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Type 1 Hemochromatosis: A Review of the History, Inheritance and Treatment of Iron Overload Disorder

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ABSTRACT

Hereditary hemochromatosis (also known as type 1 hemochromatosis, iron overload disorder, or the Celtic Curse) is a genetic disorder characterized by an autosomal recessive inheritance pattern. This review project focused on gathering comprehensive data about the history, causes, inheritance, diagnosis, and treatment of iron overload disorder. Through such research, it was discovered that type 1 hemochromatosis may occur due to one of two nucleotide sequence changes (either the C282Y mutation or the H63D mutation) in the HFE gene, which codes for the construction of the homeostatic iron regulator protein and regulates production of the hormone hepcidin. As a result of these mutations, individuals affected by hemochromatosis have elevated iron levels and excess deposits of iron in tissues and organs. Such deposits may cause a variety of symptoms and complications, including fatigue, skin discoloration, heart failure, cirrhosis, liver cancer, and diabetes. Hemochromatosis is one of the most common genetic disorders in the world, affecting one in every three hundred individuals. The majority of hemochromatosis patients are of northern European descent. Currently, there is no cure for type 1 hemochromatosis; however, the primary treatment method for this disorder is phlebotomy. Due to the widespread prevalence of the disorder, researchers continue to explore experimental treatment methods, including gene therapy and iron chelation therapy.

Introduction

Overview

Type 1 hemochromatosis is a genetic disorder which causes one's body to absorb excess iron from the environment (i.e., food that is eaten). This iron is then stored in one's tissues and organs-especially the heart, liver, pancreas, joints, and skin-where it often causes long term damage to said tissues and organs. Physicians have identified a wide variety of symptoms associated with hemochromatosis, including (but not limited to) fatigue, weakness, joint pain, abdominal pain, heart and liver failure, memory fog, increased infections, thyroid issues, weight loss, and hormonal changes. Likewise, hemochromatosis may also lead directly to the development of arthritis, cirrhosis, liver cancer, diabetes, heart disease, skin discoloration (bronze or gray skin color), and permanent tissue or organ damage (Centers for Disease Control and Prevention, 2020). Typically, most people do not begin to experience symptoms of this disorder until they are between the ages of forty and sixty. Men often experience symptoms that are more severe, and such symptoms tend to present much earlier in men than they do in women (Mayo Clinic Staff, 2020). Nevertheless, the phenotypic expression of this disorder varies tremendously, even among individuals of the same sex. For example, the severity of a hemochromatosis patient's symptoms is largely dependent on environmental factors, including alcohol consumption and the prevalence of iron in one's diet. It should be noted that this disorder is most often referred to as type 1 hemochromatosis or hereditary hemochromatosis; however, it is additionally known as genetic hemochromatosis, familial hemochromatosis, bronze diabetes, iron overload disorder, or the Celtic Curse (Health Grades, 2020).

History

Scientists and historians estimate that the genetic mutation causing hemochromatosis originated over four thousand years ago, spreading throughout northern Europe with the travel of the Vikings. Despite the longevity of this condition, research into the disorder did not start until the nineteenth century. Such research began with Dr. Rudolf Virchow, a German physician. While performing autopsies on organs with internal bleeding, Virchow discovered a mysterious yellow-brown pigment, referred to as haematin. Unsure of the contents of the pigment, Virchow chose to utilize a staining practice known as the Berlin Blue method. The distinct dark blue color that is formed through this staining method is the product of a reaction involving blood, iron sulfate, and potassium carbonate. Once Virchow realized that the haematin he'd discovered could be stained Berlin Blue, he was able to conclude that this pigment contained iron. Twenty years later (in 1867), German pathologist Max Perls improved this staining technique by utilizing potassium ferrocyanide, which reacts with iron (III) oxide. Perl's staining method (known as haemosiderin) would go on to become the standard histological technique for determining iron pigment (Alturkistani et al., 2016).

While this research into staining reactions was taking place, scientists and physicians were working to diagnose hemochromatosis in patients. The first known case of this disorder was presented by the French doctor Armand Trousseau. In Trousseau's presentation of his diabetes patient, he described his observations of liver cirrhosis, as well as an odd brown skin pigmentation. Such symptoms had never before been known to present with diabetes. Furthermore, in 1871, the second case of this genetic disease was published by Professor Charles Trosier. At the time, scientists did not yet understand that the brown skin pigmentation was due to excess iron (Ulvik, 2016). Thus, the disorder was known as "pigment cirrhosis" until 1886, when French physician and professor Victor Hanot coined the name "bronze diabetes" (The Free Dictionary, 2012).

Finally, in 1889, German physician Friedrich von Recklinghausen took the first step toward truly understanding the causes of hemochromatosis. Using Max Perls's staining technique, Recklinghausen began staining the livers of deceased patients who had suffered from "bronze diabetes." Such research definitively proved that the mysterious yellow-brown pigment which had perplexed so many physicians was caused by excess storages of iron. Recklinghausen concluded that this excess iron was the result of internal bleeding in which red blood cells broke down; thus, he referred to the disorder as "haemochromatosis." This term directly translates to "a blood disease," as the prefix haema- means blood, and the suffix -osis indicates a state of disease (Online Etymology Dictionary, 2012). Although Recklinghausen's theory about the cause of the extra iron was inaccurate (and eventually discarded), researchers and doctors continued to utilize the name Recklinghausen had established.

Following Recklinghausen's breakthrough, research into the disease slowed considerably, with the next major discovery taking place nearly fifty years later. In 1935, Dr. Joseph Sheldon, an English physician, published the book *Haemochromatosis*, a lengthy overview of all patients in medical literature that had been diagnosed with the disorder. Additionally, the book provided a complex picture of iron deposition in the human body. Within his work, Sheldon also introduced the idea that the disorder might be congenital (present from birth). Prior to Sheldon's work, specialists had believed that, since symptoms of hemochromatosis did not present until later in life, the disease was something which individuals inherited later in life. Sheldon, however, attempted to argue otherwise. Although he was incorrect about how the iron accumulated (he believed hemochromatosis was caused by a molecular defect that made it difficult for iron to leave cells), he was right about the disorder being congenital, a notion that was solidified in 1967 when researchers proved that hemochromatosis was, in fact, hereditary.

Further insight into the fundamentals of hemochromatosis was brought to light several years later. In 1937 and 1947 the iron-binding proteins ferritin and transferrin, respectively, were discovered. Ultimately, these discoveries allowed scientists to learn more about how iron was stored within the human body. Likewise, in 1937, British biological scientists Elsie Widdowson and Robert McCance found stores of iron in the intestines and kidneys of hemochromatosis patients. This provided concrete evidence that the high iron levels in patients with hemochromatosis were due to an excess absorption of iron from the environment. As a result of the research conducted throughout the late nine-

teenth and early twentieth centuries, scientists today have a reasonably solid understanding of the inheritance, diagnostic signs, and long-term effects of hemochromatosis. Still, researchers continue to work towards gaining a stronger understanding of how to effectively treat and prevent this disorder (Ulvik, 2016).

Methods

In order to complete this review, a total of 32 web-based sources were used. Such references were selected using Google as the primary search engine, and the use of keywords in the search bar ensured that only sources relating to hereditary hemochromatosis, the history of the disease, and treatment methods were found. Some keywords used include "type 1 hemochromatosis," "genetic causes of hemochromatosis," "inheritance of hemochromatosis," and "current hemochromatosis research." The information found on these websites was then organized by topic and cited in the American Psychological Association (seventh edition) format, before being included in this work.

Discussion

Genetic Cause

Hereditary hemochromatosis is caused by a missense point mutation, in which a nucleotide base pair change causes one amino acid to be replaced by another in the protein produced (Brody, 2022). In cases of type 1 hemochromatosis, such a mutation occurs in one single gene, the "high iron (Fe)"-or HFE- gene (Gene Cards, 2022). This particular gene is located on the sixth chromosome, and it codes for the construction of the homeostatic iron regulator protein (the HFE protein). The HFE protein interacts with other proteins on the surfaces of cells (primarily liver, intestinal, and immune system cells) to detect the amount of iron in the body (National Library of Medicine, 1998). Furthermore, the HFE protein binds to a signal-receiving protein known as transferrin receptor 1 (Miller & Lappin, 2022). This interaction between the HFE protein and transferrin, a blood plasma glycoprotein, ensures that iron traveling through the blood is properly regulated (Ogun & Adeyinka, 2022). Similarly, the HFE gene regulates the production of hepcidin, a hormone produced by the liver. In the human body, hepcidin is the protein which determines how much iron is absorbed from one's diet and released from storage sites in the body (Medline Plus Genetics, 2019). On average, the body absorbs about ten percent of the iron eaten, when the HFE gene is left unmutated. However, mutations cause the HFE protein produced to contain a different strand of amino acids. As a result of this change, the homeostatic iron regulator protein cannot accurately detect the amount of iron in the body. In addition to this, mutations in the HFE gene prevent the HFE protein from interacting with transferrin as it typically does. Thus, excess iron is able to enter liver cells. Furthermore, when the HFE protein becomes mutated, the hormone hepcidin does not function properly. Due to this, the body absorbs more than the standard ten percent of iron eaten, and excess deposits of iron begin to form (Medline Plus Genetics, 2019).

Currently, scientists are aware of two specific mutations (both of which are missense point mutations) that cause type 1 hemochromatosis to occur. One such mutation is the Cys282Tyr, or C282Y, mutation. This mutation becomes present when the 282nd amino acid in the HFE protein, cysteine, is replaced by the amino acid tyrosine. Ultimately, this prevents the homeostatic iron regulator protein from fully reaching the surface of cells. Likewise, hereditary hemochromatosis may also be caused by the His63Asp, or H63D mutation, in which the 63rd amino acid histidine is replaced by aspartic acid. As a result of this mutation, the three-dimensional structure of the homeostatic iron regulator protein is disrupted. While it should be noted that each of these mutations is distinct, both change one amino acid in the HFE protein, causing the body's iron regulation to be disrupted. Nonetheless, a limited number of individuals with type 1 hemochromatosis have neither the C282Y mutation nor the H63D mutation, suggesting that there are more mutations causing this disorder which have yet to be discovered (National Library of Medicine, 1998).

Mode of Inheritance

Type 1 hemochromatosis is characterized by an autosomal recessive inheritance pattern (All About Hemochromatosis, n.d.). Therefore, in order for an organism to demonstrate symptoms of this disorder, the individual must inherit a mutated HFE gene (which may be either the C282Y or H63D mutation) from both biological parents. Since the allele causing hemochromatosis is recessive, an organism must contain two copies of said allele for the condition to be expressed (Centers for Disease Control and Prevention, 2020). Those with only one mutated HFE gene are known as carriers.

Neither Parent Carries Gene

	H	H
H	HH	HH
H	HH	HH

Chance of Having Disorder: 0%
Chance of Being a Carrier: 0%
Chance of Being Unaffected: 100%

One Parent Heterozygous for Gene, Other Parent Does Not Carry Gene

	H	h
H	HH	Hh
H	HH	Hh

Chance of Having Disorder: 0%
Chance of Being a Carrier: 50%
Chance of Being Unaffected: 50%

One Parent Homozygous Recessive, Other Parent Does Not Carry Gene

	h	h
H	Hh	Hh
H	Hh	Hh

Chance of Having Disorder: 0%
Chance of Being a Carrier: 100%
Chance of Being Unaffected: 0%

Figure 1-Punnett squares demonstrating the inheritance of type 1 hemochromatosis.

Both Parents Heterozygous for Gene

	H	h
H	HH	Hh
h	Hh	hh

Chance of Having Disorder: 25%
Chance of Being a Carrier: 50%
Chance of Being Unaffected: 25%

One Parent Homozygous Recessive, Other Parent Heterozygous for Gene

	h	h
H	Hh	Hh
h	hh	hh

Chance of Having Disorder: 50%
Chance of Being a Carrier: 50%
Chance of Being Unaffected: 0%

Both Parents Homozygous Recessive

	h	h
h	hh	hh
h	hh	hh

Chance of Having Disorder: 100%
Chance of Being a Carrier: 0%
Chance of Being Unaffected: 0%

Figure 2-Punnett squares demonstrating the inheritance of type 1 hemochromatosis (continued)

Nevertheless, the inheritance of this disorder truly begins not during fertilization (when the two parental HFE genes are passed to an offspring), but rather during meiosis, when alleles are distributed to gametes. Meiosis is the process by which the cells of eukaryotic organisms divide for the purpose of sexual reproduction (producing gametes). During this proceeding, the alleles for each of an organism's genetic traits are distributed to gametes (eggs and sperm) independently of one another, a phenomenon known as independent assortment. Therefore, at the conclusion of meiosis, each of the daughter cells produced will contain one allele for each of an organism's traits. In terms of the inheritance of hemochromatosis, this means that each of the gametes produced will contain either a mutated or a non-mutated HFE gene. If, during the process of fertilization, an egg and sperm both containing a mutated HFE gene are combined, then the offspring produced will inherit hemochromatosis (Scitable, 2014).

Geographical Distribution and Risk Factors

Despite the fact that hemochromatosis is a purely genetic disorder, the expression of this condition is unquestionably affected by environmental factors. Most notably, one's diet may contribute to the prevalence of symptoms, as consuming foods which are high in iron (including red meat and spinach) will further raise an individual's iron levels.

Along with this, symptoms of type 1 hemochromatosis tend to be expressed most prominently, as well as from an earlier age, in males. This is due to the fact that, through pregnancy and the menstrual cycle, women lose more blood, causing their iron levels to be lower overall (Anderson & Bardou-Jacquet, 2021).

Ethnicity is another risk factor that may have an effect on the inheritance and expression of hemochromatosis. This disorder is particularly pervasive in Caucasians and individuals of Northern European descent (Mayo Clinic Staff, 2020). Ultimately, it is the prevalence of hemochromatosis in people of Irish descent, especially, which has led to this disease being called the Celtic Curse. Although this disorder can be found most prominently in northern Europe, it remains tremendously common worldwide. Internationally, approximately 1.9 percent of all people carry at least one C282Y mutation, while 8.1 percent of people possess at least one H63D mutation (Duchini et al., 2017).

Furthermore, type 1 hemochromatosis is one of the most common genetic disorders in the United States, directly affecting close to one million people at any given time (Medline Plus Genetics, 2019). It is estimated that the probability of inheriting this disorder is approximately one in three hundred. Of the individuals in the United States that have been tested for hemochromatosis, 0.26 percent are homozygous for the C282Y mutation, while 1.89 percent of people are homozygous for the H63D mutation. Approximately 1.97 percent of individuals are compound heterozygotes (Duchini et al., 2017), indicating that they possess one C282Y mutation and one H63D mutation (Marks, 2021). In general, patients possessing two C282Y mutations have the most severe hemochromatosis symptoms, and individuals with two H63D mutations tend to have the least severe case of this disorder (meaning iron levels are lower and there is less organ damage). Compound heterozygotes display symptoms of a fairly intermediate severity (Lewis, 2016). Nonetheless, although inheriting hemochromatosis is tremendously common, carriers of the disorder are found even more frequently. Currently, experts estimate that about 10 percent of the United States' population possesses one mutated HFE gene (Bacon & Kwiatkowski, 2022).

Diagnosis

As a result of the continued prevalence of hereditary hemochromatosis, accurate diagnosis of the disorder remains a critical aspect of improving national and global public health. Oftentimes, hemochromatosis is rather challenging to diagnose, for symptoms do not present until later in life. Consequently, many do not realize this disorder is something they should be tested for. Still, however, multiple methods do exist for diagnosing type 1 hemochromatosis. One of the most common means of diagnosis is through blood tests. When seeking to diagnose hemochromatosis, physicians will perform serum transferrin saturation blood tests. This method measures the amount of iron bound to the protein transferrin, as it carries iron through one's blood. If a patient's serum transferrin saturation is higher than 45 percent, a serum ferritin blood test will be performed, which measures the amount of iron stored in the liver. While individuals may be specifically tested for hemochromatosis, most people discover they have this disorder while getting blood work for other reasons (Bacon & Kwiatkowski, 2022).

Furthermore, hereditary hemochromatosis may also be diagnosed through MRIs, liver biopsies, and liver function tests, which a physician will choose to perform if a patient proves to have elevated iron levels (Mayo Clinic Staff, 2020). Such tests are used to detect tissue iron overload. Similarly, some physicians may choose to perform genetic testing in order to diagnose hemochromatosis. Through this method, patients' DNA is scanned specifically for mutations in the HFE gene. Not only does genetic testing allow those with hemochromatosis to be detected, it also allows physicians to detect carriers of the mutated gene, as well as determine whether a patient carries a C282Y mutation or an H63D mutation (Bacon & Kwiatkowski, 2022). Such genetic testing is recommended for individuals with a first-degree relative (a relative with which the individual shares approximately fifty percent of their DNA, including parents, siblings, or children) that has hemochromatosis (Sapp, 2022). While physicians tend to focus less on the detection of carriers, it is an important step in determining how likely one's family is to be affected by this disorder (Canadian Hemochromatosis Society, n.d.).

Treatment and Management

As of October 2022, there is no cure for type 1 hemochromatosis. Nevertheless, there exists a plethora of means through which physicians and patients may treat or manage this disorder. Phlebotomy (blood removal) is the most common procedure for treating hereditary hemochromatosis (Mayo Clinic Staff, 2020). Typically, one unit of blood (500 mL) is removed during each session, and most patients must have blood drawn every two to four months, in order to effectively manage iron levels. Some patients are able to maintain healthy iron levels without undergoing phlebotomy regularly. However, those with exceedingly high iron levels will have a unit of blood removed weekly or biweekly. Such intense treatment continues until excess iron stores have been removed (which may take anywhere from four to fifty phlebotomy sessions), at which point the patient may be able to assume a more typical treatment schedule (National Health Service, 2018). Despite the fact that phlebotomy is unable to completely cure those affected by hemochromatosis, it is vastly effective at preventing complications that have yet to occur (Bacon & Kwiatkowski, 2022). Similarly, phlebotomy is known for its ability to resolve numerous symptoms of the disorder, including fatigue, weakness, skin discoloration, lethargy, heart disease, and early-stage liver disease. Phlebotomy may additionally improve liver function in individuals with cirrhosis (Mayo Clinic Staff, 2020).

Moreover, several methods exist for treating the complications that arise as a result of type 1 hemochromatosis. For instance, the excess stores of iron that accumulate because of mutations in the HFE gene may cause liver cancer. Treatment options for this complication tend to vary depending upon the severity of the cancer; however, chemotherapy and radiation remain the standard approach for eliminating this unregulated cell growth. Along with this, type 1 hemochromatosis may lead to the development of diabetes, a disease which occurs when the pancreas is no longer able to make sufficient amounts of insulin or when the body cannot make use of the insulin that is produced (International Diabetes Federation, 2022). As a result of this, high glucose levels in the blood can occur-a condition known as hyperglycemia-which often causes tissue and organ failure. However, physicians are effectively able to treat diabetes using insulin injections or an insulin pump (American Diabetes Association, 2020).

Outside of medical facilities, type 1 hemochromatosis patients are able to lower their iron levels (and, thus, lessen the severity of symptoms) by making changes to their lifestyle. It is often recommended that those affected by hemochromatosis avoid iron-rich foods. Among such products to be avoided are red meat, vitamin C supplements, iron supplements, anything (e.g. breakfast cereals) that has been "fortified" with extra iron, and alcohol. Stopping one's use of alcohol can also help treat cirrhosis, another complication of hemochromatosis (Morganette, 2017). Likewise, it is recommended that type 1 hemochromatosis patients avoid uncooked seafood, as it may contain bacteria that thrive in an environment (such as the internal systems of one with high iron levels) that is rich in iron (Mayo Clinic Staff, 2020).

Recent Advances

Although certain methods of treating and diagnosing hemochromatosis do exist, scientists are actively working towards uncovering new methods, as well. One treatment method being explored is gene therapy, which utilizes genetic modification to treat this disorder (Medline Plus Genetics, 2022). Currently, researchers are looking at altering the DMT-1 transporter gene, which moves iron into cells. This movement of iron occurs far more rapidly in patients with hemochromatosis. Thus, scientists believe that, if the DMT-1 transporter gene was modified so that its expression was reduced, iron uptake from the gut would simultaneously be lessened. Ultimately, this would decrease the amount of iron that reaches an individual's cells, effectively lowering iron levels without the use of regular phlebotomy. Conjointly, scientists are researching a method of gene therapy which would cause hepcidin (an iron regulatory hormone that becomes impaired when the HFE gene is mutated) to be overexpressed. If this were to occur, iron absorption would be more strongly regulated, thus eliminating the excess iron deposits that occur as a result of hemochromatosis (Ezquer et al., 2006).

Moreover, those hemochromatosis patients that also have anemia or heart conditions are not able to safely undergo phlebotomy. Therefore, researchers and physicians are actively seeking out other treatments for type 1 hemochromatosis that do not involve the removal of blood. One possible alternative treatment is iron chelation therapy. This approach would involve the hemochromatosis patient receiving either an injection or a pill containing the medication deferoxamine, deferasirox, or deferiprone. Scientists are hopeful that this medication would bind together the excess iron that is found within individuals affected by hemochromatosis. Following the binding of this iron, it would then exit the body through urine or stool (National Health Service, 2018). Such a process is known as chelation, hence the hemochromatosis treatment being named iron chelation therapy (Mayo Clinic Staff, 2020).

Likewise, in addition to researching treatments for type 1 hemochromatosis, many scientists and physicians remain intently focused on resolving complications of this genetic disorder. Most prominent among this type of advancement is the development of the drug ebselen. Recently developed by biologists at Stanford University, ebselen is believed to be capable of preventing heart failure (caused by iron overload cardiomyopathy) in patients that are affected by hemochromatosis (White, 2020). Ebselen works by inhibiting the function of the DMT-1 transporter, thus decreasing the amount of iron that is moved into cells. Such a decrease effectively eliminates excess iron deposits within the human myocardium, improving heart function considerably (Rhee et al., 2020).

Conclusion

Type 1 hemochromatosis is one of the most common genetic disorders within the United States, as well as internationally. This disorder, caused by a missense point mutation in the HFE gene, results in one amino acid replacing another, ultimately impeding the function of the HFE (homeostatic iron regulator) protein, as well as the hormone hepcidin. As a result, those affected by hemochromatosis have high iron levels, along with excess deposits of iron in tissues and organs. Said excess iron leads to tissue and organ damage, which may cause a multitude of other symptoms to present. Through strenuous efforts, scientists, physicians, and medical researchers have definitively identified the genetic causes and means by which hemochromatosis is inherited. Considerable research relating to diagnostic and treatment methods has additionally been conducted. Still, type 1 hemochromatosis remains a major research and discussion topic, for techniques to manage the disorder exist, but a cure has yet to be identified. Recent advancements in the fields of genome mapping and gene therapy, however, provide scientists with hope that an effective cure for type 1 hemochromatosis might be found within the coming years. Such a discovery would be life-changing for the millions of individuals currently affected by hemochromatosis.

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