Hemochromatosis

Genetics, pathophysiology, diagnosis, and treatment

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A brief history of hemochromatosis

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Introduction

In 1847, Virchow reported the occurrence of golden brown granular pigment in sites of hemorrhage and congestion; this pigment was soluble in sulfuric acid, yielded a red ash on ignition, and then produced a Prussian blue reaction[1]. Eighteen years later, Trousseau first described the syndrome of hepatic cirrhosis, pancreatic fibrosis, and cutaneous hyperpigmentation[2], but he did not recognize the involvement of iron in its pathogenesis. In 1867, Perls formulated the first practical acid ferrocyanide reaction for histologic analysis of iron, and applied the staining reaction to a variety of tissues[3]. Trousseau's report was followed by Troisier's account of 'diabète bronzé et cirrhose pigmentaire' in 1871[4]. In 1889, von Recklinghausen reported the use of the methods of Virchow and Perls to identify excess iron in tissues obtained at autopsy of persons who had 'hämochromatose'[5]. Following the theories of Virchow, von Recklinghausen erroneously believed that the iron-containing pigment was derived from blood (due to hemorrhage or hemolysis), rather than from primary iron deposition, but he also described another finely granular yellow pigment that occurs with hemosiderin in the liver and other tissues in hemochromatosis that does not react to the iron methods (hemofuscin = lipofuscin)[5]. During the next several decades, additional cases were reported using variations of the terminology of the French and German physicians. In 1935, the English gerontologist Sheldon summarized 311 carefully selected 'haemochromatosis' cases from the literature, establishing this as the name for the disorder and for his detailed monograph[6].

Etiology

Sheldon concluded that the absorption of iron and possibly that of other metals is increased in hemochromatosis, suggested that the disorder is an inborn error of metabolism that primarily affects men, and rejected hypotheses that diabetes, infections, intoxication, alcoholism, and other conditions cause hemochromatosis[6]. Clinical case series published in the interval 1935–1955 hinted that the disorder was more common than had been appreciated previously[7]. In the 1960s, MacDonald diverted attention from the true etiology of organ and tissue injury in hemochromatosis by concluding incorrectly that hemochromatosis and iron overload are consequences of alcoholism and other nutritional factors[8]. However, many other investigators reported additional evidence for central roles of a heritable factor and absorption of excess iron in hemochromatosis, and recognized that the clinical phenotype of hemochromatosis was variable and depended on sex, age, and coincidental occurrence of other disorders. Nonetheless, alcohol can increase the absorption of iron and lower the threshold for hepatic injury in hemochromatosis, alcoholism is common among case series of hemochromatosis patients, and excess alcohol use frequently mimics the primary abnormalities of iron metabolism typical of hemochromatosis. In most target organs of iron overload in hemochromatosis, a sequence of subcellular injury, cell death, and fibrosis occurs due to the excessive production of injurious free radicals in the presence of ever-increasing iron burdens. A murine genetic knockout model of hemochromatosis now provides an additional important means to assess the pathogenesis of iron overload[9, 9a].

Metal absorption and transport

The absorption of both inorganic and organic forms of iron is inappropriately increased, mechanisms to eliminate excess body iron are extremely limited, and transfer of iron

from enterocytes to the blood is the rate-controlling step in abnormal iron absorption in hemochromatosis. By demonstrating that the absorption of inorganic cobalt is also increased in hemochromatosis, Valberg and colleagues confirmed Sheldon's postulates regarding increased absorption of non-ferrous metals[10]. Other metals are also absorbed or retained in increased amounts in hemochromatosis, although their possible role in the pathogenesis of clinical abnormalities remains obscure. Enterocyte iron and non-ferrous metal uptake from the intestinal lumen probably depends on divalent cation transporters such as *Nramp2*/DCT1 and calreticulin[11–13], and on the interaction of wild-type and mutant *HFE* gene products with transferrin receptor at the basolateral membranes of enterocytes[14]. This provides a unifying concept of abnormal metal absorption in hemochromatosis. Further, the persistent deficiency of unsaturated transferrin and behavior of non-transferrin-bound plasma iron in hemochromatosis largely explain the histologic patterns of excess iron and non-ferrous metal deposition, especially in the liver[15, 16].

Diagnosis

In the first few decades after its original descriptions, hemochromatosis was often diagnosed at autopsy, primarily by recognition of the 'classic' triad of end-stage iron overload: cutaneous hyperpigmentation, diabetes mellitus, and hepatic cirrhosis. In 1962, Scheuer and colleagues reported a method of histologic grading of hepatic biopsy specimens prepared using Perls' technique. This study emphasized the characteristic gradient of iron distribution in hepatocytes in hemochromatosis, made it possible to semi-quantify hepatic iron content with minimal apparatus and thus diagnose the disorder ante-mortem, and demonstrated that some relatives of index cases had similar abnormalities of hepatic iron deposition[17]. Hepatic histology also provided prognostic information. The availability of reliable clinical measurements of serum iron, total serum iron-binding capacity, and serum ferritin in the 1960s and 1970s provided a basis for ascertaining the clinical phenotype of hemochromatosis. Consequently, variability of the phenotype among probands and affected family members became more apparent[18]. The hepatic iron index distinguished presumed homozygotes from heterozygotes and persons with alcoholism and other forms of iron overload and hepatic disease[19], and became the standard of diagnosis for more than a decade.

In 1975, Simon and colleagues reported that the genetic factor associated with hemochromatosis was closely linked to the human leukocyte antigen (HLA)-A locus[20]. By the late 1970s, HLA immunophenotyping was used to identify relatives of probands who also inherited two HLA-linked hemochromatosis alleles, sometimes before iron overload occurred. In 1996, Feder and colleagues discovered two missense mutations in an unusual major histocompatibility (MHC) class I gene on 6p known as *HFE*. The C282Y mutation is present in homozygous configuration in approximately 80% of persons with heavy iron overload attributable to hemochromatosis[21]. The H63D mutation, although more frequent in the general population, is much less frequently associated with iron overload. The ability to detect C282Y and H63D mutations now makes possible the detection and diagnosis of many asymptomatic, healthy persons from the general population likely to develop iron overload.

Complications of iron overload

Sheldon's compilation of histologic observations explained or presaged identification of virtually all complications of iron overload recognized today in untreated patients. However, data accumulated on patients and their families in the 20 years after the publication of Sheldon's *Haemochromatosis* indicate that many affected persons had symptoms and signs other than those of the classic diagnostic triad, and that many of these preceded the development of the classic features. Bassett and coworkers demonstrated that the hepatic iron concentrations had a direct relationship with the occurrence of hepatic cirrhosis[19]. Further, the incidence of primary hepatic cancer is markedly increased among persons with hemochromatosis with hepatic cirrhosis[22], but cancer of the liver almost never develops in persons without cirrhosis. Now, the most common causes of death among persons with hemochromatosis are cirrhosis and its complications[23]. Before insulin therapy was available, diabetes mellitus was a major cause of acute illness and death. Today, the clinical picture of diabetes mellitus in hemochromatosis is more complex. Its clinical expression depends on pancreatic iron overload, the degree of hepatic disease, coincidental inheritance of other diabetogenic genes, and other factors. Vasculopathy and neuropathy, rarely observed by early investigators, are now as common in hemochromatosis patients as in others with diabetes mellitus. Accordingly, diabetes is now the second most common cause of death in modern hemochromatosis case series[23]. Once a common form of acute illness and death in hemochromatosis, cardiac siderosis with cardiomyopathy and arrhythmias is increasingly rare[24], but remains a common presentation and potentially avoidable cause of

death in young persons with severe iron overload, especially those with 'juvenile' hemochromatosis. Schumacher described the distinctive forms of arthropathy that affect approximately one-half of persons with hemochromatosis[25]. However, some cases are diagnosed before iron overload has developed, and most fail to improve after iron depletion, suggesting that factors other than inheritance of hemochromatosis alleles is responsible for this common and often disabling sequel. Even the cutaneous abnormalities of hemochromatosis are more diverse than the hyperpigmentation described in the nineteenth century[26].

Abnormal immunity and susceptibility to infection

Over many years, reports of unusual fulminant bacterial infections that occurred in persons with chronic hepatic disease or increased iron stores have included some hemochromatosis patients. Although these incidents are clinically important, the commonness of hemochromatosis and the rarity of the reports suggest that the occurrence of some of these infections in persons with hemochromatosis is coincidental. In 1978, however, de Sousa and co-workers began to discover more fundamental relationships of hemochromatosis, iron overload, and immunity[27]. Their subsequent investigations and those of others demonstrate the direct effects of excess iron on cells of the immune system, the decreased expression of CD8+ lymphocytes in hemochromatosis, and the role MHC class I-like proteins in intestinal iron absorption[28]. Further, discovery of the *Nramp* family of divalent cation transporters reveals additional relationships in the absorption and metabolism of iron with cellular immunity in experimental animals and humans[11, 12, 29].

Treatment

In 1952, Davis and Arrowsmith reported treating three persons with hemochromatosis with repeated phlebotomy[30]; long-term studies demonstrated thereafter that treated patients lived longer[31, 32]. In a prospective trial, Niederau and colleagues demonstrated that persons without hepatic cirrhosis or diabetes mellitus who undergo iron depletion have normal actuarial survival[23]. Early diagnosis and treatment prevent hepatic cirrhosis and diabetes mellitus in those who do not have other risk factors for the development of these disorders, although therapeutic phlebotomy does not reverse established hepatic or pancreatic injury. Cardiac disease and hypogonadism are sometimes reversed by aggressive phlebotomy therapy, but arthropathy is usually unaffected. Lingering questions about the role of iron overload in the pathogenesis of certain hemochromatosis-associated complications or the effectiveness and cost-effectiveness of therapy in subgroups of patients are only answerable with randomized control therapeutic trials. However, the overall success of phlebotomy trials indicates that treatment must now be recommended for most patients[33].

Population genetics

The original descriptions of hemochromatosis from countries of western Europe suggested its prevalence in this geographic area. Extension of Simon's original work revealed that HLA-A and -B and other MHC types mark haplotypic variants among hemochromatosis patients in different populations, and provided indirect evidence that hemochromatosis alleles occur frequently in many European population groups. In 1988, a report of the evaluation of 11 065 healthy blood donors in Utah using phenotypic criteria revealed convincingly that hemochromatosis genes are common[34]. After's Feder's 1996 publication[21], other investigators confirmed that approximately 12% and 25% of western Caucasians in many geographic locations are heterozygotes for the C282Y and H63D mutations, respectively[35], confirming the conclusions of the Utah survey[34]. *HFE* mutations, especially the C282Y allele, are associated primarily with western Caucasians. The origins, dissemination, and population frequencies of *HFE* alleles are associated with old northern European peoples, especially the Vikings or Celts, and have been reconciled with the hemochromatosis-associated HLA haplotypes discovered by Simon and others. However, the cause(s) for the prevalence of hemochromatosis alleles remains obscure.

Social issues

At a meeting at the Centers for Disease Control and Prevention in Atlanta in early 1996, international experts in hemochromatosis, geneticists, epidemiologists, and patient advocates collectively recommended initiation of population-based screening and treatment for hemochromatosis in western European and derivative countries based on its frequency, its susceptibility to early diagnosis, the availability of a meaningful treatment intervention, and evidence of cost–benefit. Soon thereafter, discovery of the *HFE* gene caused these recommendations to be reconsidered, and raised new questions about the optimal

diagnosis strategies[36]. These included the social and ethical consequences of hemochromatosis diagnosis (particularly on a large scale), the disparities of phenotyping and genotyping, and the availability of adequate numbers of diagnosticians and genetic counselors familiar with hemochromatosis to mount population-based screening programs.

Conclusions

Since its discovery in the nineteenth century, hemochromatosis has fascinated and challenged basic and clinical scientists. Long-held notions of its rarity have yielded to increasing recognition of its prevalence among Caucasians of western European descent, and of its place among several heritable iron overload disorders that occur frequently among large population groups. It has become possible to diagnose affected persons before they develop multisystem iron overload disease, and provide simple, effective, and inexpensive treatment. However, there are unrecognized mechanisms of iron absorption and homeostasis, additional ill-effects of iron overload, unforeseen consequences of altered immunity and limited expression of HLA types, and adverse (or beneficial) effects of increased non-ferrous metal absorption in hemochromatosis that remain undefined. In aggregate, the many persons who are heterozygous for hemochromatosis-associated alleles could be at increased risk to develop heart disease, cancer, or other common disorders; answering these questions is possible now that *HFE* genotyping can identify most hemochromatosis gene carriers. Genetic maneuvers to restore normal iron absorption in affected persons await discovery. Further, hemochromatosis is likely to be the disorder by which new social and ethical standards surrounding revelation of personal genetic information are formulated in western populations. Truly, hemochromatosis is 'the genetic disease of the twenty-first century'[37].

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