SEVERE HEREDITARY HEMOCHROMATOTIC CARDIOMYOPATHY RESPONSIVE TO SMALL-VOLUME VENESECTIONS COMBINED WITH DEFEROXAMINE

Tariq A. A. Madani, FRCPC; Janis Bormanis, FRCPC

Several reports of patients with mildly to moderately severe hereditary hemochromatotic cardiomyopathy (HC) that responded well to venesections have been published. [1-7] There is, however, no emphasis in the literature on the potential of even the most severe HC to respond as well to venesections, and on the advantage of combining iron-chelation therapy with small-volume venesections in the initial treatment of such patients who are usually unable to tolerate large-volume venesections.

We report two cases of severe hereditary HC that responded remarkably well, and are currently leading a normal life off all cardiac medications, following small-volume phlebotomies for a combination of two years, in the first three and six months of treatment, with subcutaneous deferoxamine. The first case presented with a cardio-embolic stroke, a unique presentation of HC that has not been previously reported.

Case 1

A 36-year-old male engineer presented to the Ottawa Civic Hospital with a three-hour history of confusion, expressive aphasia and right hemiparesis. He had been on erythromycin for a flu-like illness in the preceding five days. He had noticed mild pedal edema during the preceding two months, with no other symptoms of heart failure. The patient had never smoked or drunk alcohol in excess. Three years earlier he had been diagnosed as having isolated hypogonadotrophic hypogonadism, for which he had been receiving monthly injections of testosterone. Four months prior to presentation the patient was diagnosed as having insulin-dependent diabetes mellitus. There was no family history of hemochromatosis.

Physical examination revealed a conscious but inattentive patient with aphasia, a tanned bronze clammy skin, a pulse rate of 102 beats/minute with frequent ectopics, a blood pressure of 120/80 mmHg, a respiratory rate of 22 breaths/minute, and a temperature of 36.7 °C. He had no stigmata and a jugular venous pressure of 4 cm above the sternal angle. A gallop rhythm with a loud third heart sound was audible on cardiac auscultation, but no heart murmurs. Chest examination revealed bilateral stony dullness with no crepitations. The abdomen was soft with no organomegaly or ascites. The patient had expressive aphasia, right facial droop and right hemiparesis of 4/5 power and an extensor right plantar reflex. Fundal examination was normal.

Investigations included hemoglobin 149 g/L, white blood count 9.8×10^9/L, platelets 230×10^9/L, serum iron 26 μmol/L (N:5-25), ferritin 5213 μg/L (N:22-447), TIBC 31 μmol/L (N:42-71), transferrin saturation 84% (N:20-45), moderately elevated liver enzymes, normal total proteins, albumin, and prothrombin (PT) and activated thromboplastin (PTT) times, normal T_4 and TSH, negative rheumatoid factor, antinuclear, anti-Sm, anti-RNP, anti-La and anti-Ro antibodies. ECG showed sinus tachycardia, left axis deviation of -30, left atrial enlargement, poor R-wave progression, nonspecific T-waves changes and no Q-waves. Chest x-ray showed bilateral pleural effusion, mild cardiomegaly and no signs of pulmonary edema. Computerized tomography (CT) scan of the brain showed a hypodensity extending through the insula and a small segment of the posterior frontal region of the sylvian fissure on the left with gray and white matter involvement.

A diagnosis of congestive heart failure with cardio-embolic left hemispheric stroke was made. A few hours after admission to the hospital, the patient developed florid pulmonary edema and worsening of his right hemiparesis. Echocardiogram revealed a dilated left ventricle with severe global hypokinesia and an ejection fraction of 15%. A transesophageal echocardiogram two days later showed a left ventricular apical thrombus and severe tricuspid regurgitation. The patient was therefore fully anticoagulated and was treated with diuretics and captopril. When the iron study results became available, CT scan of the liver was undertaken. This showed hyperdensity of the liver with a CT attenuation measuring 85 to 90 Hounsfield Units consistent with

From the Basic Sciences Building, Winnipeg, Manitoba (Dr. Madani) and the Ottawa Civic Hospital, Ottawa, Ontario (Dr. Bormanis).

Address reprint requests and correspondence to Dr. Bormanis: Ottawa Civic Hospital, 1053 Carling Avenue, Ottawa, Ontario, Canada K1Y 4E9. Accepted for publication 9 July 1996. Received 26 February 1996.

hemochromatosis. Liver biopsy was not done because the patient was anticoagulated. The clinical, biochemical and liver CT scan features were deemed adequate to establish a diagnosis of hereditary hemochromatosis causing severe cardiomyopathy that had resulted in a cardio-embolic stroke. The patient was treated with a 250 cc phlebotomy every week, combined with daily subcutaneous infusion of 3.5 gm of deferoxamine. The patient had some improvement of his cardiac failure and neurological deficits during the 20 days of hospitalization, after which period he was transferred to a rehabilitation center. After three months of combined therapy, his serum ferritin level decreased to 1463 μg/L. Deferoxamine was then discontinued and the volume of the phlebotomy was gradually increased to 400 cc per week. The patient continued to improve. Three months later the serum ferritin was down to 750 μg/L and the patient had an ejection fraction of 50%, with a normal left ventricular size. At the end of the first year, he was taken off all cardiac medications, namely captopril, furosemide and coumadin. After 18 months of treatment and an estimated iron loss of 12 g, serum ferritin was down to 51 μg/L and the left ventricular size and function were normal, with an ejection fraction of 70% on echocardiogram. The patient has since been on phlebotomy three times per month to prevent iron reaccumulation. The right hemiparesis and expressive aphasia had almost completely resolved and the patient was back to work, enjoying a normal life on insulin and a monthly injection of testosterone.

Case 2

A 42-year-old male outdoor physical instructor presented to the emergency room of the Ottawa Civic Hospital with a two-day history of dyspnea on minimal exertion, progressing to dyspnea at rest, orthopnea, and right hypochondrial pain. He was diagnosed as having idiopathic congestive cardiomyopathy for three months, and insulin-dependent diabetes mellitus and pancreatic insufficiency for six months prior to presentation to another hospital. He also had a 10-year history of hepatomegaly and arthritis of the 2nd and 3rd metacarpophalangeal joints, and lately of the shoulder and knee joints, as well. There was no history of hypertension or hyperlipidemia. He had stopped smoking 20 years before presentation. He drank alcohol in small to moderate amounts and had no family history of hemochromatosis.

Physical examination revealed a bronze skin complexion, moderate respiratory distress, an irregularly irregular pulse of 110 beats/minute, and a blood pressure of 90/70 mmHg. He had no stigmata of chronic liver disease. Jugular venous pressure was elevated 12 cm above the sternal angle. A gallop rhythm with 3rd and 4th heart sounds without any murmurs were audible. Chest auscultation revealed bilateral basal fine crepitations up to the mid-scapulae. The liver edge was 4 cm below the costal margin with a span of 19 cm. The rest of the physical examination was normal.

Laboratory investigations included hemoglobin 133 g/L, white blood count 6.4×10^9/L, platelets: 94×10^9/L, serum iron 31 μg/L (N:5-25), ferritin 3192 μg/L (N:22-447), TIBC 37 μg/L (N:42-71), transferrin saturation 79% (N:20-40), glucose 24.2 mmol/L, normal PT, PTT, albumin, liver enzymes, total bilirubin, cholesterol, triglycerides, urea, and creatinine. ECG showed atrial fibrillation, left axis deviation of -70, generalized flattening of T-waves with T-wave inversion in L_1, aVL, V_4, V_5 and V_6. Chest x-ray showed cardiomegaly and moderate pulmonary edema. Echocardiogram showed dilatation of both ventricles and both atria, an ejection fraction of 17%, and normal valves. Liver biopsy showed excessive iron deposition and Laënnec's cirrhosis.

The patient was admitted to the hospital and was treated with furosemide, captopril, digoxin, quinidine and coumadin. The patient had some symptomatic improvement, particularly after reverting to sinus rhythm. After establishing the diagnosis of hemochromatosis, an attempt at a 400 cc phlebotomy caused marked weakness in the patient. He was therefore treated with a smaller volume (300 cc) phlebotomy weekly in combination with deferoxamine 3 g subcutaneous infusion overnight daily. The patient was discharged 24 days after admission in stable condition. He was subsequently readmitted three times in a two-month period because of severe congestive heart failure and intermittent atrial fibrillation.

He was, therefore, enrolled in the urgent cardiac transplantation waiting list. Subsequently, however, the patient started to improve steadily. Four months after treatment with phlebotomies and deferoxamine, the ejection fraction increased to 37% and serum ferritin decreased to 2130 μg/L. After completing six months of treatment, deferoxamine was stopped, phlebotomy was increased to 400 cc per week, and the patient was gradually taken off all his cardiac medications, namely furosemide, captopril, digoxin and coumadin. The patient continued to improve and by the end of the first year, his exercise tolerance was virtually normal, being able to walk several miles daily and swim 5000 yards weekly; the ejection fraction was up to 45% and the ferritin was down to 175 μg/L. He is presently enjoying a normal active life on daily insulin and a 400 cc phlebotomy every other month.

Discussion

Hemochromatosis is an autosomal recessive hereditary disorder of iron metabolism characterized by excessive intestinal absorption of iron with subsequent deposition in

various body tissues and organs, leading eventually to their damage and functional failure. The liver, pancreas, pituitary gland and heart are the organs most commonly involved. One-third of untreated patients with histologically proven hemochromatosis die of congestive heart failure.[8]

The removal of iron by repeated phlebotomy for the treatment of hemochromatosis has substantially increased the five-year survival rate from 33% to 89%, and if instituted before organ damage has occurred, the survival may not be different from the normal population.[9] Buja et al.[10] suspected that iron deposition in the heart occurs after the other organs have been saturated with iron. Reversal of cardiac function by iron removal suggests that the cardiac impairment, at least in the early stages, is a result of a direct local cardio-depressant effect of excessive myocardial iron rather than an irreversible myocardial damage or fibrosis.[2] The mechanism by which iron deposition impairs the cardiac function is not known, but the degree of impairment seems to be directly related to the amount of iron deposited in the myocardium. We postulate the presence of a myocardial iron threshold, above which functional impairment would be clinically evident with subsequent rapid deterioration. Iron may thus deposit in the myocardium without any clinically demonstrable deleterious effect, as long as this postulated myocardial iron threshold has not been exceeded. This may explain the clinically-proven erroneous conclusion of Macdonald and Mallory,[11] and Keschner,[12] that iron deposition in the heart does not cause heart failure. The myocardial vulnerability to iron deposition may also be affected by such factors as excessive alcohol intake and coronary artery disease.

The first case reported here presented with a cardioembolic stroke, a unique presentation of hemochromatosis that has not been previously reported. These two cases with very severe HC clearly demonstrated excellent response to small-volume (200-300 cc) phlebotomies combined with a chelating agent in the first three and six months of treatment. We conclude that severe heart failure due to HC is a reversible disease if diagnosed and treated early.

References

1. Krumholz HM. Congestive heart failure in a middle-aged man. Hospital Practice 1990;25:63-66.
2. Rivers J, Garraby P, Robinson W, Murphy A. Reversible cardiac dysfunction in hemochromatosis. Am Heart J 1987;113:216-7.
3. Dabestani A, Child J, Henze E, et al. Primary hemochromatosis anatomic and physiologic characteristics of the cardiac ventricles and their response to phlebotomy. Am J Cardiol 1984;54:153-9.
4. Candell-Riera J, Lu L, Seres L, et al. Cardiac hemochromatosis: beneficial effects of iron removal therapy; an echocardiographic study. Am J Cardiol 1983;52:824-9.
5. Short EM, Winkle RA, Billingham ME. Myocardial involvement in idiopathic hemochromatosis; morphologic and clinical improvement following venesection. Am J Med 1981;70:1275-9.
6. Skinner C, Kenmure ACF. Hemochromatosis presenting as congestive cardiomyopathy and responding to venesection. Br Heart J 1973;35:466-8.
7. Easley RM, Schreiner BF, Yu PN. Reversible cardiomyopathy associated with hemochromatosis. N Engl J Med 1972;287:466-88.
8. Finch SC, Finch CA. Idiopathic hemochromatosis, an iron storage disease. Medicine (Baltimore) 1955;34:381-430.
9. Neiderau C, Fischer R, Sonnenberg A, Stremmel W, Trampisch HJ, Strohmeyer G. Survival and causes of death in cirrhotic and in noncirrhotic patients with primary hemochromatosis. N Engl J Med 1985;313:1256-1262.
10. Buja LM, Roberts WC. Iron in the Heart, Etiology and Clinical Significance. Am J Med 1971;51:209-221.
11. MacDonald RA, Mallory GK. Hemochromatosis and hemosiderosis: study of 211 autopsied cases. Arch Int Med 1960;105:686-700.
12. Keschner HW. The heart in hemochromatosis. South Med J 1951;44:927-930.