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Discussing Why Hemochromatosis is Ignored
(A Common but Rarely Diagnosed Disease)

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Abstract

Hereditary Hemochromatosis is the most common, life threatening genetic disorder in the Western World. It is an autosomal recessive disorder, which means it is passed on to an individual by both parents who each have the HFE gene. When this gene mutates, it causes the small intestine to absorb high levels of iron from the diet into the bloodstream. The iron is commonly deposited in the liver, but it can also accumulate in the heart, lungs, brain, and the pancreas. This excessive accumulation of iron in the body can lead to toxicity and eventually to organ failure. Although, quite common, there is little public awareness of the disease with only 4 known cases diagnosed in the Grand Cayman. Some affected individuals have no symptoms. Those that have early signs and symptoms have nonspecific ones that resemble those of other common conditions. In a survey, conducted by the Centers for Disease Control and Prevention (CDC), 67% of those with the right symptoms had initially received various multiple diagnoses, including arthritis, liver disease, hormonal deficiencies, and diabetes (Centers for Disease Control and Prevention, 2008). Since, according to CDC, it takes approximately 9.5 years after the onset of symptoms for a patient to be diagnosed, early diagnosis and treatment is essential to prevent the development of severe complications such as diabetes mellitus, hepatocellular carcinoma, liver failure, cardiomyopathy, and even death. Consequently this raises the question, of whether the small number of known cases in Grand Cayman was due to lack of awareness or misdiagnosis of this common, but rarely diagnosed disease.

Key words: *cirrhosis, Hemochromatosis, HFE = High Iron, Mutation, Phlebotomy, Transferrin*

Introduction and Historical Background

In 1865, the first medical description of a patient with hemochromatosis was first described in a French pathology publication, by legendary diagnostician and educator Dr. Armand Trousseau [1]. He described it as an unrecognized illness involving the triad skin bronzing, cirrhosis, and diabetes. Two decades later in 1889, the German Pathologist Friedrich von Recklinghausen autopsied a series of patients dying of mysterious "bronze diabetes." He noted that what Trousseau described was related to iron accumulation leading to the pigment changes in tissues, this prompted him to name the disorder hemochromatosis. Joseph Sheldon later explained the inherited nature of the disease in 1935. He organized a detailed written study of published cases of hemochromatosis, in which he concluded that the disease was not a complication of diabetes, cirrhosis, or excess copper but a familial disorder.

For more than 125 years, hemochromatosis was thought to be extremely rare [1]. Treatment for this disease was not effective until 1950 when Davis and Arrowsmith cleverly suggested phlebotomy as a treatment option. At the same time, progress was made when autopsy studies showed a much higher prevalence of the disease in the general population than previously known. Unfortunately, numerous supporting studies did not lead to changes in clinical practice. Nearly 150 years later in 1996, after Dr. Trosseau's initial report, researchers identified the genetic culprit: a mutated HFE gene encoding a tyrosine molecule instead of the intended cysteine at the 282nd position of the protein chain (a mutation abbreviated as C282Y by biochemists). Since then, researchers have estimated that the C282Y mutation occurring on the HFE gene originated 60-70 generations ago. This means that the appearance of Hemochromatosis can be traced back between 600 to 1100 C.E. [2]

While hemochromatosis is prevalent worldwide, the likelyhood of carrying at least one copy of the HFE gene was most common in people of Western European descent. Specifically the chance of carrying this gene for people of Western European ancestry is about one in three individuals. Yet, only one in two hundred actually have hemochromatosis and its symptoms. This is particularly important since Caymanians not only have African ancestry and European ancestry as well.

In the United States, approximately 1 in 10 Caucasian population are heterozygous for the C282Y mutation while 4.4 per 1000 are homozygous for this same mutation [3]. Roughly, one million people have this disease in the USA. Since this is an autosomal-recessive condition, a difference in disease rates between the sexes would not be expected. Nonetheless, the clinical disease is more common in men, other than women because it is thought that women are protected from it by the loss of iron by their bodies during menses and pregnancy [3].

In the Grand Cayman, there were four confirmed cases of the disease 2 men and 2 women in 2013. One of the females was recently diagnosed and all four of them were light skin Caymanians from the district of West Bay [4]. Although the number of people with hemochromatosis is quite low, there could be cases out there that have yet to be diagnosed or that have been mistaken for other chronic diseases.

Iron is an essential part of our diet. Although it is mainly found in red meat, it is also found in green leafy vegetables and fortified foods such as cereal and breads. Iron is essential to the human body because it is required for vital functions. For example, it is crucial for the transportation of oxygen through the bloodstream, energy production, formation of the hemoglobin in the red blood cells and myoglobin in muscles, DNA synthesis, and numerous enzymatic metabolic processes. Normally, iron is absorbed in the duodenum located in the small intestine. Once absorbed, the iron is transported by a glycoprotein called Transferrin and is thereby distributed to sites of iron utilization and storage. This carrier protein plays a role in regulating the transport of iron from the site of absorption to virtually all tissues [5]. Depending on the need for iron, the body is able to increase or decrease the amount absorbed by the intestinal tract and thus maintain iron homeostasis. Hepcidin is the hormone responsible for controlling iron homeostasis. It controls how much iron is absorbed by the intestines, how iron is used in various body processes, and how it is stored in various organs [6].

Initially, iron is stored in ferritin molecules abundantly found in the heart and liver. A single one of these molecules can store up to 4000 iron atoms [5]. When excess iron from the diet is absorbed, the body responds by producing more ferritin to facilitate iron storage. On average, 3.5 g of iron is contained within the body and is maintained such that mucosal absorption of iron is equal to the iron loss. Men lose only about 1 mg of iron daily through the shedding of skin cells and secretions of the gut and skin. Women end up losing an additional milligram of iron due to menstrual bleeding and can lose approximately 500 mg when pregnant.

The daily intake of iron is about 10mg. Healthy people usually absorb about 10% of this iron, which is enough to meet normal requirements. In a person with hemochromatosis, 30% is absorbed because mucosal absorption is greater than body requirements. The mutated HFE gene causes a false signal that iron stores are low and thus, dietary iron is absorbed 2-4 times the normal rate amounting to approximately 4mg or more of iron per day [7] . This leads to accumulation of 0.5-1.0g of iron per year [5]. The progressive accumulation of iron increases plasma iron, saturation of transferrin, and results in a progressive increase of plasma ferretin. Although iron absorption is greater, the excretion rate remains the same. As there is no natural way for the body to excrete excess iron other than through blood loss, it is stored in synovial joints and various tissues, such as the liver, heart, pancreas, brain and lungs [8]. Over many years, this excess stored iron accumulates to toxic levels and can damage and bring about organ failure. The iron overload can cause many health problems, most frequently a form of diabetes that is often resistant to insulin treatment [9].

The gene responsible for regulating iron absorption from the diet is called the HFE gene which stands for High Fe (iron). Hemochromatosis is caused by the mutations in the HFE gene. As mentioned previously, hemochromatosis is an autosomal recessive disease and thus an individual must inherit two mutated genes for the disorder to manifest. This is termed homozygous. While researchers have identified more than 20 mutations in the HFE gene, only two in particular are responsible for this disorder. Each of these mutations changes one of the protein building blocks (amino acids) used to make the HFE protein [10]. The two main mutations that can occur on the HFE gene are the C282Y mutation, which accounts for 90 to 95% of cases, and the H63D mutation. C282Y is associated with a more severe form of iron absorption than the H63D mutation. Individuals who inherit one of the mutated genes and a normal gene are heterozygous for hemochromatosis. They are generally asymptomatic, but in rare cases they may also display signs and symptoms of the disease [9].

Signs and Symptoms

The signs and symptoms of this disease are so varied, non-specific and so vague that proper diagnosis is often difficult. Some of the early signs and symptoms include fatigue, weakness, weight loss, abdominal pain, and arthralgia. As iron accumulation progresses, patients may also experience arthritis, shortness of breath/ dyspnea or symptoms of gonadal failure such as amenorrhea, early menopause, loss of libido, and impotence. Iron accumulates in the parenchymal cells of several organs; the liver is a major site, followed by the heart and pancreas. Conditions associated with advanced stages of hemochromatosis include: arthritis, abnormal liver function such as elevated transaminase and clinical liver disease, glucose intolerance and diabetes, chronic abdominal pain, severe fatigue, hypopituitarism, hypogonadism, cardiomyopathy (enlargement of heart) and arrhythmia (abnormal heart beat), cirrhosis, liver cancer, heart failure, and gray or bronze skin pigmentation similar to a suntan [5].

Obviously, as seen by the extensive list of symptoms, hemochromatosis can be extremely difficult to diagnose. Most advanced hemochromatosis complications are also common primary disorders. Therefore, a hemochromatosis diagnosis can be missed even in advanced stages unless it is looked for specifically. Looking back at the low number of cases diagnosed in the Grand Cayman and some hospitals in the United States, one has to wonder if physicians in the Cayman Islands (Territory of Briatain) and their counter parts from all over the world are actively screening for hemochromatosis or mistaking its signs and symptoms for other common primary disorders. In speaking with a handful of physicians, most of them were vaguely aware of what hemochromatosis is. Most noted that it was “too much iron in the blood”. However, when asked about signs, symptoms, and treatments, none could recall any.

Some complications of hemochromatosis are not clearly related to excess iron, yet, when excess iron is removed, many individuals report feeling better [5]. Manifestations of iron accumulation can vary from person to person. The most common presenting symptom is chronic fatigue which occurs in about 50-75% of individuals. Over 70% of patients have liver function abnormalities, weakness, and lethargy at the time of diagnosis. Excessive skin pigmentation is present in more than 90% of symptomatic patients at diagnosis. The liver is usually the first organ affected. Hepatomegaly is one of the most frequent findings in clinical presentation, followed by cirrhosis. Primary hepatocellular carcinoma is more common in those with hemochromatosis than those in the general population. Diabetes mellitus occurs in 25%-75% of people and is more likely to develop in those with family histories

of diabetes, suggesting that direct damage to pancreatic islets by iron absorption occurs in combination with genetic predisposition. Arthropathy develops in 25%-50% of people and usually occurs after age 50, but it may also occur as a first manifestation. Cardiac involvement is another presenting manifestation in about 15% of people, but the most common manifestation is palpitations as symptoms of arrhythmia [5].

The signs of hereditary hemochromatosis usually do not appear until about age between 40 and 60 years, when iron in the body has reached damaging levels. The reason for this is that it takes many years for iron to accumulate to the level at which clinical manifestations occur. Because women lose iron to a greater extent than men because of menses, pregnancy, and lactation, they tend to become symptomatic slightly later in life than men, often after menopause [8]

Penetrance is a term indicating the likelihood that a given gene will actually develop into disease. Thus, an individual with two mutated HFE genes does not necessarily mean have to exhibit symptoms and may actually remain symptom-free for life. Early studies that used both self-reported symptoms and clinical signs to define hemochromatosis, reported clinical penetrance estimates ranging from 40% to 70%. In contrast, more recent studies that used clinical signs or objective laboratory measures to define hemochromatosis have reported clinical penetrance estimates ranging from 1% to 50%. Inconsistencies regarding penetrance estimates persist and so further studies are needed to more fully understand the role of genetic and environmental factors that may affect penetrance [5]. Of people with the HFE mutations, only a subset will develop elevated transferrin saturation (TS). Of these, only a subset will develop an elevated serum ferritin (SF), only a further subset will develop hemochromatosis symptoms. Of those with symptoms, only a subset will develop clinical signs consistent with hemochromatosis. Thus, diagnosis is reserved for those whose signs and symptoms are clearly referable to documented iron overload [5].

Diagnosis

Currently, the clinical guidelines recommend that testing for hemochromatosis should be performed in individuals with any unexplained signs or symptoms associated with hemochromatosis, those with porphyria, hepatitis, or other liver diseases, and those with abnormal blood tests consistent with hemochromatosis. Individuals that have a family member with the condition should specially be examined for this inherited disorder because these individuals have an increased risk of developing iron overload and are an ideal group for targeted prevention efforts.

A number of laboratory tests are available to measure the amount of iron in the blood and diagnose iron overload. Biochemical tests include: Serum iron (SI), total iron-binding capacity (TIBC), unsaturated iron-binding capacity (UIBC), transferrin saturation (TS), and serum ferritin (SF). The Centers for Disease Control and Prevention (CDC) has established a testing protocol involving 3 steps to determine a diagnosis of hereditary hemochromatosis. Involving a transferrin saturation test, a serum ferritin test, and a confirmation of the hemochromatosis diagnosis.

Transferrin is a blood protein that measures the amount of iron absorbed by the intestines and transports if from on location to another. When iron absorption is abnormally high, transferrin proteins become more saturated with iron. An elevated TS value therefore reflects an increase in iron absorption. This transferrin saturation test (TS) is a sensitive and relatively inexpensive biochemical measure of iron overloading [5]. When interpreting the results of a fasting transferrin saturation (TS), it is important to keep in mind that several factors can falsely elevate TS values, including the use of vitamin C, dietary supplements containing iron, medicinal iron, and estrogen preparations. Individuals should be advised to avoid these products for 24 hours prior to the fasting blood draw. On the other hand, colds, inflammation, liver disease, and malignancies can falsely lower TS values. Pathologic blood loss or a history of frequent blood donations should be considered reasons for normal iron status in those who have symptoms consistent with hemochromatosis [5].

Those with elevated TS values should proceed with serum ferritin testing and additional workup as needed. As mentioned before, ferritin is a protein that stores iron. The body increases serum ferritin production when excess iron is absorbed. Serum ferritin levels therefore reflect the body's iron stores. It is important to note that because serum ferritin is also an acute phase reactant affected by cancer and inflammatory or infectious processes, SF values may increase if these underlying conditions are present.

The final test involves acquiring additional biochemical evidence of iron overload and is typically required before the hemochromatosis diagnosis can be made. This confirmation can be achieved in three ways: indirectly by quantitative phlebotomy, HFE genotyping, and directly by liver biopsy.

Quantitative phlebotomy is considered as a confirmatory test choice because the amount of mobilizable iron removed from the body by weekly or biweekly phlebotomy aids in measuring the degree of iron overload. This typically requires approximately 15 phlebotomies, each removing 500ml of blood. Each 500mL of blood extracted then removes approximately 200mg of iron. The goal is to reduce the ferritin level.

Genotyping for HFE mutations can provide additional confirmatory evidence though this information should be combined with clinical history, examination, and laboratory assessment. Identifying any HFE mutation alone is insufficient for diagnosing hereditary hemochromatosis [5]. Other genes involved in iron metabolism may also be responsible for iron overloading. Therefore, if a patient is negative for an HFE mutation yet has disease symptoms and iron overload, phlebotomy treatment and proper management of the patient's iron overload are still important.

Another method of confirming hemochromatosis after getting elevated iron levels is liver biopsy. Since liver biopsy directly evaluates the amount of iron per gram of liver tissue, it is more commonly used for prognostic reasons to determine the level of damage [5].

Once used as the definitive confirmation test for hemochromatosis, liver biopsy is now recommended for those with high risk of liver involvement or liver damage. Most health care providers use liver biopsy in patients with elevated liver enzymes and serum ferritin levels greater than 1,000 ng/mL.

Screening

The screening process is the main thrust of this paper**,** since the disease is common and complications can be easily prevented with early diagnosis and treatment, the question of community screening has been raised and much debate has ensued. Concerns include: incomplete knowledge about disease penetrance, the potential for discrimination with insurance and employment, potential for increased anxiety in people who may never develop manifestations of the disease, the cost effectiveness of screening, compliance with clinical management, and whether screening should be by iron studies or genetic testing [11]. One major concern regarding screening is that people who test positive may never return for confirmation testing or may not take action to treat their disease. A study performed in Italy found that 67% of people who had elevated iron levels upon screening did not return for definitive testing [11]. Talking with the Genetic Councilor at Health Service Authority (HSA) of Cayman Islands, it was determined that HFE screening in the Grand Cayman was non-existent due to similar concerns.

Here in the USA a number of medical doctors (from Graves Gilbert hospital in Bowling green Kentucky, Wood county hospital in Bowling green Ohio, University of Toledo Medical center in Toledo Ohio, Toledo Hospital in Ohio) whom I interviewed for condition have indicated they don't really "screen" people in the typical sense of the word, "screening" is usually reserved for asymptomatic individuals. One named hematologist said he usually checked for iron overload in patients with unexplained liver disease or in patients with underlying hematologic diseases that predispose to iron overload such as hemolytic anemia and transfusion dependent conditions. One cardiologists said, there was no current recommendation to screen for hemochromatosis unless they have symptoms or disease. Definitely there are several genotypes as well as accompanying phenotypes. Some patients are quite unlikely to have an end organ damage even with a quite elevated ferritin whereas other patients may have evidence of an end organ damage with moderate elevations in ferritin. The public health departments throughout USA and even in the Cayman Islands (territory of Britain) do conduct sporadic screening of certain diseases such as Hypertension, Diabetes, in public places (Myers stores here in USA, Foster's food fair in Cayman Islands), this is good because people can be treated early once they have been diagnosed with these diseases and make informed decisions regarding their diets. May be the Department of public health in conjunctions with hospital hematologists, cardiologists could come up with a similar program that could implement the screening of people for hemochromatosis. People that have been diagnosed with diabetes, hypertension etc as a result of screening programs, take precaution regarding what they eat and they go back to the hospital for regular checkups to make sure the blood sugar levels or blood pressure is within normal range.

Individuals diagnosed with hemochromatosis can modify their diet accordingly; again each person is unique which must be taken into consideration before using the following suggested diet modifications in Table 1 below. This is exactly what happens with individuals diagnosed with hypertension (take low or no salt diet) or diabetes mellitus (on sugar substitutes or no sugar) do once they have known their status.

Table 1: Iron Fe (mg) content of selected foods per common measure

Food	common measure	content per measure
Alcohol beverage, beer	12 fl oz	0.11
Apples raw with skin	1 apple	0.17
Apple raw without skin	1 cup	0.08
Asparagus, canned drained solids	4 spears	1.32
Asparagus, cooked boiled drained	4 spears	0.55
Bananas, raw	1 banana	0.42
Beans, baked, canned plain	1 cup	3.00
Beans, baked, canned with pork/ tomato	1 cup	8.20
Beef, chuck	3 oz	3.13
Beef, ribs	3 oz	1.99
Beef, round	3 oz	2.09
Beef, ground	3 oz	2.21
Blackberries raw	1cup	0.89
Broccoli raw	1 spear	0.23
Broccoli raw	1 cup	0.64
Carrots raw	1 carrot	0.22
Carrot raw	1 cup	0.33
Chicken, broilers, cooked, roasted	3 oz	0.96
Chicken, broilers, cooked meat/ skin	1 thigh	1.25
Fish, salmon smoked	3 oz	0.72
Fish, salmon , pink, solids/bone	3 oz	0.71

Treatment and Management

Initial treatment and long-term management of hemochromatosis often depends on the level of iron in the body and associated symptoms at the time of diagnosis. In addition to treatment, diseases caused by hemochromatosis also need separate management, such as liver disease and diabetes mellitus [12]. Phlebotomy is the most common treatment and management method. Phlebotomy works by stimulating the bone marrow to make new red blood cells as old ones are extracted. Iron is moved out of iron stores in the body to make more hemoglobin. Therefore, phlebotomy reduces the patient's iron level and can restore it to a healthy level.

In the initial de-ironing phase, normalization of iron stores involves weekly removal of blood by phlebotomy until mid hypoferritinemia occurs. That is, ferritin should equal 20ng/ml. This phase usually takes from 3 months to 1 year. The volume of blood to be removed varies among patients. Typically, 1 unit (500ml) of blood is removed per week but those who are smaller in size (less than 110lbs), elderly, and those with anemia, heart and lung problems can only manage 250ml of blood removal per week [5]. Careful monitoring of each patient throughout treatment is essential. If the treatment is too aggressive, anemia may result. Post-treatment monitoring is required and is key to appropriate patient management. Phlebotomy should be performed throughout a patient's life to keep ferritin levels between 25 and 50ng/ml. Table 2: indicates the expected benefits from the pre-

treatment state of individuals experiencing symptoms from hemochromatosis.

Table 2: Symptoms and benefits of Hemochromatosis management

Pretreatment State	Expected Benefit
No symptoms	prevention of complications of iron overload; normal life expectancy.
Weakness, fatigue, lethargy	Resolution or marked improvement if iron related.
Elevated serum concentrations of hepatic enzyme.	Resolution or marked improvement
Diarrhea	Cessation if iron related
Hepatomegaly	Resolution often occurs
Hepatic cirrhosis	No change or slower progression of liver failure
Right upper quadrant pain	Resolution or marked improvement
Arthropathy	Some improvements in arthralgia, change in joint deformity; progression sometimes seen.
Hypogonadotrophic hypogonadism	Resolution is rare

Chelation therapy is an option for patients who are not allowed to bleed due to other heritable and acquired anemias [13]. Iron chelation is the pharmacological removal of metals by chemicals that bind metal so that it is excreted in urine. However, the only pharmacological iron-chelating agent approved by the FDA for use in humans is intravenous deferoxamine, or desferrioxamine or Desferal. This approach lacks the complete efficacy of phlebotomy and should be used only when absolutely necessary [5].

There are lifestyle and home remedies that may reduce the risk of complications from hemochromatosis. Those with hemochromatosis should avoid iron supplements and multivitamins containing iron because these can further increase the iron levels. Individuals with the disease need to limit their intake of alcoholic beverages to lessen the effects of liver cirrhosis. They should also refrain from consuming Vitamin C which increases the absorption of iron from within the intestinal tract, and consume minimal amounts of red meat which is high in iron. They should avoid eating raw shellfish because individuals with hemochromatosis are susceptible to infections, especially those caused by certain bacteria in raw shellfish [6]. Also, increasing intake of substances that inhibit iron absorption, such as high tannin tea, and calcium may help slow the accumulation of iron in the body.

Conclusion

Hemochromatosis is a common yet rarely diagnosed genetically disorder. It is more common than the well-known sickle cell disease. Left untreated this disease leads to certain end organ damage and consequently death. Fortunately, if the condition is diagnosed and treated early, the damage from hereditary hemochromatosis is completely preventable. The HFE gene mutation responsible for hemochromatosis is found in a small but significant proportion of the general Caucasian population. Although it is rare to find HFE mutations in African Americans who have iron overload, these mutations have been found in a few individuals. It has been suggested that their appearance is due to admixture [5]. This might also hold true for Caymans. However, it is important to remember that only 4 known cases were in the Cayman Islands in 2013, thus, the disease might be under recognized by both physicians and individuals. It would thus be beneficial for Countries of the world to become more aware of the symptoms and management of this condition. The ongoing under diagnosis of hemochromatosis exhibited by screening individuals who have an end organ damage is not enough, or hematologists have a low sensitivity to the condition when symptoms compatible with the early stages of the disease are present and even sometimes when late complications are present. With early screening and diagnosis, preventive therapy can be instituted in the form of regular phlebotomy. If treatment is begun before end organ damage (cirrhosis or diabetes) has occurred, the prognosis is good. However, late and missed diagnoses lead to under- utilization of this readily accessible preventive treatment. This is worse in developing countries in Africa and elsewhere where the screening of hemochromatosis is never done and where most patients due to end organ damage die of the preventable diseases.

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