A case of alcaptonuria with fatal cardiovascular disturbance

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Abstract

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A CASE OF ALCAPTONURIA WITH FATAL CARDIOVASCULAR DISTURBANCE

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Abstract. A case of alcaptonuria combined with aortic insufficiency was found in a 28-year-old male. The patient was palpitating at admission. The daily excretion of homogentisic acid was 2.0-6.0 g. Electrocardiography indicated atrial fibrillation and left ventricular hypertrophy with a ST-T change and right axis deviation. Cartilage tissues in the knee-joints showed no pigmentation. Vertebral X-ray revealed no calcification. The patient's history disclosed a family intermarriage in his grandparents. The patient's mother noticed the presence of black stains on diapers in his infancy and brown pigmentation on the skin and sclera in childhood. No kin had similar symptoms.

Alcaptonuria is a rare inherited metabolic disease characterized by the excretion of homogentisic acid in the urine and is due to a defect in the metabolism of tyrosine. Boedecker (1) was the first to scientifically describe the alcaptonuric patient. Homogentisic aciduria arises as a consequence of the absence of the enzyme homogentisic acid oxidase (homogentisate 1,2-dioxygenase) and is present almost always from birth. Homogentisic acid is considered to be converted to maleylacetoacetic acid by the enzyme (2).

Alcaptonuria is not fatal probably because of the easy excretion of homogentisic acid by urine. It is frequently noticed in infancy by stainings on the diapers (3). Homogentisic acid in connective tissue is considered to be readily oxidized and polymerized. This auto-oxidation polymer appears to become irreversibly bound to collagen (4, 5). The affinity between homogentisic acid and collagen might account for arthritis, skin pigmentation and calcification of the spine disc often found in the disease. More than 600 cases have been reported from 35 countries (6).

In this report, a male alcaptonuria case is described with fatal cardiovascular disturbance whose exact diagnosis was established at the age of 28 years. This report covers clinical and laboratory studies in addition to the...
The patient was first admitted to Mitoyo General Hospital at the age of 23 years (November 1966) with occasional palpitation and fatigue. His past history obtained from his mother revealed that black stains were present during infancy on his diapers, particularly when the diapers were exposed to soap and air. Brown pigmentation on the skin and sclera were later noted. A diastolic murmur in the aortic valve area was found at 17 years of age. Arthralgia was never noted. The family history disclosed an intermarriage at his grandparent’s generation. None of his relatives were reported to have similar symptoms.

Physical examination at 28 years of age revealed: focal brown pigmentation on the skin and scleras, no edema on the legs and no hepatosplenomegaly. A diastolic murmur on aortic valve area was confirmed, and diastolic blood pressure fell to zero. Aortic insufficiency was diagnosed. A freshly passed urine sample was normal in appearance but rapidly turned dark-brown on addition of sodium hydroxide solution. The urine reduced Benedict’s reagent suggesting the existence of alcaptonuria, but this was not examined further. Radiologic examination disclosed a left ventricular enlargement but calcification typical for ochronosis was not found.

Laboratory examination performed at this time disclosed: hemoglobin, 14.1 g %; white blood cell count, 5,700 per mm³; total serum protein, 8.6 g %; albumin/globulin ratio, 0.56; urinary protein, 1-plus; urinary cast, negative; antistreptolysin-0 titer (ASLO), 166 Todd units; latex fixation test (RAT), negative; blood urea nitrogen (BUN), 15 mg %; and serum glutamic pyruvic transaminase (S-GPT), 10 Karmen units. Digitalization was instituted. The patient recovered after 5 months hospitalization and was discharged on April 7, 1967.

In June 1971 an electrocardiogram revealed atrial fibrillation accompanied with palpitation and epigastric pain. He was treated only symptomatically as an outpatient and apparently recovered in a week.

In February 1973, dyspnea with palpitation occurred. An electrocardiogram revealed severe atrial fibrillation, and the patient was readmitted. His body weight was 51 kg and his height, 165 cm. Physical examination disclosed slight cyanosis on the skin and lips. Anemia was present on the conjunctiva. An enlarged heart markedly deviated to left with the point of maximal impulse in the sixth intercostal space 3 cm outside of the left midclavicular line. The blood pressure was 120/48 mmHg. The pulse rate was 90 beats per minute and irregular. Systolic and diastolic murmur were heard in the second and third right intercostal space. No edema was present on the legs.
A chest roentgenogram (Fig. 1) taken on admission (February 28, 1973) showed a markedly enlarged heart. The white blood cell count was 5,800 per mm$^3$ with 59%
polymorphonuclear leukocytes, 39% lymphocytes and 2% band forms. Laboratory examination revealed a hematocrit value of 37%; hemoglobin, 13.1 g%; erythrocyte sedimentation rate, 9 mm in the first one hour; urinalysis, normal; BUN, 15 mg%; serologic test for syphilis (VDRL), negative; C-reactive protein (CRP), 1-plus; ASLO, 80 Todd units; RAT, negative; total bilirubin, 0.4 mg%; S-GPT, 16 Karmen units; alkaline phosphatase, 3.2 Bodansky units; lactate dehydrogenase (LDH), 395 Wroblewski units; serum total cholesterol, 126 mg%; serum gamma globulin, 1.18 g%; and Triosorb test and Tetrasorb test, normal. An electrocardiogram taken on admission showed atrial fibrillation and left ventricular hypertrophy with a ST-T change and right axis deviation (Fig. 2). A spinal X-ray examination revealed no osteochondrosis.

Right heart failure developed gradually in spite of daily administration of 0.1 mg of digitoxin. The patient complained of severe palpitation and dyspnea.

Fig. 3. A paper chromatogram of the urine. Color was developed according to Neuberger (8). Solvent system: Water saturated n-butanol with several drops of formic acid. 1 and 4, authentic homogentisic acid (standards); 2, urine; 3, homogentisic acid extracted from the urine with ethyl ether.
Alcaptonuria with Fatal Cardiac Disease

An electrocardiogram taken on March 26 showed atrial fibrillation with tachycardia. Liver function test disclosed serum total bilirubin of 0.7 mg %; S-GOT, 460 Karmen units; S-GPT, 430 Karmen units; LDH, 1,560 Wroblewski units; CRP, 2-plus; proteinuria, 2-plus; and serum total protein, 7.0 g % with a gamma globulin fraction of 1.1 g %. Administration of digitoxin and furosemide in an oxygen tent resulted in improvement of laboratory values, except for positive CRP. The patient showed considerable improvement in April.

In the beginning of May, palpitation with dyspnea appeared. Physical examination revealed hepatomegaly at 6 cm below the costal margin, and edema on the legs and face. Laboratory examination disclosed S-GOT, 145 Karmen units; S-GPT, 210 Karmen units; LDH, 1,280 Wroblewski units; serum total bilirubin, 4.6 mg %; CRP, 2-plus; serum total protein, 6.8 g % with gamma globulin fraction of 1.6 g %; and proteinuria 2-plus without cast. Electrocardiographic results were the same as in the previous examination. The

Fig. 4. Thin layer chromatogram of the urine. 1 and 4, authentic homogentisic acid (standards); 2, urine; 3, ether extract of the urine.
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heart showed progressively severe decompensation and the patient died on May 21. Autopsy was refused by his family.

Identification and quantitation of homogentisic acid. Urinary homogentisic acid was determined by the colorimetric method (7, 8). This method requires a large volume of urine (25 ml), and readings were taken with an absorptiometer with a red filter. The method used in the present study was modified at several points. The reaction mixture was composed of 5 ml of water solution containing 0.1-1.0 micromole of homogentisic acid, 0.5 ml of 5% ammonium molybdate in 5N H₂SO₄ and 0.5 ml of 1% monobasic potassium phosphate. The mixture was incubated at 37°C for 30 minutes and absorbance at 700 nm was read by a spectrophotometer. The daily excretion of homogentisic acid was 2.0-6.0 g. For identification of homogentisic acid, descending paper chromatography (9) was performed on Whatman No.1 paper in a solvent of water saturated n-butanol containing several drops of formic acid (Fig. 3). Thin layer chromatography on a plate coated with silica gel was performed with the same solvent to confirm the presence of urinary homogentisic acid (Fig. 4).

DISCUSSION

Alkaptonuria is usually first suspected by dark diaper stainings, and rarely by ochronosis and arthritis. The clinical diagnosis is usually made from a combination of arthritis, ochronotic pigmentation and urine which darkens on addition of strong alkali (10). In this case the characteristic brown pigmentation on the skin and sclera and the dark brown urine were found but not arthritis. The arthritis in this disease usually begins at middle age (10). O'Brien, La Du and Bunim (6) reviewed the disease based on analysis of 604 cases reported from 35 countries. They estimated the average patient affected by ochronotic arthropathy was 41 years of age and was more likely to be a male than a female. Our patient was younger than average and arthritis was absent at 29 years of age.

The diagnosis should be established on the basis of urinary homogentisic acid identified by appropriate methods (11). Thin layer chromatography and paper chromatography were employed in this study. Quantitative analysis of urinary homogentisate was performed on a smaller scale than by the original method. The large amounts of acid excretion (as much as 2.6-6.0 g per day) are consistent with the values reported in the literature (8, 12).

A review of the reported cases of the disease disclosed that correct diagnosis was made in 252 cases but was initially missed in 97 other cases (6). The review also stated that one patient first noted dark urine at the age of 93 and that a diagnosis was not made in 28 patients until postmortem. The mother of the present patient noticed brown staining during the patient's infancy but a
physician was not consulted on this condition until he had palpitation at 23 years of age, probably because alcaptonuria \textit{per se} is benign and without obvious symptoms. A definitive diagnosis was finally established at 28 years of age.

O'Brien, La Du and Bunin (6) reported cardiovascular lesions of ochronosis including diffuse bluish pigmentation of the heart valves, endocardium and intima of the aorta. Discoloration was especially prominent at the base of the mitral and aortic valves and annulus fibrosus. The edges of cusps were roughened, fused for 1 to 2 mm at the base and minimally calcified. These changes were found in only 2 of 13 patients below 50 years of age. These investigators also stated that although striking pigmentation of arteriosclerotic plagues was seen, the alcaptonuria did not seem to contribute significantly to the arteriosclerosis or cause clinically discernible cardiac disease. We could not explain the aortic insufficiency in our patient, since he previously did not show evidence of rheumatic fever, sepsis, syphilis or congenital valvular disease.

Richman, Dalman and Grep (13) showed that the liver function indices could be deranged in congestive heart failure (13). They examined the liver function in 175 patients with right-side congestive heart failure due to various causes and found that four-fifths of patients with elevated levels of S-GOT indicated measures between 40 and 80 Karmen units, but that the remainder had values as high as 1,250 Karmen units, and that the highest value of S-GPT was 530 Karmen units. Therefore, the elevation of S-GOT and S-GPT in this patient might be due to aortic insufficiency, since liver function indices returned to the normal range when the congestive condition was improved.

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