Phlebotomies as a treatment of serious heart failure due to haemochromatosis: a case report

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Haemochromatosis is a disturbance in the iron metabolism leading to excessive accumulation of iron in various organs such as the liver, pancreas, joints, skin, pituitary, testes and heart, with the last mentioned leading to heart failure. In this report we describe a patient with serious heart failure, attributed to homozygosity for C282Y in the haemochromatosis (HFE) gene, in whom repetitive phlebotomies led to normalisation of left ventricular function. (Neth Heart J 2009;17: 438-41.)

Keywords: heart failure, haemochromatosis, phlebotomy

Cardiomyopathy is in general a late complication of ischaemic heart disease or significant valvular disease. However, it is not uncommon to see normal coronary arteries and only minor valvular heart disease, hence categorised as idiopathic cardiomyopathy.

Hereditary haemochromatosis (HHC) is a common genetic disorder of iron metabolism characterised by increased absorption of dietary iron from the gastro-

intestinal tract. This condition leads to excessive iron accumulation in various organs. The fact that a number of these patients, in whom haemochromatosis is initially overlooked, may develop congestive heart failure is illustrated by the presented case.

Case report

A 54-year-old, non-smoking man had progressive dyspnoea without chest pain. His weight had increased by 7 kg in the last three weeks. His mother had suffered a myocardial infarction at the age of 60 years. He had a three-year history of hypogonadotropic hypogonadism and adult-onset type insulin-dependant diabetes mellitus.

At physical examination he was moderately dyspnoeic and had a respiratory frequency of 24 breaths/min, a blood pressure of 107/70 mmHg and a heart rate of 90 beats/min. The peripheral oxygen saturation was 88% in outer air and his body temperature was 36.9°C. The central venous pressure was elevated. The heart sounds were normal and no murmurs were heard and the lungs revealed basal crepitations. The liver was not enlarged and only slight pitting oedema was present at the lower extremities.

The electrocardiogram is presented in figure 1. Arterial blood gas analysis, haematology and blood chemistry are presented in table 1. The X-ray of the thorax showed a right-sided pleural effusion, cardiomegaly and pronounced pulmonary artery vessels. Pulmonary ventilation scan showed two segmental defects in the right mid and lower lung, highly suggestive of pulmonary embolism. In addition, echocardiographic evaluation showed a poor systolic left ventricular function (left ventricular end diastolic/systolic diameters: 52 and 49 mm, respectively), without signs of hypertrophy, a moderate right ventricular function (tricuspid annular plane systolic excursion (TAPSE) 12 mm) and a moderate mitral and tricuspid valve regurgitation. The atrial dimensions were normal. Low-molecular-weight heparin (LMWH), oxygen, diuretics and ACE inhibitors were started. A multigated acquisition scan (MUGA) showed a left ventricular ejection fraction of 16%. The coronary angiogram was normal.

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Figure 1. ECG of this patient at presentation.

Because of coexisting diabetes mellitus and hypogonadotropic hypogonadism, which are well-known endocrine features of iron storage disease, haemochromatosis was suspected and confirmed by a highly elevated serum ferritin of 8547 µg/l (normal values 30 to 300) with an increased serum iron of 34.6 µmol/l (normal values 10.0 to 30.0) and increased transferrin saturation index of 92% (normal values 20 to 40). Further, magnetic resonance imaging (MRI) of the liver (T2 weighted, 1.5 Tesla) confirmed excessive iron storage by an increased liver/muscle intensity ratio of 0.19, corresponding with 0.54 mmol iron per gram

liver, which is highly predictive for haemochromatosis¹ (figure 2). DNA confirmed primary haemochromatosis: homozygosity for C282Y mutation of the HFE gene. Regular phlebotomies were started after which his serum ferritin decreased to 31 µg/l and heart function

Table 1. Arterial blood gas analysis, haematology and blood chemistry.

Arterial blood gas analysis

PH	7.43	(7.35-7.45)
PCO ₂ (KPa)	5.0	(4.6-6.0)
PO ₂ (KPa)	7.1	(9.5-13.5)
Bicarbonate (mmol/l)	24.2	(21.0-25.0)
Oxygen saturation (%)	88	(96-100)

Haematology

Haemoglobin (mmol/l)	8.7	(8.7-10.6)
Leucocyte count (x 10 ⁹ /l)	7.1	(4.0-10.0)
Platelet count (x 10 ⁹ /l)	228	(150-350)

Blood chemistry

Sodium (mmol/l)	130	(132-144)
Potassium (mmol/l)	4.5	(3.6-4.8)
Creatinine (mmol/l)	126	(62-10)
Alkaline phosphatase (U/l)	102	(12-120)
Aspartate aminotransferase (U/l)	89	(0-40)
Alanine aminotransferase (U/l)	61	(0-30)
γ-glutamyltransferase (U/l)	29	(0-65)
Glucose (mmol/l)	9.1	(4.0-5.4)
Creatine kinase (U/l)	66	(0-50)
Myocardial band (U/l)	6	(0-10)
Troponin (µg/l)	0.49	(0.00-0.04)
d-dimer (ng/l)	5727	(0-500)

Normal values given in brackets.

Figure 2. MRI of the liver (T2 weighted, 1.5 Tesla), showing a liver/muscle intensity ratio of 0.19. This corresponds with 0.54 mmol iron per gram liver.

Figure 3. Effect of phlebotomy on ferritin (—□—) and left ventricular ejection fraction (LVEF) measured with MUGA.

improved remarkably to a left ventricular ejection fraction to 46% after two years of treatment (figure 3).

Discussion

Although cardiomyopathy in the absence of coronary and/or valve disease is often categorised as idiopathic, other diseases, which are easy to diagnose, could also be the cause. In our patient, a hereditary haemochromatosis caused heart failure that improved after adequate treatment to an almost normal left ventricular function.

Symptoms

Haemochromatosis was classically described as the 'diabète bronzé', a middle-aged person with pigmented skin due to iron storage and an unknown type of diabetes, which could be complicated by liver cirrhosis and cardiac manifestations: heart failure due to deposits in the myocardium and bradyarrhythmia and tachyarrhythmia due to deposits in the conducting system. The prevalence of hereditary haemochromatosis was increased in a recent series of patients with dilated cardiomyopathy (DCM).^{2,3} Atrial fibrillation described in idiopathic DCM patients with heterozygosity for HHC is not more common than in patients without heterozygosity for HHC (about 7 to 19%).³ Other organ manifestations as such as arthropathy, hypogonadism by a combination of primary (testicular) and secondary (pituitary) failure and diabetes mellitus were all present in our patient. The fact that the type of diabetes could not be categorised in combination with testosterone substitution for hypogonadism, was an early warning sign of a systemic disease. This only came to mind after the patient developed heart failure, as a further manifestation.

Prevalence and genetics

Hereditary haemochromatosis is one of the most common genetic disorders in European countries. Only a few case reports of HHC and cardiac complications have been described,^{4,7} which is remarkable because one in 300 healthy persons has homozygosity for C282Y mutation in the HFE gene and thus approximately one out of ten is a carrier of this defect. In the vast majority of patients with HFE-related hereditary haemochromatosis, it is due to C282Y or H63D mutation.⁸⁻¹⁰ Other mutations leading to hereditary haemochromatosis in the HFE gene and non-HFE-related genes are rare. Secondary causes involving iron overload are mentioned in table 2.

Diagnosis

Initial screening includes determination of ferritin and transferrin saturation (TS). A normal TS ($\leq 45\%$) in combination with a normal ferritin ($\leq 400 \mu\text{g/l}$) almost excludes haemochromatosis.¹¹ When ferritin exceeds $400 \mu\text{g/l}$ in combination with a TS of more than 45%, further DNA research on the HFE gene is recommended as 90% of haemochromatosis patients are carriers of a HFE-gene mutation. If homozygosity for

Table 2. Classification of iron overload.

Hereditary haemochromatosis

Classic hereditary haemochromatosis: HFE protein (Type I)
Juvenile haemochromatosis: haemojuvelin (Type IIa),
Hepcidin (Type IIb)
TfR2 haemochromatosis (Type III)
Ferroportin disease (Type IV)
Hereditary hyperferritinaemia (Type V and VI)

Secondary iron overload

Haematological

- β -Thalassaemia
- Sideroblastic anaemia
- Chronic haemolytic anaemia

Dietary iron overload

Chronic liver disease

- Chronic viral hepatitis B and C
- Alcohol-related liver disease
- Non-alcoholic steatosis hepatitis
- Porphyria cutanea tarda

Transfusional iron overload

Miscellaneous

- African iron overload
- Neonatal iron overload
- Aceroplasminaemia

Figure 4. Diagnostic diagram in suspicion for haemochromatosis.

the C282Y or heterozygosity for C282Y and H63D is found, the diagnosis of primary hereditary haemochromatosis is certain (figure 4). Magnetic resonance imaging (MRI) of the liver is recommended if the aforementioned gene defects are not found. MRI is an accurate method for non-invasive measurement of iron concentration in the liver. The liver/muscle signal intensity ratio is inversely related to the hepatic iron concentration.¹ If the MRI is suggestive of haemochromatosis further DNA research is warranted to look for other HFE-related, non-HFE-related genes and secondary causes of iron overload. Liver biopsy is seldom necessary to confirm the diagnosis.¹²

Treatment

The primary treatment of haemochromatosis is mobilisation of iron stores by regular phlebotomy weekly until the ferritin is <50 µg/l.⁴⁻⁷ This will halt the progression of future organ failure, which is also considered for the heart.^{13,14} This treatment can sporadically lead to regression of heart failure. If iron mobilisation treatment fails and serious heart failure remains, a heart transplantation might be a reasonable option.¹⁵ ■

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