sciendo Acta Marisiensis - Seria Medica 2022;68(4):179-182 DOI: 10.2478/amma-2022-0031

RESEARCH ARTICLE

Hereditary hemochromatosis: Retrospective study on clinical data from Emergency County Hospital Mures

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Objective: Hereditary hemochromatosis, or primary hemochromatosis, is a recessive genetic liver disorder caused by iron accumulation in tissues. This study evaluates patients with hereditary hemochromatosis to determine correlations between clinical and laboratory data. **Methods**: The data analyzed in this study was gathered from the discharge records from 2019 to 2021 of the Gastroenterology Department of the Mures Country Emergency Clinical Hospital. 15 patients with hemochromatosis were sampled during the studied period. **Results**: Hepatic cirrhosis is present in 67% of the studied group of patients, 40% of patients presented hypertension and 20% of patients showed diabetes mellitus and portal hypertension. Positive correlations were obtained between serum iron and alkaline phosphatase (r=0.8536), between serum iron and lactate dehydrogenase (r=0.7381), and between serum iron and urea (r = 0.79). Positive, strong correlation between ferritin and serum iron (r=0.7719), GOT (r=0.778) and GPT (r=0.6108). total bilirubin and direct bilirubin (r = 0.85), between total bilirubin and GOT (r = 0.68) and GPT (r = 0.82). **Conclusions**: Excess iron stored is influencing organ function trough reactive oxygen species, the hepatic signs being a main participant in the clinical presentation, while serum iron cause damage to other tissues such as myocardium, pancreas and kidneys. Treatment for hemochromatosis includes phlebotomies, and iron chelation with Deferoxamine.

Keywords: hemochromatosis, iron, cirrhosis, reactive oxygen species, phlebotomy

Received 10 October 2022 / Accepted 11 December 2022

Introduction

Genetic liver diseases are disorders caused by specific genetic defects that cause metabolic anomalies and they evolve with chronic liver disease. Examples of such inherited disorders include hereditary hemochromatosis, Wilson's disease and AAT deficit [1].

There are 2 main types of hemochromatosis: hereditary hemochromatosis and acquired hemochromatosis. Hereditary Hemochromatosis, also known as primary hemochromatosis, is a genetic condition, involving the iron metabolism, that follows a recessive inheritance pattern. The cause of the condition is an increase in iron absorption because of the mutation of the HFE gene. Acquired hemochromatosis, or secondary hemochromatosis, on the other hand, is caused by an excessive parenteral administration of iron [2].

The most common HFE mutations are C282Y, a homozygous mutation involving the fourth exon of the HFE gene, which results in changing of cysteine to tyrosine at the 282 position, H63D, a mutation related to the second exon of the HFE gene where aspartate replaces histidine at the 63 position, and S65C. The HFE gene encodes membrane protein similar to MHC class I proteins. This protein function is to regulate the hepatic synthesis of hepcidin. The defect of the HFE gene results in the deficit of hepcidin up-regulation, resulting in low levels of hepcidin. 90% of Hereditary hemochromatosis in Western Europe result from defects in this gene [3].

The aim of this retrospective study is to evaluate laboratory and clinical data on patients with hemochromatosis and to determine correlations between specific biomarkers involved in hemochromatosis pathology.

Methods

Data for this retrospective study was obtained from the discharge records of the patients with hemochromatosis that were admitted in the Gastroenterology Department of the Mures Country Emergency Clinical Hospital between 2019-2021. Authorization from ethics committee of the hospital was obtained prior to data gathering. Data extracted contains laboratory values such as the blood count, the international normalized ratio, ferritin, serum iron, total and direct bilirubin, cholesterol, creatinine, glutamic pyruvic transaminase, glutamic oxaloacetic transaminase, lactate dehydrogenase, gamma GT, alkaline phosphatase, urea, uric acid. Other non-numerical data collected included reasons for hospitalization, treatment and other conditions. For the statistical analysis, p values of less than 0.05 are considered significant, so the alternate hypothesis will be accepted, and p values greater than 0.05 will be consider not significant, so the null hypothesis will be accepted.

Results

After reviewing the discharge records from the years from 2019 to 2021, a total of 15 patients were found with hemochromatosis. Out out them, 11 were males and 4 were females, resulting in gender ratio of 2.75:1. The average age at presentation is 52, with the lowest age being 33, and the oldest patient being 69.

Hepatic cirrhosis is the one of the most frequent conditions associated with hemochromatosis, present in 67% of the studied group of patients. Likewise, chronic alcoholism

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was diagnosticated in 5 patients, associated with cirrhosis in 4 patients and with steatosis in 1 patient, it being a key factor in the progression of fibrosis and development of cirrhosis in patients with hemochromatosis. Other conditions associated with hemochromatosis include hypertension (40% of patients), diabetes mellitus (20% of patients) and portal hypertension (20%).

From the studied population of 15 patients with hemochromatosis, 13 presented with INR modifications, showing a correlation between hemochromatosis and high INR. Serum iron was elevated in 53% of cases at the moment of hospitalization. Because of the reduced sample and the high variations between patients, for determining the correlations only patients admitted for hospitalization will be considered for the next correlations.

Strong, positive correlations were obtained between serum iron and alkaline phosphatase (r = 0.8536), between serum iron and lactate dehydrogenase (r=0.7381), and between serum iron and urea (r = 0.79), suggesting a direct relationship between iron accumulation and damage in other tissues such as bile ducts or kidneys. No correlation was found between serum iron and gamma GT (r = 0.1731). Ferritin levels were compared with serum iron, GOT (glutamic pyruvic transaminase) and GPT (glutamic oxaloacetic transaminase). After removing outliers and applying Pearson's test, R values of 0.7719, 0.778 and 0.6108 were obtained, respectively, resulting positive, strong correlation between ferritin and serum iron, GOT and GPT, suggesting a direct relationship between liver damage and iron stores, respectively serum iron.

The relationship between transaminases and iron stores is represented in Figure 1, showing GOT values more elevated than GPT in relationship to ferritin.

The relationship between alkaline phosphatase and serum iron is represented in Figure 2.

Liver enzymes are also modified in hemochromatosis, with 60% presenting elevated GPT (glutamic pyruvic transaminase) and 66 % elevated GOT (glutamic oxaloacetic transaminase) at hospitalization. Alkaline phosphatase and lactate dehydrogenase were elevated in 46.6% of patients, and gamma GT was elevated in 60% of patients. Means of transaminases values from laboratory data, for admission and discharge, were compared, and T test for paired data was applied for GPT values, resulting a p value of 0.569, considered not significant. Wilcoxon test for matched pairs was performed for GOT values, resulting a not significant p value of 0.812. Furthermore, 60% of patients presented with elevated bilirubin and r value of 0.85 shows a strong, positive correlation between total bilirubin and direct bilirubin.

Figure 3 shows the correlation between total bilirubin and GOT.

From the patient sample studied, only 5 had phlebotomies, with blood emissions between 300ml and 500ml. Among the reasons why patients did not had venesection are anemia, upper digestive hemorrhage caused by cirrhosis, lower digestive hemorrhage or kidney failure.

Discussion

The small patient sample obtained in the studied period and the lack of some categories of laboratory data from the discharge reports could have resulted in some source of bias in the final statistical results.

The most common presentation of patients with hemochromatosis in the studied group is related to hepatic related symptoms, such as alteration to the general condition,

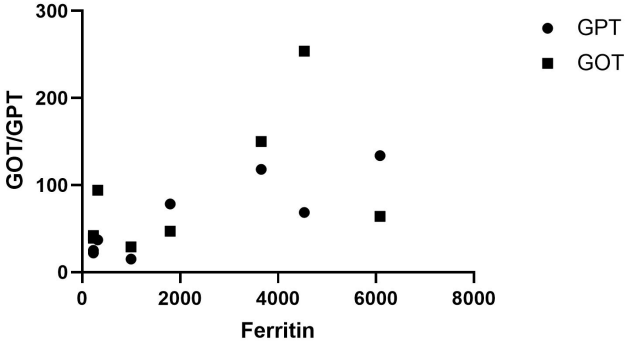

Fig. 1. The correlation between ferritin and transaminases

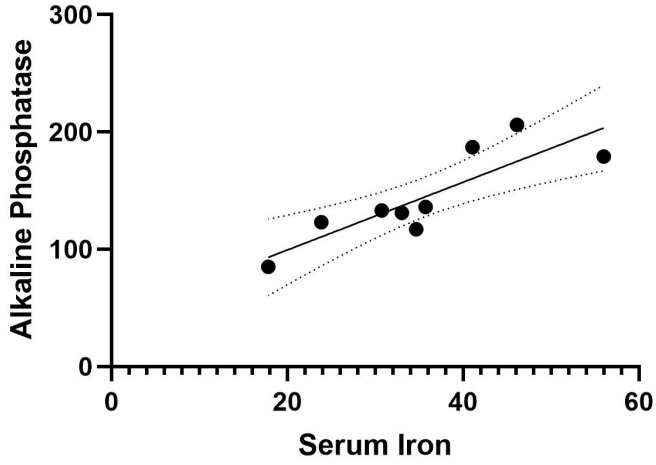

Fig. 2. The correlation between serum iron and alkaline phosphatase.

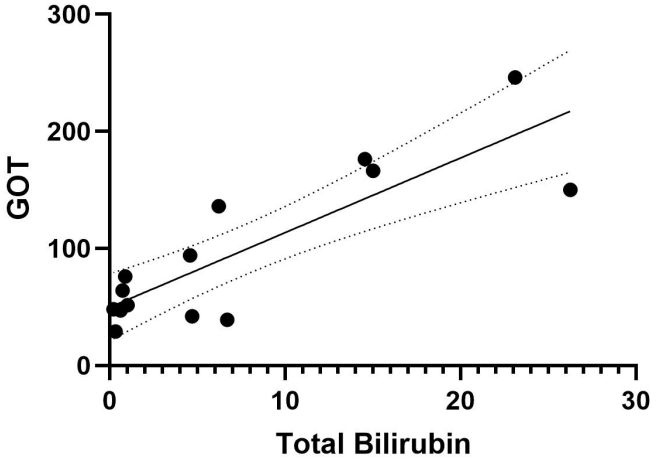

Fig. 3. The correlation between total bilirubin and GOT

abdominal pain, fatigue, loss of appetite, jaundice, hepatic encephalopathy. Associated conditions include steatosis, cirrhosis, toxic and viral hepatitis, portal hypertension, coagulation dysfunction, cardiac and renal illness.

A study conducted on C282Y homozygous hemochromatosis patients showed that drinking more than 60g of alcohol per day render patients with hemochromatosis 9 times more likely to develop cirrhosis [4]. On the other hand, a study which included 386 homozygotic hemochromatosis patients, only 23.4% presented cirrhosis, with a greater prevalence in men [5].

In hemochromatosis, liver damage caused by iron accumulation leads to a decrease in the hepatic synthesis of coagulation factors and an increase in the prothrombin time, observed through an increase in INR. It is also a possible indicator of the severity of the disease, as patients with higher values associate cirrhosis, diabetes and even hepatic encephalopathy [6].

Total and direct bilirubin suffered modifications in a significant number of hemochromatosis patients, as strong, positive correlations were obtained between total bilirubin and direct bilirubin, showing that bilirubin is an indicator of liver damage in hemochromatosis, beside transaminases.

In-patient treatment includes phlebotomies, also known as venesection, to reduce serum iron. Anemia and severe heart disease are relative contraindications for phlebotomies, so not all patients had phlebotomies during hospitalization [7].

The reduced prevalence of female patients in hemochromatosis could be explained by the fact that females can remove the excess iron through menstruation. As a result, females tend to become symptomatic later in life, in general post menopause, while men will develop symptoms earlier [8].

In hemochromatosis, the low levels of hepcidin lead to increased iron absorption by overexpression of ferroportin. Increased free intracellular iron generates reactive oxygen species through Fenton and Haber-Weiss reaction, leading to tissue lesions and cirrhosis. The superoxide ion (O2-) reacts to ferric iron, and the resulting ferrous iron reacts with hydrogen peroxide (H2O2), resulting hydroxyl radicals (OH), which are highly reactive. Hydroxyl radicals lead to phospholipids peroxidation within cellular membranes, oxidation of amino acid side-chains, protein fragmentation, DNA mutation and, eventually, cell death [9]. The death of hepatocytes leads to the release of ferritin and transaminases in circulation, leading to the increase in their values specific to hereditary hemochromatosis.

The increasing of transferrin saturation is the prime biochemical modification in hereditary hemochromatosis. This is followed by the increase of ferritin as the parenchymal cells are overloaded with iron [10]. Studies conducted on hemochromatosis and other iron overload conditions showed a correlation between onset of cirrhosis and ferritin values [11,12]. However, as ferritin is an acute phase reactant, its levels will be elevated in neoplasia and inflammatory conditions such as rheumatoid arthritis, autoimmune disorders. Patients are diagnosticated after evaluating elevated transferrin saturation and serum ferritin and molecular genetic testing for C282Y, H63D, and S65C can be used for confirmation [12].

Current treatment options for hereditary hemochromatosis include therapeutic phlebotomy, iron chelators such as Deferoxamine I.V., and diet containing mainly non-hemin iron, which is harder to absorb. Future treatment could include mini-hepcidin analogs, consisting of 7–9 N-terminal amino acids with a single cysteine, therapy to reduce intestinal iron absorption [13]. The current treatment of hemochromatosis represents a challenge in particular in Romania caused by the lack of chelators and absence of a national programme to support the cost of this therapy.

Conclusions

Excess iron stored is influencing organ function trough reactive oxygen species, the hepatic signs being a main participant in the clinical presentation, while serum iron cause damage to other tissues such as myocardium, pancreas and kidneys. Damage to hepatocytes can be also evaluated with bilirubin, alkaline phosphatase and lactate dehydrogenase. Moreover, INR, a possible indicator of the severity of the condition, was elevated in 86% of patients. Alcohol consumption is a key factor in evolution of the disease. For diagnostic, transferrin saturation and ferritin are the main biomarkers. Current treatment options include Deferoxamine for iron chelation and therapeutic phlebotomies to reduce free iron.

Author contribution

VS - Conception and design, acquisition of data, analysis and interpretation.

Conflict of interest

None to declare.

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