HETEROZYGOUS HEMOCHROMATOSIS: A RARE CASE REPORT

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Abstract

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ABSTRACT

Hereditary hemochromatosis is a common autosomal recessive iron storage disease. The classic clinical triad of liver cirrhosis, hyperpigmentation, and diabetes is nowadays rare, most probably because of early recognition. Usually, the homozygous C282Y mutation in the HFE gene is responsible for most cases of hereditary hemochromatosis. Here a 31-Year-Old, otherwise healthy female with no significant past medical history presented to the ED with complaints of yellow discoloration of her urine followed by yellow discoloration of her eyes associated with headache, nausea, and vomiting. History of family, liver disease, autoimmune disorders, IV drug use, recent NSAIDs use, and recreational medications were negative. USG abdomen and MRCP show gallbladder wall thickening. The Work-up of her gamma globulin, autoimmune, Monospot, hepatitis A, B, and C, and HIV screen was negative but showed conjugated hyperbilirubinemia with transaminitis, and to rule out the cause of this we decided to do a liver biopsy and it shows subtotal hepatic necrosis and a small collection of iron in the liver. PCR of blood shows a single mutation C282Y identified. To our knowledge, this is the first report of this presentation that she has no family history and usually, patients do not manifest symptoms if they are heterozygous. Individuals heterozygous for C282Y who have a coexisting insult to the liver, associated with the use of medications, may present with overt manifestations of iron overload.

INTRODUCTION

Hereditary hemochromatosis (HH), is an autosomal recessive disorder with Iron overload in different organs, especially in the liver. The monoallelic genetic disease was first described by Trousseau in 1889 as a triad of glycosuria, cirrhosis, and hyperpigmentation of the skin. The term hemochromatosis was first used by Von Recklinghausen in 1889. HH is commonly due to two histone family E1 (HFE1), gene mutations-C282Y, and H63D. HFE gene is located within the human leukocyte antigen (HLA) class 1 region on chromosome 6 between the genes coding for HLA-A and HLA-B. Two mutations in the HFE gene have been described. The first, C282Y, comprises the substitution of tyrosine for cysteine at amino acid position 282. In the second, H63D, aspartic acid is substituted for histidine in position 63. C282Y/H63D is found in most patients with HH. Secondary hemochromatosis is caused by disorders of erythropoiesis and treatment of the diseases with blood transfusions. Hereditary hemochromatosis is characterized by abnormal iron absorption from the diet resulting in progressive iron overload, causing tissue damage in several organs, particularly the liver. Historically, HH has been regarded as an extremely rare inborn error of metabolism resulting in the causation of bronze diabetes, liver cirrhosis, and hepatocellular carcinoma due to heavy iron overload in the liver and pancreas. HFE gene mutations are strongly associated with predisposition to HH and are also implicated in other disorders such as rheumatoid arthritis, type 2 diabetes mellitus, porphyria cutanea tarda, and coronary heart disease. Considerable ethnic variation is observed in the frequency distribution of HFE mutations.

CASE REPORT

31 Year Old, otherwise healthy female with no significant past medical history presented to ED with complaints of yellow discoloration of her urine followed by yellow discoloration of her eyes associated with headache, nausea, and vomiting. Before that, she had decreased appetite and some vague abdominal pain for the past 2 days along with the sensation of constipation. She took a probiotic and some cranberry pills which didn't seem to help improve her urine color and abdominal discomfort. She denies a history of liver disease, autoimmune disorders, IV drug use, recent NSAIDs use, and recreational medications such as ecstasy or amphetamines or cocaine. She had Opthalmology/optometry exam in August 2019 and no Kaiser-Fleischer rings were seen.

USG abdomen and MRCP shows gallbladder wall thickening with gallbladder wall measuring up to 4.5 mm and no cholelithiasis/choledocholithiasis. Her gamma globulin level was normal, the workup for autoimmune has been negative, Monospot negative, negative for hepatitis A, B, and C and HIV screen.Liver enzymes remain elevated (>1000) in a predominantly hepatocellular pattern with cholestasis and decided to do the outpatient liver biopsy next week and discharged, but the Patient began to develop RUQ pain, nausea, vomiting, and worsening jaundice yesterday which prompted her to return to ED. To differentiate the suspicious cause of conjugated hyperbilirubinemia with transaminitis in 1000s we decided to do a liver biopsy. Biopsy shows subtotal hepatic necrosis with severe inflammation, a very small amount of iron, no fat, and fibrosis.PCR of blood shows single mutation C282Y identified

CASE DISCUSSION

Hereditary hemochromatosis is characterized by abnormal iron absorption from the diet resulting in progressive iron overload, causing tissue damage of several organs, particularly the liver. Two different mutations C282Y and H63D in the HFE gene are associated with over 93% of HH cases. HH can be either asymptomatic or symptomatic. Some individuals who test positive for HH remain asymptomatic throughout their life. In the present case, the patient presented with icterus, yellowish discoloration of urine, nausea, vomiting, and negative family history. The diagnosis of HH is based on the measurement of transferrin saturation, serum ferritin levels, and mutation analysis of HFE. In the present case, total iron (326 mg/dL) and serum ferritin (2506 mg/dL) were increased with a marked increase in transferrin saturation- (88%), >1.9 iron-age-index which is diagnostic of hemochromatosis. The patient had conjugated hyperbilirubinemia with transaminitis, a common clinical finding in hemochromatosis. Liver biopsy confirmed the deposition of iron. Liver biopsy is used to evaluate the underlying disease, determine the fibrosis and degree of iron load. The importance of liver biopsy also lies in the fact that documentation of extensive bridging fibrosis or cirrhosis has a pro-

found impact on the prognosis in HH patients. Given the prevalence of the condition, some specialists suggest screening to detect HH before it causes problems. The following approaches to screening have been suggested.

- Transferrin saturation testing in all adults at age 20, and every five years thereafter for anyone who has a family history of the disease
- Genetic screening of newborns to potentially benefit both the child and the rest of the family
- Routine iron testing of all kids at age 4, those who have a genetic risk, but remain symptom-free, continue to be tested every five years thereafter.

The absence of symptoms is nonetheless common, particularly in young individuals, due to the variable phenotypic expression of the disease and variations of lifetime accumulation of iron stores. Early detection, in conjunction with routine screening procedures, is of utmost importance because effective therapy is available through phlebotomy.

In patients with unexplained liver dysfunction, look for underlying causes, such as hemochromatosis, especially in the presence of skin pigment changes, recent-onset diabetes, or cardiomyopathy. Individuals heterozygous for C282Y who have a coexisting insult to the liver, including associated with the use of medications, may present with overt manifestations of iron overload. In hemochromatosis, a normal life expectancy can be achieved if early diagnosis and treatment are given before irreversible damage can occur.

RESULTS:-

Diagnosis of HH is based on measurement of transferrin saturation, serum ferritin levels, and mutation analysis of HFE.In the present case, total iron and serum ferritin were 326 mg/dL,2506 mg/dL respectively with marked increase in transferrin saturation- (88%) and >1.9 iron-age-index which is diagnostic of hemochromatosis. A single mutation of C282Y also identified.

CONCLUSION

Hemochromatosis can be detected incidentally by routine examination and blood analysis, and its diagnosis can be made easily by mutation analysis. Today, C282Y and H63D mutations are detected in whole blood by polymerase chain reaction (PCR). Accumulation of iron in the body and detection of homozygous C282Y mutation is sufficient for the diagnosis of the disease. C282Y *homozygosity* is the most common mutation for hemochromatosis and proceeds with maximum iron accumulation. While the patients with both C282Y/H63D *heterozygosity* show moderate iron accumulation, H63D *homozygotes* , and C282Y *heterozygotes* are usually normal.

CONSENT

The authors certify that they have obtained all appropriate patient consent forms.

COMPETING INTEREST

There are no conflicts of interest.

REFERENCE

1. *Hayashi, H., Wakusawa, S., Yano, M., & Okada, T. (2007). Genetic background of Japanese patients with adult-onset storage diseases in the liver. Hepatology Research, 37(10), 777–783. https://doi.org/10.1111/j.1872-034x.2007.00114.x*
2. *Hollán, S. R. (1997). Transfusion-associated iron overload. Current Opinion in Hematology, 4(6), 436–441. https://doi.org/10.1097/00062752-199704060-00014*
3. *Steiner, M., Meier, P., & Schuff-Werner, P. (2005). Hemochromatosis in a young female: The picture continues to broaden. International Journal of Cardiology, 104(2), 229. https://doi.org/10.1016/j.ijcard.2004.10.036*

4. *Turkmen, E., Yildirim, T., Yilmaz, R., Hazirolan, T., Eldem, G., Yilmaz, E., Aybal Kutlugun, A., Altindal, M., & Altun, B. (2017). HFE gene mutation is a risk factor for tissue iron accumulation in hemodialysis patients. Hemodialysis International, 21(3), 359–366. https://doi.org/10.1111/hdi.12537*
5. *Yeap, B. B., Divitini, M. L., Gunton, J. E., Olynyk, J. K., Beilby, J. P., McQuillan, B., Hung, J., & Knuiman, M. W. (2014). Higher ferritin levels, but not serum iron or transferrin saturation, are associated with Type 2 diabetes mellitus in adult men and women free of genetic haemochromatosis. Clinical Endocrinology, 82(4), 525–532. https://doi.org/10.1111/cen.12529*