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# HAEMOCHROMATOSIS IN A YOUNG FEMALE

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In 1951 one of us reported a case of idiopathic haemochromatosis in a young European male, aged 21 years.[1] The salient features were myocardial failure, sexual hypoplasia and enlargement of the liver. The cardiac disability was the major presenting feature and was the cause of the patient's sudden death 1 year after the onset of the symptoms. Recently a sister of the patient was found to be suffering from the same disease and the clinical presentation was very similar to that of the first case.

The occurrence of idiopathic haemochromatosis in siblings is uncommon and, moreover, the disease is extremely rare in young females.[2] For these reasons the present case is reported in detail.

## CASE HISTORY

*First Admission*

The patient, a female of 25 years of age, was admitted to another unit of the Johannesburg hospital in March 1954. The major complaint was that during the previous 2 years she had developed amenorrhoea, diminished libido and increasing skin pigmentation. Before this her periods had been irregular. She had been married for 6 years but had never become pregnant.

She was a young, thin woman with patchy pigmentation of the face and forearms. The breasts were poorly developed and hair was scanty in the pubic and axillary regions. There was no obvious hepatomegaly. The blood pressure was 120/60 mm. Hg and the cardiovascular system appeared normal. On vaginal examination the uterus was felt to be hypoplastic.

*Laboratory data.* Full blood count normal. Serum electrolytes normal. 'Liver function' tests: Thymol turbidity 8·5 units, thymol flocculation ++++, cephalin cholesterol ++++, Takata Ara (Ucko's modification) ++, zinc-sulphate turbidity 26·8 units, total lipids 984 mgm. per 100 ml., alkaline phosphatase 15·8 King-Armstrong units, total bilirubin 0·3 mg. per 100 ml., total protein 7·8 g. per 100 ml., 17 ketosteroids in 24-hour specimen of urine 3·1 mg. Follicle-stimulating hormone less than 6 mouse units (normal 6-12 mouse units). Kepler-Robinson-Power test negative. Skin biopsy: increased melanin pigmentation in the basal layers.

The patient was discharged from hospital with no definite diagnosis made.

*Second Admission*

The patient was readmitted to hospital in September 1956 complaining of severe bouts of abdominal pain during the previous few weeks. She had also noticed increasing breathlessness on exertion over the same period and a sudden attack of severe palpitation, lasting a few hours, had occurred on the day before admission.

The physical findings were similar to those on the first admission except for signs in the cardiovascular system. She was dyspnoeic at rest and was found to be in congestive cardiac failure. The heart rate was 200 per minute and the rhythm was grossly irregular. The blood pressure was 90/60 mm. Hg. Cardiomegaly was present and a gallop rhythm was heard at the apex. The liver was tender and enlarged to 3 fingers' below the costal margin. An electrocardiogram taken on admission showed a sinus rhythm with runs of nodal extrasystoles and occasional ventricular ectopic beats, and there was a generalized depression of T-waves in the precordial leads. An X-ray of the chest taken at the same time showed some generalized cardiac enlargement (cardio-thoracic ratio 56%).

The patient was treated with digoxin and a mercurial diuretic. In view of her almost moribund condition she was also given 30 mg. of prednisone daily. On this therapy she responded well and the signs of cardiac failure disappeared. While in hospital further investigations were carried out.

*Laboratory data.* Haemoglobin 13·6 g.%. 'Liver function' tests: Similar to those on the previous admission. Glucose tolerance test (50 g. by mouth) normal. Serum iron 266 gamma per 100 ml.; total iron-binding capacity 266 gamma per 100 ml. Follicle-stimulating hormone (24-hour specimen of urine) less than 6 mouse units. 17-ketosteroid 3·4 mg. in 24-hour specimen of urine. Liver biopsy: Heavy deposits of haemosiderin were present in parenchymal cells; there was also some early fibrosis of the portal tracts.

*Progress.* On discharge from hospital the patient felt much improved. There was no sign of congestive cardiac failure and there was a normal sinus rhythm. She was maintained on digitalis therapy and a regime of regular weekly phlebotomies (500 ml.) was commenced. In all, 7,500 ml. of blood was removed during the next 3 months. During this period the patient maintained a haemoglobin level between 12 and 14 g. per 100 ml. Although the cardiac control remained fairly adequate she tended to become breathless on moderate exertion. On several occasions she was found to have multiple ventricular ectopic beats. These were partially controlled by maintenance therapy with oral procaine amide.

*Third Admission*

The patient was again admitted to hospital in January 1957 because of severe breathlessness. She was found to be in severe cardiac failure and the heart rate was 200 per minute with an irregular rhythm. Pulsus alternans was present and the blood pressure was 100/80 mm. Hg. The heart was clinically enlarged and a gallop rhythm was heard at the apex. The liver was 4 fingers enlarged and extremely tender. Peripheral oedema was also present. An electrocardiogram showed auricular fibrillation with multifocal ventricular ectopic beats. The plasma-iron level on admission was 253 gamma per 100 ml.

The patient's condition improved slightly on routine cardiac care, but although the cardiac arrythmia was restored to normal she remained in congestive cardiac failure. Ten days after admission she suddenly became shocked and was found again to have auricular fibrillation with a ventricular rate of 140 per minute. During the next few hours various resuscitative measures were adopted, including intravenous strophanthin and noradrenaline. Although the heart rate slowed to 100 per minute the blood pressure remained very low, and she died in irreversable peripheral vascular failure.

The blood chemistry shortly before death was as follows: serum potassium 4 mEq.l., serum sodium 139 mEq./l., plasma chloride 93 mEq./l., blood sugar 135 mg./100 ml., serum iron 487 gamma/100 ml.

*Summary of autopsy findings:* There was a generalized brownish pigmentation of the skin and pitting oedema of the ankles. The lungs showed well-marked chronic venous congestion and there was an excess of clear fluid in the pleural cavities. The heart was slightly enlarged (weight 320 g.). It was of a brownish colour and gave a positive prussian-blue reaction for iron. The wall of the left ventricle was thickened and a mural thrombus was found at the apex. No abnormalities were noted in the gastro-intestinal tract. The liver (weight 1,860 g.) was smooth and very firm. On section it showed the typical features of haemochromatosis as well as chronic venous congestion. The pancreas was chocolate coloured and showed a well-marked fibrosis. The spleen was enlarged (weight 490 g.) and congested. The liver, spleen and pancreas all gave a well-marked prussian-blue reaction for iron. The endocrine glands were macroscopically normal. Microscopic examination of the organs showed the typical features of idiopathic haemochromatosis.

## DISCUSSION

Although idiopathic haemochromatosis is an uncommon disease, Finch and Finch[2] were recently able to review 787 cases which have been reported in the last 20 years. The disease was found to be about 10 times more common in males as in females and most subjects developed their first symptoms between the ages of 40 and 60 years. In this group the presenting features were usually related to cirrhosis of the liver and to diabetes. In a small proportion of cases the disease manifested itself at a younger age and the major impact was often on the heart and endocrine glands. The prognosis was found to be variable. Although the average expectation of life was 4.4 years, some cases lived much longer, while those with cardiac complications usually succumbed within a year.

It is generally agreed that the disease is the result of an inborn error of metabolism, which allows for an excessive absorption of iron from the gut. This excessive absorption has been demonstrated in several studies[3-5] and it has been noted that the increase is especially marked in young patients suffering from the disease.[6] In quantitative terms the derangement from normal need not be a large one to account for the massive deposits of iron found in idiopathic haemochromatosis. This is due to the fact that the body's ability to excrete iron is extremely limited, so that once iron is introduced into the body it tends to be retained. In an average daily diet there is approximately 10-15 mg. of iron. About 10% of this is normally absorbed and at this level iron balance can usually be maintained adequately. An absorption of 20-30% (i.e. 3-5 mg. daily) is therefore enough to lead to the accumulation of iron in the body. Such an absorption rate, maintained over 30-50 years, will lead eventually to a body content of between 20 and 60 g.[7] This is of the magnitude found in idiopathic haemochromatosis. In females the situation is somewhat different since the normal loss of iron from the body *via* pregnancy, lactation and menstruation may be enough to prevent, or at least retard, the development of the disease in predisposed individuals. It is thus possible to explain partly the much lower incidence of the disease in females as compared to males (1 : 10) and the tendency for it to manifest at a later age.[2]

There seems little doubt that the pathological changes in idiopathic haemochromatosis are secondary to the iron deposits. Thus the liver, which is the chief reservoir for excess iron, eventually becomes cirrhotic, while the heavy pancreatic deposits lead to diabetes in about 80% of cases.[2] In addition the skin becomes pigmented and cardiac involvement may also occur. Endocrine damage, as manifested by loss of secondary sex characteristics, testicular atrophy and amenorrhoea, is also not uncommon. It has been suggested that these changes are due to the deposition of iron in the pituitary and other glands.[8] Although this may be the mechanism in some cases it is probably more frequently a secondary effect from the advanced liver disease.[2]

In the present case the major clinical findings were related to the endocrine and cardiovascular system. The initial symptone of amenorrhoea occurring at the age of 23 years. Unfortunately only limited endocrine function studies were carried out but the levels of follicle-stimulating hormone and 17 ketosteroids were low. These findings were certainly compatible with pituitary damage. Four years after the onset of amenorrhoea, cardiac failure developed and the course from then on was rapidly downhill. The cardiac manifestations were very similar to those previously reported. The feature of such cases has been the occurrence of cardiac failure associated in most instances with disturbances of rhythm. Response to digitalis is usually poor and the majority of patients die within a year of the onset of cardiac symptoms.[1] It seems likely that the much higher incidence of heart failure in the younger age-group is due to the fact that the disease is present in a more acute form, with iron being absorbed and deposited at a rapid rate. Thus the damage to the myocardium is dependent not only on the degree of iron deposition, but on the rate at which it is laid down.[6] On this basis it is possible to explain why many older patients with heavy depositions of iron in the heart show no clinical evidence of myocardial damage.

It has been noted previously that idiopathic haemochromatosis is uncommon in females. This is especially true in the younger age-groups and it has been possible to find only isolated reports of cases similar to the present one.[6, 9-11] Three of these were siblings, each of whom developed amenorrhoea and cardiac failure,[11] and a brother in the same family died from the disease at the age of 27 years. The similarity to the present patient is striking, her brother also having suffered from idiopathic haemochromatosis. Although most cases occur sporadically, several reports have appeared of more than one case occurring in the same family.[2] It has also been found that about 20% of patients' relatives have serum-iron levels above normal.[2] These data suggest that the inherited bio-chemical defect which leads to idiopathic haemochromatosis is inherited as a dominant gene with incomplete penetrance.[12] Such findings underline the importance of examining the relatives of all patients manifesting the disease. In the present case it is extremely probable that adequate therapy could have been given had the diagnosis been made earlier.

In recent years a rational approach to treatment has become available. It had hitherto only been possible to give supportive treatment to damaged organs, e.g. insulin for

the diabetes. Since, however, the pathology is basically due to excessive iron in the body, the primary objective of therapy is to remove this iron.[13] It has now been shown by several groups of workers that this can be effectively achieved by repeated phlebotomies and it is often possible to remove as much as 500 ml. per week until the iron stores are depleted.[2] On this regime iron is mobilized from stores to supply the increased needs of the bone marrow. Such therapy has caused amelioration of symptoms and it seems probable that it will improve the prognosis of patients with the disease.[14] Whether it will prove helpful in cases with cardiac complication is, however, much more doubtful. Apart from the present subject the authors have treated two other young patients by phlebotomy and in neither did it seem to help. The poor results might, in fact, have been anticipated, as the total amount of iron in the heart is small, relative to that in the liver. The greater part of the mobilized iron therefore probably comes from the liver and little difference is is made to the iron content of the heart. Nevertheless, there is justification for trying the effects of repeated venesections in patients with cardiac complications as the prognosis without them is so desperate. Some support for this approach is contained in one recent report where striking improvement in cardiac function occurred in a case treated by repeated phlebotomies.[14]

Shortly before death the present patient exhibited one last feature worthy of comment. The serum-iron level was found to be 487 gamma per 100 ml. Since the total iron-combining capacity had previously been shown to be only 266 gamma per 100 ml. it appears likely that a proportion of the iron in the plasma was circulating in a form not attached to beta globulin. The most probable explanation for this would seem to be the release of ferritin into the circulation from damaged liver cells. In animal studies ferritin has been shown to be a powerful vasodepressor agent[15] and it may well have been the cause of the irreversible shock in our patient. There are only isolated reports of extreme hyperferraemia in idiopathic haemochromatosis.[16, 17] In two of these cases it was noted shortly before death, but a third patient remained well in spite of a serum-iron level of between 7,000 and 8,000 gamma per 100 ml.[17] The reason for this discrepancy is not clear. It may, however, be possible that in the third case the iron compound was inactivated by being bound onto some plasma protein.

SUMMARY

A case of idiopathic haemochromatosis occurring in a young adult female is described. The salient clinical features were amenorrhoea, skin pigmentation and cardiac failure. Response to repeated venesections was poor and the patient died within a year of the onset of the cardiac symptoms. Of special interest was the fact that the patient's brother had previously succumbed to the same disease.

The pathogenesis of idiopathic haemochromatosis is briefly discussed with special reference to cardiac involvement and genetic aspects.

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