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Alkaptonuria and Ochronosis

Jozef Rovenský[1*], Richard Imrich[2] and Tibor Urbánek[1]
[1]*National Institute of Rheumatic Disease, Piestany, Slovakia*
[2]*Biomedical Research Centre, Bratislava, Slovakia*

Abstract

Alkaptonuria (AKU) is a rare inherited genetic disorder of phenylalanine and tyrosine metabolism. AKU represents an autosomal recessive condition caused by a defect in the enzyme homogentisate 1,2-dioxygenase, which participates in the degradation of tyrosine. As a result, homogentisic acid and its oxide, accumulate in the blood and are excreted in urine in large amounts. The polymer of homogentisc acid called alkapton, impregnates bradotrophic tissues such as cartilage. A clinical trial aimed at proving efficacy of nitisinone in AKU is currently underway.

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History

Scientists have found alkaptonuria in Egyptian mummies Harwa 1500 years BC. The name alkaptonuria (AKU) was first used in 1859 in a patient, whose urine contained areducing compound (alkapton), which was later identified as the homogentisic acid. In 1902, Sir Archibald Edward Garrod postulated the hypothesis that AKU is an inherited metabolic disease and that deficiency of the enzyme that metabolizes homogentisic acid is the result of a defective gene. This concept was later proved correct. His article about AKU was published in Lancet in 1902 [1]. At that time it was a bold statement when one considers how little was known about enzymes, about human genetics and intermediary metabolism. His knowledge was later summarized in his book Inborn Errors of Metabolism [2]. In 1958, La Du [3] in his work brought a biochemical evidence of the defect in AKU. He demonstrated the absence of enzyme activity metabolizing the homogentisic acid in liver homogenates from a patient with AKU. He found that the defect is related to one enzyme – homogentisate 1,2-dioxygenase. He suggested that the affected persons do not synthetize the enzyme. The gene responsible for AKU was identified in 1993 by Pollak et al. [4] and so far more than 100 potential mutations of the gene is known. Due to the lack of homogentisic acid degradation in the liver, the metabolite is secreted in the urine. In the body the homogentisic acid builds an oxidized polymer, which is stored in the form of blue-black deposits in tissues (ochronosis).

The Clinical Picture

The first signs of AKU can be seen already in the newborn. Their urine turns dark and leaves brownish black spots on its diapers. In contact with alkaline soap spots are highlighted and cannot be washed away. Dark earwax is typical for newborn with AKU. Dark urine and earwax remain the only clinical symptoms of AKU for many years. In the organism affected by this metabolic disorder a much more serious process takes place in the meantime. The ochronotic pigment is produced by oxidative polymerization of the homogentisic acid, it accumulates in bradytrophic tissues and stains them dark brown. In principle, it is a benign process, which goes on unnoticed for a long time.

The first signs of the ochronotic pigment deposition can be often detected accidentally during eye exam of the anterior segment. The ochronotic pigmentation of the ocular structures is present in approximately 70 % of patients. In addition to the sclera, lumps of the ochronotic pigment can be found in the conjunctiva and cornea. Since similar pigmentation of the cornea is not present in other medical conditions, this finding is regarded as pathognomic for alkaptonuric ochronosis. Skinsnes [5] described a patient, who underwent enucleation of the only one eye (the other was lost due to injury), due to a pigment stain in the sclera deemed as melanosarcoma. After an unrelated death of the patient, however, the autopsy revealed that this was an alkaptonuric ochronosis with ocular pigmentation. Pigment spots on the sclera are mostly seen. They appear usually in the third decade of life in 2/3 of the patients with alkaptonuric ochronosis. In the advanced stage they can be seen with the naked eye. When found, chronic poisoning with phenolic substances, arsenic and lead, Addison's disease, and blue sclerae in osteopsatyrosis should be excluded. The diagnosis of AKU is confirmed by presence of homogentisic acid in urine. AKU patients do not seek medical help due to difficulties with vision; often they are without any subjective complications.

In parallel with the ocular manifestations, ochronotic changes can be found in the hearing organ. Color changes of the auricle are visible in the 10th to 15th year of life. Detailed histological examination of the temporal bone performed by Brunner [6] revealed accumulation of the ochronotic pigment in the bone and its membranous parts. The changes taking place in the ears are slowly, and patients are alerted to the blue-gray color of the ear by their relatives. On the cartilage painless, hard, rough lumps can be seen, firmly connected with the basis, and shining through the delicate skin the dark-blue-violet. The first rough ridges appear on the lower arm of the anthelix, and later throughout the anthelix, in the fossa triangularis, cavum conchae, in the cymbal and the tragus. In advanced cases sometimes auricle deformation can be found. The external auditory canal is without changes, earwax is dark brown, drum is dark, dull, often inverted, with an atypical reflex, with bluish tint, and in most cases calcium incrustations are present. Patients may also suffer from hearing loss type hypacusis mixta with a stronger involvement of the perceptive apparatus. Symptoms of alkaptonuria hearing organ are specific and often lead to the diagnosis of this disease.

Typical for alkaptonuric ochronosis are changes in the skin, mainly brownish or bluish pigmentation of the skin under the arm, in the face, neck and hands, and rarely on the nails. Given their visibility

[*]**Corresponding Author:** Prof. Jozef Rovenský, National Institute of Rheumatic Disease, Piestany, Slovakia; E-mail: jozef.rovensky@nurch.sk

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they may be relevant for the early diagnosis alkaptonuric ochronosis.Ochronotic pigment is deposited also on the internal organs. In the field of cardiovascular organs it is the myocardium and blood vessels. Statistically significant myocardial disorders were not found, but earlier atherosclerotic changes in the aorta were observed. Urolithiasis was found in more than half of the patients and rarely cases of nephropathy were seen.

From a clinical point of view, the most serious process takes place in the joints and is called ochronotic arthropathy. It represents a degenerative process with a known genesis and with an increased risk of disability. From the early stages of the disease the basic clinical manifestation of ochronotic arthropathy is related to the spine. The first subjective difficulties appear at the end of the third decade of age. Gender is significant with a predominance of men relative to women 2:1. Objective findings include flattening of thoracic kyphosis and lumbar lordosis, mild rigidity with a tendency to deterioration. Later, in an advanced stage, the contours of the spine worsen with irregular spinous processes and a complete ankylosis of the entire lumbar and thoracic spine. The spine is rigid, irregular and at bending forwards, the contours do not change. Cervical spine maintains its mobility for a relatively long time despite significant sciagraphic changes. In an advanced stage dorsal flexing and rotational movements become limited, while the head moves forward. As a result of degenerative changes to the plates in then arrowing intervertebral space, body height decreases up to 8 cm in 20 years.

Typical calcification of intervertebral discs can be diagnosed using X-ray of the spine. Osteolytic and hyperplastic changes and secondary reactive bone formation can be found on the vertebral bodies. Osteophytes are created, sometimes even massive bone bridges of the type of ankylosing hyperostosis. Calcification of some peripheral bundles of the connective rings may be similar to pseudosyndesmotic bridges. Already in the early stages hollow formations in the plates are formed, this is called the vacuum phenomenon. In the intervertebral joints the gap is narrowed and reactive subchondral sclerosis is present.

Sometimes, calcification is found in the ligaments between the spinous processes. Occasionally, osteoporotic vertebral fractures are found. On the other hand, thickening of bone structure is not unusual. This resembles Paget osteitis.

While the spine is affected in all patients with ochronotic arthropathy, peripheral joints are affected less frequently. Based on the analysis of 26 patients with ochronotic arthropathy it may be noted that small joints are spared and large joints are affected in the following order: knee (64 %), shoulders (42.3 %) and hips (34.6 %) [6].

The finding in the knee is basically of arthrotic nature. It differs from genuine osteoarthrosis by an earlier start (average of 39 years), faster progress and larger deformations. Hydrops occurred in 30.4 % of our patients. Based on a series of investigations Hüttl et al. [7] have found that the synovial effusion is of a non-inflammatory, irritating and degenerative nature. The effusion has a yellowish color that remains unchanged even after prolonged standing in air, suggesting a low concentration of homogentisic acid. From the nosographic point of view it is important to find histiocytes with brown-violet and blue black cytoplasmic inclusions, which can be assumed to be the phagocytosed ochronotic pigment. The finding of histiocytes with pigment inclusions in the cytoplasm described Hüttl et al. [7] for the first time in the world literature. The X-ray image in ochronotic arthropathy shows similar changes as in osteoarthrosis, and this is often asymmetric. The characteristic sign is the formation of free calcified and ossificated pea sized or even larger bodies of a diverse shape. These are signs of ochronotic chondromatosis. Occasionally, narrow strips of calcified soft tissue pars of the extremities are detected, that resemble Thieberg-Weissenbach syndrome. The main difference between genuine arthrosis and ochronosis of the knee is in a more rapid progression and in advanced findings in relation to age of the patient with ochronosis.

In the early stages of ochronosis there are painful episodes of the type of humeroscapular periarthropathy In the shoulder joints which are probably related to the deposition of pigment and lime deposits tendons in the rotator. Gradually, the mobility gets limited due to the retraction of the joint capsule, destruction of the cartilage and the adjacent bone structures. X-ray image of the shoulder joints shows already at an early stage signs of ossificating enthesopathy. Siťaj [8] proves with an analysis of 42 patients with ochronosis that the calcareous deposits in the shoulder rotators are present more than 25 % of patients. In the next stage, around the 50th year of life, patients develop degenerative changes with exostosis on the bottom of the joint fossa, and later with cystoid translucency, usures and destruction on the humerus head. This finding is completely different from genuine osteoarthrosis and pathognomic for ochronotic arthropathy of the shoulder. The hip joints are affected only in later stages of ochronosis and approximately one third of patients. The course is faster than in coxarthrosis and results in an almost complete restriction of the mobility. The X-ray examination shows a severe, in some patients destructive coxarthrosis. Červeňanský et al. [9] describe ochronotic enthesopathy in the hip area and highlight the selective deposition of the ochronotic pigment in the tendons.

Coincidence of AKU with other diseases

The metabolic disorders in ochronotic arthropathy of the spine and large joints of the limbs include osteoporosis. It is assumed, that this a secondary form of osteoporosis, due to immobilization of severely affected individuals. Barel et al. [10] describe an affected family with alkaptonuria, phenylketonuria and congenital cataract. Occasionally alkaptonuria occurs concurrently with psoriasis. In 1955, Urbánek et al. [11] described a unique coincidence of alkaptonuric ochronosis and Bechterev's disease in a 51-year-old man. The patient had family history of AKU in four of five siblings. Based on an the clinical and X ray findings in the spine the authors assumed presence of ochronotic arthropathy and Bechterev's disease. Typical ochronotic changes were present in the patient, especially calcifications of the intervertebral discs, but less marked in comparison with other patients with ochronosis in advanced disease stages. Maybe the premature rigidity of the spine due to the Bechterev's disease prevented age-related development of ochronotic changes. On the other hand, despite standard Bechterev's disease symptoms (the affected sacroiliac joints, paraspinal ligament ossification and obliteration of intervertebral joints) the patient had disproportionately low pain throughout the course of the disease. The long-term observation of a large number of patients with ochronosis revealed that the relatively subtle pain is characteristic for ochronotic arthropathy [8].

Japanese authors Kihara et al. [12] described the coexistence of ochronosis and rheumatoid arthritis in 64-year-old woman. Magnetic

resonance imaging of intervertebral discs showed typical changes suggestive of ochronotic arthropathy. At the same time, symptoms of rheumatoid wrists arthritis were identified with positive rheumatoid factor and nodules, which histologically were compatible with the diagnosis of RA. Authors suggest that the pre-existing ochronotic arthropathy could have masked the manifestation of RA and caused a delay in diagnosis.

In conclusion, these two case reports suggest that the process of ochronosis delays development of inflammatory symptoms and is associated with less severe clinical course of Bechterev's disease and rheumatoid arthritis.

Diagnosis

Although diagnosis of ochronosis is based on finding pigment spots on ocular structures, on the blue-gray discoloration of the auricles and skin in the armpit and on the Xray findings on the calcified intervertebral discs, the AKU diagnosis is confirmed by presence homogentisic acid in urine. In the advanced stage of the disease irregularly protruding spinous processes of the thoracic and lumbar spine are typical for ochronotic arthropathy and specific is the finding of pigmented inclusions in the cells of the synovial effusion.

Differential diagnosis

The fresh urine of a patient with alkaptonuria has a normal pale yellow color and after prolonged standing in air or in contact with alkali (soaps, etc.) darkens to dark gray to black. This sign of alkaptonuria is specific and it will almost always distinguish it from some other diseases associated with changes of urine color. For example, the urine in the hereditary disease - congenital erythropoietic porphyriai (m. Günther), which also begins shortly after birth, has a very typical red color. Similarly, inhaematuria or haemoglobinuria urine has a pinkish red color. Decisive importance for the diagnosis has the analysis of the urinary sediment. In bilirubinuria the urine has a reddish-brown color (resambling black beer) and in melanuria a dark brown color. Urine is always already colored when it is fresh, with the exception of AKU, when the urine darkens in the air after hours or immediately after the addition of alkali.

Ochronosis may be endogenous (on the basis of AKU) and exogenous, caused by the contact with certain chemicals. Several authors have described yellowish pigmentation of the skin and cartilage caused by carbolic acid (phenol), which was previously used to treat leg ulcers and in other cases. This exogenous "karbolochronosis" was not associated with spondylosis and arthropathy. More recently, exogenous ochronosis in the skin and sclera was described, associated with myxedema caused by long-term use of resorcinol. Anderson [13] described the pigmentation of the eye conjunctiva and cornea due to working in the production of hydroquinone. The sclera was dark and spots on the cornea caused blindness. Sugar and Waddi [14] found a pigmentation of the sclera and cartilage similar to ochronosis after long-term use of atebrin. Skinsnes [5] describes a case of incorrect melanosarcoma diagnosis in a patient with ochronosis, which led to a tragic solution – enucleation of a single eye of the patient (see above).

To differentiate ochronotic changes in the spine from other spondylopathies is crucial to find calcified intervertebral discs, which are pathognomic for alkaptonuric ochronosis. Spondylopathies in chondrocalcinosis could cause certain problems in differential diagnosis, but this disease is characterized by painful process with episodes of attacks of inflammatory nature, by calcifications of small joints, especially at the wrists, and the spondylopathy has an easier course with no tendency to ankylosis. In rare cases, a distinction from calcified discs in hemochromatosis can be considered. When in doubt, analysis of the urine for the presence of homogentisic acid is decisive, as well as comprehensive view of the patient and evaluation of eye, ear and skin. Alkaptonuric ochronosis has a characteristic polytope symptomatology that usually does not cause greater differential difficulties. Rather, it is necessary to exclude other diseases that may require more urgent intervention before the full clinical picture develops.

Therapy

Currently, there is no effective treatment available for AKU; therapeutic interventions essentially can be summarized:

- reduction of the excretion of homogentisic acid into the urine,
- restriction of the onset of ochronosis,
- therapeutic and preventive interventions to influence ochronotic arthropathy.

To reduce the formation homogentisic acid and its excretion into urine in recent decades various dietary interventions have been tested, vitamins, hormones and other substances. Ascorbic acid, low protein diet and physiotherapy have been tried but do not alter the underlying metabolic defect [15].

Since 1992, nitisinone – a derivate of triketone herbicides – has become potentially an effective pharmacological treatment of AKU by inhibiting the enzyme 4- hydroxyphenylpyruvate dioxygenase. The first 3-year randomized therapeutic trial of nitisinone in AKU was performed by Introne and coworkers [16]. Clinically, primary and secondary parameters did not prove benefit from the medication very likely due to high age of patients. However, the trial demonstrated the remarkable tolerability of nitisinone, its biochemical efficacy, and the need to investigate its use in younger individuals prior to development of debilitating arthritis. Recently, a multicentre, randomised, open-label, notreatment controlled, parallel-group, dose-response study showed that nitisinone therapy decreased urinary homogentisic acid excretion to low levels in a dose-dependent manner and was well tolerated within the studied dose range [17]. Currently, a clinical trial aimed at proving efficacy of nitisinone in AKU is currently underway. Nitisinone is marketed by Sobi (Swedish orphan international, which after its merger with Biovitrum in 2010 became Sobi) in Europe and the rest of the world (excluding the USA – where i tis marketed by RDT) under the trade name „Orfadin“. In addition to hereditary tyrosinemia type 1, there are other diseases where the potential role of nitisinone has been investigated and may be useful, for example – alkaptonuria. A systematic clinical development programme in alkaptonuria is underway [15].

Competing Interests

The authors declare that they have no competing interests.

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