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Research Article

IRON OVERLOAD TURMOIL" AND "MANAGEMENT OF HEMOCHROMATOSIS

Raghavendra Rao M.V[1], Kumar Ponnusamy[2], Balaramiah[3], M. M. Karindas[4], Ilie Vasiliev[5], Rekha A[6], Hitesh Lakshmi Billa [7], Mahendra. K. Verma [8], Sreedhar[9] and Srilatha Bashetti[10],

[1]Central Research Laboratory, Apollo Institute of Medical Sciences and Research, Jubilee Hills, Hyderabad, Telangana, India
[2]Department of Biochemistry, Avalon University School of Medicine, Curacao, Caribbean Islands
[3]Department of Internal medicine, Avalon University School of Medicine, Curacao, Caribbean Islands
[4]Department of Oncology, world Academy of Medical sciences,Netherlands
[5]Department of Internal Medicine, world Academy of Medical sciences, Netherlands
[6]Department of Surgery and Dean, Apollo Institute of Medical Sciences and Research, Jubilee Hills, Hyderabad, Telangana, India
[7]Department of Interventional Pulmonology, Apollo Institute of Medical Science and Research, Hyderabad, TS, India
[8]Department of Basic medical sciences, American University of School of Medicine, Aruba, Caribbean Islands
[9]Department of Microbiology, Maheswara Medical College and Hospital, Patancheru,Hyderabad,T.S,India
[10]Department of Biochemistry, Dr Patnam Mahendra Reddy Institute of Medical Sciences, Chevella, TS, India

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A B S T R A C T

It is known that Toxic iron overload can be fatal. Iron poisoning is one of the most common toxic ingestion and one of the most deadly among children. "Excess of iron is harmful to the body as it may lead to deposition of iron in organs and cause organ failure. Hemochromatosis Is an iron-overload disease in which iron is directly deposited in the tissues (Liver,spleen,heart,pancreas and skin) .An abnormal gene on chromosome 6 is linked with hemochromatosis. The amino acid tyrosine in the normal protein encoded by this gene is replaced by cysteine. This abnormal protein is responsible for excessive iron absorption from the intestine which accumulates in various tissues leading to their damage and malnutrition. A gene called HFE is most often the cause of hereditary hemochromatosis. Primary hemochromatosis is unusual in India.

INTRODUCTION

Recent advances in the monitoring and treatment of iron overload appear to have had a positive impact on iron burden, morbidity, and mortality in chronically transfused patients with thalassemia.(1) Cardiac T2* MRI, which enables accurate prediction of the risk of developing iron-related cardiac disease, is increasingly utilized to tailor iron chelation treatment in patients with thalassemia.(2) The human body has no effective physiological mechanism for excreting excess iron.(3)Anemia, hypoxia, and erythropoiesis decrease hepcidin gene expression, thereby stabilizing ferroportin and increasing circulating iron available for erythropoiesis (4) Hereditary iron overload includes several disorders characterized by iron accumulation in tissues, organs, or even single cells or subcellular compartments (5) A common diet daily provides about 14 mg of iron as inorganic or organic (heme) iron. In the steady state in adults 1–2 mg are absorbed each day to maintain body iron balance.(6)

Iron absorption can be increased up to 25–30% of dietary iron content in response to increased iron demand , but this cannot always match iron requirements in children, young and pregnant women, and elder people that are more exposed to iron deficiency (7). Although still not fully clarified, heme absorption and transport at both the cellular and systemic levels involve several proteins (8,9). Non-heme iron requires it to be converted into ferrous iron by the apical ferric reductase duodenal cytochrome-B to enter the cytoplasm via DMT1 (10).

Currently, hemochromatosis (without further specification) is mostly defined as iron overload with a hereditary or primary cause, or originating from a metabolic disorder (11) Hereditary hemochromatosis is an autosomal recessive disorder with estimated prevalence in the population of 1 in 200 among patients with European ancestry, with lower incidence in other ethnic groups(12)

The gene responsible for hereditary hemochromatosis (known as HFE gene) is located on chromosome 6 (13) Iron overload indicates increased total accumulation of iron in the body from

Corresponding author:* **Raghavendra Rao M.V
Central Research Laboratory, Apollo Institute of Medical Sciences and Research, Jubilee Hills, Hyderabad, Telangana, India

any cause and resulting organ damage [14] The most important causes are hereditary hemochromatosis, a genetic disorder, transfusional iron overload, which can result from repeated blood transfusions [15] There are 5 types of hereditary hemochromatosis: type 1, 2 (2A, 2B), 3, 4 and 5, all caused by mutated genes. [16]

Hereditary hemochromatosis is the most frequent, and unique related to the HFE gene.[17] The diagnosis of haemochromatosis is often made following the incidental finding on routine blood screening of elevated serum liver.(18) Heterozygotes for either allele can manifest clinical iron overload, if they have two of any alleles. This makes them compound heterozygous for hemochromatosis [19] A novel experimental approach to the hereditary hemochromatosis treatment is the maintenance therapy with polymeric chelators.[20]

HISTORY

Virchow, 1847, described a golden brown granular pigment that was soluble in sulfuric acid and produced red ash on ignition [21] Armand Trousseau, described the disease in 1865 in a report on diabetes in patients presenting with a bronze pigmentation of their skin [22]

Trousseau did not associate diabetes with iron accumulation, the recognition that infiltration of the pancreas with iron might disrupt endocrine function resulting in diabetes was made by Friedrich Daniel von Recklinghausen in 1890.[23]

Joseph Sheldon,in 1935 described the cases of haemochromatosis. He established this as the name of the disorder and his detailed monograph. [24] Hemochromatosis disease as an inborn error of metabolism where this inherited disorder can increase the absorption of iron and thus cause tissue damage due to iron deposition. [25] Moreover, he rejected theories that alcohol, drug, and other factors contribute to the disorder [26] MacDonald in the 1960s, at Boston City Hospital, believed that hemochromatosis was a nutritional condition because he observed many drunken patients of Irish ancestry [27,28] In1976, Marcel Simon and his collaborators confirmed that haemochromatosis is an autosomal recessive disorder that has a link to the human leukocyte antigen (HLA) region of the genome. [29]

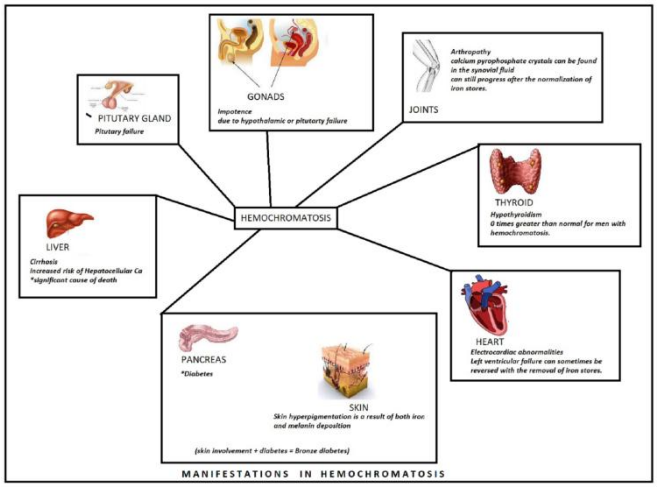
In 1996, Feder et al. identified HFE, which is a major histocompatibility complex (MHC) gene. They found that 83% of patients have homozygosity for a missense mutation (C282Y) in the HFE gene [30]

Increased gastro-intestinal absorption of iron

Normal intestinal iron absorption is about 1–2 mg/day. In patients with thalassemia who do not receive any transfusion, iron absorption increases several-fold.

Manifestations in hemochromatosis

It includes liver damage, liver cirrhosis, pancreatic islet cell damage, diabetes, hypothyroidism, and hypogonadism, Skin, Heart, Joints and gonads.

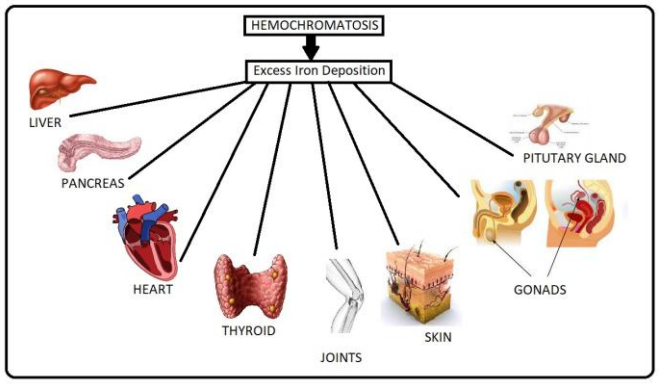


End-organ damage

Iron is stored in the liver, pancreas and heart. Long-term effects of haemochromatosis on these organs can be serious, even fatal when untreated. Toxins may accumulate in the blood and eventually affect mental functioning due to increased risk of hepatic encephalopathy.

Arrhythmia or abnormal heart rhythm can cause heart palpitations, chest pain, and light-headedness, and is occasionally life-threatening.

The pancreas, which also stores iron, is very important in the body's mechanisms for sugar metabolism. Diabetes affects the way the body uses blood sugar, and diabetes is, in turn, the leading cause of new blindness in adults and may be involved in kidney failure.



Haemochromatosis may lead to cirrhosis and its complications, including bleeding from dilated veins in the esophagus (esophageal varices) and stomach (gastric varices) and severe fluid retention in the abdomen (ascites). Severity of periodontal disease is associated with high transferrin saturation in haemochromatosis patients.(31,32)

Hemochromatosis in India

Although there are several reports of primary hemochromatosis from India, it has not been possible to identify the associated gene. Specifically, the HFE gene C282Y mutation has not been found except in one family from Andhra Pradesh. Only one recent study from Chandigarh investigated the hemojuvelin (HJV) gene in primary hemochromatosis, and 4 unrelated cases with significant mutations were found (33).

Can excessive iron in the body harm your health?

While iron is an important mineral and the lack of it can lead to many issues, did you know that excessive consumption of iron can be harmful, too?

Dr Satish Koul, Director, Internal Medicine, Fortis Memorial Research Institute, Gurugram explained, "Excess of iron is harmful to the body as it may lead to deposition of iron in organs and cause organ failure." He added that due to multiple transfusions, thalassemia patients develop endocrine disorders.(34)

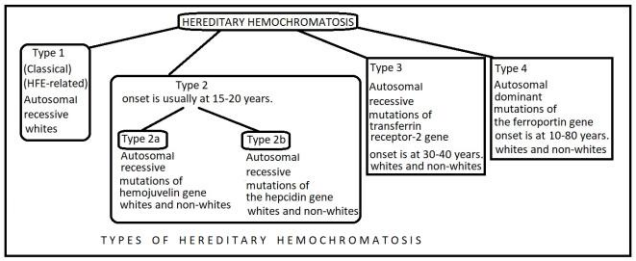
Hereditary hemochromatosis

Type-1-Autosomal recessive
Type-2 a and b

Autosomal recessive mutations of hemojuvelin gene white and non-whites and autosomal recessive mutations of the hepacidin gene whites and non-whites

Type-3-Autosomal recessive mutations of transferr in receptor-2 gene

Type-4 Autosomal dominant mutations of the ferroportin gene



High iron levels may help lower cholesterol

The study, published in the journal PLOS Medicine, looked at the role that iron plays in 900 diseases, uncovering the impact of both low and high iron levels. People with high iron levels are not only protected against anaemia but are also less likely to have high cholesterol, according to a global study. The researchers from Imperial College London in the UK also found that too much iron in the body may increase the risk of bacterial skin infections, such as cellulitis and abscesses. The study, published in the journal *PLOS Medicine*, looked at the role that iron plays in 900 diseases, uncovering the impact of both low and high iron levels.(35)

Excess iron in body may cause liver damage

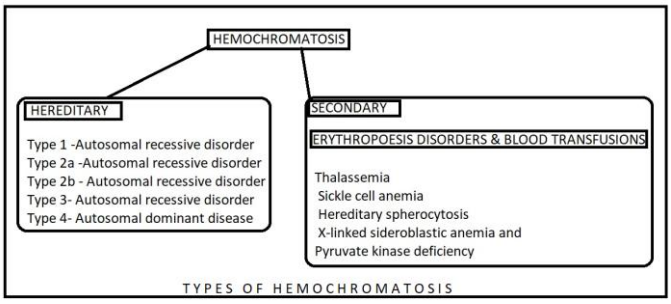
When the levels of iron are high it leads to damaging every organ and tissue. Excess build-up of iron in the body - Hemochromatosis –can damage the liver.

Types of Hemochromatosis

It is by hereditary and secondary by erythropoisis disorders and blood transfusions.

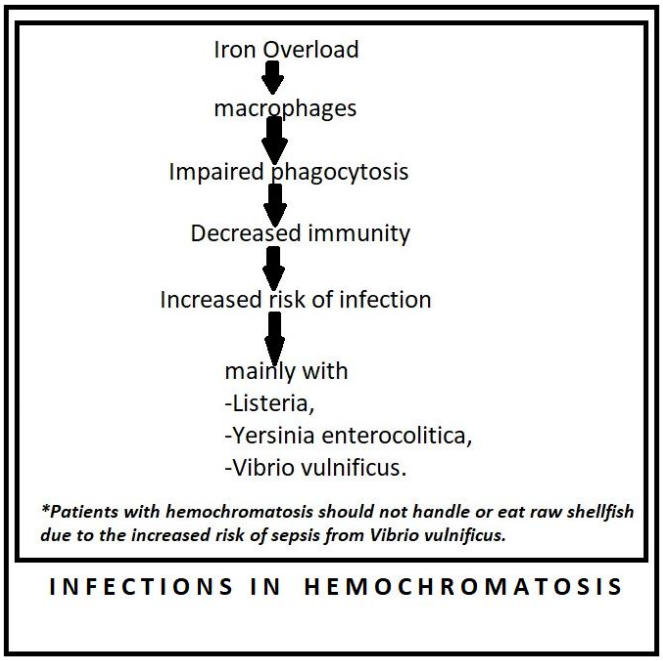
HFE Hemochromatosis

A gene called HFE is most often the cause of hereditary hemochromatosis Persons with clinical *HFE* hemochromatosis, in whom manifestations of end-organ damage secondary to iron overload are present; Individuals with biochemical *HFE* hemochromatosis, in whom transferrin-iron saturation is increased and the only evidence of iron overload is increased serum ferritin concentration. (36)



Infections in Hemochromatosis

Increased risk of infections mainly with *Listeria monocytogenes, Yersinia enterocolitica, and Vibrio vulnificus.* Patients with Hemochromatosis should not handle or eat raw shellfish due to increased risk of sepsis from *Vibrio vulnificus.*



The Role of Iron in Fried Reich's Ataxia

FRDA is an inherited disease with an autosomal recessive pattern caused by an insufficient amount of the nuclear-encoded mitochondrial protein frataxin, which is an essential and highly evolutionary conserved protein whose deficit results in iron metabolism deregulation and mitochondrial dysfunction [(37)]

Iron overload drug might help improve leukaemia treatment

A new study found that a drug already approved to treat iron overload has a protective effect on the blood vessels in leukaemia patients, allowing the rescue of healthy blood stem cells.Chemotherapy for one type of leukaemia could be improved by giving patients a drug currently used in the treatment of iron overload, new research has showed.Acute myeloid leukaemia (AML) is an aggressive cancer that stops healthy blood cell production. Chemotherapy is the standard treatment, but improvements are needed as the five-year survival rate in patients older than 60 is only 5-15%.The findings, from Imperial College London, showed that special regions of blood vessels – where blood stem cells that

generate billions of new cells every day of our life reside – are the hardest hit by leukaemia.(38)

IGIB team finds a new target to reverse iron overload disease

Using zebrafish, researchers at the Institute of Genomics and Integrative Biology (CSIR-IGIB) have successfully discovered a pathway that regulates hepcidin hormone production. There is no therapy currently available," says Sandeep Basu from CSIR-IGIB and first author of a paper published in *ACS Chemical Biology*. "Hepcidin gene is controlled by many factors, many of them not well understood. So, instead of picking one target for our drug screen, we focused on the symptoms of the disease - excess accumulation of iron," says Dr. Sachidanandan. "We knew that hepcidin hormone is low in the hemochromatosis patients, and that this causes iron overload." Since the researchers knew hepcidin production is regulated by many signalling pathways, they selected 80 compounds that specifically target signalling pathways in zebrafish. (39)

'Watch out for early signs of a sick or damaged liver'

On the eve of World Hepatitis Day (on July 28), doctors from Kauvery Hospital explained the various types of liver conditions with a focus on chronic viral hepatitis (A to E) that are treatable and curable, but often ignorance and delay lead to complications.K. Elankumaran, senior consultant and head, Liver Diseases and Transplantation Centre, at the Chennai unit of the hospital, and Kumaragurubaran, consultant Hepatologist in Trichy, were speaking at *The Hindu Wellness* webinar on "Hepatitis Can't Wait".(40)

Biochemical risks of excessive iron

Iron overload is the most significant problem reported as complication of repeated transfusions. Many studies in thalassemia patients had well established the association of Iron overload to mortality (41)

Currently it is noted that patients with thalassemia are able to survive up to 50 to 60 years of age but, endocrine and heart failure is replaced by malignant transformation this is the consequences of oxidatively active iron (42)

It is well established that iron loading rate of the total body is proportional to the number of transfusions administered. Rate of iron load various from organ to organ and occurs at specific rate for instance, the iron loading rate for pituitary gland, pancreas and heart majorly depends on bone marrow activity and different organ specific iron transporters (43)

Liver unloads iron much quicker than heart and endocrine organ. This reasons the presence of normal total body iron stores in patients after chelation (Liver iron concentration [LIC]) but substantial residual iron load is noticed in heart and endocrine organ. Studies state that it takes about 4-6 months to remove LIC by 50% by administration of intensive iron chelation but may take approximately 14 months to reduce 50% of the iron from heart (44)

In a prospective study by Ballas et.al; had collected the data of 247 adult sickle cell anemia patients. Further correlated the results with laboratory markers of iron overload versus clinical outcomes. The team observed significantly higher incidence of organ failure contributed by increased levels of serum ferritin (19% vs 71%) and also reported significantly high mortality rate too (5% vs 64%) (45)

Transfusion mediated iron overload

Chronic anemia requires multiple transfusions and currently is the only available therapy. There are various causes of chronic anaemia like decreased production of RBC,Leukemia Aplastic anemia, bone marrow aplasia, bone marrow replacement, Fanconi anemia, Maintenance chemotherapy (suppression of DNA synthesis), etc; patients on regular transfusions will invariably and unavoidably develop mounting iron overload further would be at risk for toxicity of iron (46)

A transfusion-dependent anemia patient receives about 2U of blood/ month, would be receiving about 24U of RBC/ year. If this calculated over a period of 4 years then the patient receives 84U of RBC and about 20gm of iron. Is many folds higher than the normal amount of body iron. The predictor of iron overload is the number of transfusions administered. (47)

The half-life of transfusion RBC is short when compared to the normal RBC, further undergoes erythrophagocytosis eventually liberates iron which gets accumulated or overloads macrophages. (48)

In a study conducted in 174 thalassemia patients receiving regular transfusions and chelation the clinical significance of NTBI was asssed and learnt that NTBI is the independent predictor of saturation of transferring and noticed the iron overload causing heart disease (49)

A study was conducted in patients with myelodysplastic syndrome to evaluate the transfusion dependency as an independent prognostic value and iron overload. (50)

Laboratory measurements and diagnosis of iron overload

The first step taken to prevent the iron toxicity in patients dependent on transfusions is monitoring and routine screening of iron levels. This helps in proper diagnosis and management of the therapy effectively. The tests include indirect measurement of iron like clinical laboratory tests and image studies.

Serum Ferritin: This test estimates total body iron stores (TBI) and till date this is proven to be the most convenient laboratory test as it is widely available, non-invasive and inexpensive (51)

Large population studies had stated that the results of serum ferritin are approximately proportional to TBI. The established ranges for serum ferritin are as follows. Men >300ng/ml, female > 200ng/ml in premenopausal women. This when combined with serum transferring saturation then fasting value is >60% in men and >50% in women

Yet another study stated that mean serum ferritin values were of 2698± 1444ng/ml for a decade of thalassemia major patients life had predicted short stature impression of hypogonadism. It is suggested that if serum ferritin is repeatedly > 1000ng/ml then this is a threshold alarming to start with iron reduction therapy (52,53)

However, serum ferritin is an acute phase reactant and it is known that serum level increases even in infections and inflammation also. Serum ferrtin values are learnt to be increased in malignancies, chronic liver diseases,

hemophagocytosic syndrome and adult still's disease. In addition to this the levels may also get effected by different iron toxicity treatments. Nonetheless, serum ferritin test is considered as significant screening tool and is used to monitor iron burden changes effectively (54)

Serum transferring saturation

This test measures the proportion of transferring bound to iron and used as an adjunctive test along with serum ferritin. It is derived by dividing serum iron/ total iron binding capacity (TIBC). It cannot estimate the TBI hence, not proven to be useful test in patients with transfusional iron overload [(55)]

Other laboratory tests include serum transferring receptor concentration, liable plasma iron, quantifies plasma NTBI and serum ferritin iron [(56)]

These tests are useful to understand the pathophysiology of iron overload but are not sufficiently sturdy for routine clinical applications and are not available as common tests.Tissue iron can be visually quantified by various imaging techniques like nuclear resonance scattering (NRS), computed tomography (CT), superconducting quantum interference device (SQUID) and magnetic resonance imaging (MRI).

Management of iron overload

1. Transfusion iron loading calculated annually.
2. Ferritin should be measured between one- to three-monthly intervals.
3. MRI for assessment of cardiac/liver iron should be performed at regular intervals
4. MRI of the heart and liver to assess iron burden should be undertaken in transfused patients
5. Cardiac and liver should be assessed annually either by echocardiography or MRI
6. Patients presenting with palpitations should be assessed for cardiac arrhythmias
7. Patients over the age of 40 should be assessed for liver fibrosis
8. Patients who have had severe liver iron overload, previous hepatitis C or fibrosis should be screened six monthly for HCC with ultrasound

Treatment

Deferoxamine, Deferiprone, and Deferasirox are the drugs of choice. These drugs were approved.By the United States Food and Drug Administration-accepted as iron chelators. Each of these iron chelators is well known for the treatment of iron overload in various clinical conditions.

SUMMARY

Hemochromatosis is a rare hereditary disease that is characterised by iron accumulation or overload in various tissues. The symptoms are non-specific and hence difficult to diagnose. Current options only manage the disease by removing excess iron. "One method is to bleed the patients and the other is to absorb iron using iron chelation, which is toxic to liver and kidney and may also cause hearing problems.Noted iron overload due to multiple transfusions was indepent reason for reduced survival rates and increased risk for transformation to acute myeloblastic leukemia It is established that symptoms of iron overload would not appear until significant organ damage occurred. Hence, it is mandate for routine screening and monitoring the iron levels.

CONCLUSION

Different inherited iron metabolism defects can lead to iron overload, iron deficiency, and abnormalities of serum ferritin levels. Iron overload occurs when iron intake is increased over a sustained period of time, either as a result of red blood cell transfusions or increased absorption of iron through the gastrointestinal tract (GI) When the levels of iron are high it leads to damaging every organ and tissue.Excess build-up of iron in the body.Hemochromatosis –can damage the liver.
Studies stated that transfusions in thalassemia patients helped in maintaining the haemoglobin levels at least between 7 to 8g/dL thus contributed for the improvement of the survival rate of children.

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