Review Article

Evaluation of Hemochromatosis, Diagnosis and Management: Simple Literature Review

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Abstract

Background: Hemochromatosis is an autosomal recessive genetic disorder characterized by abnormal iron regulation in the body leading to excessive iron deposition in multiple organs. Most of the patients of hemochromatosis are presymptomatic or asymptomatic. Nevertheless, a minority of patients presents with severe complications. **Objective:** In this study, we aimed to discuss the published literature focused on diagnosing and managing hemochromatosis. **Method:** PubMed database was used for articles selection, and the following keys were used in the mesh ((“hemochromatosis”[Mesh]) and (“hemochromatosis management”[Mesh])). The articles' selection was based on the relevance to the topic as their primary endpoint. **Conclusion:** The stage of the disease and particularly the extent of iron overloading should be the parameters that are dependent on assessment and treatment. Phlebotomy is the mainstay of treatment in hemochromatosis cases. It improves insulin sensitivity, fatigue, and skin pigmentation. Initiating the phlebotomy before the development of liver cirrhosis has shown a significant decrease in morbidity and mortality rates. Iron chelation therapy can be an option when the hemoglobin of the patients cannot tolerate therapeutic phlebotomy.

Keywords: Hemochromatosis, Diagnosis, Management Approach

Introduction

Hemochromatosis is an autosomal recessive genetic disorder [1, 2] characterized by abnormal iron regulation in the body [3, 4]. It is associated with excessive iron deposition in multiple organs, which may lead subsequently to multiple organ dysfunction. Different life-threatening complications can develop, such as diabetes, cirrhosis, and heart failure. It has been called “bronze diabetes” because it affects the pancreas and causes discoloration of the skin. Hereditary hemochromatosis is still considered as the most common genetic disorder in Caucasians. It most commonly arises from a mutation in the human hemochromatosis protein (HFE) gene and this gene was first described in 1996 [5-7]. It is common in people with northern European descent, Nordic or Celtic origin in particular with a prevalence of 1 per 220-250 individuals [8, 9]. In this article, we aimed to review the published literature that tackled this disease and discussed its complications and management.

Method:

PubMed database was used for articles selection, and the following keys were used in the mesh ((“hemochromatosis”[Mesh]) and (“hemochromatosis management”[Mesh])). The articles' selection was based on the relevance to the topic as their primary endpoint. Regarding the inclusion criteria, the articles were selected based on including one of the following topics: hemochromatosis, clinical manifestations, diagnosis, and management. Exclusion criteria were all other articles which do not have one of these topics as their primary endpoint.

Discussion:

Traditionally, it has been thought that all individuals, who are genetically susceptible to develop iron overload syndromes,

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will develop phenotypic expression. Later, HFE-related hereditary hemochromatosis, with the advancement of genetic testing, got more identified in asymptomatic individuals. It also appeared in presymptomatic relatives of the previously diagnosed patients [7]. Therefore, HFE-related hereditary hemochromatosis patients might be diagnosed by genetic testing without or before developing any manifestations [10, 11]. Recent studies have clarified that around 70% of C282Y homozygotes develop phenotypic expression and the severe complications of hemochromatosis will appear in less than 10% of C282Y homozygotes [7, 10]. Therefore, the European Association for the Study of Liver Diseases in 2000 staged hemochromatosis into 3 different stages based on the genetic susceptibility and the disease course [11].

These stages are defined as follows:

1. Patients with a genetic disorder with no increase in iron stores who have ‘‘genetic susceptibility’’.
2. Patients with the genetic disorder who have phenotypic evidence of iron overload but are without tissue or organ damage.
3. Individuals who have the genetic disorder with iron overload and have an iron deposition to the degree that tissue and organ damage occurs.

Clinical Presentation:

As we implied earlier, most of the patients of hemochromatosis are diagnosed presymptomatic due to the advancement in diagnostics. This changed our look at the disease and made it an easy and early detected disease after it was only considered as severe and life-threatening [12]. Nevertheless, a minority of patients presents with severe complications, such as heart failure, liver function impairment, or diabetes [13, 14]. Hemochromatosis in children is associated with more cases of symptomatic heart failure and other endocrinopathies than adults. Hypo-gonadotrophic hypogonadism is one of the common endocrinopathies in juvenile hemochromatosis [12, 15]. It will lead eventually to impotence and decreased libido in men [16]. The reason behind it is the deposition of iron in the anterior pituitary causing a significant decrease in trophic hormones secretion. In females, amenorrhea may develop but it is much rarer than hypogonadism in men [17, 18].

Hepatomegaly, progressive liver fibrosis and potential cirrhosis may arise in the liver but in the early stages, they can be reversible. Other associated liver diseases can worsen the complications but the most harmful co-factor is excessive alcohol consumption. Liver involvement may not appear in liver function laboratory tests in the beginning because the iron deposition in hepatocytes may not be inflammatory at the start and may not lead to fibrosis [19, 20]. Hepatic liver enzymes elevations are mostly seen when there is another liver disease. The most dangerous complication of the hepatic iron overload is hepatocellular carcinoma [21].

Other than liver involvement, there are several common symptoms, such as weakness and easy fatigability, and skin hyperpigmentation [22]. Half of the symptomatic patients develop diabetes mellitus because the iron deposition in the pancreas occurs in beta cells [16]. In addition, there is also a possibility for deposition of iron within the joints that may lead to arthritis involving most commonly metacarpophalangeal joints. The involvement of joints may develop chronic inflammation of the joints leading eventually to Pseudogout or Chondrocalcinosis [16, 23].

Diagnosis:

In cases of suspected hemochromatosis, the next step is testing serum ferritin and transferrin saturation levels [5]. In hemochromatosis, it is expected to have high ferritin and transferrin saturation of more than 45% [7, 24]. Nevertheless, they cannot be used to confirm the diagnosis because they can be raised in cases of excessive alcohol intake or severe inflammation. Next, HFE genotype has to be tested in the suspected patients who have compatible clinical features with hemochromatosis, and patients’ first degree relatives even if there were no symptoms [5].

In general, the minimum criteria for the diagnosis of hereditary hemochromatosis are increased storage of iron and C282Y HFE gene mutation [25]. As we mentioned earlier, the presence of a gene mutation does not mandate considering the case as an active disease and it does not require unnecessary aggressive intervention. The extent of iron overloading should be the parameter that is dependent on assessment and treatment [26, 27].

Treatment:

Phlebotomy is the mainstay of treatment in hemochromatosis cases. It might be required even twice weekly to lower the ferritin level to <50 ug/l. After that, maintaining the ferritin levels between 50-100 ug/l is cardinal in the treatment process [7, 28]. Initiating the phlebotomy before the development of liver cirrhosis has shown a significant decrease in morbidity and mortality rates. Normal life expectancy is expected in patients who did not develop liver cirrhosis. The risk of cirrhosis significantly increases with a prevalence of 20-45% in patients who present with a ferritin level of >1000 ug/l. Moreover, the risk of hepatocellular carcinoma is increased in patients with cirrhosis with an annual incidence of 3-4%. Therefore, liver biopsy should be considered in such patients. Early detection of potential malignancy can lead to early detection and probable prevention of some serious complications, such as esophageal varices [5, 7]. Phlebotomy improves insulin sensitivity, fatigue, and skin pigmentation. Unfortunately, it can rarely reverse preexisting end-organ damage. Treating the associated end-organ dysfunction is indicated as insulin for pancreatic dysfunction. Cessation of bad habits like alcohol intake is mandatory because alcohol can significantly worsen hepatic and pancreatic complications.

Iron chelation therapy can be an option when the hemoglobin of the patients cannot tolerate therapeutic phlebotomy. Iron-chelating agents help in mobilization and excretion of iron. They are available as intravenous agents, such as Deferoxamine and there are oral iron chelators, such as Deferiprone and Deferasirox [28].

Conclusion:

The stage of the disease and particularly the extent of iron overloading should be the parameters that are dependent on assessment and treatment. Phlebotomy is the mainstay of treatment in hemochromatosis cases. It improves insulin sensitivity, fatigue, and skin pigmentation. Initiating the phlebotomy before the development of liver cirrhosis has shown a significant decrease in morbidity and mortality rates. Iron chelation therapy can be an option when the hemoglobin of the patients cannot tolerate therapeutic phlebotomy.

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