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Letter to the Editor

A brief communication of patients with homozygous C282Y mutation-related hereditary hemochromatosis

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Abstract

Hereditary hemochromatosis is an autosomal recessive inherited iron-loading disorder and is characterized by chronic hepatitis, cirrhosis, diabetes, and bronze skin. The hemochromatosis gene (C282Y homozygosity)-related hemochromatosis is the most common form of hereditary hemochromatosis. The prevalence of hereditary hemochromatosis varies. Here, we defined six cases with C282Y homozygosity-related hereditary hemochromatosis in a single center in Turkiye.

Introduction

Hereditary hemochromatosis (HH) is an autosomal recessive disorder of iron metabolism that is characterized by inadequate hepcidin synthesis, increased intestinal iron absorption, and iron release from macrophages, leading to progressive parenchymal iron accumulation with potential for multiorgan damage. Excess iron is deposited in the liver, pancreas, heart, endocrine glands, and joints.[1] HH mainly manifests in the liver and can result in fibrosis, cirrhosis, and hepatocellular carcinoma (HCC).[2] Homozygotes for the hemochromatosis gene (HFE) C282Y are the most common genotype in HH and are seen in 80% to 95% of cases of typical HH among European individuals.[3,4] In Turkiye, HFE-associated HH is rarely seen.[5] Moreover, this brief study represents the largest series reporting HFE-associated hemochromatosis due to C282Y homozygosity in a single center in Turkiye.

MATERIALS AND METHODS

We investigated hereditary HFE-associated hemochromatosis due to C282Y homozygosity in patients followed by the Liver Disease Outpatient Clinic, Ankara University School of Medicine, between January 2015 and December 2023. The diagnosis of hemochromatosis was based on clinical features, biochemical tests, including transferrin saturation (TS) (normal range: 13-45%) and serum ferritin level (normal range: female 13-150 ng/mL, male 30-400 ng/mL), imaging methods (magnetic resonance imaging [MRI]), genetic screening, family history, and histological evaluation when available. Secondary causes of iron overload, such as hematological disorders, history of multiple transfusions, parenteral iron therapy, alcohol-related liver disease (ALD), and metabolic dysfunction-associated steatotic liver disease (MASLD), were also reviewed for differential diagnosis.

Genomic DNA was isolated from a whole blood sample in an EDTA tube using a genomic DNA isolation kit (Roche, California, USA). The DNA region containing the HFE gene was amplified by PCR using appropriate primers. The amplified PCR products underwent sequencing using a genetic analyzer (BigDye terminator kit, ABI 310 Genetic Analyzer, California, USA).

MRI was performed on 1.5 Tesla MRI devices (Optima 450w, GE Healthcare, and Aera, Siemens Healthcare). The liver-to-muscle signal intensity ratio method, a calculation tool from the University of Rennes in France, was used to estimate liver iron concentration in a subset of patients.[6] The normal liver iron concentration (LIC) value is less than 36 µmol Fe/g. In HH, it is greater than 80 µmol Fe/g.[7] For the remaining patients, quantitative T2* and its reciprocal R2* (R2* = 1000/T2*) maps were obtained using a multi-echo spoiled gradient-echo single-breath-hold MR sequence. In healthy individuals, the T2* value is above 14 ms, and the R2* value is below 70 s^{-1}.[8]

MR-based fat quantification [proton density fat fraction (PDFF)] was mainly measured using a chemical shift (CS)-based MRI method known as multi-echo Dixon for Siemens. This method employs six echoes and can generate a comprehensive PDFF map of the entire liver. An FF threshold of 6.3% was accepted as the upper normal limit.[9]

Results

Six patients had been diagnosed with C282Y homozygous HH: four were male and two were female. The mean age at diagnosis was 48.6 ± 16.5 years. Their median TS and serum ferritin levels were 77.5% (range: 43-82) and 1757.5 ng/mL (range: 256-5264), respectively. The characteristics of the patients with HH are given in Table 1.

Cases 1 and 6 were siblings. Cases 1, 2, 3, and 6, all male patients, represented a clinical expression of HH. However, the female cases (Cases 4 and 5) had no phenotypic manifestation of hemochromatosis. Two patients (Cases 2 and 3) had cirrhosis: one had hepatocellular carcinoma (HCC), three patients (Cases 1, 4, 6) had hepatosteatosis (two MASLD, one ALD), and the remaining patient (Case 5) had chronic hepatitis B virus (HBV) infection.

Cases 2 and 3 represented typical clinical expressions of HH. Case 2 had diabetes mellitus, hypopituitarism (hypothyroidism, libido loss), congestive heart failure (due to cardiomyopathy), and atrial fibrillation. Case 3 had bronze diabetes and arthropathy.

Case 4 had a family history of HH, and her sister was diagnosed with HH in another center. Her TS and ferritin levels were 82% and 256 ng/mL, respectively. Case 5, a female patient, had a TS of 43% with high ferritin levels (1501 ng/mL).

On the other hand, the C282Y heterozygous (C282Y/N) mutation was found in five patients (Cases 7, 8, 9, 10, and 11), and the compound C282Y heterozygous (C282Y/H63D) mutation was found in one patient (Case 12). Four patients (Cases 7, 8, 10, and 12) had hepatosteatosis (two MASLD, two ALD). Case 7 had chronic hepatitis C and had undergone renal transplantation. Case 9 was diagnosed with polycythemia vera, and Case 11 had ALD. Cases 10 and 11 were the parents of Cases 1 and 6. Demographic and laboratory data of patients based on HFE gene mutations are presented in Table 2.

DISCUSSION

This study determined the largest series of HFE-associated hemochromatosis due to C282Y homozygosity in a single center in Türkiye. The frequency of C282Y homozygosity differs across Europe depending on the geographical region. It is most common in individuals of Northern European descent, particularly in Ireland and Scandinavia.[3,4,10] Patients with C282Y homozygosity are at risk of developing hemochromatosis, but disease penetrance depends on age and gender. The prevalence of the disease increases with age, and male gender is predominant.[1,11] HFE-related HH is a multifactorial disease characterized by stepwise disease progression from biochemical test abnormality to organ damage. The altered HFE gene plays an essential role in disease progression. However, host-related factors such as age, gender, other genes, and acquired factors (diet and alcohol consumption) also play important roles in the phenotypic penetrance of the genetic defect.[12] These factors may lead to biochemical abnormalities, symptoms, and signs, or organ damage with/without overt organ failure. Many patients are asymptomatic and have been followed up for many years, while some patients present with cirrhosis or bronze diabetes.[13] In this series, four of six patients with C282Y homozygosity were male, and they had clinical expression of hemochromatosis. However, two female patients with C282Y homozygosity were asymptomatic and had no significant iron overload.

The clinical impact of C282Y heterozygotes and compound C282Y/H63D heterozygotes appears limited. Patients with these mutations have slightly increased serum iron parameters and hepatic iron load and seem predisposed to expression of the disease.[14,15] In these cases, secondary causes of iron overload, such as MASLD, alcohol consumption, iron-loading anemias, parenteral iron administration, ferroportin disease, aceruloplasminemia, or atransferrinemia, should also be investigated.[4,11] In the present report, we found five patients with C282Y heterozygosity and one with compound C282Y/H63D heterozygosity. Hepatosteatosis was the most common clinical expression in these cases.

The initial step in the diagnosis of hemochromatosis is to suspect the disorder in patients with unexplained liver injury test abnormalities, bronze diabetes, arthralgia, cardiomyopathy, or hypogonadism. Family history, especially first-degree relatives, should be investigated. High transferrin saturation and serum ferritin levels can be used to screen and diagnose HFE-related HH. These tests occasionally lead to missed diagnoses and some false-positive results. HFE mutation analysis is typically the initial genetic test conducted in individuals with hemochromatosis, especially in European countries due to a high prevalence of HH [1, 11]. In Türkiye, HFE gene mutation analysis should not be considered an initial test in the diagnosis of hemochromatosis because of its low prevalence. MRI techniques are available for quantifying liver iron concentration and have shown a good correlation with liver biopsy.[16] Confounder-corrected R2*-based liver iron content (LIC) quantification is the most clinically useful method, with the strongest supporting evidence for providing a precise and reliable measurement of LIC. This technique is commonly available in many MRI scanners. Although liver biopsy is currently the preferred diagnostic and prognostic indicator method for iron overload disorders, in countries with a low prevalence of HH, it is feasible to evaluate organ iron accumulation with MRI first to exclude the disease.

In conclusion, hemochromatosis has been a life-threatening disease with high morbidity and mortality in some cases. Patient and physician awareness of hemochromatosis is the first step toward the successful management of the disease

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Figure Legends

Figure 1. Correlation of non-invasive fibrosis markers with the liver biopsy fibrosis stage

Figure 2. Median (95% CI) values of non-invasive fibrosis indicators at different stages of liver biopsy

Figure 3. Relationship between stage in liver biopsy and non-invasive indicators in patients with autoimmune hepatitis

Figure 4. Relationship between stage in liver biopsy and non-invasive indicators in patients with overlap syndrome

Figure 5. Relationship between stage and non-invasive indicators in liver biopsy in MASLD patients

Table 1. Characteristics of patients with C282Y homozygotes hemochromatosis

Case	Age at diagnosis	Sex	Diagnosis date	Hepatic manifestation at diagnosis	Extrahepatic manifestation at diagnosis	TS (normal range: 13-45%) / Ferritin (normal range: female 13-150ng/mL, male 30-400ng/mL)	MRI at diagnosis	Liver biopsy at diagnosis	Family history
1	25	M	2021	Hepatosteatosis		76/1442	Severe Hepatosteatosis (Dixon FF= 24%) Mild-moderate iron accumulation (R2 *=245s-1 T2 *=4.5ms	60% macrovesicular steatosis, HIC:1600 µg/gram dry weight HII:1.6	Sibling of case 6
2	52	M	2015	Cirrhosis	Diabetes mellitus Hypopituitarism Libido loss Hypothyroidism Heart failure Atrial fibrilation	79/3332	Severe iron accumulation (LIC at PD sequence= 350 µmol/g)	Grade 4 iron staining	
3	67	M	2016	Cirrhosis with HCC	Bronze Diabetes Arthropathy	72/5264	N/A	N/A	
4	52	F	2018	Hepatosteatosis		82/256	N/A	N/A	Sister
5	63	F	2014	Chronic HBV infection		43/1501	No iron accumulation LIC at GRE sequence= 30µmol/g	N/A	
6	33	M	2021	ALD		81/2014	Severe hepatosteatosis (DixonFF= 20%) Moderate iron accumulation (R2 *=241s-1	40% macrovesicular steatosis, HIC:2500 µg/gram HII:1.35	Brother of Case 6

							T2 *=3.8ms		

TS: Transferrin saturation; MRI: Magnetic resonance imaging; FF: Fat fraction; HIC: Hepatic iron concentration; HII: Hepatic iron indeks; LIC: Liver iron concentration; HCC: Hepatocelular carcinoma; HBV: Hepatitis B virus; ALD: Alcoholic liver disease.

Table 2. Demographic and laboratory data of patients based on the HFE gene mutation

C282Y homozygous								**C282Y heterozygous/ C282Y compound heterozygous**						
Case	**1**	**2**	**3**	**4**	**5**	**6**	**Mean±SD/ Median**	**7**	**8**	**9**	**10**	**11**	**12**	**Mean±SD/ Median**
Age	25	52	67	52	63	33	**48.6±16.5**	42	55	28	60	61	73	**53.1±15.8**
Gender	M	M	M	F	F	M		F	M	M	F	M	M	
Hemoglobin (g/L)	15.7	13.0	15.2	14.0	14.0	14,7	**14.4±0.96**	12.3	14.5	17.4	14.3	14.1	16.1	**14.7±1.76**
AST(U/L)	40	52	104	17	19	67	**46 (17-104)**	33	68	16	27	23	33	**30 (16-68)**
ALT (U/L)	106	31	94	20	16	143	**62.5 (16-143)**	53	60	11	34	25	35	**34.5 (11-60)**
GGT (U/L)	37	175	85	22	13	34	**35.5 (13-175)**	16	226	10	21	23	81	**22 (10-226)**
Albumin(g/dL)	48.4	36.0	33.3	43.0	42.0	47.0	**41.5±6.0**	46.7	47.6	51.6	47.9	46.3	47.0	**47.8±1.9**

INR	1.12	1.23	0.98	0.95	0.99	0.98	**1.04±0.1**	0.84	0.84	1.03	1.02	1.1	0.97	**0.96±0.1**
Bilirubin(mg/dL)	0.34	1.30	0.88	1.10	0.56	0.6	**0.79±0.36**	1.23	0.98	1.91	0.5	0.5	0.81	**0.98±0.53**
TS (%)	76	79	72	82	43	81	**77.5 (43-82)**	71	61	52	43	38	40	**47.5 (38-71)**
Ferritin (ng/mL)	1442	3332	5264	256	1501	2014	**1757.5 (256-5264)**	952	1106	36	262	76	580	**421 (36-1106)**

Abbrevations: M: Male; F: Female; AST: Aspartat aminotransferase; ALT: Alanine aminotransferase; GGT: Gamma glutamil transferase; INR: International normalized ratio TS: Transferrin saturation.