, as he denied

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nightly pain, morning stiffness, fever, and weight loss. He had no symptoms of nerve root compression, and all peripheral joints were asymptomatic.

On physical examination, we found a slight scoliosis. Spine mobility was slightly restricted by fingertip-floor distance measurement (22 cm) and a positive Schober test (13 cm). All other joints had a normal range of motion and no deformity or crepitation. Chest expansion and neurologic examination results were normal, as were his sclerae and auricles. Serum alkaline phosphatase, calcium, creatinine, phosphorus, ferritin, C-reactive protein, and the erythrocyte sedimentation rate were within normal limits.

Radiographic images of the lumbar spine revealed narrowed intervertebral spaces and calcifications at the periphery of several intervertebral disks (Fig. 1). Radiographs of both knees were completely normal. Magnetic resonance images of the spine showed Modic type II signal intensity changes in vertebral body marrow (Fig. 2). Modic type II changes are thought to result from fatty changes in the bone marrow due to chronic disk degeneration [8]. The patient then reported that he had noted an abnormal darkening of his urine exposed to air and been diagnosed with alkaptonuria in his infancy. We confirmed the diagnosis

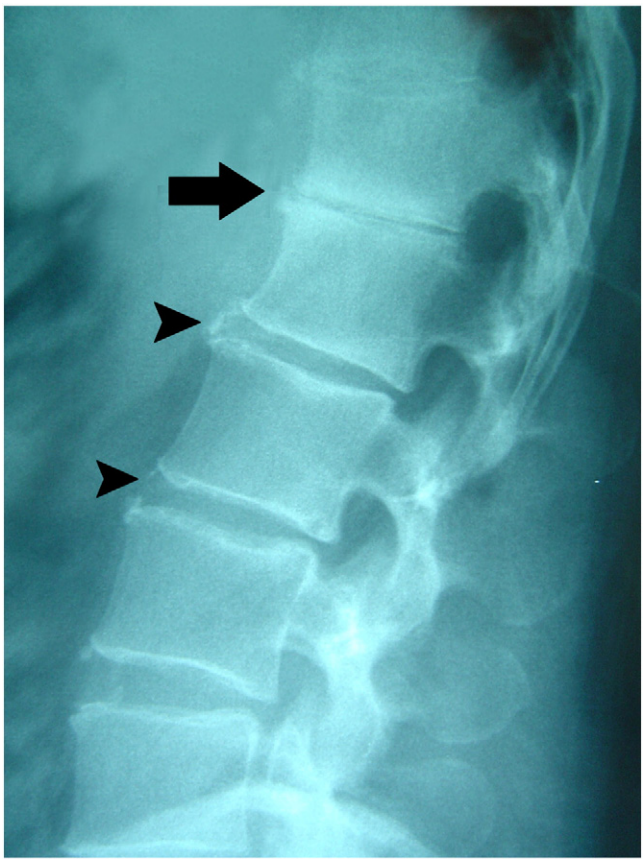

Fig. 1. Lumbar spine radiography demonstrating narrowing of the intervertebral space between the last thoracic and the first lumbar vertebral body (arrow), as well as calcifications of the annular rings of several intervertebral disks (arrowheads).

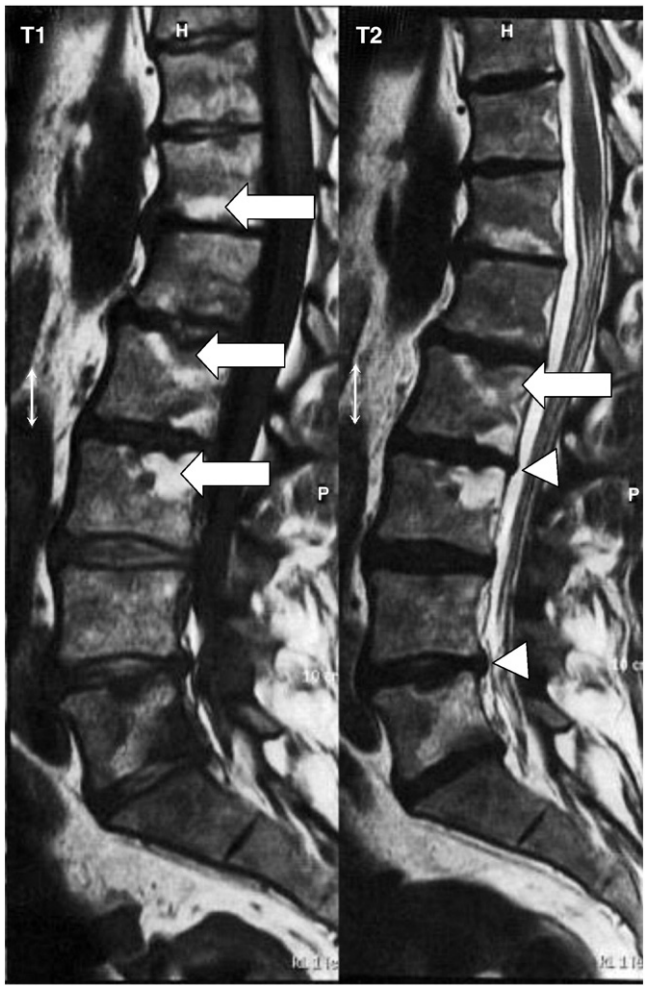

Fig. 2. Magnetic resonance T1-weighted (left) and T2-weighted (right) images of the lumbar spine demonstrating Modic type II changes (arrow) and intervertebral disk bulging (arrowhead).

of alkaptonuria by means of gas chromatography mass spectrometry that detected massively elevated levels of HGA in the patient's urine. The radiomorphology of the spine is typical for this diagnosis.

We treated the patient conservatively with nonsteroidal anti-inflammatory drugs and ambulant physiotherapy. He was briefed on how to behave in everyday life to preserve his back. The limited knowledge of the clinical effects of a dietary restriction of tyrosine and phenylalanine was discussed [9].

3. Discussion

We present the case of a 38-year–old man who presented with back pain due to spinal involvement of alkaptonuria.

Accumulation of HGA in patients with alkaptonuria starts at birth. The only sign present in childhood may be dark staining of diapers in some instances, but this occasionally passes unnoticed. The clinical symptoms of the musculoskeletal system are typically not seen before

the third decade [4]. Ochronotic pigment is deposited in the large joints as well as in the spinal disks, typically in the lumbosacral region. Collagen-rich ligaments and meniscal tissues also turn dark and lose elasticity, and their resistance to mechanical strain decreases [10]. The pigment is considered to irritate and accelerate age-associated degenerative processes [5,11]. The spine is more frequently affected than nonaxial articulations [5]. In the spinal column, ochronosis especially affects the annulus fibrosus. Radiologic investigations demonstrate wafer-like disk calcifications, narrowing of intervertebral spaces, bony bridges between vertebral bodies, or osteoporotic rarefaction [5]. Kyphosis and scoliosis can lead to loss of height. Despite the high incidence of disk involvement, radicular symptoms and myelopathies are rare [12,13]. Proximal joints are more severely affected than distal joints [5]. The small joints of the hands and feet, wrists, elbows, and ankles are rarely affected and without apparent calcification. Patients may develop joint contractures, joint space loss, and alterations in alignment. Some patients have tendon-related symptoms, such as thickening and even rupture of the Achilles tendons [14]. On ultrasonography, the pigment may be detected as hyperechoic deposits in the insertional tracts tendons [15]. Eventually, all patients will develop dark brown to black pigment, accumulating in the ear cartilage or the sclera at the position where the eye muscles attach. The appearance of this sign may be observed at the age of 30 years but can also be delayed beyond the fifth decade [4,16]. Another clinical appearance of alkaptonuria is the formation of kidney and prostate stones, probably due to the high levels of urinary HGA excretion. Cardiac involvement in alkaptonuria manifests with aortic dilatation, valve calcifications, or regurgitation [4,17].

The clinical manifestations of ochronosis can be misinterpreted as a result of overuse or aging, and ochronotic backache may be confused with ankylosing spondylitis because of its specific involvement of the spine and major joints and the pathologic Schober test [4,18]. Ochronosis however typically spares the sacroiliac joints. The peripheral joint involvement in ochronosis can also resemble inflammatory or infectious arthritis. The physician should especially consider the differential diagnosis of ochronosis if a degenerative arthropathy is far more advanced than would be expected for the patient's age. Disk calcifications are particularly found in the periphery of the disks, whereas the nucleus pulposus is spared. The disk calcifications seen on the radiographs can however also be seen in the context of hemochromatosis and diffuse idiopathic skeletal hyperostosis [19]. The diagnosis of alkaptonuria is usually confirmed by demonstrating elevated concentrations of HGA in either plasma or urine.

The natural evolution of ochronosis is progressive. Joint replacement is required at a relatively early age. Currently, there is no proven therapy. There are no specific dietary recommendations for patients with alkaptonuria, although it has been recommended that a low-protein diet with restriction of tyrosine and phenylalanine be used to reduce HGA formation and disease progression [9]. This notion has however not been investigated in a clinical trial. Ascorbic acid was studied because it was thought to enhance HGA degradation [9].

Nitisinone inhibits the enzyme that produces HGA. Nitisinone is an orphan drug used in the treatment of hereditary tyrosinemia type 1 [20]. In mice and humans with alkaptonuria, oral nitisinone lowered urinary HGA excretion [4,21,22]. Because of its mechanism of action, nitisinone causes elevated plasma tyrosine concentrations that can be toxic to the cornea, conjunctiva, skin, and nervous system. To prevent this toxicity, the dietary intake of tyrosine and phenylalanine needs to be restricted. In a small open-label study, nitisinone reduced joint pain in alkaptonuria [22]. A prospective randomized trial is currently examining the safety and efficacy of nitisinone on the long-term evolution of joint mobility in ochronosis. The results of this trial are expected in 2009, at a time when all patients on study will have completed their final 3-year visit (W Gahl, personal communication). We decided to then reevaluate the patient and his therapeutic options.

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