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MINIREVIEWS

- 373 Adrenal ganglioneuroma: What you need to know

Mylonas KS, Schizas D, Economopoulos KP

CASE REPORT

- 378 Hydrogen peroxide ingestion with injury to upper gastrointestinal tract

Martin JV, Sugawa C

- 381 Juvenile hemochromatosis: *HAMP* mutation and severe iron overload treated with phlebotomies and deferasirox

Lescano MA, Tavares LC, Santos PCJL

- 384 Prosthodontic management of hemimandibulectomy patients to restore form and function - A case series

Lingeshwar D, Appadurai R, Sswedheni U, Padmaja C

Contents

World Journal of Clinical Cases
Volume 5 Number 10 October 16, 2017

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Juvenile hemochromatosis: *HAMP* mutation and severe iron overload treated with phlebotomies and deferasirox

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Abstract

Juvenile hemochromatosis (JH) is a rare condition classified as an autosomal recessive disorder that leads to severe iron absorption. JH usually affects people under the age of 30 and presents symptoms such as chronic liver damage, hypogonadotropic hypogonadism, cardiac diseases and endocrine dysfunctions. The present case reports a 29-year-old Brazilian woman with JH condition due to *HAMP* mutation (g.47G>A), treated with phlebotomies and deferasirox. She presented symptoms such as weakness, skin hyperpigmentation, joint pain in the shoulders and hands and amenorrhea. First laboratory tests showed altered biochemical parameters [serum ferritin (SF): 5696 ng/mL, transferrin saturation (TS): 85%]. After sessions of phlebotomies (450 mL every 15 d), the patient presented partial symptomatic improvements and biochemical parameters (SF: 1000 ng/mL, Hb: 11 g/dL). One year later, deferasirox (15 mg/kg per day) was introduced to the treatment, and the patient showed total symptomatic improvement, with significant clearing of the skin, SF: 169 ng/mL, and TS: 50%. Furthermore, after the combined deferasirox-phlebotomy therapy, magnetic resonance imaging measurements revealed normalized level for liver iron (30 μ mol/g; reference value < 36 μ mol/g). In conclusion, combined deferasirox-phlebotomy treatment was able to normalize iron levels and improve symptoms.

Key words: Genetic disease; Juvenile hemochromatosis; *HAMP* gene; Mutation; Iron chelation

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Core tip: A 29-year-old Brazilian woman, from a city in the countryside of the State of Bahia, Brazil, was referred to our service in 2015 because of a hepatomegaly clinical condition, detected by imaging exam. This case study reports a patient with juvenile hemochromatosis condition due to *HAMP* mutation (g.47G>A) treated with phlebotomies and deferasirox, which were able to normalize iron levels and improve symptoms.

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INTRODUCTION

Juvenile hemochromatosis (JH), also known as type 2 hemochromatosis, is a rare condition classified as an autosomal recessive disorder that leads to severe iron absorption. JH usually affects people under the age of 30 and presents symptoms such as chronic liver damage, hypogonadotropic hypogonadism, cardiac diseases and endocrine dysfunctions. JH is subdivided into two groups: Type 2A (associated to *HJV* - hemojuvelin gene mutation) and type 2B (associated to *HAMP* - hepcidin gene mutation). Both genes are involved in the production of hepcidin, a peptide that regulates iron homeostasis by adjusting its absorption and storage. *HJV* and *HAMP* mutations, therefore, lead to decreased hepcidin levels, and consequently to iron overload in the body^[1-3].

CASE REPORT

A 29-year-old Brazilian woman, from a city in the countryside of the State of Bahia, Brazil, was referred to our service in 2015 because of a hepatomegaly clinical condition, detected by imaging exam. In the anamnesis, symptoms such as weakness, skin hyperpigmentation and joint pain in the shoulders and hands were observed. The patient had reported amenorrhea since she was 25 years old, whereas transvaginal ultrasound showed uterus and ovaries were not developed. She also reported that her father died before the age of 50 because of non-alcoholic cirrhosis and diabetes. Furthermore, one of her three brothers, who was 31 years old, died because of the same reported father diseases. The patient's other two brothers, on the other hand, are healthy.

The patient's first laboratory tests results were: Serum ferritin (SF) of 5696 ng/mL, transferrin saturation (TS) of 85%, hemoglobin (Hb) of 13.3 g/dL, international normalized ratio of 1.3, aspartate transaminase of 91 U/L, alanine transaminase of 69 U/L, alkaline phosphatase of 288 U/L, gamma-glutamyl transferase of 84 U/L, blood glucose of 72 mg/dL, creatinine of 0.7 mg/dL and albumin of 4.3 g/dL. Her echocardiogram was normal

and secondary causes of iron overload (hepatitis, chronic hemolysis, oral or parenteral iron overload, metabolic syndrome and alcohol abuse) were excluded. Genetic analysis for mutations in the *HFE* gene (p.C282Y, p.H63D and p.S65C) revealed a heterozygous genotype for the p.H63D. Taking in account the patient's age and the absence of relevant genetic alteration for hereditary hemochromatosis (HH), the *HJV* (exons 1-4) and *HAMP* (exons 1-3) genes were sequenced^[4], as iron overload in a young individual who presents endocrine dysfunctions is suggestive of a JH diagnosis. The *HAMP* sequencing revealed the homozygous genotype for the mutation 5'-UTR G>A at position +14 (g.47G>A), confirming the prior suspicion.

In January 2015, the patient started phlebotomies of 450 mL every 15 d. After 12 mo of treatment, there was partial improvement of weakness, skin hyperpigmentation and joint pain symptoms. In addition, the hemoglobin level was never below 11 g/dL and, despite an observed decrease in ferritin level, the values were always above 1000 ng/mL. In January 2016, deferasirox (15 mg/kg per day) was introduced to the treatment, concomitantly with the phlebotomies. No side effects were observed and the serum creatinine values remained normal. In September 2016, the patient showed total symptomatic improvement, with significant clearing of the skin, SF values of 169 ng/mL and TS of 50%. The study protocol was approved by the Ethics Committee of Hospital das Clínicas (HC) of University of São Paulo Medical School (FMUSP), Brazil, and consent was obtained from the participants prior to entering the study.

DISCUSSION

When compared with *HFE*-hemochromatosis, the frequency of the JH condition with *HAMP* gene mutation is considered very rare. However, some cases were reported^[5,6]. Here, we report one case of a Brazilian patient with JH condition due to *HAMP* mutation (g.47G>A), first identified in a Portuguese family^[7]. She presented significant improvement of symptoms through combined treatment with deferasirox and phlebotomies.

Phlebotomy is the choice treatment for hemochromatosis. However, iron chelator has been suggested as an alternative treatment option for iron overload, especially when patients have severe iron overload, did not have tolerance to phlebotomies or where it is contraindicated. The dose used in the present case report was previously evaluated in hemochromatosis patients^[8]. Cançado *et al*^[9] (2015) evaluated the efficacy and effectiveness of deferasirox (doses of 5-10 mg/kg per day) for treatment of hemochromatosis patients. They showed that chelation was safe and effective^[9].

It is possible to estimate the quantity of liver iron removed using magnetic resonance imaging (MRI) measurements (given as mg of Fe/g of liver). Santos *et al*^[10] (2010) performed a study that measured liver iron concentration before and after combined deferasirox-



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