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Hereditary hemochromatosis.

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ORIGINAL ARTICLE

Hereditary Hemochromatosis

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ABSTRACT

Objective: To describe the clinical and laboratory features of hereditary hemochromatosis associated liver disease in a tertiary care hospital.

Study Design: Observational study.

Place and Duration of Study: The Aga Khan University Hospital, Karachi, from January 2002 to October 2012.

Methodology: Charts of patients with Hereditary Hemochromatosis (HHC) were reviewed. Data collected and analyzed consisting of clinical presentations, liver function tests, serum ferritin, transferrin saturation, hepatic imaging and histology in patients with HHC.

Results: A total of 22 patients were identified as having hemochromatosis. All subjects were men with a mean age of 53 ± 9.2 years at the time of diagnosis. The most common presentation was skin pigmentation seen in 17 (77%), followed by loss of libido/ impotence in 11 (50%) and then arthralgias in 10 (45%) and weakness in 6 (27%). Eleven (50%) subjects had diabetes mellitus and one subject had concomitant cardiac involvement. Patients with diabetes were diagnosed earlier as compared to those without it. Eighteen (81%) subjects had cirrhosis at the time of diagnosis. Serum iron was 164 ± 53 ug/dl, ferritin 3391 ± 1960 ug/L, TIBC 202 ± 61 ug/dl and transferrin saturation 76.8 ± 14%. Liver biopsy was done in 10 (45%) and using Pearls' stain histopathological features were consistent with hemochromatosis and none had carcinoma. Only 3 (14%) patients had regular phlebotomy.

Conclusion: Hemochromatosis is not a rare disease in Pakistan and should be looked in those subjects whose liver function tests are deranged.

Key Words: *Hemochromatosis. Cirrhosis. Child score. Pakistan.*

INTRODUCTION

Liver diseases are a major global health problem affecting millions of people worldwide.[1] Among the liver diseases, cirrhosis is the most common liver disorder caused by a variety of causes like viral hepatitis, alcohol, autoimmune and metabolic causes.[2,3] Cirrhosis is common in Pakistan.[4] In Pakistan, most common cause of cirrhosis is hepatitis C followed by hepatitis B and then non B non C (NBNC) related cirrhosis.[5-6] NBNC entity is not very well addressed in Pakistan which might include the metabolic causes such as hemochromatosis.

Hereditary Hemochromatosis (HHC) is the most common inherited disorder of iron metabolism in which there is an inappropriate increase in intestinal iron absorption.[7] Unregulated iron traffic causes excessive iron deposition in parenchymal cells of the liver, heart, pancreas, and other endocrine organs, sometimes leading to organ damage.[8]

Most data on HHC is from west and there is very limited data from Pakistan. The present case record review of the subjects with HHC was done in a tertiary care hospital in Pakistan to review clinicopathological manifestations and recognition of its importance in subjects with deranged liver function tests.

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METHODOLOGY

Study was done in the Section of Gastroenterology, Department of Medicine, The Aga Khan University and Hospital. Twenty two charts were identified as having hemochromatosis from medical records (Health information and management system) by using the ICD code 9CM. These 22 HHC cases were retrospectively analyzed for clinical presentations, liver function tests, serum ferritin, transferrin saturation, hepatic imaging and histology. Ethical exemption was sought because it was chart review. All cases were diagnosed from January 2002 to October 2012. Patient's data was recorded on proforma.

Statistical analysis was done by using the Statistical Package for Social Science (SPSS). Mean ±SD were used for continuous variables and numbers and percentages were used for categorical variables.

RESULTS

Twenty two charts were identified as having hereditary hemochromatosis. All of them were males with a mean age of 53 ± 9.2 years at the time of diagnosis. Two presented before the age of 40 years. The most common presentation in this group of patients was skin pigmentation in 17 (77%), followed by loss of libido/ impotence in 11 (50%) and then arthralgias in 10 (45%) and weakness in 6 (27%). Eleven (50%) had diabetes

mellitus and only one patient had concomitant cardiac involvement. Patients with diabetes were diagnosed earlier as compared to those without diabetes. Eighteen (81%) had cirrhosis at the time of diagnosis. Fifteen (68.2%) patients had ascites and two subjects had hemetemesis secondary to esophageal varices shown in Table I. Among the 15 subjects with ascites, 5 had spontaneous bacterial peritonitis. None had hepatocellular carcinoma. Only 3 (14%) patients had regular phlebotomy.

The serum Iron studies are summarized in Table II. Serum iron was 164 ± 53 ug/dl (normal range = 50 - 170 ug/dl), ferritin 3391 ± 1960 ug/L (normal ranges = 5 - 365 ug/L), TIBC 202 ± 61 ug/dl (normal range = 250 - 400 ug/L), and transferrin saturation was 76.8 ± 14% (normal range = 15 - 55%).

Liver biopsy was done in 10 (45%) patients using percutaneous route in 9 subjects while transjugular route was used in one. Biopsy specimens were stained with hematoxylin and eosin for routine histology, with Masson's trichrome for collagen, and with Pearls' Prussian blue for iron. Facility for hepatic iron concentration and genetic testing is not available in study center. Pearls' Prussian blue stain showed excessive (grade IV) iron deposition in all biopsy specimens.

Table I: Clinical characteristics, signs and symptoms at identification.

Age (mean±SD)	53 ± 9.2
Male	22 (100%)
Skin pigmentation	17 (77%)
Loss of libido/impotence	11 (50%)
Arthralgias	10 (45%)
Weakness	6 (27%)
Diabetes	11 (50%)
Cirrhosis	18 (81%)
Ascites	15 (68.2%)
SBP	5 (22.7%)
UGI bleed	2 (9.1%)

DISCUSSION

Hereditary Hemochromatosis (HHC) is the most common inherited disorder of iron metabolism in which there is an inappropriate increase in intestinal iron absorption.[7] Iron deposition in the liver may result in hepatomegaly, cirrhosis, hepatocellular carcinoma and premature death.[9,10] Cardiac deposition may result in cardiomyopathy, arrhythmias and heart failure.[11] Other manifestations are skin pigmentation, bronze diabetes, arthralgias and impotence.[12] HHC is most commonly identified in Caucasians. It is much less common in Hispanic, Asians and black persons.[13]

The present study of chart review of hemochromatosis cases seen over a period of 10 years showed a male predominance, iron overload on biopsy and advanced liver disease. This is the largest case series from Pakistan on HHC in which most of these patients presented with advanced liver disease. The mean age at onset was slightly higher in this cohort compared to other comparison studies in which HHC is detected earlier (Table II). The reason of late presentation may be because of lack of awareness of disease itself by the patients or local physicians (Internists) whom they approach initially with early, non-specific symptoms and signs rather than advanced disease.[8] It is prerequisite to exclude secondary forms of iron overload, such as those caused by repeated red blood cell transfusions or anemia owing to ineffective erythropoiesis. Although all lead to raised serum iron parameters, they are treated differently.[14] It has generally been acknowledged that women present with symptomatic HHC about 10 years later in life than men, presumably because of physiological iron loss from menstruation and pregnancy. Preponderance of males in the present study could be due to men having more access to health facilities in Pakistan. Symptoms and signs of HHC are initially non-specific, so the disease is often diagnosed at

Table II: Comparison of HHC with different countries.

	Pakistan	Iran[27]	Ireland[28]	USA[29]
Year	2013	2012	2004	1997
Study period	2002 - 2012	2006 - 2010	2004	1990 - 1995
Place of study	Karachi, Pakistan	Tehran, Iran	Dublin, Ireland	Missouri, USA
Number of cases	22	12	209	40
Male (%)	100	92	51	65
Mean age at onset	53 ± 9.2	39 ± 12.6	42 (14 - 79)	46 ± 2
How patients were identified	Symptomatic index cases	Symptomatic index cases	Family screening	Family screening
Symptoms / signs				
Skin pigmentation	17 (77%)	9 (75%)	17 (8.1%)	2 (5%)
Loss of libido / impotence	11 (50%)	5 (41.7%)	NA	3 (12%) male
Arthralgias	10 (45%)	8 (66.7%)	15 (7.2%)	5 (13%)
Weakness / fatigue	6 (27%)	NA	77 (36.8%)	10 (25%)
Diabetes	11 (50%)	7 (58.3%)	3 (1.4%)	2 (5%)
Cirrhosis	18 (81%)	6 (50%)	9 (5%)	3 (7.5%)
Serum iron studies				
Ferritin (ug/L)	3391 ± 1960	2642 ± 1257	809 M, 283F	1,025 ± 155
Transferrin saturation (%)	76.8 ± 14	79 ± 18.8	≥ 52	84 ± 3

a late stage when substantial organ damage has already occurred.[15] HHC burden was higher in male population from Iran and USA but same in both the gender from Ireland. With a greater proportion of patients identified on screening, the age of diagnosis for women and men has equalized.[13,16] The most common mode of presentation in present cohort was darker skin and loss of libido/impotence which is consistent with the study from Iran. However, in the studies from Ireland and USA, majority of the patients (upto 73%) were asymptomatic or had nonspecific symptoms. Eighteen (81%) patients had already developed cirrhosis at the time of presentation in this cohort as compared to Irish and American studies. In the studies from Ireland and USA, most patients were identified earlier because of family screening. Thus, as more patients with HHC are identified by screening, they are more likely to be asymptomatic and without significant disease. Early diagnosis and treatment of HHC can prevent end-stage complications of cirrhosis, diabetes and hepatocellular cancer.[17] Patients with HHC can have a normal life expectancy if treatment is started before cirrhosis occurs.[18] In this cohort of patients, higher ferritin level was seen as compared to the study from Iran, USA and Ireland due to late presentation when majority developed the decompensated liver disease.[19-22]
Diagnostic strategies for HHC are serum iron markers including serum ferritin levels and transferrin saturation, liver histology and genetic testing for HFE mutations.[23] The diagnostic markers in this study showed high serum ferritin and transferrin saturations. The results are comparable with the other three studies as shown in (Table II).

HHC should be suspected in patients who have unexplained deranged liver function tests and diabetes mellitus or positive family history for liver disease. A clinician should check for at least serum ferritin and transferrin saturation in case of unexplained abnormal LFTs to rule out HHC. HHC is inherited in an autosomal recessive disease, with variable penetrance.[24] A homozygous mutation in the hereditary hemochromatosis gene, HFE is responsible for HHC.[14] HFE gene was identified on chromosome 6 in 1996. Two major mutations responsible for HFE-related HHC are C282Y and H63D.[25] Discovery of the genetic defect has allowed for early detection through screening of family members of known cases.[19] We have found this major limitation in this study that none of the patients had genetic analysis for HFE mutation.

CONCLUSION

Hemochromatosis is not a rare disease in this part of world and should be looked in those subjects whose liver function tests are deranged especially when viral serology is negative. HHC can easily be detected early in patients with deranged liver functions by doing the serum iron studies and, therefore, prevent the later development of chronic liver disease. All physicians should further evaluate patients with abnormal iron studies on screening chemistry panels.

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