CURRENT STATUS OF HEMOCHROMATOSIS

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This is to acknowledge that Dr. Burton Combes has not disclosed any financial interests or other relationships with commercial concerns related directly to this program. Dr. Burton Combes will not be discussing off-label uses in his presentation.

INTRODUCTION

In the past decade, enormous advances have been made in our understanding of diseases related to iron overload. Good insights can be gleaned in a recent issue of Seminars in Liver Disease.

(1) *Bruce R. Bacon (guest editor). Iron and the Liver. Seminars in Liver Disease 2005 (November issue), 25:1-472. Thieme, New York, Stuttgart.*

In the present Grand Rounds, we shall focus on

(1) the disease

(2) the etiologies of iron overload with emphasis on genetic causes of iron overload

(3) the scientific highlights which serve as the basis of our understanding of the development of iron overload

(4) management of the disease

(5) various tidbits.

THE DISEASE

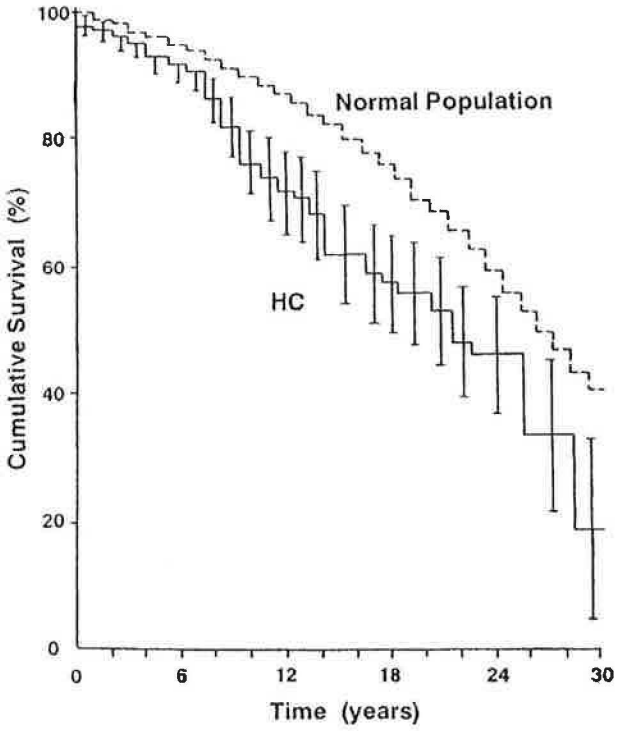
A valuable reference that provides an overview of the natural history of hereditary hemochromatosis is the publication of Niederau and colleagues.

(2) *Claus Niederau, Rudolf Fischer, Ariane Puerschel, et al. Long-term survival in patients with hereditary hemochromatosis. Gastroenterology 1996;110:1107-1119.*

SURVIVAL IN HEREDITARY HEMOCHROMATOSIS

(251 patients)

From Niederau et al, Gastroenterology 1996;110:1107-1119



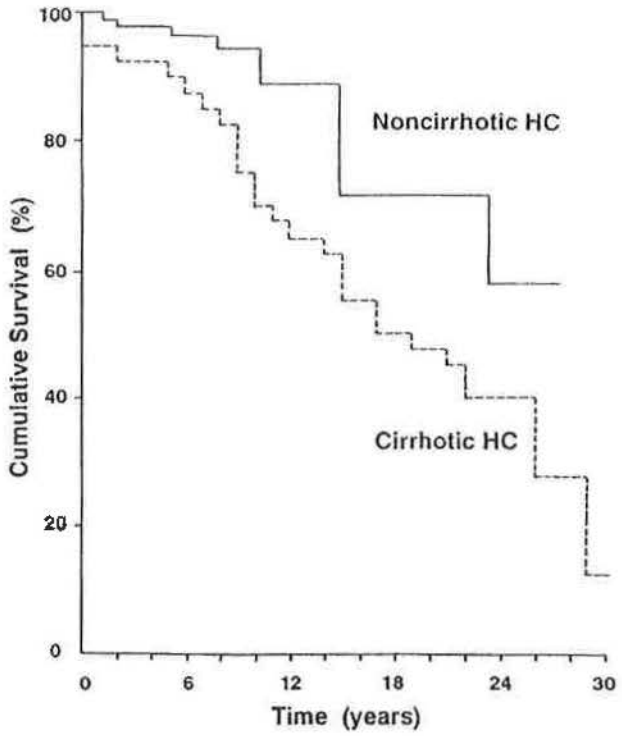
The cumulative survival of patients with hereditary hemochromatosis was reduced when compared with the expected survival rates for an age- and sex-matched normal population (Figure 1 in reference 2).

Moreover, cumulative survival was significantly reduced in their cirrhotic when compared to their non-cirrhotic patients (Figure 2 in reference 2).

SURVIVAL IN HEREDITARY HEMOCHROMATOSIS

(142 cirrhotic; 109 non-cirrhotic patients)

From Niederau et al, Gastroenterology 119;110:1107-1110



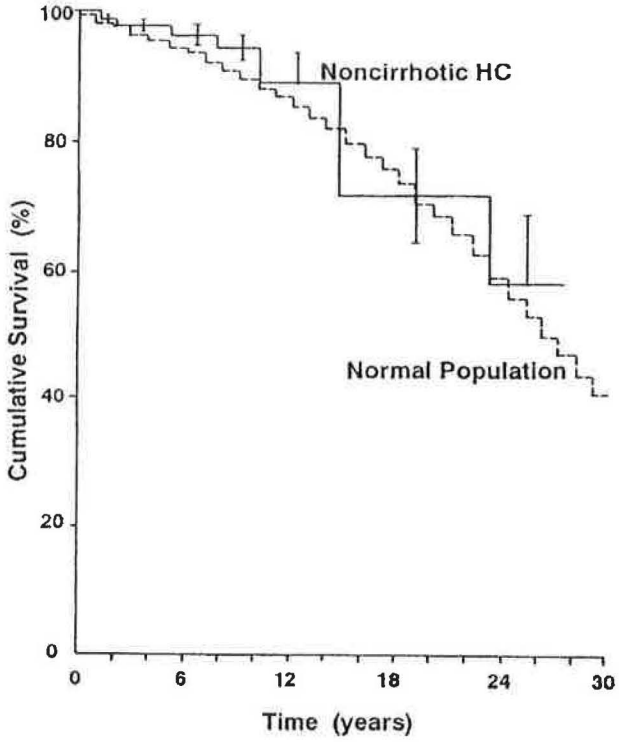
Cumulative survival was significantly reduced in the cirrhotic patients when compared with the non-cirrhotic patients.

Of additional importance, the cumulative survival rate was comparable in non-cirrhotic patients and in the rates expected for an age- and sex-matched normal population (Figure 3 in reference 2).

SURVIVAL IN NON-CIRRHOTIC PATIENTS WITH HEREDITARY HEMOCHROMATOSIS

(109 patients)

From Niderau et al, Gastroenterology 1996;110:1107-1119



The cumulative survival rate was comparable in non-cirrhotic patients and in the rates expected for an age- and sex-matched normal population

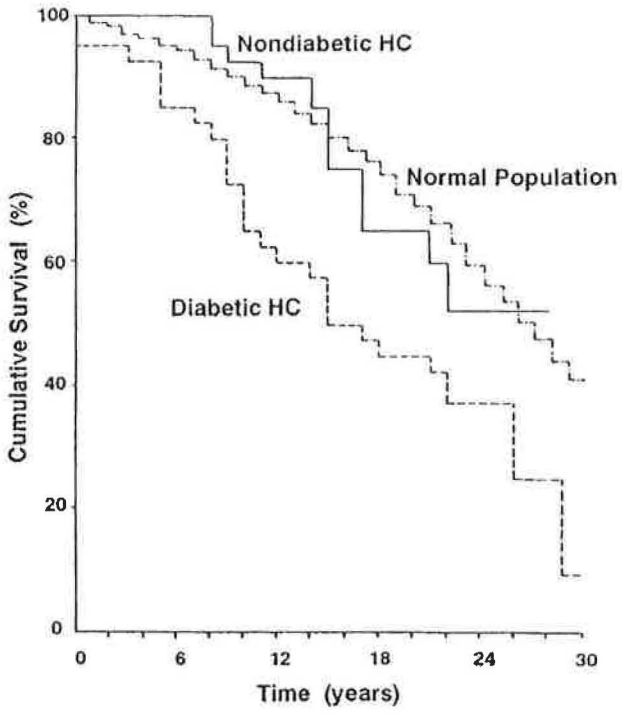
Thus, progression to cirrhosis imparts a poorer prognosis.

Diabetes is another serious complication of hereditary hemochromatosis, imparting, like cirrhosis, a poorer prognosis (Figure 4 in reference 2)

SURVIVAL IN DIABETICS WITH HEREDITARY HEMOCHROMATOSIS

Diabetic (n=120) versus non-diabetic (n=131)

From Niederau et al, Gastroenterology 1996;110:1107-1119



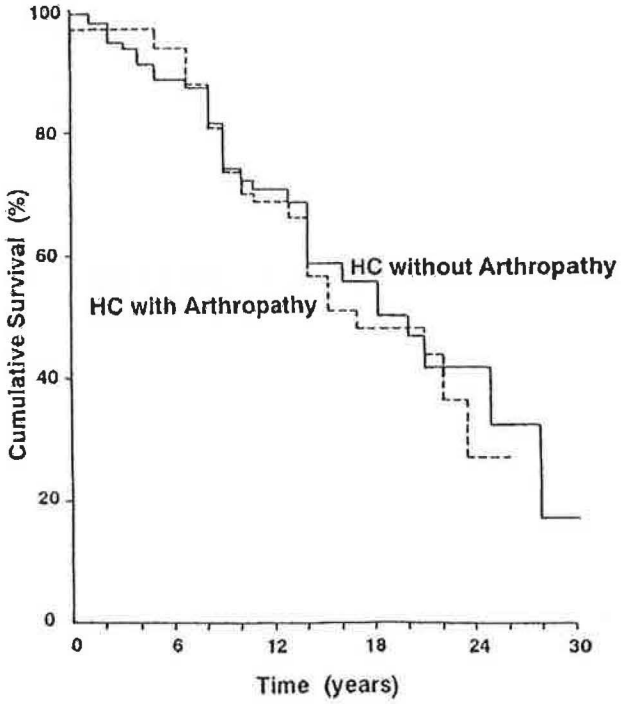
Diabetes occurs with much higher frequency in the cirrhotic than non-cirrhotic patients. Thus, the effects of cirrhosis and diabetes on survival are not cumulative.

By contrast, arthropathy, although a common complication of iron overload, did not impact on survival (Figure 5 in reference 2)

RELATIONSHIP OF ARTHROPATHY TO SURVIVAL IN HEREDITARY HEMOCHROMATOSIS

With arthropathy (n=111) versus without arthropathy (n=140)

From Niederau et al, Gastroenterology 1996;110:1107-1119



Much greater iron loads could be removed by phlebotomy in those patients whose (a) survival was reduced, (b) who had cirrhosis, or (c) who had diabetes than in their non-cirrhotic, non-diabetic counterparts.

A reasonable conclusion is that severe iron load induces complications that shorten survival.

CLASSIFICATION OF IRON OVERLOAD DISORDERS

I Genetic hereditary hemochromatoses

A. (Autosomal recessive inheritance)

Mutations affect production of the important sensors of iron load in hepatocytes. All lead to a decrease in the wild type peptide compound referred to as HEPCIDIN.

1. TYPE 1: HFE-associated hemochromatosis
   C282Y homozygosity
   C282Y/H63D compound heterozygosity

2. TYPE 2:
   (a) Mutations in hepcidin (Type 2A)
   (b) Mutations in hemojuvelin, a compound that has important influence on hepcidin formation (Type 2B)

3. TYPE 3: Mutations in transferrin receptor 2
   Effective transferrin receptor 2 required for formation of hepcidin

B. (Autosomal dominant inheritance)

Mutations affect the compound (FERROPORTIN) that responds to hepcidin and is important for release of iron from enterocytes, reticuloendothelial cells, muscle and placenta.

1. TYPE 4: Ferroportin disease

II **Acquired iron overload**

A. Iron-loading anemias
- Thalassemia
- Sideroblastic anemia
- Chronic hemolytic anemias

B. Parenteral iron overload
- Iron supplementation
- Multiple transfusions

C. Dietary iron overload (African)
- Many of these patients have mutations in ferroportin.

III **Miscellaneous causes of iron overload**

A. Chronic liver disease
- Hepatitis C
- Alcohol-related liver disease
- Non-alcoholic fatty liver disease
- Porphyria cutanea tarda
- Post portocaval shunting

B. Very rare
- Aceruloplasminemia
- Congenital atransferrinemia

The autosomal recessive mutations involve genes that regulate the synthesis of hepcidin.

HEPCIDIN

CHARACTERISTICS

- 25 amino acid polypeptide
- Synthesized by liver
- Secreted into blood
- Excreted in urine
- Increased synthesis with iron overload
- Decreased synthesis with iron deficiency

FUNCTIONS

- Binds to ferroportin, a transmembrane iron transporter necessary for iron transport out of intestinal epithelium, macrophages (? out of liver).
- Leads to internalization of hepcidin-ferroportin and to degradation of ferroportin.
- Leads to decreased iron absorption.

MUTATIONS

- Regulators of hepcidin synthesis
  - (a) HFE 1
  - (b) HFE 2
  - (c) TRF 2
- In hepcidin *per se*

All of these mutations lead to:

Loss of function
Increased iron absorption
Increased serum iron (i.e. transferrin saturation).
Increased iron in hepatocytes

HEPCIDIN

Park CH, Valore EV, Waring J, et al. Hepcidin, a urinary antimicrobial peptide synthesized in the liver. J Biol Chem 2001;276:7806-7810.

Bridle KR, Frazer DM, Wilkins SJ, et al. Disrupted hepcidin regulation in HFE-associated haemochromatosis and the liver as a regulator of body iron homeostasis. Lancet 2003;361:669-673.

Ganz T. Hepcidin - a regulator of intestinal iron absorption and iron recycling by macrophages. Best Practice and Research Clinical Haematology 2005;18:171-182.

Nemeth E, Tuttle MS, Powelson J, et al. Hepcidin regulates cellular iron efflux by binding to ferroportin and inducing its internalization. Science 2004;306:2090-2093.

Ganz T and Nemeth E. Iron imports. IV. Hepcidin and regulation of body iron metabolism. Am J Physiol Gastrointest Liver Physiol 2006;290:G199-G203.

Papanikolaou G, Tzillanos M, Christakis JI, et al. Hepcidin in iron overload disorders. Blood 2005;105:4103-4105.

HFE 1 HEMOCHROMATOSIS

Feder JN, Gnirke A, Thomas W, et al. A novel MHC class 1-like gene is mutated in patients with hereditary hemochromatosis. nature Genet 1996;13:399-408

Borot N, Roth M-P, Malfroy L, et al. Mutations in the MHC class 1-like candidate gene for hemochromatosis in French patients. Immunogenetics 1997;45:320-324.

Piperno A, Sampiertro M, Pietrangelo A, et al. Heterogeneity of Hemochromatosis in Italy. Gastroenterology 1998;114:996-1002.

Camaschella C, Fargion S, Sampietro M, et al. Inherited HFE-unrelated hemochromatosis *in Italian Families. Hepatology 1999;29:1563-1564.*

Steinberg KK, Cogswell ME, Chang JC, et al. Prevalence of C282Y and H63D mutations in the hemochromatosis (HFE) gene in the United States. JAMA 2001;285:2216-2222.

Beutler E, Felitti VJ, Koziol JA, et al. Penetrance of 845G→A (C282Y) HFE hereditary haemochromatosis mutation in the USA. Lancet 2002;359:211-218.

Lazarescu A, Sinvely BM and Adams PC. Phenotype variation in C282Y homozygotes for the hemochromatosis gene. Clin Gastroenterol Hepatol 2005;3:1043-1046.

HEMOJUVELIN (HFE 2)

Papanikolaou G, Samuels ME, Ludwig EH. Mutations in HFE2 cause iron overload in chromosome 1q-linked juvenile hemochromatosis. Nature Genetics 2004;36:77-82.

Koyama C, Hayashi H, Wakusawa S, et al. Three patients with middle-age-onset hemochromatosis caused by novel mutations in the hemojuvelin gene. J Hepatology 2005;42:740-742.

Lin L, Goldberg YP and Ganz T. Competitive regulation of hepcidin mRNA by soluble and cell-associated hemojuvelin. Blood 2005;106:2884-2889.

TRANSFERRIN RECEPTOR 2

Roetto A, Totaro A, Piperno A, et al. New mutations inactivating transferrin receptor 2 in hemochromatosis type 3. Blood 201;97:2555-2560.

Lebrón JA, Bennett MJ, Vaughn DE, et al. Crystal structure of the hemochromatosis protein HFE and characterization of its interaction with transferrin receptor. Cell 1998;93:111-123.

Nemeth E, Roetto A, Garozzo G, et al. Hepcidin is decreased in TFR2 hemochromatosis. Blood 2005;105:1803-1806.

The autosomal dominant mutations involve the synthesis of ferroportin.

FERROPORTIN 1

Roetto A, Merryweather-Clarke AT, Daraio F, et al. A valine depletion of ferroprotein 1: a common mutation in hemochromatosis type 4? Blood 2002;100:733-734.

Devalia V, Carter K, Walker AP, et al. Autosomal dominant reticuloendothelial iron overload associated with a 3-base pair deletion in the ferroportin 1 gene (SLC11A3). Blood 2002;100:695-697.

Pietrangelo A. The ferroportin disease. Blood Cells, Molecules, and Diseases 2004;32:131-138.

COMPARISON OF FEATURES OF CLASSICAL HEREDITARY HEMOCHROMATOSIS AND FERROPORTIN DISEASE

Adapted from Pietrangelo, Blood Cells, Molecules and Diseases 2004;32:131-138

	Hemochromatosis	Ferroportin Disease
Gene	HFE 1	Iron-regulated transporter (SLC 40AI)
Chromosome	6p21.3	2q32
Protein function	Interact with transferrin receptor 1 (TRF1)	Iron export from intestine; RE cells, hepatocytes, placenta
Pathogenesis	Increased tissue iron influx through down-regulation of hepcidin.	Increased retention of iron due to decreased release from cells.
Biochemistry	Increased transferrin saturation from second decade. High ferritin from third to fourth decade.	Variable transferrin saturation increasing in third to fourth decade. High ferritin from first decade.
Histological features (Liver biopsy)	Predominantly in hepatocytes	Predominantly in RE cells
MRI	Decreased liver signal intensity	Decreased liver and spleen signal intensity
Main clinical features when fully expressed	Liver fibrosis - cirrhosis Diabetes Hypogonadism Arthropathy Cardiac disease	Mild liver disease Marginal anemia
Response to phlebotomy	Well tolerated with aggressive regimen	Need to proceed more slowly because of risk of anemia, even in face of high ferritin.
Inheritance	Autosomal recessive	Autosomal dominant

The other autosomal recessive mutations induce iron overload at an earlier age, and induce what is called "juvenile hemochromatosis".

MANAGEMENT OF HEREDITARY HEMOCHROMATOSIS

Adapted from AASLD Practice Guidelines:
Tavill, Hepatology 2001;33:1321-1328

Early diagnosis to prevent organ damage and dysfunction due to tissue iron toxicity.

Screening and early detection of asymptomatic HH cases to reduce mortality.

Recognition and diagnosis of symptomatic cases of HH, to minimize progression and complications of the disease.

Adequate treatment of HH to promote rapid, safe, and effective removal of iron.

Vigilant follow-up and maintenance treatment of all cases of HH.

TREATMENT OF IRON OVERLOAD

Adapted from AASLD Practice Guidelines:
Tavill, Hepatology 2001;33:1321-1328

Hereditary Hemochromatosis:

One phlebotomy (removal of 500 ml of blood) weekly or biweekly

Check hematocrit prior to each phlebotomy; allow hematocrit to fall by no more than 20% of prior level.

Check serum ferritin level every 10-12 phlebotomies.

Stop frequent phlebotomy when serum ferritin falls below 50 ng/ml.

Continue phlebotomy at intervals to keep serum ferritin to between 25 and 50 ng/ml.

Avoid vitamin C supplements.

It is now possible for blood banks to transfuse blood obtained from patients with hereditary hemochromatosis, provided the blood is processed in the same way as any other blood volunteered for donation. Blood banks must apply for this opportunity. For the patient, no costs are levied for phlebotomy treatment. Blood considered satisfactory for transfusion can be administered without disease labeling (**see Guidance Document of the US Food and Drug Administration entitled "Guidance for industry. Variances for blood collection from individuals with hereditary hemochromatosis", August 2001**).

CONCLUSIONS

Too much iron in the body is not a good thing. Iron can damage organs and produce major disease.

Major causes of iron overload are related to genetic mutations of proteins that regulate iron metabolism.

Discovery of many of these mutations has led to development of laboratory tests that can identify persons at risk of developing iron overload. Risk alone does not invariably lead to sufficient iron overload to induce organ damage. Thus, we have developed strategies that may be unnecessary to pick out the person with increased iron stores before irreparable organ damage occurs.