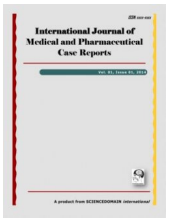

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Hereditary Juvenile Haemochromatosis and Idiopathic Dilated Cardiomyopathy

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Authors' contributions

This work was carried out in collaboration between all authors. Authors FD and AZ wrote the draft of the manuscript. Author FG managed the literature searches. Authors RC and AD designed the figures, managed literature searches and contributed to the correction of the draft. Author MMC provided the case, the figures and supervised the work. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Hereditary hemochromatosis (HH), a common autosomal recessive disease, is characterized by excessive iron overload/toxicity in multiple organs (joints, liver, heart, pancreas, pituitary, adrenals and skin). Symptoms and signs depend upon the location of the excess iron deposition. Dilated cardiomyopathy is a typical complication of HH. Juvenile haemochromatosis is a rare disorder of iron metabolism with clinical manifestations before 30 years of age. Two common mutations of the haemochromatosis associated gene (HFE), cys282tyr (C282Y) and his63asp (H63D), have been implicated in the HH. These genes also appear to be modulators in cardiovascular disease. In fact the HFE gene defects are related to idiopathic dilated cardiomyopathy (IDCM) in some patients, even though the results of genotype analyses were conflicting. In this case report we investigate a 21 year-old male patient affected by juvenile haemochromatosis associated with heterozygosity for the H63D mutation with an idiopathic dilated cardiomyopathy.

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1. INTRODUCTION

Hereditary hemochromatosis (HH) is a common autosomal recessive disease characterized by an abnormal iron accumulation in multiple organs, including the heart [1]. Over time the abnormal iron uptake may cause organ failure. It is therefore not surprising that cardiomyopathy is one of the most severe complications of HH. The HFE gene defects have been related to idiopathic dilated cardiomyopathy (IDCM) in some patients, even though the results of genotype analyses were contradictory [1].

Myocardial siderosis was present in 33% of newly presenting genetically confirmed HFE-HC patients with ferritin >1000 µg/L, and was the commonest cause of reduced ejection fraction [2]. It remains to be defined if the excessive uptake of iron or immunological processes contribute to the pathological mechanisms of IDCM [3].

Two missense mutations (C282Y and H63D) seems to be responsible for the majority of cases of HH. The first is a cysteine/tyrosine aminoacids substitution at position 282 (C282Y) and the second is a histidine/aspartate substitution at position 63 (H53D). The highest proportion of HH related to HFE mutations is in the Northern European population [4].

The frequency of HFE H63D is increased in patients with dilated cardiomyopathy. As H63D has a relatively minor effect on iron status, the mechanism of this association may be related to immunological mechanisms [5].

Juvenile haemochromatosis is a rare congenital defect of iron metabolism. Clinical manifestations appears before 30 years of age and, unlike adult haemochromatosis which principally affects men, juvenile haemochromatosis affects men and women equally. It causes early endocrine diseases, articular disease and dilated cardiomyopathy [6].

2. PRESENTATION OF CASE

A previously healthy 21-year-old male was admitted to our cardiology Intensive Care with a two-day history of malaise, orthopnoea, oliguria, palpitations and right hypochondriac pain. The patient had no history of alcohol habitude. At the general examination there were no cutaneous stigmata of chronic liver disease, and abdominal palpation not evidenced hepatosplenomegaly. Cardiac examination showed signs of congestive heart failure. The blood pressure was in the standard. Electrocardiography confirmed sinus rhythm with some ventricular extrasystoles and signs of left ventricular hypertrophy. Transthoracic echocardiography showed biventricular dilatation with poor systolic function (LVEF: 26%) and moderate mitral insufficiency. The patient underwent further investigations for dilated cardiomyopathy at our Hospital: right ventricular biopsy revealed overt myocardial haemochromatosis with extensive iron deposition in myocytes.

Serum ferritin was 1343 ng/ml, serum iron was 380 mcg/dl, with serum transferrin iron saturation of 74% and normal serum liver-related tests apart from total bilirubin: 1.1 mg/dl (normal<1,0), alanine aminotransferase (ALT): 88 IU/l (normal <40). Subsequent serological testing for hepatitis B, hepatitis C and autoimmune liver disease was all negative. He had normal levels of thyroid stimulating hormone (TSH) and thyroid hormones (FT3, FT4), prolactin and adrenocorticotropic hormone. The patient had no signs of inflammation and inflammatory markers were normal.

Liver ultrasound scanning was normal but liver biopsy revealed severe (Grade 4) liver cell siderosis with the appearances of haemochromatosis with extensive fibrosis. Abdominal computerized tomography showed increased liver density (80 Hounsfield units, normal <75) and pancreatic atrophy.

Coronary examinations evidenced that coronary vessels were free from stenotic lesions.

The final diagnosis was 'Idiopathic dilated cardiomyopathy' and the patient was subjected to single-chamber Implantable Cardioverter Defibrillator (ICD) implantation in primary prevention, according to "2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy" [7]. Genetic testing for common mutations in the HFE gene (the gene most commonly implicated in the hereditary haemochromatosis) showed that he did not carry the C282Y mutation. He was heterozygous for

the H63D mutation. DNA sequence analysis of the haemojuvelin gene on chromosome 1 identified a single base substitution, changing the amino acid at codon 99 from glycine (GGG) to arginine (AGG); this missense mutation, designated p.G99R, is associated with juvenile haemochromatosis [8].

The patient received drug therapy with Bisoprolol 1,25 mg/die, Ramipril 1,25 mg/die and diuretics. He was allergic to Deferasirox, than he didn't assume chelation therapy for iron.

After six months from the implantable cardioverter defibrillator (ICD) implantation, patient underwent to electronic control of the device that showed a single episode of monomorphic ventricular tachycardia (230 bpm), treated by defbrillation theraphy. For this reason drug therapy was increased with a dose of beta-blocker (bisoprolol) from 1,25 mg/die to 2.5 mg/day.

One year after admission, patient reported an improvement of general clinical conditions: in fact he was asymptomatic for dyspnea and palpitations. He performed 24-hour dynamic electrocardiogram, that did not show any arrhythmia and a transthoracic echocardiography, that showed an improvement of LV ejection fraction (33%).

3. CONCLUSION

The purpose of this case report is to support the correlation between idiopathic dilated cardiomyopathy and HH in a heterozygous patient for the H63D mutation with a positive phenotype.

It is interesting to note that, although the patient was not in chelation therapy, he responded positively to cardiac drug therapy with beta-blockers, ACE inhibitors and diuretics.

This case underlines the importance of cardiac drug therapy in patient with HH and severe cardiac impairment.

CONSENT

All authors declare that written informed consent was obtained from the patient for publication of this case report and accompanying images.

ETHICAL APPROVAL

All authors declare that written informed consent was obtained from the patient for publication of this case report and accompanying images.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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