Case Study: Iron Overload in a 53-Year-Old Male with HFE Heterozygous Mutation

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Abstract

HFE Genetic Haemochromatosis (GH) is a genetic disorder that follows an autosomal recessive pattern, leading to abnormal iron absorption and accumulation in the body. The majority of GH cases are caused by three specific mutations in the *HFE* gene: C282Y (c.845G>A), H63D (c.187C>G), and S65C (c.193A>T). These mutations alter the expression, structure, or function of the HFE protein, resulting in impaired regulation of iron absorption. The way these mutations manifest can vary significantly between individuals.

This case report focuses on a 53-year-old caucasian man with a long-standing raised Serum Ferritin (SF) with no other identified causes. Genetic testing confirmed that he was heterozygous for the C282Y mutation. His laboratory results showed chronically elevated serum ferritin levels with a normal transferrin saturation (TSAT). Significant debilitating fatigue over the preceding 6 years, cognitive difficulties/ brain fog and mood swings and depression. To manage this and prevent the onset of further complications, the patient was recommended to commence a regimen of regular therapeutic phlebotomy following hepatology advice.

Although some existing literature suggests that HFE carriers do not load iron, this case demonstrates the importance of regularly monitoring TSAT and SF levels in C282Y carriers, as iron overload can be unpredictable due to various genetic and environmental factors.

This case has shown that therapeutic phlebotomy, has likely played a key role in managing his health outcomes and improvement of his symptoms (fatigue and cognitive difficulties/ brain fog).

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Introduction

HFE Genetic Haemochromatosis (GH) is a genetic disorder that follows an autosomal recessive inheritance pattern, leading to excessive iron absorption and deposition in various organs, including the liver, pancreas, heart, joints, and pituitary gland (Haemochromatosis UK, 2024). The condition is particularly prevalent in white populations. Clinical symptoms can vary greatly depending on both genetic and environmental factors, such as blood loss (through menstruation or blood donations), alcohol consumption, diet, or underlying liver health conditions, all of which can influence the degree of iron overload and its effects (Kanwar & Kowdley, 2013).

The majority of GH cases are linked to mutations in the *HFE* gene, specifically C282Y, H63D, and S65C (Cukjati et al., 2007). According to these authors, compound heterozygotes with C282Y and another *HFE* mutation like H63D can develop iron overload (Gochee et al., 2002), while the S65C mutation has been associated with milder cases when combined with C282Y (Holmstrom, 2002) (Mura et al., 1999). These mutations disrupt the production of hepcidin, a protein critical for regulating iron balance. Hepcidin controls iron levels by binding to ferroportin, a receptor responsible for iron export, leading to its degradation and reducing further iron absorption. When hepcidin levels are deficient, as in *HFE* mutations (Radford-Smith et al., 2018), unregulated iron absorption leads to iron accumulation and potential damage to various organs.

GH diagnosis is typically based on the genetic predisposition, often accompanied by biochemical evidence of iron overload measuring serum ferritin (SF) and transferrin saturation (TSAT). Elevated SF (greater 200 µg/L) and/or a TSAT level over 45% for women and an elevated SF (greater 300 µg/L) and/or TSAT level over 50% suggests the need for genetic testing for *HFE* mutations

(Fitzsimons et al., 2018). According to these authors, genetic testing is recommended in individuals of Northern European descent or first-degree relatives of those with GH.

Most GH cases are due to homozygous *HFE* mutations, but other genotypes involving *HFE* have been documented. Approximately 5% of GH cases are found in compound heterozygotes, 1.5% in those homozygous for H63D, 3.6% in C282Y heterozygotes, and 5.2% in H63D heterozygotes (Hanson et al., 2001). Studies have shown that compound heterozygous mutations result in milder forms of the disease compared to homozygous C282Y mutations (Aguilar-Martinez et al., 2008) (De Valk et al., 2000). Individuals with a single C282Y heterozygous mutation are often at a lower risk for developing iron overload (Aguilar-Martinez et al., 2008).

The phenotypic expression of GH can occur in stages, from no symptoms to elevated TSAT without changes in SF, and eventually to increased TSAT and SF with or without organ damage. Early symptoms include fatigue, joint pain, palpitations, and abdominal discomfort. Over time, iron accumulation in organs can cause serious complications, such as cirrhosis, liver cancer, diabetes, heart disease, impotence, hypogonadism, darkening of the skin, and arthritis, particularly affecting the second and third knuckle joints (Haemochromatosis UK, 2024). Hepatomegaly (enlarged liver) is often the first sign of iron buildup. SF levels over 1000 µg/L are associated with an increased risk of hepatomegaly, elevated liver enzymes, cirrhosis, and higher mortality rates (Beaton, 2002).

According to Jackson et al. (2001), around 90% of GH cases in individuals of Northern European descent are due to homozygous C282Y mutations. However, in this case study, a 53-year-old caucasian man was found to be heterozygous for the C282Y mutation. He had moderately elevated ferritin levels, with normal TSAT, and required regular therapeutic phlebotomy to manage his condition.

Background

A 53-year-old male contacted Haemochromatosis UK (HUK) following a 3-year history of progressively increasing serum ferritin levels and significant symptoms, including extreme fatigue, brain fog, mood swings, depression and joint pain. These symptoms had severely impacted his quality of life. Previously diagnosed with chronic fatigue syndrome (CFS), the patient's symptoms persisted despite treatment. His CFS consultant suggested the possibility of genetic haemochromatosis (GH) due to a family history of the condition. His mother had been recently diagnosed with GH, prompting the patient to undergo genetic testing through HUK, following reluctancy of genetic test from his general practitioner.

Diagnostic evaluation

The patient reported severe fatigue, which interfered with daily activities; and chronic joint pain, which had worsened over time, particularly in large joints.

His serum ferritin levels had been consistently elevated over the last three years, most recently reaching 573 µg/L and fasting TSAT at 46.3% (Table 1 – iron indices from 2018). He reported no significant alcohol consumption or history of liver disease, with normal Liver Function Tests (LFT's).

Given his mother's diagnosis of genetic haemochromatosis, genetic testing was conducted through HUK. Results confirmed the presence of a heterozygous C282Y mutation in the HFE gene.

To assess liver iron overload, the patient underwent a Liver Multiscan - T2* MRI of his liver after seeking advice from Haemochromatosis UK (Figure 1 – Liver Multiscan results). This is a sensitive tool for detecting iron deposition in the liver and other organs (St Pierre et al., 2004). The scan revealed a T2* value of 12 milliseconds (ms), which is below the normal range of 12.5 ms, indicating significant iron accumulation in the liver. Though T2* MRI does not directly measure hepatic iron concentration, the decreased T2* time is strongly suggestive of iron overload.

Management and Follow-up

Following a consultation with an hepatologist, the patient was referred for therapeutic phlebotomy, aimed at reducing the body's iron stores. The patient was started on phlebotomy sessions, with a goal of lowering his serum ferritin to a target range of 50-100 µg/L, which was achieved following 8 phlebotomies.

The patient was advised to make lifestyle modifications to reduce his risk of further iron accumulation, including reducing consumption of iron-rich foods, avoiding vitamin C supplements (which enhance iron absorption), and continuing his limitation of alcohol intake, which can exacerbate liver damage in the context of iron overload.

Regular follow-up appointments were scheduled

to monitor serum ferritin, transferrin saturation, and liver function tests. These tests will help guiding ongoing care.

Discussion

Existing literature highlights similar cases that might shed light on our patient's condition. One study on C282Y carriers suggested that individuals with a heterozygous C282Y mutation tend to have SF and TSAT levels that lie between those of individuals with a C282Y/H63D compound heterozygous mutation and those with no genetic mutations (De Valk et al., 2000). The most severe cases of iron overload are usually found in those with homozygous C282Y mutations.

In cases where C282Y carriers do develop iron overload, it is often thought to be caused by other genetic mutations or influenced by environmental factors like alcohol use (Sozen & Shah, 2024), liver disease or metabolic syndrome (Aguilar-Martinez et al., 2011). Other studies have suggested that blood transfusions, high iron intake, alcohol consumption, non-alcoholic fatty liver disease, metabolic syndrome and viral hepatitis can also contribute to iron overload (Pinyopornpanish et al., 2023). In our patient's case, he had no history of blood transfusions, excessive alcohol consumption, iron supplements, anaemia, viral hepatitis, non-alcoholic fatty liver disease (normal liver fat fraction on Multiscan perfomed) or metabolic syndrome (as previously investigated by his General Practitioner). This implies that other genetic or environmental factors may be contributing to his iron overload.

It has been suggested that certain single nucleotide polymorphisms (SNPs) in genes related to iron metabolism, or other genetic modifiers unrelated to iron metabolism, may impact how genetic haemochromatosis presents in people with C282Y mutations, leading to higher SF and TS levels (Fairweather-Tait et al., 2007) (Kanwar & Kowdley, 2013). One study identified C282Y carriers with iron overload who also had additional mutations in the *HFE* gene, which could be a factor in our patient as well (Aguilar-Martinez et al., 2011).

The NHS National Genetic Test Directory recommends further genetic testing for mutations in other iron metabolism genes on a presence of a negative HFE test (National Health Service, 2024). This additional testing could be beneficial for our patient.

This case demonstrates the importance of regularly monitoring TSAT and SF levels in C282Y carriers, as iron overload can be unpredictable due to various genetic and environmental factors. Since our patient's SF levels did not exceed 1000 µg/L, he was at a lower risk of cirrhosis and mortality. Regular monitoring of his SF and TSAT levels, along with therapeutic phlebotomy, has likely played a key role in managing his health outcomes and improvement of his symptoms (fatigue and cognitive difficulties/brain fog).

The author declares that there are no conflicts of interest related to this work.

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Figures:

Table 1 – Iron indices from year 2018 to 2024

Date	Serum Ferritin ug/L	Serum Transferrin Saturation
31-July-18	369	35%
17-Jun-20	413	-
28-Jan-21	440	38%
06-Jul-23	506	41%
06-Feb-24	573	46.3%

Figure 1 – Liver Multiscan results



