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– CASE REPORT –

Juvenile Hereditary Hemochromatosis: A Case Report

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Abstract

Introduction*: Hereditary hemochromatosis is an inherited condition where an excess of iron is absorbed from the diet, causing its accumulation in vital organs and subsequent organ damage. Very few cases of hereditary hemochromatosis have been reported, and reports of genetic studies are rare. Genetic mutations and environmental factors regulate iron absorption, which modulates the manifestation of disease.*

Case presentation*- A 30-year-old male presented to the Endocrinology outpatient clinic with a complaint of decreased facial and axillary hair and reduced sexual desire since puberty. The patient was diagnosed with hypogonadotropic Hypogonadism, and magnetic resonance imaging suggested Pituitary hemosiderosis. Mutation analysis revealed the presence of an HFE2 gene mutation, indicating Hereditary Haemochromatosis type 2A.*

Conclusion*- Early diagnosis and timely phlebotomy are the key to preventing end-organ damage.*

Keywords*- Hereditary hemochromatosis; Hypogonadism; HFE gene; hepcidin; iron*

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Introduction

Hereditary hemochromatosis (HH) is an inherited condition where an excess of iron is absorbed from the diet, causing its accumulation in vital organs and subsequent organ damage. The disease manifestations vary, including cardiomyopathy, Liver Cirrhosis, Hypogonadism secondary to iron deposition in the pituitary gland, arthropathy, and diabetes mellitus that does not respond to oral hypoglycemic agents (OHA).[1,2] It is an autosomal recessive condition in the majority of cases, with variable penetrance in families. So far, four types of hereditary hemochromatosis have been identified, with type I being the most common, characterised by the HFE gene mutation.[3] Very few cases of hereditary hemochromatosis have been reported, and genetic studies are rare. Genetic mutations and environmental factors regulate iron absorption, which modulates the manifestation of disease. The genetic causes of hemochromatosis primarily include mutations in the HFE gene and non-HFE mutations. Hepcidin deficiency is a common factor that leads to organ iron overload by increasing cellular iron entry. Types I–III are associated with decreased or altered expression of hepcidin, whereas type IV results from a ferroportin mutation. The FE mutation-associated Type 1 is more prevalent in European and American populations and is the classic form of hemochromatosis. Types 2, 3, and 4 are collectively known as non-HFE-associated hemochromatosis and are the primary types found in Asia.[4]

Iron is absorbed from the duodenum via DMT1 (Divalent Metal Transporter 1), then transported to various iron storage sites from the basolateral membrane of intestinal cells via transferrin under the influence of Hepcidin, a protein synthesised by the liver in response to iron needs. It is the hepcidin-ferroportin interaction that determines the fate of iron absorption.[5] Other mutations present in HH include non-HFE mutations, which affect different co-transporters, leading to variable presentations of HH. Since iron overload and hyperferritinaemia are common in other conditions as well, clinical suspicion for HH as a differential diagnosis is not a priori

ty for physicians. In Asian countries, the prevalence of haemoglobinopathy and repeated transfusions, along with endemic diseases like tuberculosis that cause high ferritin levels due to underlying infections, makes physicians less likely to consider HH.

Family history may suggest a diagnosis of HH, as these patients often have a family history of cardiomyopathy and sudden death. These symptoms result from prolonged, unopposed iron absorption and its buildup in vital organs, leading to dysfunction that is unfortunately only detected once it becomes irreversible. We present a case of a 30-year-old male who exhibited reduced secondary sexual characteristics and loss of libido and was ultimately diagnosed with hereditary hemochromatosis.

Case report

A 30-year-old male presented to the Endocrinology Outpatient Department (OPD) with complaints of reduced facial and axillary hair, decreased sexual desire since puberty, and concerns about infertility. On examination, there was no pallor, icterus, cyanosis, clubbing, palpable lymph nodes, or oedema. His family history revealed the death of two elder brothers, one in a road traffic accident. At the same time, another, a known case of Diabetes Mellitus with recurrent jaundice, succumbed due to an unknown acute cardiac illness. On examination, he was affaire, with a thin build and sparse facial hair, exhibiting hyperpigmentation over the nail beds. A liver palpable on deep inspiration was noted, with a smooth, soft surface 1 cm below the costal margin. Axillary and pubic hairs were sparse, and testicular size was decreased. There was no palpable splenomegaly, ascites, or signs of liver failure or encephalopathy; no joint tenderness or swelling was noted. The patient's blood pressure (BP) was 118/76 mmHg, pulse rate (PR) was 96/min, respiratory rate (RR) was 18/min, and SpO2 was 98% on room air. His routine investigation and hormonal assay revealed low levels of serum testosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) (Table 1). He had raised liver enzymes, and an ultrasound showed hepatosplenomegaly with a prominent portal vein. He was also found to be diabetic and hypothyroid on follow-up. His Magnetic Resonance Imaging (MRI) indicated Pituitary hemosiderosis (Image 1). Hypogonadotropic hypogonadism with transaminitis, hypothyroidism with Pituitary hemosiderosis, along with high ferritin and transferrin saturation, and the family history of death due to cardiac ailment point towards the presence of hereditary Hemochromatosis.

Parameters	**Result**	**Normal range**
Haemoglobin	14.4 gm/dl	13-17gm/dl
Total Leucocyte count (TLC)	8700/µl	4000-10000/µl
Platelets	102000/µl	150000-410000/µl
Bilirubin	0.56 mg/dl	0.2-1.3mg/dl
SGOT	106 U/L	15-46 U/L
SGPT	138U/L	13-69 U/L
ALP	202U/L	37-143 U/L
HbA1C	10.4 %	
Ferritin	9766 ng/dl	10-210 ng/ml
Serum Iron	292.88 µg/dl	65-175 µg/dl
TIBC	320 µg/dl	261-495 µg/dl
Transferrin saturation	91 %	25-30%
Viral markers HIV/HBsAg/Anti-HBC	Negative	
IgA Anti TTG	1.06 (Negative)	
Anti-Nuclear Antibody (ANA)	Negative	
Serum Ceruloplasmin	25.69 mg/dl	20-40 mg/dl
Hormonal Assay		
FSH	0.24 mIU/ML	2.5-7 mIU/ML
LH	0.44 mIU/ml	0.57-12.07 mIU /ml
Testosterone	9.54 ng/dl	400-1080 ng/dl
Cortisol	12 µg/dl	5-15 µg/dl
TSH	2.86 µIU/ml	0.35-4.94 µIU /ml
T4	10.26 µg/dl	4.87-11.72 µg/dl
Prolactin	7.61 ng/ml	3.46- 19.40 ng/ml

Table 1. *Summary of routine and Hormonal assay investigation*

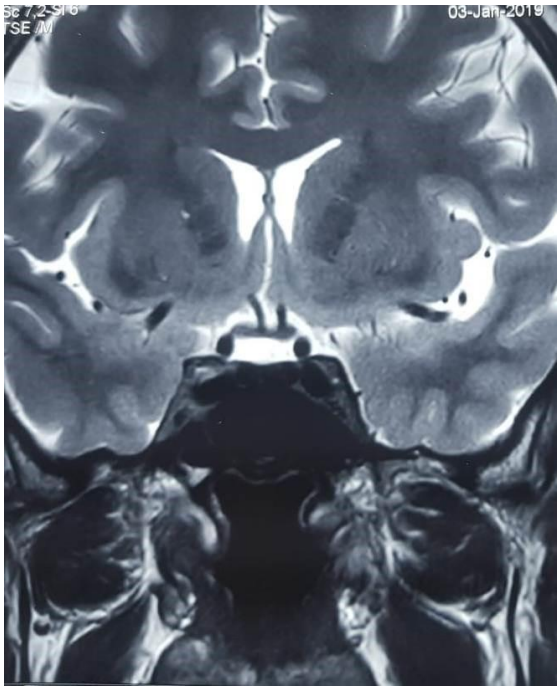

Image 1. *Magnetic resonance imaging of pituitary hemosiderosis*

He was started on androgen replacement therapy and an oral hypoglycemic agent (OHA); however, due to poor glycaemic control with OHA, during a subsequent visit, the patient was initiated on insulin injections. MRI of the abdomen revealed a dark, hypo-intense appearance of the liver, pancreas, and pericardium, suggestive of iron deposition in these tissues (Image 2). Using a more sensitive imaging technique with MRI at different R2 values, we were able to measure hepatic and cardiac iron content as follows: liver iron content (LIC) - 7.59 mg/g of liver tissue and myocardial iron content (MIC) - 8.49 mg/g of myocardial tissue. His 2D echo showed a restrictive filling pattern with an Ejection fraction (EF) of 45% and left ventricular diastolic dysfunction (LVDD) Grade 3.

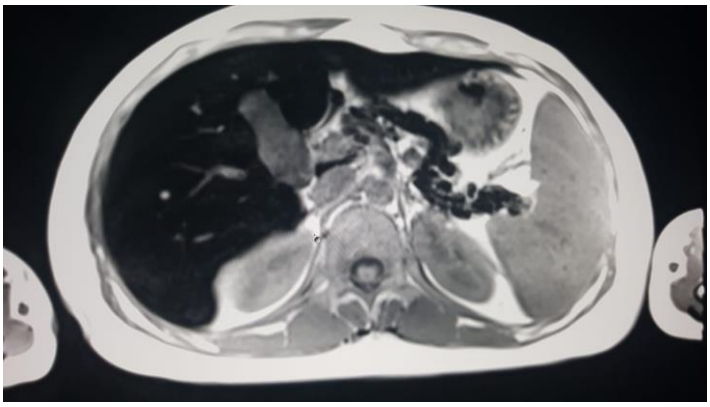

Image 2. *Magnetic resonance imaging - Iron deposition in the Liver*

His upper gastrointestinal endoscopy (UGIE) was normal. Liver biopsy showed grade 4 iron deposition in liver cells (Image 3), and a gene panel confirmed the presence of a homozygous HEF2 gene mutation at Exon 4. A definitive diagnosis of Hereditary Haemochromatosis Type 2A (Juvenile Haemochromatosis) due to a pathogenic mutation in Hemojuvelin (HJV) was made.

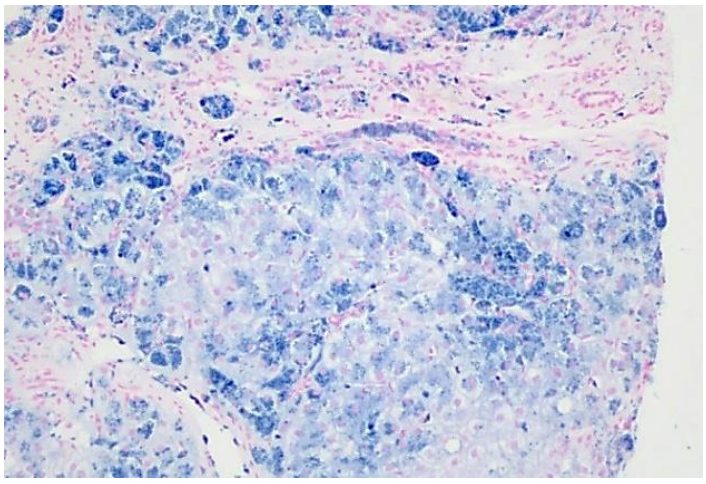

Image 3. *Liver Biopsy suggesting Iron accumulation*

He was managed with regular phlebotomies of 350 ml each week, maintaining a haemoglobin level above 11 g/dL, and monitored with ferritin, TIBC, and serum iron every four weeks. Additionally, he received LH/FSH replacement for hypogonadotropic hypogonadism, basal-bolus insulin for bronze diabetes, thyroxine for

hypothyroidism, a proton pump inhibitor to reduce iron absorption, and a low-iron diet. He was also advised to undergo regular clinical and biochemical monitoring for signs of decompensation by a gastroenterologist and close clinical follow-up for the development of dilated cardiomyopathy (DCM) and arrhythmias by a cardiologist. His clinical condition gradually improved with regular phlebotomies. Serum Ferritin gradually decreased to 200 ng/ml. His 2D echo showed an improved left ventricular ejection fraction (LVEF) from 45% to 55%. The patient has been in follow-up with us for the last two years and is the father of a son.

Discussion

The earliest documented case of primary hemochromatosis was described by Dr. Armand Trousseau in 1865.[6] Since then, cases have been reported worldwide. In India, the first case was reported in a woman in 2000, who exhibited porphyrins in her urine and abnormal findings on kidney imaging.[7] While the presence of porphyrins in urine in cases of hemochromatosis is rare, it can be explained by hepatic dysfunction caused by iron accumulation and subsequent disturbances in porphyrin metabolism, leading to the accumulation of intermediate products and their subsequent excretion in urine. While the presentation of HH patients varies, our patient presented with a lack of secondary sexual characteristics, with normal height for age.

Hemojuvelin (HJV) is a co-receptor in the Bone Morphogenetic Protein (BMP) pathway and acts as a suppressor of the Mother Decapentaplegic (SMAD) signalling pathway. This pathway controls the production of Hepcidin. A mutation in the HJV gene causes early termination of protein synthesis, leading to decreased Hepcidin levels and, consequently, excessive iron absorption, as seen in our case. Our patient had a p.Gly336Ter mutation, where a stop codon at amino acid position 336 replaces Glycine. [8]A study by Dhillon BK in North Indians screened 258 patients with chronic liver disease and 19 patients with high transferrin saturation, Serum ferritin levels> 1000 ng/L, and Liver siderosis (biopsy-proven). These patients underwent DNA sequencing, which revealed a homozygous mutation at p.Gly336Ter in four patients; the same mutation was also found in our patient.[9]

In developing countries, nutritional deficiency is widespread. According to the World Health Organisation, around 51.5% of Indian females are anaemic.[10] Menstruation acts as a physiological check for women to regulate iron levels. Therefore, suspecting hemochromatosis in the Asian population, especially among Indians, is challenging and often concealed. Among those of European descent, the prevalence of anaemia is lower due to dietary habits, making diagnosis more likely. Moreover, the C282Y mutation is the most common in individuals of European descent. In contrast, other mutations—HJV, HAMP, TFR2, and SLC40A1—are called non-HFE mutations and are found in individuals of Asian descent. [11] However, Shukla P et al reported the presence of primary hemochromatosis without any of the non-HFE mutations in patients with clinically and biochemically suspected HH, emphasising the role of polymorphisms in these mutations.[12]

While the most common mutation, C282Y, presents with features of iron overload such as diabetes mellitus, skin pigmentation, endocrine dysfunction, and arthropathy, the presentation of other non-HFE mutations varies. Patients with type IIA typically have an early onset before 30 years of age, with prevalent hypogonadism and cardiomyopathy. Type III also manifests with the same spectrum of symptoms due to the TFR2 mutation. In contrast, type IV, known as ferroportin disease, is inherited in an autosomal dominant pattern and characterised by splenic iron deposits and a lower tolerance to phlebotomy. In our case, the patient presented at age 30 with hypogonadotropic gonadism, restrictive cardiomyopathy, and grade III diastolic dysfunction, which improved following phlebotomy. Additionally, the presence of a family history of the elder brother with diabetes mellitus and death due to acute cardiac illness suggests a familial inheritance of the disease. [13]

In patients with Type 2A HH disease, serum ferritin and transferring saturation are proportionally higher compared to Types I, III, and IV. Therefore, aggressive phlebotomy is necessary to lower the target ferritin level (50-100 ng/ml). In some cases, if phlebotomy is poorly tolerated, iron chelation can be considered. Since the liver is the most commonly affected organ in iron overload, and HH disease has a high risk of hepatocellular carcinoma, regular screening is recommended, along with the avoidance of tobacco chewing and alcohol consumption, which can reduce the phenotypic expression of the disease.[14]

Conclusion

Hereditary hemochromatosis is a rare autosomal recessive condition. Every patient with high ferritin and transferrin saturation should be screened for HH. The presence of a gene mutation confirms the diagnosis, and the treatment modality is primarily phlebotomy. Iron chelation is

reserved for patients with anaemia or intolerant to phlebotomy.

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Ethical considerations: The research was conducted in accordance with the Declaration of Helsinki, and patient consent was obtained.

Conflict of interest: We certify that we do not have any financial or personal relationships that might bias the content of this work.

References

1. D Daniłowicz-Szymanowicz L, Świątczak M, Sikorska K, Starzyński RR, Raczak A, Lipiński P. Pathogenesis, Diagnosis, and Clinical Implications of Hereditary Hemochromatosis-The Cardiological Point of View. Diagnostics (Basel). 2021;11(7):1279. doi: 10.3390/diagnostics11071279.

2. Peter Capell; Case Study: Hemachromatosis in Type 2 Diabetes. Clin Diabetes. 2004; 22 (2): 101-102. https://doi.org/10.2337/diaclin.22.2.101

3. Crawford DHG. Hereditary hemochromatosis types 1, 2, and 3. Clin Liver Dis (Hoboken). 2014;3(5):96-97. doi: 10.1002/cld.339.

4. Lok CY, Merryweather-Clarke AT, Viprakasit V, Chinthammitr Y, Srichairatanakool S, Limwongse C et al. Iron overload in the Asian community. Blood 2009; 114 (1): 20–25. doi: https://doi.org/10.1182/blood-2009-01-199109.

5. Yin X, Zhang Y, Gao H, Jin QL, Wen XY. A case report of hereditary hemochromatosis caused by mutation of SLC40A1 gene. Medicine (Baltimore). 2019 Nov;98(44):e17526. doi: 10.1097/MD.0000000000017526.

6. Ginzburg YZ. Hepcidin-ferroportin axis in health and disease. Vitam Horm. 2019;110:17-45. doi: 10.1016/bs.vh.2019.01.002.

7. Trousseau A. Glycosurie, diabète sucré. Clinique Médicale de l'Hôtel-Dieu de Paris. 1865;2:663-98.

8. Sood A, Jain R. Idiopathic haemochromatosis with unusual CT findings. Trop Gastroenterol. 2000;21(2):73-4.

9. Malyszko J. Hemojuvelin: the hepcidin story continues. Kidney Blood Press Res. 2009;32(2):71-6. doi: 10.1159/000208988.

10. Dhillon BK, Chopra G, Jamwal M, Chandak GR, Duseja A, Malhotra P et al. Adult-onset hereditary hemochromatosis is associated with a novel recurrent mutation in the Hemojuvelin (HJV) gene among North Indians. Blood Cells Mol Dis. 2018 Nov;73:14-21. Doi: 10.1016/j.bcmd.2018.08.003.

11. Goodarzi E, Beiranvand R, Naemi H, Darvishi I, Khazaei Z. Prevalence of iron deficiency anaemia in the Asian female population and human development index (HDI): an ecological study. Obstet Gynecol Sci. 2020;63(4):497-505. doi: 10.5468/ogs. 19196.

12. Anderson GJ, Bardou-Jacquet E. Revisiting hemochromatosis: genetic vs. phenotypic manifestations. Ann Transl Med. 2021;9(8):731. doi: 10.21037/atm-20-5512.

13. Shukla P, Julka S, Bhatia E, Shah S, Nagral A, Aggarwal R. HFE, hepcidin and ferroportin gene mutations are not present in Indian patients with primary haemochromatosis. Natl Med J India. 2006 Jan-Feb;19(1):20-3.

14. Kowdley KV, Brown KE, Ahn J, Sundaram V. ACG Clinical Guideline: Hereditary Hemochromatosis. Am J Gastroenterol. 2019;114(8):1202-1218. doi: 10.14309/ajg.0000000000000315. Erratum in: Am J Gastroenterol. 2019;114(12):1927. doi: 10.14309/ajg.0000000000000469.

15. Grosse SD, Gurrin LC, Bertalli NA, et al. Clinical penetrance in hereditary hemochromatosis: Estimates of the cumulative incidence of severe liver disease among HFE C282Y homozygotes. Genet Med 2018;20(4):383–9.

16. Duduveche AE,Baluta G,Gika LI,Ocroteala L.Prevalence and impact of hepatitis B and C in haematological patients. Documenta Haematologica - Revista Romana de Hematologie 2024;2(3):135–142. doi:10.59854/dhrrh.2024.2.3.135.