Penetrance in hereditary hemochromatosis

Ajoka and Kushner\(^1\) make the point that ascertainment bias is the reason for the finding of low clinical penetrance in some studies of the incidence of hemochromatosis. They explain how they have avoided ascertainment bias in their study of hemochromatosis families by studying clinically unselected relatives homozygous for the \(HFE\) Cys282Tyr mutation and also by comparing 2 groups of probands—those presenting clinically and found to have hemochromatosis and those detected through screening of blood donors or through annual health assessment visits. For the clinical cases, the possibility of selection bias by referral to a tertiary center is acknowledged by the authors but not considered to be a source of bias. Furthermore all the “detected” probands had a transferrin saturation more than 62%. All probands were therefore selected either by disease or iron phenotype and are not representative of those in the general population who are homozygous for Cys282Tyr.

The study of 10,500 blood donors from South Wales\(^2\) referred to in the “Rebuttal to Beutler”\(^3\) was not designed to determine clinical penetrance, as blood donors must declare that they are not being treated for any medical condition before giving blood. The study was designed to determine \(HFE\) genotype frequencies and iron status within the several genotype groups. Of the 72 donors homozygous for Cys282Tyr, only 60% of males and 30% of females would have been identified if the selection was based on a transferrin saturation more than 62%. After interviewing 63 of the blood donors, a surprising finding emerged—none was aware of any family history of iron overload.

Since completion of the blood donor study, further work in South Wales has also confirmed our belief that the penetrance of the \(HFE\) gene is indeed low. A survey of hemochromatosis as a clinical condition in 2 health authorities (included in the blood donor survey region, population approximately 1 million) concluded that only 1.2% of adult Cys282Tyr homozygotes had received a confirmed diagnosis.\(^4\) Restricting the study to men older than 45 years, the figure rose to 2.8%.

Recently, we have been able to study the families of those blood donors homozygous for Cys282Tyr. Iron status and morbidity have been compared with families of Cys282Tyr homozygotes presenting clinically (C.A.M. et al., in preparation). Despite 32% of all female Cys282Tyr\(^+/+\) relatives and 72% of all male Cys282Tyr\(^+/+\) relatives having both a raised transferrin saturation and serum ferritin, serious morbidity directly attributable to iron overload was low.

These studies, and those reviewed by Beutler\(^5\) and Ajoka and Kushner,\(^1\) all point in the same direction. Most men and about 50% of premenopausal women who are homozygous for \(HFE\) Cys282Tyr have biochemical evidence of iron accumulation (raised transferrin saturation). However, this cannot simply be equated with iron overload or morbidity and is not reflected in a significant, identifiable burden of disease for health services.

There have now been many reports of the frequency of homozygosity for Cys282Tyr in patients with diabetes, cardiac disease, liver disease, and arthritis. With the exception of hepatoma, there is no increase in frequency in such patients.\(^6\) The urgent need is to identify the factors that, in addition to homozygosity for Cys282Tyr, cause significant iron accumulation and disease. The male blood donors from South Wales had given a mean of 1 unit per year and the female donors 0.5 units. If regular blood donation at this frequency is found to prevent morbidity in Cys282Tyr homozygotes, then a universal system of disease prevention already exists.

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**References**


Response:

**Morbid complications of hemochromatosis**

Dr McCune has misinterpreted the significance of an elevated transferrin saturation. An elevated transferrin saturation is not biochemical evidence of iron accumulation. The serum ferritin concentration is the laboratory study that most accurately reflects an increase in liver iron stores. An elevated transferrin saturation has proved to be a remarkably reliable phenotypic marker of homozygosity for the Cys282Tyr \(HFE\) mutation. Dr McCune states that only 60% of men homozygous for the Cys282Tyr mutation...
were found to have an elevated transferrin saturation in her study of 10 500 blood donors from South Wales. This result differs from results in other studies in which an elevated transferrin saturation detected the predicted frequency of Cys282Tyr homozygotes in both a population of blood donors\(^1\) and in 65 000 individuals older than 20 years in a Norwegian county.\(^2\) The precise value of the transferrin saturation to be used as a “threshold” value in screening studies has been modified since our original study of blood donors. A value for the transferrin saturation of 50% for women and 55% for men is now widely accepted, recognizing that a small proportion of heterozygotes will be identified using these values.

Our previous report describing clinical penetrance of the Cys282Tyr homozygous genotype involved the study of 214 homozygous relatives of 291 homozygous probands.\(^3\) Our study differs from most published studies in that criteria for penetrance were restricted to a limited set of objective findings. Nearly every homozygote identified underwent liver biopsy, and fibrosis or cirrhosis was considered an indicator of penetrance. Many individuals with abnormal liver biopsies were completely asymptomatic. We also used radiographic evaluation of the metacarpal-phalangeal joints and found that hemochromatotic arthropathy was quite common and that the presence of arthropathy did not correlate well with total-body iron burden. We recognized the importance of familial factors influencing penetrance, and calculated our minimal estimate of the incidence of clinical penetrance to homozygous relatives of healthy probands who had been detected in screening studies. In this population, we estimated the incidence of clinical penetrance of 29% in men older than 40 years and 11% in women older than 50 years. We believe this estimate does reflect the incidence of penetrance in the white population.

Our results have been confirmed by Dr Sigvard Olsson and colleagues, who identified 297 potential homozygotes in central Sweden using an elevated transferrin saturation as the screening probe (written personal communication, June 2003). Liver biopsy was part of the evaluation, and fibrosis was found in 12.8% and cirrhosis in 5%. Thus, approximately 18% of the homozygotes identified had histologic evidence of iron-associated liver damage. These values approach the results we reported, indicating that our findings in the population of Utah are likely applicable to Cys282Tyr homozygotes elsewhere.

Defining the incidence of clinical penetrance of hemochromatosis is important in order to justify large-scale screening programs, but the key issue is that some fraction of homozygotes clearly suffer morbidity complications. Until modifier genes are identified, it will be difficult to determine which homozygotes are destined to develop morbidity complications and which are not. Thus, it remains important to identify homozygotes and initiate iron-depletion treatments before disease-related morbidity develops.

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References

To the editor:

Guidelines for the use of epoetin in cancer patients: a much-needed step forward in standardizing anemia treatment

Recently, clinical practice guidelines for the use of epoetin alfa in cancer patients were published.\(^1\) Although based on high-quality evidence, the rapid pace of research in anemia management requires that such guidelines be reviewed and updated regularly. This letter reviews new data, specifically on anemia-related quality of life (QOL) and optimal hemoglobin (Hgb) management, which are relevant to, and may serve to augment, the guidelines.

Although the guidelines endorse epoetin alfa’s ability to improve hematologic outcomes, they do not support a relationship between epoetin alfa treatment and QOL improvements, primarily due to methodologic concerns regarding critical studies; however, there is new evidence to consider. An a priori, planned, multivariate analysis of QOL data from Littlewood et al.\(^2\) accounting for possible confounding variables including disease progression, still indicated significant \((P < 0.05)\) improvements in QOL for all 5 cancer-specific scales.\(^3\) Another conservative analysis by Fairclough et al.,\(^4\) using joint-mixed effects modeling to account for nonrandom missing data, produced significant between-group differences in QOL scores comparable with those previously reported.

There were 2 studies published after the guidelines based on Littlewood et al’s data\(^2\) that examined the clinical significance of QOL improvements in patients receiving epoetin alfa. Patrick et al used change in Hgb level as an internal standard to determine the clinically meaningful difference in QOL that could be considered clinically meaningful.\(^5\) Differences in QOL scores between the epoetin alfa and placebo groups exceeded these minimally important differences, supporting their clinical relevance. Cella et al compiled population-based reference QOL data from 1078 persons in the United States via an internet survey.\(^6\) Comparison of the survey results with the Littlewood et al data\(^2\) showed that epoetin alfa treatment overcome 49% to 95% of the QOL deficit seen in anemic cancer patients compared with the population-norm sample. The Patrick et al and Cella et al analyses address the concerns of the guidelines and provide additional support for the beneficial effects of epoetin alfa on QOL in anemic cancer patients.

Selecting the optimal Hgb level for intervention is critical for maximizing patient benefits related to epoetin alfa treatment. The guidelines make a conservative recommendation (Hgb ≤ 100 g/L [10 g/dL]) based on published reports from clinical trials meeting strict criteria. However, the guidelines also state that epoetin alfa administration in patients with Hgb levels of 100 to 120 g/L (10-12 g/dL) should be determined by clinical circumstances.

One retrospective analysis\(^7\) and 2 prospective trials published as abstracts\(^8\) provide strong evidence that early intervention with epoetin alfa prevents declines in Hgb level and QOL. A retrospective analysis of the Littlewood et al data\(^2\) prospectively stratified by