Iron overload diseases

IAGH monthly meeting Jan 2013
Reza Malekzadeh M.D AGAF
DDRC/TUMS
Iron Over Load Disorder

IAGH Day 1391
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هم اکنون که در حال نفس کشیدن هستید، کس دیگری دارد نفس‌های آخرش را می‌کشد، پس رست از گله و شگایت بردارید و بیاموزید پرچونه با راشته‌هایی‌تان زنگ‌گلی کنید.
وصية مولانا جلال الدين محمود

أوصيكم بِتَقْوِيَّة الله في السَّرِّ وَ العَلَانِيَّة
شما را در نهان و آشكر به تقواه خداوند سفارش مي كنم
وٌ بِقِلَّة الطَّعَام وَ قِلَّة المَنَام وَ قِلَّة الكَلام
و به غذائ اندك و كم خوابيدن و كم سخن گفتنت
و هِجْرَانِ المَعَاشِي وَ الآثَام
و دورى گزيدن از گناهان و لغشها
و مَوْاطِبَة الصَّيَام
و نگهداری روزه
و دُوَام الْقِيَام
و مداومت بر نماز
و احتمال الجفاء من جميع الآلام و تحميل جفا از جانب همّة مخلوقات و ترك مجاليّة السفهاء و العوام و ترك همّيّنا با فرومايگان و عوام و مصاحبة الصالحين و الكرام و همّيّنا با نيكوكاران و بزرگواران [سفارش می کنم]
حافظ از باد خزان در چمن دهر مرنج
فکر معقول بفرما گل بی خار کجاست
• غنچه از خواب پرید ... و گلی تازه به دنیا آمد ...
• خار خنديد و به گل گفت : سلام ... و جوابی نشئید ...
• خار رنجید ولي هیچ نگفت ...
• ساعتی چند گذشت ... گل چه زیبا شده بود ...
• دست بی رحمی آمد نزدیک ... گل سراسیمه ز وحشت افسرد ...
• لیک آن خار در آن دست خلید ... و گل از مرگ رهید ...
• صبح فردا که رسید ... خار با شبنمی از خواب پرید ...
• گل صمیمانه به او گفت : سلام
Classification of Chronic Hepatitis

• Non-Biliary
  1- Viral: HBV, HCV, HBV+HDV
  2- Non-Viral: AIH, NASH, Wilson's, Hemochromatosis

• Biliary
  1- PBC
  2- PSC
  3- AIC (Overlap Syndrome)
Etiology of CH in 413 Patients Shariati Hospital
Tehran 1371-1374

Viral----------------------------------- -61%
  1- HBV------------------- 54%
  2- HCV------------------- 7%

Non-Viral-------------------------- ---30%
  1- AIH--------------------- ----16%
  2- PSC,PBC-------------------6.5%
  3- Alcohol,Drugs----------4.5%
  4- NASH----------------------2.5%
  5- Wilson’s---------------------2.5%
  6- Hemochromatosis....>0%

Cryptogenic------------------------- 9%
Non-Viral Hepatitis

162 Patients in Shariati Hospital

AIH--------------------- 40%
Drugs--------------------- 8%
NASH---------------------- 7%
PSC------------------------ 7%
Wilson’s------------------ 6%
Hemochromatosis---------- 0%
Alcohol,----------------- 4%
PBC----------------------- 4%
Others--------------------- 24%
Inherited Causes of Cirrhosis In USA

- Hemochromatosis
- Familial intrahepatic cholestasis
- Wilson's
- CF
- Other
- $\alpha_1$ – antitrypsin deficiency

Newborn and infants

Adults

Bacon BR and Britton RS, 2002
Inherited Causes of Cirrhosis in Iran

- Wilson's Disease
  - Familial intrahepatic cholestasis
- Hemochromatosis
- Other
Normal Iron Metabolism

Ingested
10-20 mg/day

Total body iron - 4g

Absorbed
1-2 mg/day

Lost
Gut, skin, urine - 1-2 mg/day
Menses - 30 mg/month

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Iron Transport and Storage

Transport
Transferrin - two iron atoms

Intracellular storage
Ferritin - thousands of iron atoms

Total body iron – 4g
500 ml of blood contain 250 mg of Iron
Liver plays a major role in iron homeostasis in humans.
Other sources of Iron

- **Muscle**: as myoglobin
- **Heme-containing enzymes** anywhere in the body.
- **Reticuloendothelial cells. Spleen, BM, Marophage**. In the form of ferritin or hezzmosidrin
The survival of living organisms depends on their ability to maintain "constancy in the internal milieu".

1865 Claude Bernard

Any system regulates its internal environment and tends to maintain a stable, constant condition: homeostasis.

1932 Walter Bradford Cannon
Iron Hemostasis

- Sensor: HFE, Hemojuvelin and TfR2
- Target: Ferroportin
- Effector: Hepcidin
Comparing the hemostatic system for Iron to Glucose

- Glucose
  - Glucose receptor
  - Insulin
  - Insulin receptor

- Iron
  - Hemouvelin
  - Hepcidin
  - Ferroportin

Homeostatic components:
- Sensor
- Effector
- Target
Iron sensing
Iron sensing: Role of BMP
Effector: The analogy between Insulin and Hepcidin

Hepcidin Model

C. Normal

Liver
HFE

Ferritin-iron

Villus enterocyte

Hepcidin

Plasma
Ferroportin

Iron

Macrophage

D. HFE-Related Hemochromatosis

Liver
Mutant HFE

Ferritin-iron

Villus enterocyte

Hepcidin

Plasma
Ferroportin

Iron

Uncontrolled release of iron from macrophage and duodenal enterocytes

Macrophage

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Disruption of glucose Hemoestasis

reduced INSULIN synthesis/activity

DIABETES

Insulin deficiency
(Gene defects, toxic, viral and immune-mediated beta-cell destruction)

Insulin resistance
(Gene defects and environmental factors)
Disruption of Iron Hemoestasis

**reduced HEPCIDIN synthesis/activity**

**HEMOCROMATOSIS**

- Hepcidin deficiency
  - (Genes defects, hypoxia, toxic, viral and immune-mediated hepatocyte destruction)

- Hepcidin resistance
  - (Gene defects and environmental factors)

Liver → Ferroportin
# Disruption of Hemoestasis

<table>
<thead>
<tr>
<th>Glucose</th>
<th>Glucose receptor</th>
<th>Insulin</th>
<th>Insulin receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRON</td>
<td>Hemouvelin</td>
<td>Hepcidin</td>
<td>Ferroportin</td>
</tr>
<tr>
<td></td>
<td>HFETfR2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Homeostatic components</th>
<th>Sensor</th>
<th>Effector</th>
<th>Target</th>
</tr>
</thead>
</table>

Many genes....one disease

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Hepcidin*

- Hepcidin which was discovered in (2001) is a circulating small peptide which is secreted by the liver.
- Has an inhibitory effect on iron absorption in the small intestine.
- Mutations in the gene coding for Hepcidin called HAMP have now been associated with juvenile hemochromatosis.

*Krause A et al FEBE Lett 2000
*Nemeth E et al Science 2004
Hepcidin

- Is clearly central to iron absorption and iron metabolism and work as messenger between the liver and the intestine
Hepcidin and Iron Metabolism

- Antimicrobial peptide
- Synthesized in the liver
- Expression related to body iron stores
- Hepcidin deficient mice $\rightarrow$ iron overload
- $\downarrow$ expression in iron deficient mice
- Overexpression $\rightarrow$ severe anemia
- Circulating hepcidin inhibits iron absorption
What was unknown up to 2009?

• The signals that actually lead to transduction of hepcidin message and synthesis of hepcidin were still unknown.

Billy Andriopoulos Jr et al NATURE GENETICS APRIL 2009
Bone morphogenetic proteins (BMP6) is a key endogenous regulator of hepcidin expression and iron metabolism*

- New data support a key role for BMP6 as a ligand for hemojuvelin and an endogenous regulator of hepcidin expression and iron metabolism in vivo

Billy Andriopoulos Jr et al NATURE GENETICS APRIL 2009
Reza Malekzadeh DDRC/TUMS
BMPs induction of hepcidin expression

• Expression of hepcidin, a key regulator of intestinal iron absorption, can be induced in vitro by several bone morphogenetic proteins (BMPs), including BMP2, BMP4 and BMP9.

Billy Andriopoulos Jr et al NATURE GENETICS APRIL 2009
Bmp6 is critical for iron homeostasis

• Targeted disruption of Bmp6 in mice causes a rapid and massive accumulation of iron in the liver, the acinar cells of the exocrine pancreas, the heart and the renal convoluted tubules with markedly reduced hepcidin synthesis.
Mutations in BMP6*

- The iron burden in Bmp6 mutant mice is significantly greater than that in mice deficient in the gene associated with classical hemochromatosis (HFE).
- Mutations in BMP6 might cause iron overload in humans with severe juvenile hemochromatosis for which the genetic basis has not yet been characterized.

Meynard D et al. Nature Genetics 2009
Hemochromatosis publications (1950-2009)
A Prospective Study of the Clinical and Paraclinical Features of Wilson’s Disease in Iran

Reza Ansari MD, Reza Malekzadeh MD, Naser Ebrahimi-Daryani MD, Mohammad Javad Mirdamadi MD, Masoud Reza Sohrabi MD, Seyed Abdolreza Mortazavi-Tabatabaei MD

Digestive Diseases Research Center, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran

• Abstract

Objective- Wilson’s disease (WD) is an autosomal recessive disease with different manifestations. This study was aimed to assess the clinical and paraclinical features of this disease in different groups of patients in order to reach a diagnostic algorithm.

Methods- Over a period of 10 years (1990-1999), 84 patients with WD (mean age 27 years, 54 males) were studied in 6 referral university hospitals. The presenting features were chronic liver disease in 37, acute hepatitis in 9, hepatocerebral involvement in 10 and neurological disease in 11 patients. Further seventeen patients were detected by a family screening program. Diagnosis was based on clinical evaluation including ophthalmologic and neurologic examinations, positive laboratory investigations such as abnormal liver function tests, serum ceruloplasmin level below 20 mg/dl, and urinary copper excretion levels above 100 μg/day. The patients underwent treatment with a daily dose of 1-2 g D-penicillamine.

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The First case of HH from Iran

ARCH IRANIAN MED 2006; 9 (1): 78 – 80

Case Report

HEREDITARY HEMOCHROMATOSIS: A RARE DISEASE IN IRAN

Hossein Nobakht MD*, Shahin Merat MD**, Reza Malekzadeh MD* **

Hereditary hemochromatosis is a common cause of chronic liver disease in western countries. No report of this disease has appeared from Iran and the few studies which have focused on chronic liver disease have failed to identify a single case of hemochromatosis. In this report, we present the first case of hereditary hemochromatosis during our 25 years of gastroenterology practice in Iran.

Archives of Iranian Medicine, Volume 9, Number 1, 2006: 78 – 80.

Keywords: Hemochromatosis • hereditary • Iran • liver disease

Reza Malekzadeh DDRC/TUMS
For much of the 20th century, hereditary hemochromatosis was regarded as a clinically and genetically unique entity. The classic findings on presentation — diabetes, bronze pigmentation of the skin, and cirrhosis — were first described in the 19th century, when the term “hemochromatosis” was first used; by 1935 it had become clear that the disease was hereditary and was caused by excess deposits of iron in the tissue. In the 1970s and 1980s, it was recognized as an autosomal recessive disorder linked to the region of the short arm of chromosome 6 encoding HLA-A*3, and in 1996 “the hemochromatosis gene,” HFE, was finally identified.

In the few years since the discovery of the HFE gene, our understanding of hereditary hemochromatosis and of human iron metabolism in general has become much more complete (Fig. 1). We know that mutations in other genes that control iron metabolism can cause similar forms of iron overload (defined in terms of excess body iron levels) that lead to deposits of iron in the tissues with distinct patterns and organ-damaging potential. Genetic testing has revolutionized the diagnosis of hereditary hemochromatosis and has revealed that the phenotypic expression of a given mutation in an iron-metabolism gene may vary widely. These advances have stretched the boundaries of the historical definition of hereditary hemochromatosis.
New Understanding

• We know that mutations in other genes that control iron metabolism can cause similar forms of iron overload that lead to deposits of iron in the tissues with distinct patterns and organ-damaging potential.
Variation in phenotypic expression of a given mutation

• Genetic testing has revolutionized the diagnosis of hereditary hemochromatosis and has revealed that the phenotypic expression of a given mutation in an iron-metabolism gene may vary widely.

• These advances have stretched the boundaries of the historical definition of hereditary hemochromatosis.
## Comparative Overview of the Primary Iron-Overload Disorders Classified as Hereditary Hemochromatosis

<table>
<thead>
<tr>
<th>Feature</th>
<th>HFE-Related Hereditary Hemochromatosis†</th>
<th>Juvenile Hereditary Hemochromatosis</th>
<th>TfR2-Related Hereditary Hemochromatosis</th>
<th>Ferroportin-Related Iron Overload‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>OMIM classification</td>
<td>Type 1</td>
<td>Type 2, subtype A</td>
<td>Type 2, subtype B</td>
<td>Type 3</td>
</tr>
<tr>
<td>Implicated gene and its chromosomal location</td>
<td>HFE, 6p21.3</td>
<td>HJV (originally called HFE2), 1q21</td>
<td>HAMP, 19q13.1</td>
<td>SLC40A1, 2q32</td>
</tr>
<tr>
<td>Gene product</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Name</td>
<td>HFE</td>
<td>Hemojuvelin</td>
<td>Hepcidin</td>
<td>Ferroportin (also iron-regulatory protein, or metal-transporter protein)</td>
</tr>
<tr>
<td>Known or postulated function†</td>
<td>Interaction with transferrin receptor 1, probably facilitating uptake of transferrin-bound iron; possibly modulation of hepcidin expression</td>
<td>Unknown; possibly modulation of hepcidin expression</td>
<td>Down-regulation of iron release by enterocytes, macrophages, or placental cells</td>
<td>Possibly uptake of iron by hepatocytes</td>
</tr>
<tr>
<td>Pattern of inheritance</td>
<td>Autosomal recessive</td>
<td>Autosomal recessive</td>
<td>Autosomal recessive</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>Evidence of expanded plasma iron compartment (high transferrin saturation)</td>
<td>Earliest detectable biochemical anomaly</td>
<td>Earliest detectable biochemical anomaly</td>
<td>Earliest detectable biochemical anomaly</td>
<td>Only in advanced stages</td>
</tr>
<tr>
<td>Main organs accumulating iron</td>
<td>Liver, endocrine glands, heart</td>
<td>Liver, endocrine glands, heart</td>
<td>Liver, endocrine glands, heart</td>
<td>Liver, spleen</td>
</tr>
<tr>
<td>Predominant cell distribution of iron accumulation</td>
<td>Parenchymal</td>
<td>Parenchymal</td>
<td>Parenchymal</td>
<td>Reticuloendothelial</td>
</tr>
<tr>
<td>Potential for organ damage</td>
<td>Variable</td>
<td>High</td>
<td>High</td>
<td>Variable</td>
</tr>
<tr>
<td>Anemia</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Low</td>
</tr>
<tr>
<td>Response to therapeutic phlebotomy</td>
<td>Excellent: decrease in serum ferritin in parallel with transferrin saturation; no risk of anemia</td>
<td>Excellent: decrease in serum ferritin in parallel with transferrin saturation; no risk of anemia</td>
<td>Excellent: decrease in serum ferritin in parallel with transferrin saturation; no risk of anemia</td>
<td>Fair: rapid decrease in transferrin saturation with persistently high serum ferritin; substantial risk of anemia with aggressive phlebotomy regimen</td>
</tr>
<tr>
<td>Decade of onset of symptomatic organ disease</td>
<td>4th or 5th</td>
<td>2nd or 3rd</td>
<td>2nd or 3rd</td>
<td>4th or 5th</td>
</tr>
</tbody>
</table>

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Simplified classification of hereditary iron overload

<table>
<thead>
<tr>
<th>Name</th>
<th>Type</th>
<th>Gene</th>
<th>OMIM</th>
<th>Common mutation</th>
<th>Published</th>
</tr>
</thead>
<tbody>
<tr>
<td>HFE</td>
<td>1</td>
<td>HFE</td>
<td>235200</td>
<td>C282Y</td>
<td>1996</td>
</tr>
<tr>
<td>Juvenile</td>
<td>2A</td>
<td>HJV</td>
<td>608374</td>
<td>G320 V</td>
<td>2004</td>
</tr>
<tr>
<td></td>
<td>2B</td>
<td>HAMP</td>
<td>606464</td>
<td>(93delG)</td>
<td>2003</td>
</tr>
<tr>
<td>TfR2</td>
<td>3</td>
<td>TfR2</td>
<td>604250</td>
<td>Y250X</td>
<td>2000</td>
</tr>
<tr>
<td>Ferroportin</td>
<td>4</td>
<td>SLC40A1</td>
<td>606069</td>
<td>(N144H)</td>
<td>2001</td>
</tr>
</tbody>
</table>

Other: atransferrinaemia, aceruloplasminaemia, H-ferritin, neonatal.
Adult onset hereditary hemochromatosis,

• 1-Mutations in the transferrin receptor 2 gene (\textit{TfR2}) appears to be very similar to that of classic, \textit{HFE}-related hemochromatosis

• \textit{2-HFE}-related hemochromatosis Both characterize by gradual iron loading, a relatively late onset of parenchymal iron deposition, an predominantly hepatic organ damage.

• 3- Hereditary Ferroportin disease
Juvenile-onset phenotype

- The juvenile-onset phenotype is much more severe.
- Plasma iron loading and tissue iron excesses (reflected by increased transferrin-saturation values and serum ferritin levels, respectively) are evident early in life in both sexes.
Types of juvenile-onset HH

• 1-Mutation in the *HAMP* gene, which encodes hepcidin, a peptide that plays a key role in human iron metabolism.

• 2-Mutation in hemojuvelin (*HJV*) gene that originally called *HFE2*. 
Ferroportin: Iron Exporter

• Control iron release from hepatocytes and, importantly, macrophages

• Ferroportin is inhibited directly by hepcidin, a key iron-regulatory peptide
Ferroportin disease (HH type 4)

• Single missense mutations in the Ferroportin (SLC40A1) gene are associated with iron overload syndromes inherited as an autosomal dominant trait.

• An increasingly recognized cause of hepatic iron overload in patients with hyperferritinemia;
In contrast to HFE-related hemochromatosis, individuals with *SLC40A1* mutations typically have *raised* serum ferritin concentrations with normal or low transferrin saturation and excess iron storage, predominantly in macrophages.
Hereditary Ferroportin disease have been classified into two principal groups

- **1- Macrophage type** (M-type): with low transferrin saturation have what has been termed ferroportin disease, associated with loss-of-function mutations and consequent iron trapping in macrophages.

Not restricted to Caucasians

• The disorder is typified by a raised ferritin with normal or low transferrin saturation and a tendency for anaemia with poor venesection tolerance.

• Not restricted to Caucasians, the condition is recognized in Asians and a unique and common polymorphism (Q248H) in southern African populations may contribute to the iron overload observed.
Iron loading occurs predominantly within the RES

- Iron loading occurs predominantly within the reticuloendothelial system with splenic uptake visible on magnetic resonance imaging; in the liver Kupffer cells become iron-laden with relative sparing of hepatocytes.
- The Ferroportin mutation ‘locks’ iron within macrophages and it has been suggested that the reduced availability of plasma iron to bind transferrin drives increased intestinal absorption.
The ferroportin disease

The ferroportin disease: MRI

The Polygenic Nature and Phenotypic Continuum of Hereditary Hemochromatosis

Monogenic or digenic inheritance of gene mutations

Phenotypic presentation

Age at onset

Clinical severity

Contribution of host or environmental factors to expressivity

Gene

HJV

HAMP

TfR2

HFE
Diagnosis of Iron Overload Diseases
# Iron Measurements

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Hereditary HH</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serum</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iron</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(µg/dL)</td>
<td>60-180</td>
<td>180-300</td>
</tr>
<tr>
<td>(µmol/L)</td>
<td>11-32</td>
<td>32-54</td>
</tr>
<tr>
<td>Transferrin saturation %</td>
<td>20-50</td>
<td>55-100</td>
</tr>
<tr>
<td>Ferritin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males (ng/mL or µg/L)</td>
<td>20-200</td>
<td>300-3000</td>
</tr>
<tr>
<td>Females (ng/mL or µg/L)</td>
<td>15-150</td>
<td>250-3000</td>
</tr>
<tr>
<td><strong>Liver</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iron stains</td>
<td>0,1+</td>
<td>3+, 4+</td>
</tr>
<tr>
<td>Iron concentration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(µg/g dry weight)</td>
<td>300-1500</td>
<td>3000-30,000</td>
</tr>
<tr>
<td>(µmol/g dry weight)</td>
<td>5-27</td>
<td>53-536</td>
</tr>
<tr>
<td>Iron index</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(µmol/g dry weight – age in years)</td>
<td>&lt;1.1</td>
<td>&gt;1.9</td>
</tr>
</tbody>
</table>
Hepatic Iron Index

Liver iron vs. Age
(μmol/g) (yr)

Index

Liver iron index for different conditions:
- Normals
- Alcoholic
- Precirrhotic
- Cirrhotic
- Hemochromatosis
- Heterozygotes
- Homozygotes

Bacon BR and Britton RS, 2002
## Iron Balance Values

<table>
<thead>
<tr>
<th></th>
<th>Serum iron (µg/dL)</th>
<th>TIBC (µg/dL)</th>
<th>Transferrin saturation (%)</th>
<th>Ferritin (µg/dL)</th>
<th>Quantitative hepatic iron (µg/g dry wt)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normal</strong></td>
<td>60-180</td>
<td>230-370</td>
<td>20-50</td>
<td>20-200</td>
<td>300-1500</td>
</tr>
<tr>
<td><strong>Hemochromatosis</strong></td>
<td>&gt;180</td>
<td>&lt;300</td>
<td>&gt;50</td>
<td>&gt;300</td>
<td>&gt;3000</td>
</tr>
</tbody>
</table>
Genetic Diseases – Hemochromatosis – Diagnostic Testing

Family history or suspicion of hemochromatosis

Fe / TIBC - % saturation
Ferritin
% sat. >50%
Ferritin
>250 μg/L
>300 μg/L

HFE gene testing
C282Y homozygous
C282Y / H630 heterozygous

No mutations
Liver biopsy with iron stain and quantitative iron stainable Fe
Iron index > 2

Phlebotomy, response confirms diagnosis
## Global Prevalence of HFE Mutations

<table>
<thead>
<tr>
<th>Population</th>
<th>C282Y allelic</th>
<th>H63D allelic</th>
</tr>
</thead>
<tbody>
<tr>
<td>United Kingdom</td>
<td>6.4</td>
<td>12.8</td>
</tr>
<tr>
<td>Norway</td>
<td>6.4</td>
<td>11.2</td>
</tr>
<tr>
<td>Denmark</td>
<td>9.5</td>
<td>12.2</td>
</tr>
<tr>
<td>Finland</td>
<td>0</td>
<td>11.8</td>
</tr>
<tr>
<td>Former USSR</td>
<td>1.0</td>
<td>10.4</td>
</tr>
<tr>
<td>Germany</td>
<td>3.9</td>
<td>14.8</td>
</tr>
<tr>
<td>Italy</td>
<td>0.5</td>
<td>12.6</td>
</tr>
<tr>
<td>Spain</td>
<td>3.2</td>
<td>26.3</td>
</tr>
<tr>
<td>Iran</td>
<td>0</td>
<td>2.6</td>
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<tr>
<td>Saudi Arabia</td>
<td>0</td>
<td>8.5</td>
</tr>
<tr>
<td>Africa</td>
<td>0</td>
<td>2.6</td>
</tr>
<tr>
<td>Indian subcontinent</td>
<td>0.2</td>
<td>8.4</td>
</tr>
<tr>
<td>Asia</td>
<td>0</td>
<td>1.9</td>
</tr>
<tr>
<td>Australasia</td>
<td>0</td>
<td>0.2</td>
</tr>
<tr>
<td>Americas</td>
<td>0.7</td>
<td>2.6</td>
</tr>
</tbody>
</table>

## Prevalence of HFE Mutations in Tehran*

<table>
<thead>
<tr>
<th>HFE Mutation</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C282Y Homozygous</td>
<td>0%</td>
</tr>
<tr>
<td>C282Y Heterozygous</td>
<td>2.2%</td>
</tr>
<tr>
<td>H63D Homozygous</td>
<td>2.6%</td>
</tr>
<tr>
<td>H63D Heterozygous</td>
<td>11.5%</td>
</tr>
</tbody>
</table>

*Bakayev V..Zali MR J Hepat 2004
Hemochromatosis Mutations in Iranian HBV infected subjects

• The frequencies of the major HFE mutation was significantly more frequent in subjects infected with hepatitis B virus (4%) than in control subjects (0%) \( P<0.02 \)

Sendi h, Zali MR, Magnus L et al Clin Infect Dis. 2005

Reza Malekzadeh DDRC/TUMS
Provisional

- Elevated serum ferritin (>300 µg per liter for men and postmenopausal women, >200 µg per liter for premenopausal women) in association with
- elevated transferrin saturation (>55% for men and >45% for women)
Causes of the elevated transferrin saturation in the absence of HH

• High serum iron levels due to hepatic cytolysis (sever viral, alcohol, Non Alcoholic or Al hepatitis)

• Low transferrin levels due to liver failure have been ruled
Iron-Overload–Related Disease. Documented

At least one of the following:

• increased iron content shown by hepatic iron staining 3 or 4.
• Iron concentration >90 μmol per gram, or hepatic iron index >1.9 (Whitlock et al.14)
• Serum ferritin >1000 μg per liter at baseline with documented therapeutic venesection
Normal liver has the same intensity as spleen and muscle.
Iron overload occurs in the liver only in HFE-related haemochromatosis
Low signal intensity on T2-weighted magnetic resonance imaging confirms iron deposition in both liver and spleen of a patient with Ferroportin mutation.
Comparison v
a) Ferroportin disease
b) HFE HH
3) Normal
Liver biopsy of a patient with type 4 haemochromatosis shows intense Kupffer cell iron