Case Report

A young female with bronze diabetes and cardiac failure due to juvenile haemochromatosis: A case report

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Abstract

Juvenile Haemochromatosis (JH) is a form of hereditary hemochromatosis that presents with endocrine, cardiac, and liver involvement at a young age. Here we report a case of 39-year-old female who presented with diabetes mellitus, secondary amenorrhea and dilated cardiomyopathy with Mobitz type II heart block from previously unrecognized JH. JH should be suspected in young patients who present with features of iron overload. Early diagnosis of the disease is important for proper treatment with venesection**,** which can reduce the complications and improve the outcome.

Keywords: juvenile haemochromatosis, chronic liver cell disease, cardiac failure, hypogonadism, venesection

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Introduction

Hereditary haemochromatosis (HH) is a disorder of iron metabolism characterized by excess iron absorption from the intestine and excess iron accumulation in parenchymal cells of body organs leading to multi-organ failure. HH is classified into two main categories: HFE gene-related HH and non-HEF gene-related HH. HFE gene-related HH, the most typical form seen among Caucasians, is due to a mutation in C282Y and H63D genes. Non-HEF gene-related HH is rare, and it is classified into four types: type 2A juvenile HH (hemojuvelin mutation), type 2B juvenile HH (hepcidin mutation), type 3 (mutated transferrin receptor 2 TFR2), and type 4 (mutated ferroprotein 1 gene, SLC11A3) (1).

Juvenile hemochromatosis (JH) is an autosomal recessive disorder that usually occurs in the first and third decades of life. Affected individuals usually present with cardiomyopathy, impaired glucose tolerance and hypogonadism rather than liver disease. (2) The incidence among males and females is equal (3). In Sri Lanka, only a handful of such cases have been reported. Here we report a case of JH.

Case report

A 39-year-old woman with a history of diabetes mellitus for seven years and secondary amenorrhea for five years presented to the teaching hospital Anuradhapura with NYHA class III exertional dyspnoea, orthopnoea and bilateral ankle swelling for one-month duration. In addition, she had increased fatigability, lethargy, cold intolerance and constipation. Even though she did not have any diabetes mellitus-related macrovascular or microvascular complications, her glycaemic control at presentation was not satisfactory. On examination, she was averagely built and dark-skinned. She was plethoric but not icteric. She had tachycardia with a regular pulse

rate. There were fine end-inspiratory basal crepitations in both lungs and she had pitting ankle oedema.

Regarding her investigations, the electrocardiogram showed a Mobitz type II 2nd degree heart block, and the 2D echocardiogram confirmed global left ventricular hypokinesia with an ejection fraction of 30%. We investigated the aetiology of heart failure with reduced ejection fraction. As she was dark-skinned with multiple endocrine failures, we assessed her iron stores, which revealed markedly elevated serum ferritin levels of 3127 ng/mL with high serum iron level of 215 µg/dL (37-145) and transferrin saturation of 78% (20%-50%). Liver function tests were carried out to assess the liver involvement caused by excess iron deposition, which revealed a mild elevation of aspartate transaminase (AST**)** (74 U/L) and alanine transaminase (ALT) (46 U/L) levels with reduced albumin (34 g/L) and globulin levels. Abdominal ultrasonography showed increased liver echogenicity with grade two fatty liver, but there were no features of chronic liver cell disease (CLCD). A liver biopsy was performed, which showed foci of necroinflammation of hepatic parenchyma. Iron staining (PEARL's stain) showed extensive iron deposition in the liver parenchymal cells and biliary epithelial cells (Figure 1).

The gonadal hormonal assay was carried out to assess the gonadal involvement caused by excess iron deposition, which revealed low follicular stimulating hormone (FSH) and luteinizing hormone (LH) levels (FSH 0.25 mlU/mL (1.3- 1.28), LH 0.1 mlU/mL (0.4-0.8) which is suggestive of hypo-gonadotrophic hypogonadism. Then with the suspicion of hereditary hemochromatosis, gene testing for C282Y and H63D gene mutations were carried out, and she was negative for those gene mutations. Considering the clinical presentation, patient's age, high serum ferritin levels (3000 ng/ mL), elevated transferrin saturation (78%), liver biopsy findings and 2D ECHO findings, and negative genetic testing for C282Y and H63D, we arrived at the diagnosis of juvenile hemochromatosis.

The patient was treated with venesection once a week. As the patient was in heart failure, venesection was arranged very carefully without aggravating her heart failure. Simultaneous to the venesection, an iron chelator (oral deferasirox 350 mg daily) was started. As the patient's ejection fraction was 30%, treatment for heart failure was commenced. Due to a symptomatic 2nd degree heart block, she was referred to the cardio-electrophysiologist, and a permanent cardiac pacemaker was implanted. After two months of iron chelation therapy and six cycles of venesection, her ferritin level decreased from 3167 ng/mL to 2500 ng/mL.

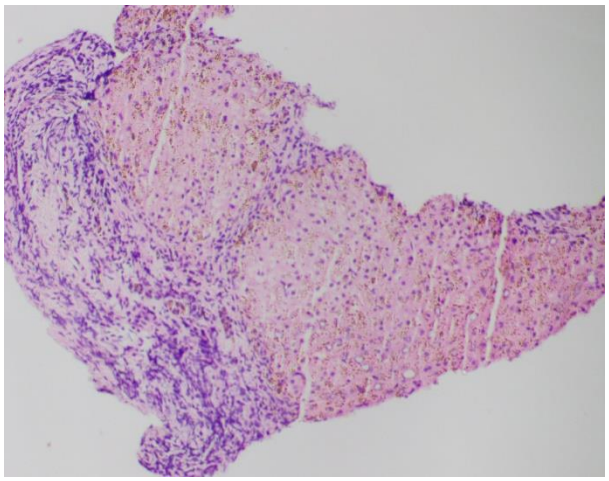

Figure 1: PEARL's stain showing extensive iron deposition in the liver parenchymal and biliary epithelial cells.

Discussion

JH is an autosomal recessive form of hereditary hemochromatosis, which is characterized by excess iron absorption from the intestine and deposition of iron in parenchymal cells in the body organs such as the liver, pancreas, gonads, thyroid, pituitary gland, heart and etc. These patients commonly present during their early 4th and 5th decades. A review suggested the average age of presentation of JH is 23.6 years (3, 4, 5). Our patient was 39-years-old when she presented to our ward, but she had diabetes mellitus since the age of 32 years and amenorrhea since the age of 35 years.

Cardiomyopathy and hypogonadism are the most frequent and earliest manifestations of JH, and the presence of cirrhosis at the initial stage is less common. Our patient had amenorrhea due to secondary hypogonadism (pituitary involvement) and heart failure due to cardiomyopathy at the presentation. However, her liver functions were minimally affected. The patient's ferritin level at the diagnosis was more than 3167 ng/mL. According to the literature, the average ferritin level at diagnosis is 3217 ng/mL. Most patients with hemochromatosis have a mutation in the HFE gene, which is found in 85-90% of patients. Others have non-HFE variants, which are rare worldwide.

JH is a life-threatening disease. Early diagnosis and appropriate treatment can reduce mortality and morbidity. When JH is suspected, iron studies with ferritin and transferrin saturation should be performed with HEF gene testing (6). A liver biopsy should be considered to confirm iron overload in patients with elevated iron saturation if the patient is negative for HFE gene mutation. The HFE2 Gly320Val is the molecular diagnostic test to confirm JH, but it is not freely

available. Therefore, JH is usually diagnosed after clinical suspicion with the help of serum biochemistry and liver biopsy results.

Venesection is still considered the treatment of choice for JH (7). If commenced sooner, it could slow down the progression of the disease, improve morbidity and reverse some of the complications**,** such as cardiomyopathy. In this patient in whom JH was suspected, on diagnosis, we initiated venesection for a better outcome, even though she had a relative contraindication for venesection: heart failure. At the diagnosis, our patient had heart failure with a reduced ejection fraction of 30%. Extra precautions were taken, and she underwent weekly isovolumic venesections. As some studies suggest the benefit of early iron chelation therapy, iron chelation with oral deferasirox at 350 mg daily was started (8). A cardiac pacemaker was inserted as the patient had developed a symptomatic 2nd degree heart block.

The patient had hypo-gonadotropic hypogonadism. Hence, hormone replacement therapy is beneficial for her, but at the moment, her current cardiac status is unsuitable to start hormone replacement therapy to prevent osteoporosis and post-menopausal symptoms. She is currently on follow-up at a medical clinic and is otherwise clinically stable**.**

Conclusion

When a young patient presents with endocrine or cardiac dysfunction with relatively spared liver function tests in the background of iron overload**,** JH should be suspected. It should be confirmed with genetic testing whenever it is available. Early treatment with regular venesection and iron chelation can reduce the complications of iron overload and improve prognosis. This case report highlights how far the quality of life and prognosis of a patient with JH could be improved if a prompt diagnosis is made and treatment is initiated.

Informed consent

The patient has given verbal and written consent to publish her history and images as a case report

References

1. Pietrangelo A. Non-HFE hemochromatosis. *Hepatology.* 2004;39(1), 21–9. DOI: 10.1002/HEP.20007
2. De Gobbi M, Roetto A, Piperno A, Mariani R, Alberti F, Papanikolaou G, Politou, et al. Natural history of juvenile haemochromatosis. *Br J Haematol.* 2002;117(4):973-9. DOI: 10.1046/j.1365-2141.2002.03509x
3. Cherfane C, Lee P, Guerin L, Brown K. A Late Presentation of a Fatal Disease: Juvenile Hemochromatosis. *Case Rep Med.* 2013;2013:875093. DOI: 10.1155/2013/875093
4. Lamon J, Marynick S, Rosenblatt R, Donnelly S. Idiopathic hemochromatosis in a young female: a case study and review of the syndrome in young people. *Gastroenterology.1*979;76(1):178-83. DOI: 10.1016/S0016-5085(79)80146-8
5. Camaschella C, Roetto A, de Gobbi M. Juvenile hemochromatosis. *Sem. Hematol.*2002;39(4):242–8. DOI: 10.1053/SHEM.2002.35635
6. Tavill AS. Diagnosis and management of hemochromatosis. *Hepatology.* 2001;33(5):1321–8. DOI: 10.1053/JHEP.2001.24783
7. Bring P, Partovi N, Ford JAE, Yoshida EM. Iron Overload Disorders: Treatment Options for Patients Refractory to or Intolerant of Phlebotomy. *Pharmacotherapy.* 2008;*28*(3):331–42. DOI: 10.1592/PHCO.28.3.331
8. Fabio G, Minonzio F, Delbini P, Bianchi A, Cappellini MD. Reversal of cardiac complications by deferiprone and deferoxamine combination therapy in a patient affected by a severe type of juvenile hemochromatosis. *Blood.* 2007;109(1):362–4. DOI: 10.1182/BLOOD-2006-04-016949