ALKAPTONURIC ARTHRITIS

Report of a Case

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Alkaptonuria is a rare disease characterised by the appearance of alkapton (homogentisic acid) in the urine. It is said to be due to an "inborn error of metabolism" of certain amino acids, namely, tyrosin and phenylalanine (Garrod 1923). About 160 cases have been reported in the literature, the approximate incidence being one in ten million of population. Apart from the changes in the urine the condition does not usually give rise to any symptoms of clinical significance. However, in about 50 per cent of the reported cases these urinary changes have been accompanied by ochronosis and degenerative arthritis (Eisenberg 1950).

A further case of alkaptonuria is reported here, not only on account of its rarity, but because it displays so typically and vividly the picturesque triad of alkaptonuria, ochronosis and degenerative arthritis. It is the first case to be reported from Africa.

ALKAPTONURIA

According to Garrod (1923) cases of undoubted alkaptonuria were recorded as far back as 1584, but the first accurate description is attributed to Boedeker in 1859. He had discovered in the urine of a patient with glycosuria a second reducing substance which he called alkapton, because the urine turned black when alkalis were added to it. In 1891 Wolkow and Baumann isolated this substance and identified it as homogentisic acid.

Garrod (1923) has called alkaptonuria an "inborn error of metabolism" and has classified it together with other inborn errors of metabolism such as albinism, cystinuria and pentosuria. It is characterised by the presence of homogentisic acid in the urine and is inherited as a Mendelian recessive character due to a defect in a single gene. This is a fact of great scientific interest and is the best known example of a metabolic defect behaving in accordance with Mendelian law (Hogben et al. 1932). The condition is found more frequently in males than in females in the proportion of approximately two to one. In 42 per cent of cases reported, there has been a history of consanguineous marriages, particularly of first cousins.

Alkaptonuria is present from birth and persists throughout life. It may be suspected in infancy because of the blackening of the urine and staining of diapers or clothing. It may also be present unrecognised until later in life when ochronosis or arthritis occurs. The urine may be normal in colour when passed but turns slate-coloured, brown and finally black on standing. The colour change is first seen on the surface of the urine from oxidation and may be hastened by heating or the addition of an alkali. Copper solutions such as Benedict's or Fehling's are reduced. An erroneous diagnosis of diabetes is therefore sometimes made. However, there is no reaction to fermentation tests because the reducing substance is not a sugar but an aromatic acid. The plane of polarised light is not rotated. Silver lactate and silver nitrate solutions are reduced in the cold. A very characteristic reaction is produced by the addition of one drop of a dilute solution of ferric chloride. A transitory bluish green colouration is produced. Millon's reagent produces a yellow precipitate. All these tests signify the presence of homogentisic acid in the urine. This is an intermediate product of metabolism brought about by the incomplete oxidation of certain amino acids, namely tyrosine and phenylalanine. Gross (1914) considered that this incomplete oxidation was due to the deficiency of a specific enzyme. The final benzene ring of these amino acids thus

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cannot be split, so that homogentisic acid circulates in the blood stream and is excreted in the urine. It is also excreted by the sweat glands, and clothing coming into contact with the axillary perspiration may be stained black (chromidrosis). The blood Wassermann reaction is sometimes positive.

OCHRONOSIS

Ochronosis was first described and so named by Virchow in 1866 as a post-mortem finding in a case of which the clinical features were not accurately described. He observed pigmentation of certain tissues in the body with granules which appeared ochre in colour under the microscope, hence the name ochronosis. Albrecht (1902) was the first to suggest that alkaptonuria was the cause of ochronosis, and Osler in 1904 described the surface pigmentation of ochronosis in three elderly men who had alkaptonuria.

Most of the recorded cases of ochronosis occurring together with alkaptonuria have been in patients over the age of forty years. Poulsen's patient (quoted by Garrod 1923) with ochronosis occurring at the age of twenty-three years is the youngest recorded. The pigmentation has been found in cartilage, tendons, fatty tissue, endocardium, intima of large vessels, kidneys, tonsils, lungs and thyroid. Garrod has described a butterfly-shaped area of pigmentation on the face. The cartilages of the ears are pigmented at an early stage and appear as a slate-grey discolouration first seen in the concha and anti-helix of the ear, and later in the tragus and anti-tragus. The auriciles often feel rigid to palpation and may appear nodular. Another early sign is the appearance of brown patches in the sclera, usually triangular in shape with their bases towards the cornea. The nasal cartilages may be stained blue, and a blue tint of the knuckles and hypothenar eminence may appear at a later stage. This accumulation of pigment in the tissues is a very gradual process requiring many years before it becomes prominent and recognisable.

It is of interest to recall that there are other conditions besides alkaptonuria which can produce ochronosis. Oppenheimer and Kline (1922) classified the causes of ochronosis as follows: 1) Ochronosis associated with the excretion of homogentisic acid in the urine (alkaptonuria); 2) Ochronosis associated with the excretion in the urine of melanin (melanuria). 3) Ochronosis associated with the external use of phenol (carboluria). In all these conditions there are present in the circulation minute quantities of aromatic compounds which are not normally present. Garrod suggested that in the tissues in which the pigment is deposited these aromatic compounds are acted upon by an enzyme such as tyrosinase and a pigment is thus precipitated. It seems that the exact mode of deposition of these pigments is not quite clear, and this aspect calls for further investigation and study.

ALKAPTONURIC ARTHRITIS

Gross and Allard (1908) were the first to lay stress on the association of osteoarthritic lesions with alkaptonuria. Umber and Burger (1913) described a family of eight children of an alkaptonuric father. Four of these children had alkaptonuria and suffered severely from articular lesions. The other non-alkaptonuric members of the family did not develop arthritis. According to Garrod one should not be tempted to regard ochronosis of the articular cartilage as the starting point of the arthritis in every case, because the cartilages of affected joints have in some cases shown comparatively little staining. Moreover Jantke (quoted by Garrod 1923) has shown that intense blackening of articular cartilage can occur without other articular pathology.

The pathological process in the affected joints associated with alkaptonuria has been described by Hertzberg (1945) as follows: 'The ochronotic pigment is deposited in the articular cartilage, especially in old cartilage with poor metabolism. This becomes black, loses elasticity, becomes brittle and shows little resistance to mechanical strain. The cartilage cracks easily and small black fragments may be wrenched off into the joint where
they soon become attached to synovial membrane, gradually becoming firmly affixed to this and embedded. Mechanical strain leads to changes in articular surfaces with sclerosis, and in other parts with formation of cysts and small infarctions. The subchondral bone marrow is irritated, proliferates and grows into the diseased cartilage. Marginal exostoses are formed. Pigmented cartilage is reported to be able to become forced up into the marrow cavity, being surrounded there by growing granulation tissue (Kleinschmidt 1922). The cartilage may disappear, leading to bony ankylosis. Several investigators have also reported the presence of osteoporosis in this disease. The pigment is deposited much less in the osseous system than in the cartilage. A lacunar resorption occurs and these patients are frequently subject to fractures as a result of minor injuries. The morbid processes greatly resemble those observed in ordinary deforming osteoarthrosis.”

Osler (1904) described the peculiar stance and gait caused by involvement of the joints of the lower limbs and spine in his patients with ochronosis. Soderbergh (1915) described the changes in the vertebral columns of four patients. There were rigidity and kyphosis of the spine as in spondylitis deformans. Alternating areas of osteoporosis and osteosclerosis were noticed and he proposed the name “osteitis deformans alkaptonurica.”

Pomeranz, Friedman and Tunick (1941) in their description of alkaptonuric arthritis stated that "the patients assume the posture reminiscent of Paget’s disease. The intervertebral discs appear as elliptical opaque wafers in all of the intervertebral joints, and are most clearly seen in the lumbar areas. It is probable that the density of the intervertebral discs is due to secondary calcification following degeneration of the cartilage, resulting from the deposition of homogentisic acid.”

All these descriptions of alkaptonuric arthritis suggest that there is some metabolic injury to the articular cartilage resulting in gross degenerative osteoarthrosis. The onset of arthritic symptoms is rare before the age of forty years, and by that time the process is usually well advanced. The radiographic appearances of the spinal column differ from those in other types of degenerative osteoarthritis in that almost all the intervertebral discs appear to be calcified and show up as dense wafers between the vertebral bodies. Several patients with alkaptonuria have presented themselves with the earliest symptoms resembling those of a prolapsed disc (Eisenberg 1950). The gross destructive changes in a non-weight-bearing joint such as the shoulder joint seem to resemble only one other condition, namely a neuropathic arthritis.

**TREATMENT**

With regard to the treatment of alkaptonuria, ochronosis and arthritis very little can be done for the patient. Treatment is symptomatic. Diets high in vitamin C (Mosonyi 1939) and low in tyrosine and phenylalanine have been tried, and have to some extent lowered the quantity of homogentisic acid excreted in the urine. A similar reduction has been obtained by the parenteral use of liver (Klein and Bloch 1936), but with no decrease in pigment deposition or joint destruction. In the case to be described, intramuscular injections of desoxycorticosterone acetate and vitamin C have been employed but without any significant success. Neither has the exhibition of colchicine been of any value.

**CASE REPORT**

A white male aged sixty-six years, a building contractor, presented himself for examination in July 1950. He complained of pains in the knees, hips, elbows and back.

**History**—About eleven years previously he was involved in a road accident and he alleged that his right hip was dislocated. The dislocation was reduced at home by his doctor, and after three weeks he was walking. A few months later he began to experience pain in the right hip but he continued to get about. The pain was worse in the morning but after walking a little it lessened. Three years later he noticed that his left leg was becoming shorter and
he raised the heel of the left shoe. Thereafter he began to limp badly and at first managed to get around with sticks but later he resorted to crutches. He did not seek the advice of a doctor at this stage. During the next six years his knees and shoulders gradually became stiff and painful, and for the past four years the elbows had been similarly affected. All these joints seemed to creak. He eventually reported to the Johannesburg General Hospital in February 1947 and was treated as an in-patient in a medical ward for "osteoarthritis and rheumatoid arthritis." The hospital records of that date reveal that he was extensively
investigated. The urine and blood were examined and all his joints were radiographed. Mention was made of some pigmentation of both arms below the elbows but there was no record of the urine having been examined for alkapton, and the true nature of the condition was therefore not diagnosed. He was eventually discharged from hospital without significant improvement about three weeks later. He was readmitted in November 1948 with acute retention of urine. He then gave a history of increased frequency of micturition during the previous five years, accompanied by straining and dysuria. A suprapubic resection of the middle lobe of the prostate was performed together with the removal of prostatic calculi. No mention was made in the notes of the presence of any colour changes or alkapton in the urine. He made an uninterrupted recovery. He stated that before this operation his undergarments used to be stained black by the dribbling of urine, but after the operation this ceased. As long as he could remember his axillary perspiration had always stained his shirts a brownish colour. For the past ten years he had noticed a few bluish-black spots on his fingers and hands, and attributed these to the fact that he did a lot of gardening and often pricked his fingers with the thorns of a weed commonly known as “black-jack.” On several occasions he removed some of these “thorns” from his fingers with the point of a knife but they seemed to recur. He was unable to do much work but managed to get around with the aid of crutches and was able to drive his own car. There was a history of malaria in 1910, and pneumonia in 1927. Family history—His father and mother were not related as far as he could ascertain. His father died of old age and his mother died of pneumonia. He had five brothers of whom four were alive; and four sisters of whom two were alive. His first wife died in childbirth. He had six children by his second wife. They were all alive. Of his four daughters, two were twins. Two of his sisters each produced male twins. None of his children darkened the diapers with their urine as infants. The urine of his eldest son and that of one of his twin daughters was recently tested and found negative for alkapton.

Examination—The patient was stocky, obese, ruddy-complexioned, and of a jovial disposition despite his severe arthritic disabilities. He walked with the aid of auxiliary crutches, taking weight lightly on his everted feet and swinging along with a tripod gait. His weight was 180 lb. Eyes—There were two oval patches of brownish-black pigmentation in each eye, situated in the sclera medial and lateral to the cornea, and about two millimetres away from the corneal margins (Fig. 1). Ears—Both ears felt rigid to palpation with a slight nodularity. There was slate-grey pigmentation of the concha and anti-helix. This pigmentation was seen more readily and thrown into relief when a torchlight was held behind the auricles (Fig. 2). Face—There was a bluish pigmented nodule in the midline of the forehead. Hands—There were bluish-black pigmented spots and nodules on the ulnar borders of both hands and along the ulnar borders of the third, fourth and fifth fingers (Fig. 3). These were not tender to pressure. The nails were not pigmented. There was no swelling or limitation of movement of the wrists or fingers. Hip joints—These were held in lateral rotation and slight adduction. All passive movements were remarkably free, but painful at their extremes. Active movements were all limited by about 75 per cent. Knee joints—There was swelling of both knees with synovial and capsular thickening and mild effusion. There was gross crepitus and some fixation of the patellae. No ligamentous laxity was present. Palpable marginal and patellar osteophytes were present and there was tenderness over the articular margins. The joints did not feel warm. Flexion was limited to 50 degrees and extension was 15 degrees short of full. Ankle and foot joints—These joints were slightly stiff but not thickened or painful. Shoulder joints—All movements were markedly limited and painful. Abduction to about 30 degrees was possible actively and there was about 5 degrees of lateral and medial rotation. Passive movements caused crepitus and pain. Elbows—These joints were not very painful. Extension was about 30 degrees short of full in each joint. Flexion was possible to a right angle in the left elbow and to 110 degrees in the right elbow. Rotation was 50 per cent of full.
Fig. 5
Radiograph showing osteoarthritis of right hip and old ununited fracture of left femoral neck.

Fig. 6
Left knee showing gross osteoarthritic changes.

Fig. 7
Left shoulder. The right shoulder showed similar changes.
Fig. 8
Lower thoracic spine showing typical appearance of alkaptonuric arthritis with wafer-like calcification of the intervertebral discs, and marginal osteophytes.
Spine—There was no gross deformity of the spine except for a smooth generalised kyphosis. All lumbar and dorsal movements appeared to be completely absent, and in the cervical region movements were limited about 50 per cent in all directions. The chest, abdomen, cardiovascular and central nervous systems were free from any gross organic disease.

Special investigations—Radiographs of the joints showed evidence of extensive degenerative osteoarthritis in the hips, knees, shoulders, elbows and spine (Figs. 5 to 8). There was an old ununited fracture of the left femoral neck (Fig. 5). The spine showed the typical picture of alkaptonuric osteoarthrosis, with the wafer-like calcification of the intervertebral discs and marginal osteophytes (Fig. 8). This appearance was present in the entire spine from the cervical to lower lumbar region.

Urine—This was normal in colour when passed. On standing, the urine gradually assumed a slate-grey hue after twenty-four hours; discolouration began first on the surface and then extended throughout the specimen. Alkapton was present and all the tests previously mentioned were positive. The transient appearance of a blue colour on adding a drop of dilute ferric chloride was photographed and is shown in Figure 4. There was no significant microscopic pathology in the urine and chromatographic analysis showed no excess of amino acids.

Blood examination—Apart from a white cell count of 11,000 per cubic millimetre and a sedimentation rate of twenty-two millimetres in the first hour, there were no abnormal findings. The Wassermann reaction was negative.

I am indebted to the patient for his genial fortitude; to Dr K. Mills, Superintendent of the Johannesburg General Hospital for permission to publish this case; to Mr J. M. Edelstein, Head of the Orthopaedic Department, for his kind co-operation; and to Dr S. Komins and Miss Tomkins of the radiological department for their assistance. Mr Maxwell Deitch took the colour photographs.

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