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Review Article

Primary Non-HFE Hemochromatosis: A Review

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Abstract

Iron homeostasis is a complex process in which iron uptake and use are tightly balanced. Primary Type 1 or HFE hemochromatosis results from homozygous mutations in the gene that encodes human homeostatic iron regulator (known as human factors engineering, HFE) protein, a regulator of hepcidin, and makes up approximately 90% of all hemochromatosis cases. However, four types of hemochromatosis do not involve the HFE gene. They are non-HFE hemochromatosis type 2A (HFE2, encoding HJV), type 2B (HAMP, encoding hepcidin), type 3 (TFR2, encoding transferring receptor-2), and types 4A and B (SLC40A1, encoding ferroportin. Non-HFE hemochromatosis is extremely rare. Pathogenic allele frequencies have been estimated to be 74/100,000 for type 2A, 20/100,000 for type 2B, 30/100,000 for type 3, and 90/100,000 for type 4 hemochromatosis. Current guidelines recommend that the diagnosis be made by ruling out HFE mutations, history, physical examination, laboratory values (ferritin and transferrin saturation), magnetic resonance or other imaging, and liver biopsy if needed. While less common, non-HFE hemochromatosis can cause iron overload as severe as the HFE type. In most cases, treatment involves phlebotomy and is successful if started before irreversible damage occurs. Early diagnosis and treatment are important because it prevents chronic liver disease. This review updates the mutations and their pathogenetic consequences, the clinical picture, diagnostic guidelines, and treatment of hemochromatosis.

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Abbreviations: AASLD, American Association for the Study of Liver Disease; ACG, American College of Gastroenterology; APRI, aminotransferase-to-platelet ratio index; DMT1, divalent metal cation transporter 1; EASL, European Association for the Study of the Liver; ERK-MAPK, extracellular signal-regulated kinase and mitogen-activated protein kinase; Fe, iron; FPN, ferroportin; GPI, glycophosphatidylinositol; HAMP, hepcidin antimicrobial peptide; HFE, human factors engineering; Hgb, hemoglobin; HH, hereditary hemochromatosis; HJV, hemojuvelin protein; JH, juvenile hemochromatosis; MRI, magnetic resonance imaging; NGS, next generation sequencing; PMP6, bone morphogenic protein 6; SLC40A1, solute carrier family 40 member 1; TFR, transferrin receptor; TS, transferrin saturation; ZIP14, zinc transporter.

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Introduction

A major pathway in iron homeostasis is the absorption of dietary iron, which begins with gastric acidification of ferric reductase on the apical membrane of enterocytes, and conversion of iron from oxidized Fe^{3+} to reduced Fe^{2+} in duodenal and proximal jejunal enterocytes. Divalent metal cation transporter 1 (DMT1) internalizes Fe^{2+}, which is temporarily sequestered in the cytoplasm as ferritin or transported by ferroportin (FPN) through the basolateral membrane. Hepcidin controls the FPN membrane concentration, which triggers internalization and degradation of the transporter. Fe^{2+} is then oxidized to Fe^{3+} by ceruloplasmin and Hephaestion and binds to transferrin for transport throughout the body in the circulation.

Upon reaching the liver, the transferrin-ferric iron complex binds to the transferrin receptor 1, and enters the cell by receptor-mediated endocytosis (Fig. 1). Binding of the transferrin-Fe^{3+} complex to transferrin receptor 1 (TFR1) has two effects. Fe^{3+} acidification leads to release and transport into the cytoplasm by DMT1 and zinc transporter (ZIP14). Fe^{3+} is then used by the cell, and dissociation of the human factors engineering (HFE) protein from TFR1-HFE complex. HFE protein, encoded by the HFE gene on chromosome 6p, is a major histocompatibility complex (MHC) class I protein that is an upstream regulator of hepcidin.[1] Dissociated HFE interacts with transferrin receptor 2 (TFR2), leading to increased stabilization and activation of bone morphogenic protein 6 (BMP6). BMP6 phosphorylates SMAD 1/5/8 and recruits SMAD 1/5/8 and SMAD 4 to HAMP proximal promoter, leading to increased transcription and synthesis of hepcidin. Hemojuvelin protein (HJV), a glycophosphatidylinositol (GPI)-linked membrane protein, is a coreceptor in the BMP6 signaling pathway, and is required for the upregulation of hepcidin gene expression.[2] Additionally, the extracellular signal-regulated kinase and mitogen-activated protein kinase (ERK-MAPK) pathway transduces extracellular signals intracellularly, including stimulation of the HAMP promoter, which leads to increased synthesis of hepcidin.[3] Figure 1 shows the pathways involved in non-HFE hemochromatosis.

Mutations in genes that control the absorption of iron result in primary hemochromatosis. A homozygous mutation at a single locus in the HAMP gene that leads to downregulation of hepcidin synthesis causes 80–90% of all hemochromatosis cases.[4] The remaining cases originate from mutations of other than the HFE gene, and fall under the broad umbrella of non-HFE hemochromatosis.[5] The understanding of mutations underlying non-HFE hemochromatosis has significantly expanded with the wider availability and use of gene sequencing. In 2008, Brissot *et al*. reviewed

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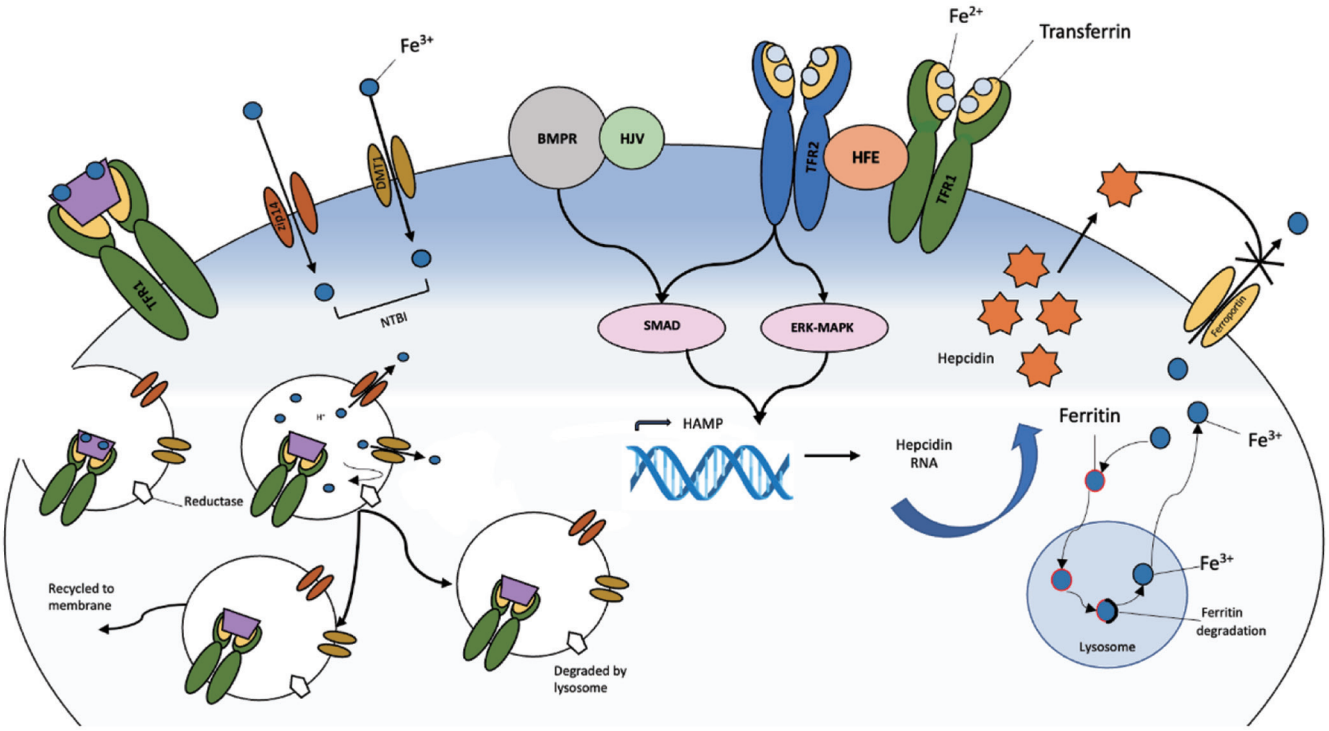

Fig. 1. Complex pathways of iron transport regulation in hepatocytes. Hepatocytes not only import and export iron, but also produce hepcidin, the master regulator of iron import through its action on FPN. FPN, ferroportin.

hemochromatosis and its diagnosis and treatment.[6] Our focus in this review is on non-HFE hemochromatosis, the mutations involved in pathogenesis, and recent guidelines on diagnosis and management.

Epidemiology

The regulation of iron homeostasis is a complicated process. Mutations of the *HOE* gene cause type 1 hemochromatosis. Mutations of several non-HFE genes result in four types of non-HFE hemochromatosis, namely *HFE2* encoding HJV (type 2A), *HAMP* encoding hepcidin (type 2B), *TFR2* encoding transferrin receptor-2 (type 3), and solute carrier family 40 member 1 (*SLC40A1*) encoding FPN 1 [6]. The allele frequencies of HJV (HFE2), TFR2, and HAMP mutations, range from 0.00007 to 0.0004.[6] The SLC40A1 variant has been associated with persons of African descent and has a reported allele frequency of around 0.0004.[7] Pathogenic allele frequencies have been estimated to be 74/100,000 for type 2A, 20/100,000 for type 2B, 30/100,000 for type 3, and 90/100,000 for type 4 hemochromatosis.[8]

Type 2A hemochromatosis

This type of non-HFE hemochromatosis, known as juvenile hemochromatosis (JH), results from either a homozygous or compound heterozygous mutation in the gene encoding HJV. The gene and mutation responsible for this presentation are located on chromosome 1q21.[9] The inheritance pattern for this type of hemochromatosis is autosomal recessive. In type 2A hemochromatosis, HJV mutation results in decreased BMPR-HJV-SMADn activity, which decreases transcription of HAMP downstream (Fig. 1). The consequent decrease in circulating hepcidin levels is severe, and accounts for presentation at an early age and the severity of disease.

Type 2B hemochromatosis

This type of hemochromatosis is also referred to as a JH and results from a homozygous or heterozygous mutation in the *HAMP* gene, which is located on chromosome 19q13. It is inherited in an autosomal recessive manner and is extremely rare. HAMP mutation leads to one of the more severe forms of hemochromatosis because of complete or nearly complete absence of hepcidin[10] and the consequent unrestrained FPN activity and iron transport (Figs. 1 and 2A) that accounts for the early age at onset, and the severity of presentation.

Type 3 hemochromatosis

This type of hemochromatosis results from a homozygous or compound heterozygous mutation in the gene encoding transferrin receptor 2 (TFR2), which is located on chromosome 7q22. It is inherited in an autosomal recessive manner.[11] Mutation in the *TFR2* gene leads to dysregulation in the interaction of the iron-transferrin complex with its receptor, and subsequent interruption in ERK-MAPK cascade, which decreased HAMP transcription and leads to low hepcidin level (Figs. 1 and 2A).

Type 4 hemochromatosis

Hemochromatosis type 4 differs from the other types of non-HFE hemochromatosis in that it results from a heterozygous mutation in the *SLC40A1* gene, which encodes FPN. It is inherited in an autosomal dominant manner. In type 4A, muta-

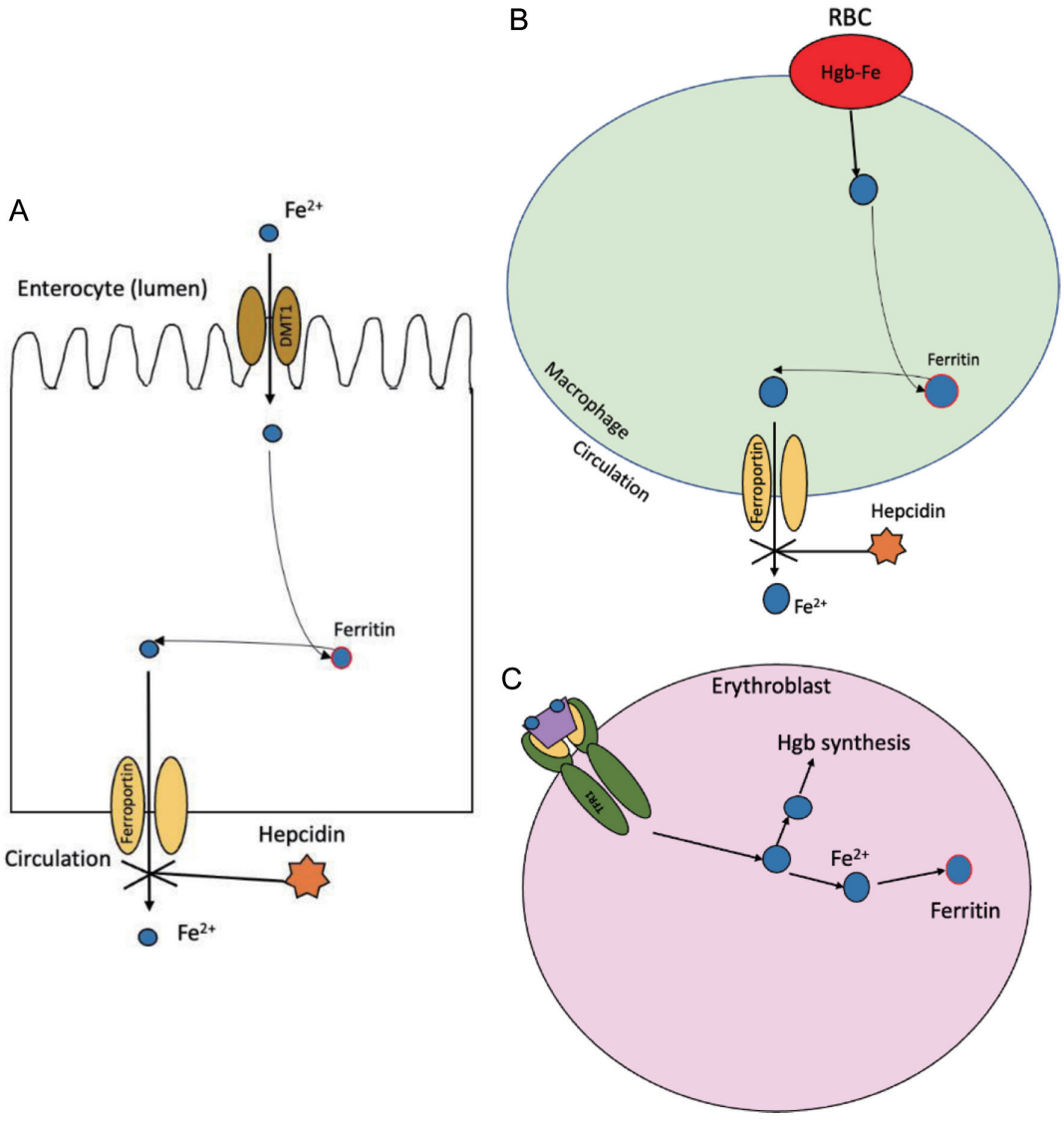

Fig. 2. Regulation of iron transport by cell type. (A) Regulation of iron transport in importer/exporter cells (e.g., enterocytes). (B) Regulation of iron transport in primarily exporter cells (e.g., macrophages). (C) Regulation of iron transport in primarily importer cells (e.g., erythroblasts and most other cells).

tions in SLC40A1 result in decreased sensitivity of FPN to hepcidin or complete loss of FPN activity[12] resulting in two major presentations. One involves early elevation in ferritin and low or normal transferrin saturation with iron predominantly stored in macrophages (Fig. 2B). The other a more classic presentation, Type 4B presents with parenchymal storage of iron and elevated transferrin levels (Fig. 2B, C).[13] Importer/exporter cells such as enterocytes, and exporter cells such as macrophages, have considerable FPN activity, which allows for iron to be exported out of the cell. Most other cells in the body are primarily importer cells and have low levels of FPN activity. If large amounts of iron are delivered to those cells, resulting in high intracellular iron, they are unable to export the excess, leading to iron overload (Fig. 2A, C).

Presentation and symptoms

Phenotypic manifestations of a particular mutation responsible for non-HFE hemochromatosis vary in the age of onset and severity of disease because each mutation affects different paths of the HAMP promoter-to-hepcidin expression biochemical signaling cascade. Life expectancy in this patient population varies and depends on the timing of diagnosis and treatment. If a diagnosis is made and treatment initiated before the development of cirrhosis, life expectancy is normal.[14]

JH

Type 2A

As discussed previously, type 2A hemochromatosis leads to severe iron overload and organ failure, usually before 30 years of age.[5] Symptoms, such as liver cirrhosis, cardiac involvement, diabetes, and dermatological changes, may be similar to adult-onset hemochromatosis, type 2A hemochromatosis frequently presents with hypogonadotropic hypogonadism. In some reports, abdominal pain was the earliest

manifestation, appearing in the first decade of life, followed by hypogonadotropic hypogonadism in the second decade, and by cardiomyopathy in the third decade.[15] The disease is not gender specific, with both males and females affected similarly. Overall, JH is associated with an early and severe iron overload state, and a more aggressive disease course compared with HFE hemochromatosis.[16] Patients with JH frequently have cardiac complications and often die of cardiovascular disease before 40 years of age.[5] For that reason, early detection is important, as timely phlebotomy can prevent significant organ damage.

Type 2B

Like type 2A, type 2B is considered a juvenile form of hemochromatosis. It is associated with severe iron overload and organ failure before 30 years of age.[17] Symptomatically, types 2A and 2B have very similar presentations.

Adult non-HFE hemochromatosis

Type 3

Type 3 hemochromatosis and HFE hemochromatosis have similar presentations,[5] with a variety of symptoms, such as abnormal liver function, skin changes, diabetes mellitus, hypogonadotropic hypogonadism, cardiac disease, and joint damage.[18] Like HFE hemochromatosis, the disease onset tends to occur later in adulthood, but if TFR2 and HFE mutations coexist in the same patient, disease onset may occur much earlier.[19]

Type 4

Type 4 hemochromatosis is a FPN disease, and unlike other types of non-HFE hemochromatosis, usually presents with low to normal transferrin saturation. The other hemochromatosis types tend to have elevated transferrin saturation. Type 4 hemochromatosis patients may have poor tolerance for therapeutic phlebotomy because impaired iron release from macrophages leads to intracellular iron overload, and mild iron deficiency anemia.[20] It is important to note, however, that there have been case reports of type 4 hemochromatosis that presented with high transferrin saturation.[21] The age of onset of type 4 hemochromatosis tends to be in late adulthood. In men, the majority of cases appear before 60 years of age. Women were noted to have a later onset of presentation.

Some studies have attempted to further characterize phenotypic presentation of non-HFE hemochromatosis mutations. Wu *et al*.[22] conducted a retrospective analysis of the correlation between genotype and phenotype of non-HFE hemochromatosis in 31 Chinese patients with non-HFE hemochromatosis. Type 2A hemochromatosis was frequently diagnosed at an earlier age, and the iron index was higher hemochromatosis type 2A and type 4 compared with other types. They also found that cirrhosis and diabetes were more prevalent in patients with type 4 hemochromatosis. They also reported that none of the hemochromatosis type 2A cases developed cirrhosis, and that arthropathy was rare in all types of hemochromatosis. Their study provides helpful insights into the phenotypic presentation of various non-HFE hemochromatosis genotypes. Its limitations included low statistical power because of the inclusion of only 31 patients, and the retrospective analysis could have introduced confounding variables.

Kumar *et al*.[22] conducted a retrospective study of the development of movement disorders with data obtained from hemochromatosis patients between 1988 and 2015. Only three of the 616 patients included in the study developed a movement disorder. One developed Parkinsonism, one developed choreiform movements, and one developed tremor. All patients had iron deposition in the brain, including the basal ganglia, dentate nucleus, red nucleus, and substantia nigra. Importantly, two of the three had non-HFE gene mutations. The study by Kumar *et al*.[22] highlighted movement disorders that is a symptom rarely described in non-HFE hemochromatosis. This study included data over a long period and was well powered, with 616 patients included, but was limited by retrospective design.

Diagnostic evaluation

The finding of an abnormal biochemical profile usually prompts a diagnostic workup of hemochromatosis. Elevated ferritin (>200 μg/L in women and >300 μg/L in men) is usually one of the first laboratory abnormalities that triggers diagnostic investigation.[23] However, ferritin is an acute-phase reactant and may be elevated for many other reasons including infection and inflammation, which should be ruled out. Another useful biochemical marker is transferrin saturation. As with primary hemochromatosis, a transferrin saturation of >45% suggests hemochromatosis. An exception is hemochromatosis type 4, in which transferrin saturation often does not exceed that threshold (Fig. 3).[24]

The 2019 guidelines of the American College of Gastroenterology (ACG) hemochromatosis recommend magnetic resonance imaging (MRI) in evaluating liver iron concentrations in this patient population, followed by liver biopsy if necessary.[25] Knowledge of the severity of iron deposition within the liver can guide therapy. With regard to establishing the type of hemochromatosis, the 2010 European Association for the Study of the Liver (EASL) guidelines recommend testing patients with high clinical suspicion of hemochromatosis (biochemical evidence or family history) for HFE mutations (C282Y) before considering screening for non-HFE mutations.[26] The ACG 2019 guidelines, on the other hand, recommend against further genetic screening in patients who test negative for type 1 hemochromatosis.[25] The same guidelines note a moderate quality of evidence for genetic counseling and screening for first-degree relatives of patients diagnosed with hemochromatosis.

Hepcidin levels are also helpful in the diagnosis of non-HFE hemochromatosis. Hemochromatosis types 2A and 2B, and type 3[27] have markedly suppressed hepcidin levels that are sometimes undetectable.[28] That differs from type 4B hemochromatosis, in which there is a lack of sensitivity of FPN to hepcidin, and levels of the latter are markedly increased.[29] Some reports suggest that the use of hepcidin levels in patients suspected of having hemochromatosis may guide genetic testing, especially for rare non-HFE types of hemochromatosis.[30] The hepcidin diagnostic kits that are commercially available are used primarily for the diagnosis of iron deficiency and have not been evaluated in hemochromatosis patients.[31] Commercial genetic tests for various types of hemochromatosis are available from Fulgent (Temple City, CA), Blueprint Genetics (Seattle, WA), Prevention Genetics (Marshfield, WI), Valencian Institute of Microbiology (Valencia, Spain), and Invitae (San Francisco, CA). However, most direct-to-consumer genetic testing kits do not yet offer testing for non-HFE hemochromatosis.

Many studies have investigated the role of genetic sequencing in the diagnosis of non-HFE hemochromatosis. A retrospective study of 36 patients by Ravasi *et al*.[32] investigated the value of next generation sequencing (NGS) for the diagnosis of non-HFE hemochromatosis. NGS identified six novel mutations in SLC40A1, three novel and one known mu-

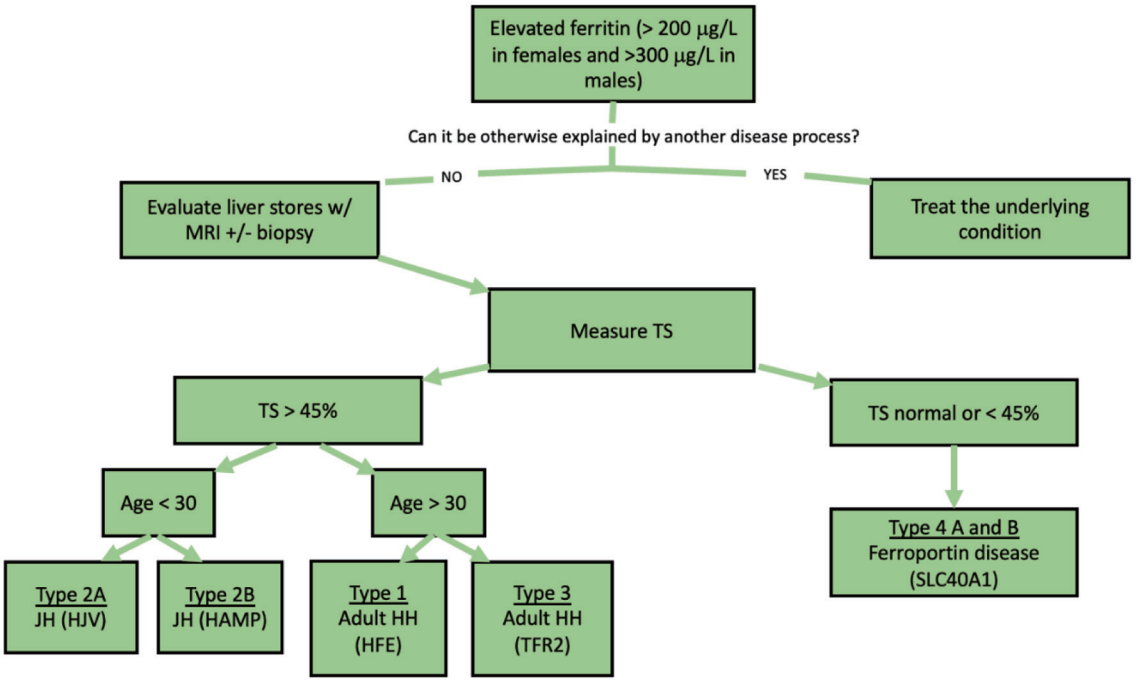

Fig. 3. Algorithm for the evaluation of hemochromatosis with a focus on non-HFE hemochromatosis. MRI, magnetic resonance imaging; TS, transferrin saturation; JH, juvenile hemochromatosis, HH, hereditary hemochromatosis; TFR, transferrin receptor; HAMP, hepcidin antimicrobial peptide; HJV, hemojuvelin protein; SLC40A1, solute carrier family 40 member 1.

tation in TFR2, one known mutation and a de-novo deletion in HJV, and a novel mutation in HAMP in 10 patients. They did not find genetic markers in 26 of the 36 patients. Genetic markers were not identified in most patients with non-HFE hemochromatosis. Wider use of NGS may identify more non-HFE mutations. The limitations of the study the small patient sample and its retrospective design. A retrospective study by Sun *et al*.[33] investigated the genetics underlying hemochromatosis in Tibetan patients. They included hospitalized patients, of whom only 73 had non-HFE hemochromatosis. They isolated non-HFE mutants, including five HJV mutations of G320V, p.Q312X, p.D249H, p.I281T, p.C321X, two TFR2 mutations: (Y250X, I238M), and two SLC40A1 mutations (V162del, N144H). The study provides an insight into specific mutations in non-HFE hemochromatosis. A study by Lv *et al*.[34] characterized mutations in hemochromatosis, including non-HFE types in 22 Chinese patients. Twenty-one of the twenty-two patients had one non-HFE mutation, and the study concluded that compound or combined heterozygous mutations of HJV or BMP/SMAD pathway genes may be a novel pattern of hemochromatosis pathogenesis. The study identified new mutations of non-HFE variants, but it was underpowered, with only 22 patients. It was also limited by being a retrospective study, which may have introduced confounding variables. Lanktree *et al*.[35] conducted a retrospective investigation of the diagnostic value of NGS in rare hemochromatosis cases. It reviewed only six patients, all of whom carried HFE2 mutations that were detected by NGS, which reaffirmed its value for advancing our understanding of non-HFE hemochromatosis. However, given the small number of patients, all of whom carried the same type of mutation, the study conclusions may not apply to mutations of other types. Badar *et al*.[36] conducted a retrospective study to assess the ability of NGS to detect five mutations associated with hemochromatosis. Their results were similar to those of McDonald *et al*.[37] that included 106 Italian patients with biochemical signs of iron overload. They found five mutations associated with hemochromatosis, which supports wider of NGS for prompt and accurate diagnosis, especially if registries with descriptions of the phenotypes of each mutation are developed. The study highlights the role of NGS in expanding our knowledge of mutations involved in hemochromatosis. Lastly, a retrospective study by Radio *et al*.[38] investigated the role of TFR2 mutations in non-HFE hemochromatosis pathogenesis in 45 Italian patients TFR2 biallelic mutations were found in seven of the 45 patients (15.6%).

The 2011 American Association for the Study of Liver Disease (AASLD) guidelines describe the evolution of the use of liver biopsy in the diagnosis of hemochromatosis over the years.[39] Liver biopsy is recommended to determine the presence of liver cirrhosis or fibrosis if the results of noninvasive tests are inconclusive. The guidelines state that the need for liver biopsy is usually guided by serum ferritin levels. Patients with serum ferritin levels of >1,000 µg/L or elevated aminotransferases are at an increased risk of developing liver cirrhosis and may benefit from a liver biopsy. Liver biopsies are recommended in patients with non-HFE hemochromatosis and elevated ferritin, aminotransferases, or other clinical indicators of liver disease. More recent guidelines published by the EASL in 2022 agree with that position. The AASLD guidelines recommend liver biopsy if serum ferritin is >1,000 µg/L or aminotransferases are elevated the EASL guidelines do not recommend liver biopsy for the diagnosis of iron overload or in patients with cirrhosis.[40] The EASL guidelines recommend that patients with hemochromatosis should be assessed for liver fibrosis with noninvasive tools such as transient elastography, serum FIB-4 level, or aspartate aminotransferase-to-platelet ratio index (APRI).[41] Liver biopsy is reserved for cases where the diagnosis of cirrhosis cannot be established noninvasively.[41]

Therapy

Therapeutic management of non-HFE hemochromatosis is similar to that of HFE hemochromatosis. The May 2022 guidelines of the Bioiron Society[8] are consistent with previous EASL recommendations. Phlebotomy remains the cornerstone of therapy, with a goal to reduce ferritin to 50–100 μg/L.[42] Because some types of non-HFE hemochromatosis may have an earlier onset and a more severe disease course, chelation therapies may be considered in addition to phlebotomy to improve iron elimination.[43] Overall, the goal for therapy in both HFE and non-HFE hemochromatosis is to decrease the iron overload burden, and phlebotomy remains the therapy of choice. The exception to that rule are non-HFE hemochromatosis types, e.g., 4A, that present with chronic anemia that precludes phlebotomy. In such cases, chelation agents are recommended.[8]

Successful lowering of ferritin levels improves survival and liver and skin manifestations, but it usually does not have a significant therapeutic effect on extrahepatic manifestations such as hypogonadism, joint symptoms, and diabetes mellitus.[42,44] Long-term survival similar to healthy controls has been reported in patients with hemochromatosis who undergo phlebotomy therapy before developing cirrhosis or diabetes.[45] According to the 2011 AASLD guidelines, any value of serum ferritin above the normal range is an indication for phlebotomy.[39] The 2019 ACG guidelines recommend phlebotomy as the first-line therapy, with chelation reserved for cases that are intolerant or refractory to phlebotomy.[25] Patients are advised to avoid supplemental iron and alcohol use, but currently there are no proven effective dietary restrictions.[46] Three chelating agents are FDA-approved for use in hemochromatosis patients, deferoxamine, deferiprone, and deferasirox. It is important to note, however, that the 2019 ACG guidelines recommend against the use of chelation as first-line therapy primarily because of treatment-associated hepatic and renal toxicity and a lack of large studies to support their effectiveness and safety. Liver transplantation is required in cases of hepatocellular carcinoma or decompensated cirrhosis.[47] Lastly, hepcidin analogs have been proposed as a therapy.[48] While there are some promising reports of their use as a maintenance therapy, data on the control of adequate iron storage disease in the liver is lacking.[49,50]

Conclusions

Advances in understanding of iron homeostasis and the cellular signaling pathway involved in hepcidin expression allow for a better understanding of the mutations involved in some of the rare types of hemochromatosis. Nonetheless, new phenotypic presentation and mutations responsible for non-HFE hemochromatosis are still being discovered. As NGS becomes more widely available, it may become a more economically viable diagnostic tool, facilitating an earlier diagnosis and providing better understanding of mutation types and incidence in the general population. Institution of therapy early in the disease process prevents progression and chronic liver disease. As we learn more about mutation types, there is an opportunity for the development of more effective targeted therapies.

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Conflict of interest

GYW has been an editor-in-chief of *Journal of Clinical and Translational Hepatology* since 2013. The other authors have no conflict of interests related to this publication.

Author contributions

Proposed concept for review and revised the manuscript with critical revisions (GYW), and drafted the manuscript (AT, DW).

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