American Journal of Clinical Case Reports

Case Report

Hereditary Hemochromatosis and Restrictive Cardiomyopathy Caused by Missense Mutation in HAMP and DSP: A Case Report

*Iokfai CHEANG[1], Shengen LIAO[1], Rongrong GAO[1], Yanli ZHOU[1], Yi XU[2], Yinsu ZHU[2] and Xinli LI[1]**

[1]Department of Cardiology, The First Affiliated Hospital with Nanjing Medical University, China

[2]Department of Radiology, The First Affiliated Hospital with Nanjing Medical University, China

Abstract

Background: The type 2 Hereditary Hemochromatosis (HH), caused by HJV or HAMP gene mutation, is an autosomal recessive disorder. HH caused by HAMP gene mutation are rarely reported in Chinese population. Herein, we reported a case with a unique inheritance pattern of HH.

Case report: An 46-year-old Chinese Han male was transferred to our center for a comprehensive evaluation of cardiomyopathy. Physical examination, ECG, Holter, Transthoracic echocardiography, and cardiac magnetic resonance indicated the diagnosis of hemochromatosis induced restrictive cardiomyopathy. Liver biopsy result further support diagnosis of Hereditary Hemochromatosis (HH). However, hereditary screening showed an untypical HH heterozygous missense mutation in HAMP:c.2T>C (HAMP:p.Met1Thr het) and DSP gene c.6309G>C (DSP:p.Lys2103Asn het).

Discussion: The compound heterozygous mutations of HAMP and DSP might represent a novel aetiological factor for HH.

Keywords: Hereditary hemochromatosis; Cardiomyopathy; Missense mutation; Case report

Background

Hereditary hemochromatosis (HH) is a disease caused by the genetic defect that leads to an abnormal systematic accumulation of iron in the cytoplasm of parenchymal cells. The clinical presentation of HH generally do not occur until after the age of 40 years in men and after menopause in women [1,2]. It is a common hereditary disease among White population [3] and the prevalence of HH in China is relatively rare. Variants on HFE, HFE2, HAMP, TFR2, SCL40A1, etc. are reported to relate with hemochromatosis. The characteristic and mode of inheritance depends on the mutant genes [4-6]. Among, HH caused by due to variants in HJV and HAMP were referred as type 2 or juvenile hemochromatosis which the symptoms usually occur at a much younger age. Juvenile hemochromatosis is an Autosomal Recessive (AR) disorder and the prevalence is extremely low in general population. Many case reports describe fatal outcomes due to delayed diagnosis and severe organ iron deposition [7,8]. Furthermore, compared with HJV gene mutation, HAMP gene mutations (type 2B HH - hepcidin gene mutation) are even rarer. It occurs more frequently in Europe and are extremely rare in Chinese population [9,10]. Herein, we report a unique case of a 46-year-old male patient with HH induced Restricted Cardiomyopathy (RCM) but with a single HAMP gene mutation and DSP mutation.

Citation: Iokfai C, Shengen L, Rongrong G, Zhou Y, Xinli LI. Hereditary Hemochromatosis and Restrictive Cardiomyopathy Caused by Missense Mutation in HAMP and DSP: A Case Report. Am J Clin Case Rep. 2020; 1(1): 1001.

Publisher Name: Medtext Publications LLC

Manuscript compiled: Feb 08th, 2020

***Corresponding author:** Xinli LI, Department of Cardiology, The First Affiliated Hospital with Nanjing Medical University, Guangzhou Road 300, Nanjing 210029, China, Tel: +86 13611573111; Fax: +86 25 68303754; E-mail: xinli3267@yeah.net

Case Presentation

In February 2019, a 46-year-old male was transferred from the local hospital with chief complaints of chest tightness, mild shortness of breath, fatigue, and bilateral lower extremity edema. He had had type 2 Diabetes Mellitus (DM) for 6 years which was managed with insulin injection. His symptoms first started after he caught "a cold" a month before admission. He first visited the primary care clinic and had a slight improvement after treatment with antibiotics. But his chest tightness and shortness of breath gradually worsened, and he developed paroxysmal nocturnal dyspnea. Therefore, patient went to local hospital for an evaluation. He was noted to have a paroxysmal atrial fibrillation, bilateral pleural effusion and cardiac dysfunction with Left Ventricular Ejection Fraction (LVEF) of 34%. After the initial treatment with diuretic, there was only little improvement therefore transferred to our centers for further management. At admission to the cardiology department, physical examination showed inconspicuous skin pigmentation (Figure 1), jugular venous distension and lower extremities edema with stable vitals and normal Body Mass Index (BMI): 24.02 kg/m^2. Haemoglobin was 134 g/L, platelet was 72 *109/L, NT-proBNP was 1819 pg/mL, and albumin was 35.7 g/L. HbA1c was 8.5%. Thyroid function, coagulating function, immunoglobulin, β2- microglobulin, immunofixation ectrophoresis were unremarkable. Admission Electrocardiography (ECG) showed sinus rhyme, V1-V3 Poor R-wave progression, and low QRS voltage in the limb leads (Figure 2A). Transthoracic echocardiogram indicated enlarged left atrium and right atrium, and left ventricular dysfunction with an Ejection Fraction (LVEF) of 25%, Fractional Shortening (FS) of 12%, and a restricted diastolic function. (Figure 3) At the night of the admission day, patient complained a sudden onset of palpitation.

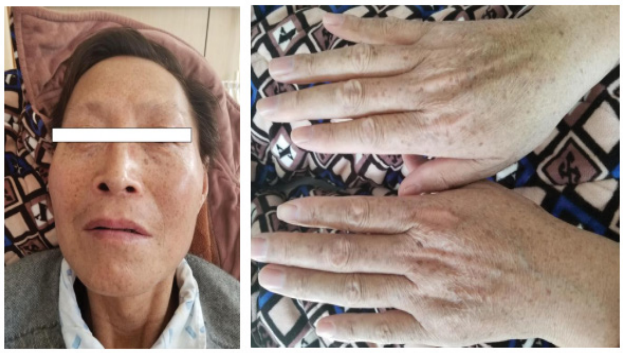

Figure 1: Skin Pigmentation.

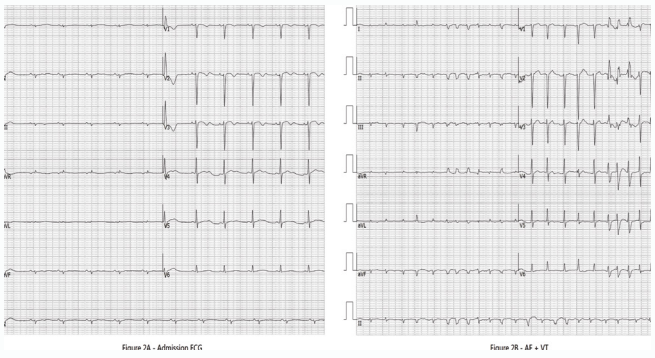

Figure 2: Electrocardiogram. 2A: Admission ECG; 2B: Atrial Fibrillation & Burst Ventricular Tachycardia.

Following ECG showed atrial fibrillation with burst ventricular tachycardia (Figure 2B). Holter showed sinus rhythm with ectopic rhythm (paroxysmal atrial flutter and atrial fibrillation, non-sustained atrial tachycardia, non-sustained ventricular tachycardia). Metoprolol and dabigatran were given for the rate control and anti- coagulation.

The computed tomography coronary angiogram showed a abnormal density changes in liver (95 Hu) and myocardium (50 Hu) without significant obstruction. Cardiac magnetic resonance showed decreased T1 signal of liver and myocardium, and the results strongly suggested an abnormal iron deposition (Figure 4A-F). The following evolution of Iron metabolism showed iron overload with serum iron 32.8 μmol/L, transferring 1.03 g/L, ferreting >15000 ng/mL (above detection), total iron binding capacity 31.4 μmol/L, transferring saturation 84.7%. His presentations were compatible with a clinical diagnosis of hemochromatosis induced restricted cardiomyopathy. The edema, chest tightness and shortness of breath shortness of breath was significantly improved after optimal volume management with furosemide, spirolactone, torasemide and tolvaptan. Furthermore, liver biopsy and gene analysis were performed for a definitive diagnosis. Liver biopsy showed inflammatory cells infiltrated around portal areas and intracellular brown particles accumulation (Figure 5). Result of the gene analysis (Figure 6) showed heterozygous missense mutation of HAMP:c.2T>C (HAMP:p.Met1Thr het) and DSP gene c.6309G>C (DSP:p.Lys2103Asn het). After the confirmation of the diagnosis, patient was transferred to hematology department for further treatment. Unfortunately, patient dies from cardiac arrest without starting the iron chelation therapy.

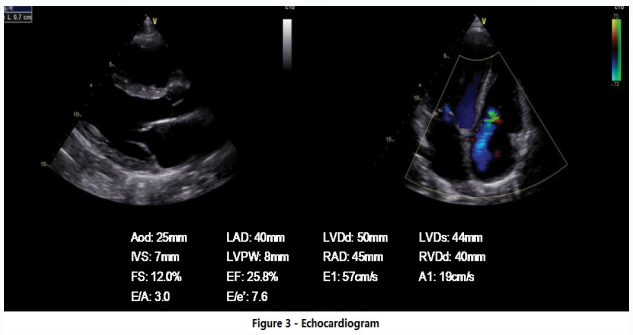

Figure 3: Transthoracic Echocardiogram.

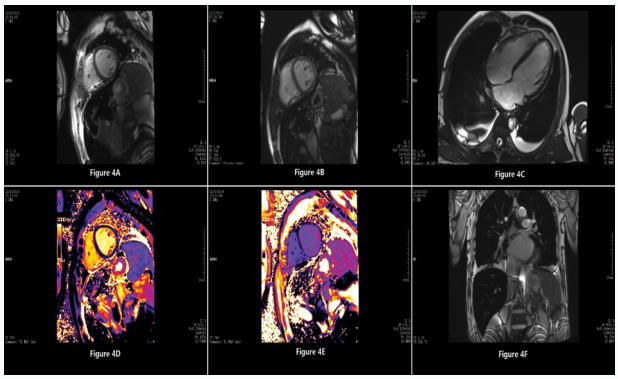

Figure 4: Cardiac Magnetic Resonance. 4A: LV short-axis cine, reduced T1 values of myocardium; 4B: Late gadolinium enhancement (LGE) of interventricular septum indicated midmyocardium fibrosis; 4C: enlarged LV on two chamber cine; 4D, 4E: T1 mapping showed reduced initial T1 value (lowest value 637ms); myocardial extracellular volume (ECV) was 37.74% ; 4F: Reduced T1 values on liver as well.

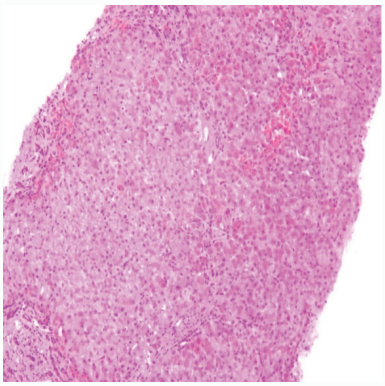

Figure 5: Liver Biopsy: cloudy swelling of hepatocytes, periportal inflammatory cell infiltration, and brown granular deposits within the portal area and hepatocytes

Discussion

Symptomatic and supportive treatments for the hepatic and cardiac dysfunction in patients with HH are essential options, but do not significantly change the clinical course and outcome. Early molecular diagnosis and initiation of iron chelation treatment for HH is lifesaving. Therefore, CMR, biopsy, and genetic screening should enable for RCM patient without specified etiology. HAMP (OMIM 613313, 606464) encoded hepcidin antimicrobial peptide (HAMP) which is a key regulator in the iron metabolism and strongly expressed

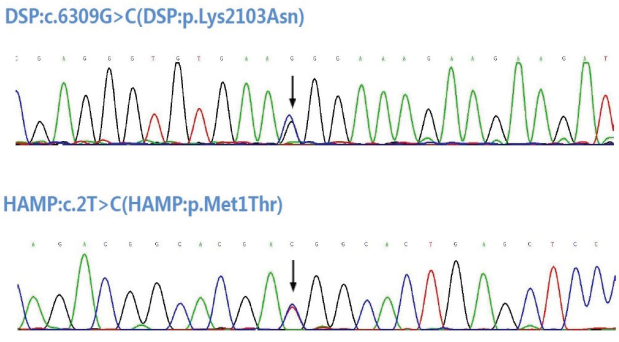

Figure 6: Gene Analysis.

in live and is associated with AR juvenile, or type 2 HH. Previous studies showed that HAMP mutation contributes to the pathogenesis of HH [11,12]. The failure of HAMP induction and disruption of iron homeostasis lead to an iron overload in tissues [13]. The distribution of iron can differ among patients causing various presentation. Cardiac iron overload can lead to different severity of cardiac dysfunction and conduction disturbances. DSP (Desmoplakin, OMIM 125647) is an essential intracellular component of the cell-cell adhesion complexes desmosomes. The heterozygous DSP mutations exhibit a complex genotype-phenotype relationship [14]. Autosomal dominant mutations of DSP variants have generally been linked to arrhythmogenic right ventricular cardiomyopathy or dystrophy, higher frequency of left ventricular dysfunction, and also exposed to a higher risk of cardiac conduction disease, but AR traits have also been reported in patients with cardiomyopathies for DSP [15-17]. In our case, single missense HAMP and DSP mutations were found, but the manifestations could not be explained by neither of the diseases. As HAMP mutation is reported as an autosomal recessive trait and DSP mutation do not showed any influences in iron metabolism, our patient exhibited a systemic manifestations of iron overload, including hyperpigmentation, DM, hepatic fibrosis, diastolic dysfunction, and arrhythmia. TGF-β signaling pathway involve in the development of cardiac fibrosis and contribute to the pathological remodeling in cardiovascular diseases [18]. Studies showed that multiple members of TGF-β superfamily are able to induce hepcidin expression and may have an individual roles in iron regulation [19,20]. DSP gene also exhibited the regulative function of TGF-β1 signaling pathway and fibrotic gene expression. We inferred that the transcription of the HAMP gene and defective hepcidin synthesis were influences by the DSP mutation causing unusual mutational mechanism. As the result, the compound heterozygous mutation therefore caused the systematic presentations and the distinctive cardiomyopathy.

Conclusion

Given that the discovered mutation in this sporadic Chinese Han case of HH, although HAMP mutation is consider as an autosomal recessive disorder, the present case highlights the above mutation might both contribute to the severe phenotype of the HH causing the cardiomyopathy and systemic presentation. Especially in patient with unspecified cardiomyopathy, the need for careful assessment and precise diagnosis for the cause of cardiomyopathy could lead to a optimal treatment and better outcome.

References

1. Brandhagen DJ, Fairbanks VF, Baldus W. Recognition and management of hereditary hemochromatosis. Am Fam Physician. 2002;65(5):853-60.
2. Crownover BK, Covey CJ. Hereditary hemochromatosis. Am Fam Physician. 2013;87(3):183-90.
3. Edwards CQ, Griffen LM, Goldgar D, Drummond C, Skolnick MH, Kushner JP. Prevalence of hemochromatosis among 11,065 presumably healthy blood donors. N Engl J Med. 1988;318(21):1355-62.
4. Sandhu K, Flintoff K. Phenotypic analysis of hemochromatosis subtypes reveals variations in severity of iron overload and clinical disease. Blood. 2018;132(1):101-10.
5. Kawabata H. The mechanisms of systemic iron homeostasis and etiology, diagnosis, and treatment of hereditary hemochromatosis. Int J Hematol. 2018;107(1):31-43.
6. Bardou-Jacquet E, Brissot P. Diagnostic evaluation of hereditary hemochromatosis (HFE and non-HFE). Hematol Oncol Clin North Am. 2014;28(4):625-35.
7. Lescano MA, Tavares LC, Santos PCJL. Juvenile hemochromatosis: HAMP mutation and severe iron overload treated with phlebotomies and deferasirox. World J Clin Cases. 2017;5(10):381-3.
8. Mantilla-Hernández JC, Amaya-Mujica J. Juvenile hemochromatosis with multi-organ involvement diagnosed at autopsy. Rev Esp Patol. 2019;52(1):45-9.
9. Matthes T, Aguilar-Martinez P, Pizzi-Bosman L, Darbellay R, Rubbia-Brandt L, Giostra E, et al. Severe hemochromatosis in a Portuguese family associated with a new mutation in the 5'-UTR of the HAMP gene. Blood. 2004;104(7):2181-3.
10. Majore S, Binni F, Pennese A, De Santis A, Crisi A, Grammatico P. HAMP gene mutation c.208T>C (p.C70R) identified in an Italian patient with severe hereditary hemochromatosis. Hum Mutat. 2004;23(4):400.
11. Merryweather-Clarke AT, Cadet E, Bomford A, Capron D, Viprakasit V, Miller A, et al. Digenic inheritance of mutations in HAMP and HFE results in different types of haemochromatosis. Hum Mol Genet. 2003;12(17):2241-7.
12. Reichert CO, da Cunha J, Levy D, Maselli LMF, Bydlowski SP, Spada C. Hepcidin: Homeostasis and Diseases Related to Iron Metabolism. Acta Haematol. 2017;137(4):220-36.
13. Favre B, Begré N, Marsili L. Desmoplakin Gene Variants and Risk for Arrhythmogenic Cardiomyopathy. Circ Genom Precis Med. 2018;11(9):e002241.
14. Kiselev A, Mikhaylov E, Parmon E, Sjoberg G, Sejersen T, Tarnovskaya S, et al. Progressive cardiac conduction disease associated with a DSP gene mutation. Int J Cardiol. 2016;216:188-9.
15. Favre B, Begré N, Borradori L. A recessive mutation in the DSP gene linked to cardiomyopathy, skin fragility and hair defects impairs the binding of desmoplakin to epidermal keratins and the muscle-specific intermediate filament desmin. Br J Dermatol. 2018;179(3):797-9.
16. Wilde AA, Behr ER. Genetic testing for inherited cardiac disease. Nat Rev Cardiol. 2013;10(10):571-83.
17. Goumans MJ, Ten Dijke P. TGF-Î² Signaling in Control of Cardiovascular Function. Cold Spring Harb Perspect Biol. 2018;10(2).
18. Lv T, Zhang W. Non-HFE mutations in haemochromatosis in China: combination of heterozygous mutations involving HJV signal peptide variants. J Med Genet. 2018;55(10):650-60.
19. Sangkhae V, Nemeth E. Regulation of the Iron Homeostatic Hormone Hepcidin. Adv Nutr. 2017;8(1):126-36.
20. Dubash AD, Kam CY, Aguado BA, Patel DM, Delmar M, Shea LD, et al. Plakophilin-2 loss promotes TGF-Î²1/p38 MAPK-dependent fibrotic gene expression in cardiomyocytes. J Cell Biol. 2016;212(4):425-38.