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Review

Do some carriers of hemochromatosis gene mutations have higher than normal rates of disease and death?

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Abstract

Some heterozygote carriers of hemochromatosis HFE gene mutations become iron loaded with ensuing increased risk of disease and premature death. Contributing nutritional, behavioral and genetic factors are beginning to be identified. Carriers of HFE gene mutations should be advised to minimize contributing factors, if possible, and to have their iron values tested periodically. If values begin to rise, a schedule of phlebotomies should be considered.

Introduction

In hereditary hemochromatosis (HH), an excessive amount of ingested iron is absorbed from the intestine. As iron loading continues, some, but not all, affected persons develop organ and tissue damage. Conditions associated with iron loading include fatigue and depression, cancers, infections, arthritis, gastrointestinal and hepatic maladies, endocrine and neurological illnesses, and, not least, cardiovascular diseases (Weinberg 1999a).

In 1996, a gene that normally prevents development of HH was identified. The gene (HFE) codes for a protein that combines with the transferrin receptor (TfR) protein to lower the affinity of TfR for the holo- transferrin (holo-Tf) molecule (Feder *et al.* 1998). However, mutations in the HFE gene can result in a protein product that has lost ability to bind TfR efficiently. The consequent increased combination of TfR with holo-Tf results in excessive cellular iron loading.

The principal mutation of HFE that can lead to HH causes replacement of cysteine by tyrosine at amino acid 282 (CY).A second mutation results in substitution of aspartic acid for histidine at amino acid 63 (HD). The CY mutation is associated with a change in conformation of the HFE protein whereas the HD mutation may decrease its stability (Roy *et al.* 2000). Homozygosity for CY is present in >83% of HH patients. Elevated risk of HH occurs also in some HD homozygous patients and, as well, in some compound heterozygotes (CY/HD) (Beckman *et al.* 1999). Presently unresolved is the amount of iron loading with increased risk of disease that might develop in simple heterozygote carriers (CY/wt or HD/wt). There is, however, an increasing awareness of specific contributing factors that could result in HH problems in either compound or simple heterozygotes.

Iron loading and disease risk in carriers of HFE gene mutations

Selected studies that have monitored the extent of iron loading or of risk of diseases associated with elevated iron in carriers are summarized in Table 1. In each of the sets of carriers examined for iron loading, a minority of the population had elevated iron values. In the sets examined for specific diseases known to be enhanced in iron loaded persons, risks to carriers often were significantly higher than those in normal controls. However, in one study, symptoms commonly

Table 1. Iron loading and increased risk of diseases in some carriers of hemochromatosis gene (HFE) mutations.

Clinical condition	HFE mutations	Contributing factors	Clinical observation	Reference
Iron loading	CY/wt	ND	In men and women, respectively, mean elevation of 15 & 18% in Tf sat % and of 3 & 8% in serum Ft	Beutler *et al.* 2002
Iron loading	CY/HD	ND	In men and women, respectively, mean elevation of 48 & 41% in Tf sat % and of 62 & 35% in serum Ft	Beutler *et al.* 2002
Iron loading	CY/HD	Alcohol	In some patients, elevated Tf sat %, serum Ft and hepatic iron	Jeffrey *et al.* 2001
Iron loading	CY/wt& CY/HD	Alcohol & red meat	In some CY/wt males, elevated Tf sat %; in some CY/HD males & females, elevated Tf sat % and serum Ft	Rossi *et al.* 2001
Infection	CY/wt	Alcohol; raw shellfish	In hepatic iron loaded patient, death due to *Vibrio vulnificus* septicemia	Gerhard *et al.* 2001
Arthritis	ND	ND	Increased risk (2.1×) for arthritis	Nelson *et al.* 2001
Vascular disease	CY/wt	Smoking	Increased risk (3.5×) for cardiovascular disease	Roest *et al.* 1999
Vascular disease	CY/wt	ND	Increased risk (2.3×) for myocardial infarction	Tuomainen *et al.* 1999
Vascular disease	CY/wt	ND	Increased risk (6.6×) for ischemic cardiomyopathy	Pereira *et al.* 2001
Vascular disease	CY/HD	ND	Increased risk (4.1×) for ischemic heart disease	George *et al.* 2001
Cancer	CY/wt	Ser/Ser mutation in TfR gene	Increased risk (2.2×, 2.2×, 1.6×) for multiple myeloma, breast cancer, colorectal cancer	Beckman *et al.* 1999
Cancer	CY/HD	Ser/Ser mutation in TfR gene	Increased risk (6.5×, 7.3×, 8.7×) for multiple myeloma, breast cancer, colorectal cancer	Beckman *et al.* 1999
Cancer	HD/wt	ND	Increased risk for malignant glioma	Montemuros *et al.* 2001
Shortened life expectancy	CY/wt	ND	Increased mortality prior to age 65	Bathum *et al.* 2001

ND – not determined; CY – cysteine282tyrosine; HD – histidine63aspartic acid; Ser – serine142glycine; wt – wild type; Tf – transferrin; Ft – ferritin; TfR – transferrin receptor; control subjects – wt/wt; Tf sat % – % iron saturation of transferrin.

associated with hemochromatosis were not significantly more prevalent among CY/HD carriers than in wt/wt controls (Beutler *et al.* 2002).

Risk of premature mortality was observed to be increased in CY/wt but not in HD/wt carriers as compared with non-carriers (Bathum *et al.* 2001). In contrast, no decrease was found in prevalence of CY/HD or CY/CY with Increasing age (Beutler *et al.* 2002).

Contributing factors

In several of the studies, investigators noted nutritional, behavioral or genetic factors that might contribute to increased iron absorption. For example, in CY/HD carriers, median ferritin values were elevated by 36% in women and 42% in men who ate red meat daily as compared with meat consumption 1-2 days per week ($P = 0.01$ and 0.001, respectively) (Rossi *et al.* 2001). Similarly, median ferritin values were 170% higher in women and 46% higher in men who drank >50 g alcohol/d as compared with those who drank 1–10 g d ($P = 0.01$ and 0.001, respectively) (Rossi *et al.* 2001).

Unlike absorption of non-heme iron, absorption of the heme content of red meat is relatively unaffected by the level of iron deposits in the body (Rossi *et al.*2001). During intake of alcohol, gastric acid secretion is enhanced; the lowered pH value promotes

reduction of non-heme ferric ions with consequent elevated absorption of ferrous iron (Duane *et al.* 1992).

A third nutritional item that can be dangerous in carriers (as well as in HH homozygotes) who have elevated iron saturation of Tf is raw shellfish. This item often is contaminated by *Vibrio vulnificus*, a bacterial pathogen that can acquire growth-essential iron, and thereby cause septicemia, only if the content of the metal in Tf is above normal (Weinberg. 2000; Gerhard *et al.* 2001).

Among behavioral factors that might contribute to an elevated iron burden in HH heterozygotes are use of iron supplements and tobacco smoking. In the series of studies in Table 1, data on supplements were not available. In a study of 12,239 women (Roest *et al.* 1999), the incidence/1000 years of cardiovascular death in wt/wt smokers was increased 1.24× over that of controls (wt/wt non-smokers). CY/wt carriers who did not smoke had an increased risk of 1.31× over that of controls. Notably, the risk in CY/wt smokers was increased 3.5× over that of controls.

Leaves of tobacco plants accumulate a large quantity of iron. In one pack/d smokers, mainstream smoke provides approximately one microgram/d to alveolar macrophages (Weinberg 1999b). These cells have been reported to contain up to 4 times as much iron as in alveolar macrophages of non-smokers. Moreover, in murine models, macrophages from the respiratory tract have been observed to migrate to the vascular system (Yang *et al.* 1995) Iron mediated oxidative stress may damage not only arterial walls but also myocardium (Tuomainen *et al.* 1999).

The role of excessive iron in initiation and promotion of cancer cell growth has long been known (Weinberg 1996). The metal is carcinogenic due to its catalytic effect on the formation of oxygen radicals, suppression of the activity of host defense cells, and promotion of cancer cell multiplication. In HH, elevation in liver iron is associated with a marked increase in hepatic carcinoma. Frequency of extra-hepatic neoplasms likewise is high (Weinberg 1996; Witte *et al.* 1996),

The presence of CY/wt or CY/HD mutations combined with homozygosity for a TfR gene mutation was significantly elevated in a set of 430 patients who had either multiple myeloma, breast cancer or colorectal cancer (Beckman *et al.* 1999). The TfR gene mutation causes a substitution of serine for glycine at amino acid 142. For the three cancers, respectively, as compared with wt/wt HFE controls, CY/wt carriers had increased risks of 2.2×, 2.2× and 1.65×; values for CY/HD carriers were 6.5×, 7.3× and 8.7×. In wt/wt HFE controls, the incidence of neoplasms was not altered by the TfR gene mutation.

Perspectives

The results of these various studies indicate that persons identified as CY/wt, HD/wt or CY/HD carriers should be advised to have their iron values (Tf Fe sat % and serum ferritin) tested periodically. Were these values to begin to rise, a schedule of phlebotomies should be considered. For all carriers, as well as for persons with homozygous HFE gene mutations, factors that contribute to iron loading should be reduced or eliminated if possible. These include consumption of red meat, alcohol and raw shellfish, and smoking of tobacco. Especially, carriers of HFE gene mutations who are burdened also with TfR gene mutations should be advised of their increased tendency to become iron loaded.

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