Hemochromatosis Induced Selective Primary Pituitary Failure: A case report

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ABSTRACT:

Hemochromatosis is a inherited disorder characterized by toxic accumulation of iron in parenchymal cells of the liver, heart, endocrine glands with normal iron driven erythropoiesis caused by a mutation that affects one of the proteins that limit iron entry into the blood. Hereditary hemochromatosis (HH) resulting from HFE gene mutation is the most common form. Four other forms of non-HFE hemochromatosis include a juvenile form, mutant genes of transferrin receptor 2 (TfR2), hemojuvelin (HJV), ferroportin 1 (IREG 1 or MTP 1) and the iron responsive element (IRE) of the ferritin H subunit. Ferroportin disease often mentioned as Type 4 hemochromatosis occurs in late adulthood. Secondary iron overload conditions are equally important while ruling out genetic etiology of hemochromatosis. Hypogonadism and cardiac involvement are seen more frequently in younger patients less than 30 years of age mostly males compared with older patients, whereas diabetes, cirrhosis, liver involvement and skin hyperpigmentation are seen less frequently. Hemochromatosis is an unusual but well-defined cause of hypogonadism. Hypogonadism is rare in females when compared with males. A 32 yr old female presented with decompensated chronic liver disease with recurrent episodes of hepatic encephalopathy past 6 months with amenorrhea and primary infertility. Investigations proved it to be a case of hemochromatosis. We report this case as a rare phenotypic presentation of hemochromatosis during adulthood, where the presentation was cirrhosis with decompensation, with hypothyroidism and hypogonadism suggestive of selective primary pituitary failure.

Key words: Hepatic encephalopathy, Iron driven erythropoiesis, hypogonadism, rare phenotype.
Introduction:

The term hemochromatosis was coined by German Pathologist Friedrich Daniel von Recklinghausen in the year 1889, describing bronze staining or slate gray pigmentation of organs attributed to blood borne pigments. Unregulated iron deposition initially causes increased saturation of transferrin (which transports iron to cells such as erythroid precursors) and then the iron accumulates in parenchymal cells of various organs resulting in cirrhosis, diabetes, thyroid dysfunction, cardiomyopathy, arthritis, dermal pigmentation, pituitary failure although the erythropoietic activity is unimpaired. [5] Deficiency or reduced activity of hepcidin an antimicrobial peptide synthesised in the liver is proposed to be an aetiology. Hepcidin downregulates entry of iron into the blood stream. Other causes being mutations of ferroportin that hamper the interaction of hepcidin with transmembrane iron export protein. [5,6] Secondary causes of iron overload are related to iron loading anemias, chronic liver disease, transfusion associated.

Case report:

A 32 yr old woman was admitted with abdominal distension and abdominal pain of 2 months duration with altered level of consciousness, oliguria and anasarca at the time of admission. There was no upper or lower GI bleed. She had no h/o fever, no melena, no breathlessness, no seizures and no visual disturbances. She was not a smoker or alcoholic, there was no history of drug intake. No H/O of native medicine ingestion, no H/O tattooing, no blood transfusion in the past, no H/O jaundice, no pale coloured stools. Similar episodes were present for which she took treatment for past 6 months, medical records were not available. Born of 3rd degree consanguineous marriage. No history of similar illness in the family. Birth history was uneventful, no siblings. She attained menarche at 16yrs of age, irregular, oligomenorrhoea, 3days/4mth initially but gradually she had amenorrhoea by 28 years of age. She was married and had primary infertility. Recurrent episodes of hepatic decompensation in the form of encephalopathy was present past 6 months.

Physical examination:

On admission patient was drowsy, disoriented, not anaemic, anasarca+, anicteric, afebrile, with pan digital clubbing of grade III with leuconychia, vitals were within normal limits except for heart rate which was 108/min, no evidence of KF ring, B/L Fundi – normal. Patient had poorly developed secondary sexual characteristics like loss of axillary hair and her breast development was inadequate.

System examination:

Abdomen was uniformly distended with dilated veins, spider naevi seen, umbilicus everted, striae albicans present. No visible VGP or VIP seen. Liver was shrunken, splenomegaly was present 5 cm below the left costal margin not
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Crossing midline. Shifting dullness was present and flow of blood in the distended veins was from below upwards, with no neurological deficits.

**Lab investigations:**

ESR increased 35/60 mm at ½ & 1 hour, Hb- 16.5 gm%, with macrocytic picture. Blood sugar values were random 162 mg/dl, FBS-124 mg/dl, PPBS-168 mg/dl, HbA1C -5.9, 75 g glucose OGTT was done which showed impaired glucose tolerance. LFT showed hypoalbuminemia with total proteins-4.2 gms, albumin 2.4 gm. Total bilirubin 1.0, direct-0.5, SGOT-112, SGPT-98. PT-14 sec, APTT-34 sec, PT INR 1.23. RFT: Prerenal azotemia was present. Creatinine- 135 mg/dl, creatinine- 2.5 mg/dl. Serum electrolytes were within normal limits, lipid profile was normal, viral markers for hepatitis B, C and HIV were done which were negative. BMD, HB Electrophoresis was normal. Echocardiogram was normal with LVEF-64%. ECG – normal sinus rhythm, WNL.

**Hormonal profile:** TSH -0.4 mIU/L, FT3-120 pg/ml, FT4 -0.4 ng/dl, anti TPO AB was negative. FSH- 0.17 mIU/ml, LH - 0.04 mIU/ml, estradiol -35 pg/ml, progesterone -10 ng/ml. Prolactin – 162.14 ng/ml (increased). ACTH and cortisol were within normal range. Serum ceruloplasmin/copper level – wnl. Interpretation was hypothyroidism, hypogonadotrophic hypogonadism, hyperprolactinemia.

**Iron profile:** Transferrin-- 181 microgm/dl, reference range (150 -280), percentage Iron saturation --87.6% (20% - 50%), TIBC -- 129 microgm/dl (250 -450), Serum Iron --343 microgm/dl (50 -150), Serum Ferritin --2224.3 ng/dl (10 -290)

**Imaging:** USG abdomen/pelvis showed cirrhosis, ascites with splenomegaly, altered renal cortical echoes CMD well maintained, ovaries were small with no evidence of follicular maturation. MRI abdomen: - Impression was visceral iron resulted in a susceptibility artifact--- t2 related signal loss(spindephasing) Low intensity signal of liver, suggestive of haemochromatosis. MRI Brain was normal. Liver biopsy was done which revealed findings consistent with cirrhosis and with a tissue iron index of 3.3. A diagnosis of hemochromatosis was made after ruling out the conditions that would cause secondary iron overload like iron loading anaemias, thalassemia, sideroblastic anemia, aplastic anemia and hemolytic anemia.

**Treatment:**

Patient was started on T. Thyroxine 100 microgram/day for hypothyroidism. Phlebotomy was done about 350 ml of blood was let out each time weekly based on 5 ml/kg body weight. Phlebotomy frequency was titrated based on serum ferritin levels which was done monthly until a value of 200 mcg/l and Hb of 12-13 g was achieved and maintained. Estrogen and progesterone were given on a cyclical basis to induce menstrual cycle and to prevent early osteoporosis. Patient was started on Deferasirox 250 mg odoral, then followed at every 2-month regular intervals with RFT, hematocrit, hemoglobin, ferritin. Alpha feto protein was checked every 6 months as the possibility of the patient developing hepatocellular carcinoma was high. Serum ferritin values and percentage iron saturation showed a declining trend from 2224.3 ng/dl to 180 ng/dl and 87.6% to 75% respectively. Dietary advice was given regarding avoidance of iron and vitamin C rich foods. There was no evidence of hepatic decompensation or cardiac compromise since then.
Discussion:

Iron is an important micronutrient needed for maintaining homeostasis. When iron is bound to transferrin, ferritin, or other transport or storage proteins, it is not available to catalyse the formation of free radicals in iron-overload patients, however the capacity of these proteins to bind with iron is overwhelmed, and tissue damage can occur. Diagnosis should be made early to avoid the specific organ damage that occurs in advanced cases. Identification of a patient with Hereditary hemochromatosis (HH) enables testing of first-degree family members, which helps to identify HH prior to the onset of symptoms. Patients with HH may also present with cardiomyopathy, diabetes (30–60%), and arthropathy, osteopenia (41%), osteoporosis (25%). The pathophysiologic predisposition to increased, disproportionate absorption of iron may lead to the development of life-threatening complications like cirrhosis, hepatocellular carcinoma (HCC). Patients with cardiac manifestations are poor responders to therapy. Clinically the severity and complications like cirrhosis and diabetes are higher in men with HH when compared with women. Patients with HH who develop cirrhosis are at a more than 200-fold risk for developing liver cancer. Heart disease presented usually as dilated cardiomyopathy with dilated ventricles, low left ventricular ejection fraction, and decreased fractional shortening, and even arrhythmias can occur. Men tend to develop HH earlier in their lifespan because they do not have the natural losses of iron experienced by females during menstruation and pregnancy this theory has poor validation though. Menstrual history, number of pregnancies, and menopausal status are important issues in a women's medical history that may affect not only HH symptom development but also other aspects of health that are relevant to a physical therapist's diagnosis and treatment decisions. A study found hypogonadism in five of 41 men with hemochromatosis but in none of 23 women with the disease, because females with hemochromatosis have a lower iron burden due to physiologic iron losses. Among men with hypogonadism, previous studies have shown that the etiology is usually pituitary failure and rarely primary gonadal failure. Phlebotomy and iron chelation remains the mainstay of therapy although other modalities like erythrocytapheresis has been in practice. With increased knowledge of genetic testing which confirms the diagnosis of hemochromatosis in patients with iron overload, the use of the hepatic iron index has been diminished. Yet in situations where genetic test could not be performed liver biopsy remains the confirmatory evidence along with other supportive laboratory investigations and treatment response. Iron accumulation in hemochromatosis occurs mainly in hepatocytes and biliary epithelial cells, with relative sparing of Kupffer cells. Typically, a gradient of hepatocyte iron accumulation is present, with prominent involvement of periportal hepatocytes (zone 1) and decreasing intensity near the central vein (zone 3). On the other hand, iron accumulation in parenteral or secondary iron overload conditions occurs predominantly in the Kupffer cells.

Conclusion:

A diagnosis of haemochromatosis with selective primary pituitary dysfunction was made in our patient based on hormonal studies, iron profile, MRI and liver biopsy. Iron chelation was effective with symptomatic improvement in general condition and restoration of menses. Hepatic decompensation and encephalopathy were not present until then. This case is a rare phenotype of hemochromatosis presenting in a female in her thirties with selective pituitary dysfunction.
dysfunction like hypothyroidism, hypogonadism, asymptomatic hyperprolactinemia. Hemochromatosis induced hypogonadism as the proposed etiology for the primary infertility.

References:

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