Reversal of cardiac complications by deferiprone and deferoxamine combination therapy in a patient affected by severe type of juvenile hemochromatosis (JH)

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Brief Report

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Abstract
Juvenile hemochromatosis (JH) is a rare autosomal recessive disorder of iron metabolism, genetically heterogeneous. In JH symptomatic organ involvement occurs as early as the second decade of life. Heart failure and/or arrhythmias are the most frequent causes of death. Phlebotomy is the safest, most effective, and most economical therapeutic approach in hemochromatosis patients but is not indicated during the treatment of a severe congestive heart failure with an unstable hemodynamic status. The treatment of iron overload in these prohibitive clinical situations has to be carried out using iron chelators. We report a case of heart failure in the setting of unrecognized juvenile hemochromatosis successfully treated by the simultaneous administration of Deferoxamine and Deferiprone. To our knowledge’s, this is the first patient affected by JH treated with combined chelation regimen.
Introduction
Juvenile hemochromatosis (JH) is a rare autosomal recessive disorder of iron metabolism, genetically heterogeneous: most families are related to the recently cloned hemojuvelin gene and a small subset of JH patients was shown to harbor mutations in the HAMP gene encoding hepcidin antimicrobial peptide that modulates intestinal iron absorption. The HAMP gene is located at chromosome 19q13. HAMP mutations are associated with a new type of severe juvenile hemochromatosis not related to chromosome 1q.1-3 Total hepcidin deficiency resulting in increased iron export to plasma, characterizes the severe iron overload of JH.
In JH, symptomatic organ involvement occurs as early as the second decade of life. Although liver involvement is a constant feature in genetic hemochromatosis, diabetes, hypogonadotrophic hypogonadism, cardiomyopathy, arrhythmias, and heart failure are far more frequent in JH than in the adult-onset form. The progression of this disease is rapid and, left untreated, heart disease may be evident by age 20-30 years, possibly resulting in death in the absence of heart transplantation. Heart failure and/or arrhythmias are the most frequent causes of death.4,5

We report a case of heart failure in the setting of unrecognized JH successfully treated by the combination of Deferoxamine (DFO) and Deferiprone (DFP).

Case Report
A 29-year-old man was admitted to intensive care unit because of cardiac failure. He lived in Albania until two months before admission when he came to Italy joining his brothers and to search for the cause of his infertility. He had been well until few days before admission when he began to notice fatigue, malaise, nonproductive cough, and progressive dyspnea.
A chest X-ray showed cardiomegaly. A two-dimensional heart ultrasound demonstrated the presence of a dilated cardiomyopathy with profound global left ventricular hypokinesis and ejection fraction of 25%. A mild increase of pulmonary arterial pressure was also detected. Shortly after admission, the patient developed atrial fibrillation. He was treated by diuretics, ACE-inhibitors and amiodarone and was started on anticoagulation with intravenous heparin followed by warfarin therapy.
Hematologic findings included a hematocrit of 38 percent, a hemoglobin concentration of 13 g/dL, a mean corpuscular volume of 91 fL, and a mean corpuscular hemoglobin value of 35 pg. Platelets were 44 x 10⁹/L and leucocytes 2.1 x 10⁹/L. Blood tests revealed the
following results: total bilirubin, 90 mg per deciliter (conjugated bilirubin, 10); aspartate aminotransferase, 132 U/L; alanine aminotransferase, 216 U/L; γ-glutamyltransferase, 79 U/L; alkaline phosphatase, 125 U/L; serum ferritin, 3773 ng/ml (normal, 15 to 250); serum transferrin saturation, 100 percent; and serum iron, 147 mcg/dl (normal, 59 to 158). Non transferrin bound iron (NTBI), evaluated by chromatographic method, was 4.91 µmol/l (normal individuals always have negative NTBI values). Glucose tolerance was normal.

The patient complained of loss of libido and decreased sexual potency since few months. Basal serum testosterone was low (<0.45 pg/ml, normal values: 8.8-27 pg/ml) as were FSH <0.1 mU/mL (normal range 0.7-11.1) and LH 0.1 mU/mL (normal range 0.8-7.6) showing pituitary hypogonadism. On physical examination there was hepatosplenomegaly. Abdominal ultrasonography showed marked liver enlargement and a portal vein diameter of 14 mm. On a sagittal ultrasonogram, the spleen measured 19.0 cm in the long dimension. No signs of portal hypertension at esophagogastroduodenoscopy were detected.

Acquired causes of iron overload were excluded (haemolytic anemias, thalassemia, blood transfusions) thus a genetic hemochromatosis was hypothesized. HFE analysis revealed a wild type genotype. Hepcidin gene was characterized and a homozygous C → T mutation was identified in exon 3 leading to a arginine substitution at position 56 with stop codon (R56X). No mutations were detected in TFR2, ferroportin, and hemojuvelin gene (Fig 1a). Parents were heterozygous carriers of the hepcidin (HAMP) mutation as were two brothers (Fig 1b). All had normal iron parameters.

Because of severe iron overload he was started on intensive iron chelation. Approval was obtained from the Ethical committee of the University of Milan, institutional review board for these studies. Informed consent was provided according to the Declaration of Helsinki, and the patient was started on combined chelation treatment with DFO and DFP (DFO ev 30mg/Kg/day and oral DFP 75mg/Kg/day in 3 administrations).

After 3 weeks of intensive chelation a marked clinical and biochemical improvement was observed: at echocardiography ventricular diameters normalized and ejection fraction raised to 40%. Anticoagulation was stopped. The chelation regimen was changed by pump subcutaneous infusion of DFO (20 mg/kg/d for 6 d/wk) maintaining oral DFP. Chorionic gonadotropin treatment (2000-3000 U/wk) was started.

Oral DFP was stopped after two months and DFO was continued until ferritin serum values decreased to 480 ng/ml (5 months), then phlebotomy treatment was started. The LVEF improved from 25% to 49% during pharmacological iron chelation and it remains
stable after a follow-up of 10 months (Figure 2). His arrhythmia disappeared and did not recur even after the antiarrhythmic drug was discontinued.

Blood counts became normal except for a persistent mild leuko and thrombocytopenia (3.20 x 10^9/L and 82 x 10^9/L); liver function tests were normal with an aspartate transaminase of 28 U/L and an alanine transaminase of 30 U/L. Abdomen ultrasonography did not show any changes in hepato-splenomegaly.

At follow-up after 5 months, testosterone concentration was partially restored with a basal serum value of 3,80 pg/ml (normal values: 8.8-27 pg/ml), then testosterone replacement was started with a return of normal sexual function, a significant improvement of the quality of life and an important effect on muscle mass and bone mineral density.

When the patient was admitted, hearth MRI T2* measurements to assess myocardial iron was not yet available at our center, however the dark tissue signal of heart was evaluated at begining and at the end of combined intensive chelation showing significant changes of signal intensity.

**Discussion**

Phlebotomy is the safest, most effective, and most economical therapeutic approach in hemochromatosis patients but is not indicated during the treatment of a severe congestive heart failure with an unstable hemodynamic status. The treatment of iron overload in these prohibitive clinical situations has to be carried out using iron chelators.

At present the 3 available iron chelators are Deferoxamine mesylate (Desferal®, Novartis), Deferiprone (Ferriprox®, Apotex) and Deferasirox (ICL670, Exjade®, Novartis).7 The major component of iron removed in iron-loaded patients by subcutaneous or intravenous DFO is thought to be NTBI iron. The liver is the organ more affected by DFO chelation, whereas other organs such as the heart are also gradually depleted of iron during DFO provided the patients can tolerate higher and continuous administration. The DFO efficacy in preventing early death from iron-induced cardiac disease and in reversing established cardiac disease especially when given continuously or ev have been extensively documented in transfusion-dependent thalassemia patients. 8-10 Although cardiac disease continues to occur and remains the most common cause of death in those patients.11 Studies in iron-loaded rat heart cells and in gerbils 12 had in the past shown the ability of DFP to remove iron from myocardial cells at concentrations that can be achieved in the circulation. DFP is smaller and more lipophilic than DFO, and therefore it could be more efficient than DFO in accessing intracellular chelatable iron.
Patients with thalassemia major switched to deferiprone therapy had a remarkably lower prevalence of cardiac disease and cardiac death than patients chelated with DFO only.\textsuperscript{13,14} Moreover combined therapy with DFO and DFP induced significant improvement in cardiac siderosis and function in those patients.

A number of \textit{in vitro} and \textit{in vivo} studies have suggested that the simultaneous use of DFO and DFP is associated with an additive or even synergistic iron excretion in patients with thalassemia major, and that combined therapy could decrease iron overload in patients who had previously been unable to achieve a satisfactory response to deferiprone or desferrioxamine alone.\textsuperscript{15} The basis for this effect could be explained by the fact that DFP easily enters cells and is subsequently able to transfer the intracellularly chelate iron to DFO in plasma.\textsuperscript{16}

Few data are available on pharmacological iron chelation in patients with GH.\textsuperscript{17}

In our patient affected by severe type of JH, we obtained the reversal of cardiac complications by DFP and DFO simultaneous administration. The aggressive pharmacological treatment was essential to induce a regression of myocardial dysfunction in a very short time, which was associated with an improvement in clinical status. To our knowledge’s, this is the first patient affected by JH treated with combined chelation regimen.

In JH patients with a poor prognosis because of the development of cardiac complications, a combination of an intense DFO treatment and oral DFP could appears to be rapid, effective and non toxic in reversing iron cardiac toxicity.
References


Figure 1 – a. Sequence chromatographs of the HAMP gene region spanning the 166C→T mutation (forward sequence show) from the indicated individuals - b. Pedigree of family carrying the R56X

a

Wild type
(Sibling 1)

Homozygous 166C→T
(Proband)

Heterozygous 166C→T
(Sibling 4)

b

Father

Mother

S1  S2  S3  S4  Proband  S5  S6
Figure 2 - Echocardiographic findings during treatment and follow-up

- **Deferoxamine** iv 30mg/kg/d
- **Deferiprone** po 75mg/kg/d

**Left ventricular end-diastolic volume**
- Day 1: 148 ml
- Day 23: 119 ml
- Day 49: 94 ml

**Ejection fraction**
- Day 1: 40%
- Day 23: 40%
- Day 49: 49%

**Serum Ferritin**
- Day 1: 3773 ng/ml

**NTBI**
- Day 1: 4.91 µmol/ml

**Days of treatment**
- 1 5 9 13 17 21 25 29 33 37 41 45 49

**Weeks of follow up**
- 17 23 33 44
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