Netherlands
The Journal of Medicine

CASE REPORT

Hypogonadism in a patient with mild hereditary haemochromatosis

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ABSTRACT

Hypogonadism is a potential complication of haemochromatosis, usually seen in patients with severe iron overload and liver cirrhosis. We describe the diagnostic workup of a patient with an early stage of hereditary haemochromatosis, presenting with only mildly elevated liver enzymes and central hypogonadism in the absence of cirrhosis or diabetes, but with concurrent sarcoidosis.

KEYWORDS

Hereditary haemochromatosis, hypogonadism, sarcoidosis, iron overload.

What was known on this topic?
Hereditary haemochromatosis is usually suspected in patients with a combination of diabetes mellitus, hepatomegaly or cirrhosis, hyperpigmentation, and arthralgias. Male patients with haemochromatosis may also suffer from hypogonadism, particularly patients with cirrhosis or severe iron accumulation.

What does this case add?
Patients with hereditary haemochromatosis without overt cirrhosis or other signs of advanced iron accumulation may still have hypogonadism. In the case of hypogonadotropic hypogonadism, MRI of the brain is able confirm the presence of iron in the pituitary gland, and differentiate iron accumulation from other causes of pituitary dysfunction.

INTRODUCTION

The classic presentation of (advanced) HFE-related hereditary haemochromatosis is a combination of diabetes mellitus, hepatomegaly or liver cirrhosis, skin hyperpigmentation, and arthralgias.[1,2] In the face of iron accumulation in several organs, patients usually present with normal haemoglobin levels.[3] We report a case of haemochromatosis presenting with anaemia and endocrine abnormalities, but without diabetes mellitus or cirrhosis. The patient was finally diagnosed with hereditary haemochromatosis and sarcoidosis, a combination that has only been described in a few cases in the literature.[1,4,5] Using magnetic resonance imaging (MRI), we were able to confirm that pituitary iron deposition caused the endocrine deficiencies. We conclude that hormonal deficiencies may also be present in patients with an early stage of haemochromatosis without signs of advanced iron accumulation, such as cirrhosis, diabetes, hyperpigmentation, or arthralgias.

CASE REPORT

A 57-year-old male with an unremarkable medical history was admitted with a six week-history of decreased appetite, nausea, and continuous abdominal pain. In addition, he reported fatigue and 10 kg weight loss. He did not smoke and consumed about two units of alcohol daily. On physical examination, his blood pressure was 107/65 mmHg with a pulse rate of 102 beats/min and a temperature of 36.7 °C. Examination of the heart, lungs and abdomen was unremarkable except for mild tenderness in the epigastric region. A few lymph nodes of up to 1 cm diameter were palpable in the cervical region, and both lower legs revealed palpable purpura. Initial laboratory investigation showed a haemoglobin of 7.8 mmol/l with an MCV of 98fl,

leucocytes 6.8 x 10^9/l, and thrombocytes of 440 x 10^9/l. C-reactive protein was 35 mg/l, aspartate aminotransferase 100 U/l, alanine aminotransferase 65 U/l, alkaline phosphatase 103 IU/l, gamma-glutamyltransferase 130 U/l, and liver and kidney function were normal. Urine analysis and a chest X-ray revealed no abnormalities.

The combination of anorexia, weight loss, lymphadenopathy, anaemia and elevated liver enzymes raised suspicion of either a metastasised malignancy or a systemic inflammatory disease. However, abdominal ultrasound and oesophagogastroduodenoscopy revealed no abnormalities, autoimmune serology (antinuclear antibodies, antineutrophil cytoplasmic antibodies, cryoglobulins, rheumatoid factor) turned out to be negative, and the vasculitis was found to be caused by a course of oral amoxicillin, and spontaneously disappeared. Surprisingly, additional laboratory tests revealed a transferrin oversaturation (>100%) with a serum ferritin of 2282 ng/ml, and an erythrocyte sedimentation rate of 96 mm/h. MRI showed extensive iron deposition in the liver (*figure 1*), and also some iron deposition in the pancreas. Eventually, the patient was found to be homozygous for the Cys282Tyr mutation, compatible with hereditary haemochromatosis type 1.

Simultaneously, 18-fluorodeoxyglucose positron emission tomography/computed tomography (18-FDG PET/CT) showed tracer-positive mediastinal and hilar lymph nodes in the thorax, and a 2 x 3 cm lymph node in the liver hilus. Subsequent blood and stool cultures did not show an infectious agent, an interferon-gamma release assay was negative for tuberculosis antigens, and serology for syphilis, viral hepatitis B and C, and HIV was negative. Cytological examination of a fine needle aspirate of the mediastinal lymph node showed noncaseating granulomas without the presence of mycobacteria. Moreover, bilateral anterior uveitis was diagnosed by a consulting ophthalmologist. The combination of these findings was compatible with a diagnosis of sarcoidosis.

In addition, hormonal tests revealed a thyroid-stimulating hormone level of 1.7 mIU/l with fT4 12.3 pmol/l, follicle-stimulating hormone 0.47 U/l, luteinising hormone 0.38 U/l, testosterone 0.55 nmol/l, insulin-like growth factor-1 45 µg/l (-2.5 SD), fasting cortisol 550 nmol/l, and an HbA1C 42 of mmol/mol. The combination of hypogonadotropic hypogonadism and growth-hormone deficiency indicated a problem in the pituitary gland, but both iron accumulation and sarcoidosis could be considered causes of pituitary dysfunction. To differentiate between these two causes, we performed an MRI of the pituitary gland, which showed the presence of pituitary iron deposition (*figure 2*), but no signs of granulomas. Finally, bone densitometry showed severe osteoporosis (T score -4.3).

The patient was discharged and started treatment with phlebotomies, which were limited due to the present anaemia. No specific treatment for the sarcoidosis was started at this stage. Testosterone suppletion was initiated, but additional testing for growth hormone deficiency was withheld, as the patient was not candidate for growth hormone suppletion. Currently, the patient's ferritin is 1269 ng/ml with haemoglobin of 8.2 mmol/l and erythrocyte sedimentation rate of 21 mm/h.

Figure 1. *Decreased signal intensity of the liver on MRI, compatible with iron deposition (>350 µmol/g liver tissue according to Yves Gandon formula)*

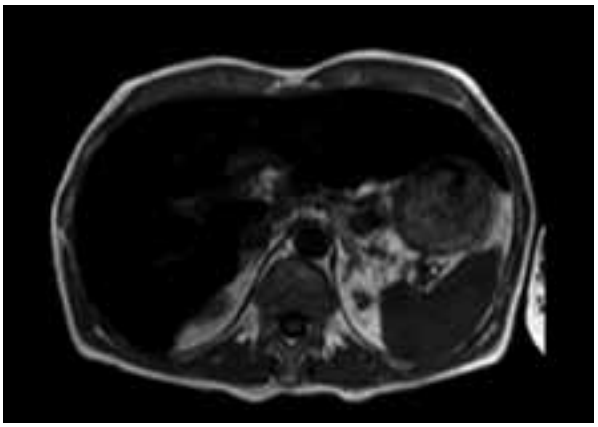
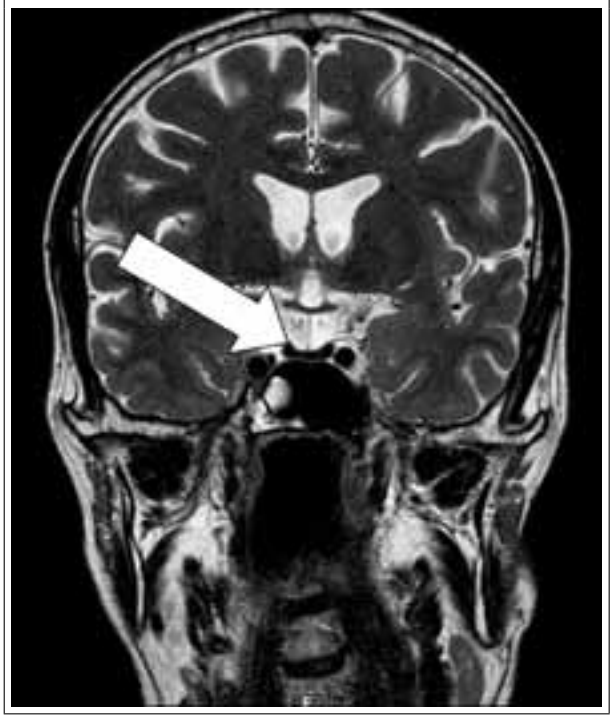


Figure 2. *Decreased signal intensity of the pituitary gland on T2-weighted MRI, compatible with iron deposition*



DISCUSSION

The present case clearly shows how the combination of three presumably independent pathophysiological processes (haemochromatosis, sarcoidosis and drug-induced vasculitis) may put the clinician on the wrong track, looking for malignancies and autoimmune diseases. Although, retrospectively, most signs of sarcoidosis are obvious in this patient, the patient's presentation of haemochromatosis is unusual, with only mild liver enzyme abnormalities, hypogonadotropic hypogonadism, and growth hormone deficiency. The co-existence of hereditary haemochromatosis and sarcoidosis has been described in a few sporadic cases,[1,5] and only once in a family: a mother and son with both haemochromatosis and hepatic sarcoidosis.[4] These studies have not shown any genetic predisposition (yet), and indicate that the co-existence of haemochromatosis and (hepatic) sarcoidosis is probably coincidental, but that this combination may increase susceptibility to cirrhosis.

Hypogonadism is the most frequent endocrine abnormality in hereditary haemochromatosis and is reported in up to 6.4% of male patients in the largest case series.[6] Although other causes such as Klinefelter's syndrome or use of androgenic anabolic steroids have also been reported,[7] hypogonadism is usually caused by iron accumulation in the pituitary gland, or sometimes in the testes. Other pituitary axes were normal in this large case series, indicating some preference of iron for gonadotropic cells.[6] Usually, patients with (central) hypogonadism also have severe (hepatic) iron accumulation and cirrhosis.

Localisation of granulomas in the central nervous system may also occur in about 10% of patients with sarcoidosis, and some case series have described granulomas in the hypothalamus and pituitary gland.[8] These lesions usually cause hypogonadotropic hypogonadism, but also failure of other pituitary axes and manifest diabetes insipidus. Most patients have multivisceral localisations and sinonasal involvement.

Our patient showed an atypical presentation with failure of two pituitary axes, without cirrhosis or diabetes, but also without severe (neurological) manifestations of sarcoidosis. Therefore, pituitary iron deposition and central granulomas were both considered possible causes of pituitary dysfunction, along with a pituitary adenoma or tumour. Eventually, MRI confirmed the presence of iron deposition in the pituitary gland and ruled out other causes. Despite its low prevalence, hypogonadism is an important complication of haemochromatosis. Testosterone replacement therapy together with phlebotomies can considerably improve the quality of life of these patients by restoring sexual function.[1,6] In addition, testosterone deficiency may have detrimental effects on bone mass and may cause mild anaemia, as shown in our case. In conclusion, we have shown that hypogonadism in haemochromatosis is an important complication that is not only confined to patients with overt signs of advanced iron accumulation. When laboratory investigations have indicated a central cause of hypogonadism, MRI may provide definitive proof of pituitary iron deposition.

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