Correspondence

Letter Regarding Article by Ellervik et al, "Hereditary Hemochromatosis and Risk of Ischemic Heart Disease: A Prospective Study and a Case-Control Study"

To the Editor:

We were interested to read the report of Ellervik et al,[1] which did not find a connection between ischemic heart disease and the presence of the common hemochromatosis mutations. There is, however, no proof of the presence or absence of clinical hemochromatosis in the homozygotic patients.

In a study from Australia of 16 subjects identified from a population screening study who had either elevated transferring saturation or C282Y homozygosity, only half were found to have clinical features of hemochromatosis, and only 3 of 11 had fibrosis on a liver biopsy.[2] Furthermore, in a study from Kaiser Permanente of more than 41 000 patients attending a health appraisal clinic in San Diego, Calif, 152 (0.4%) were found to be C282Y homozygotic.[3] Only 1 of the 152 was found to fit criteria usually applied for the clinical diagnosis of hereditary hemochromatosis, which suggests a penetrance of less than 1%.

We have previously reported a lack of association of the hemochromatosis mutations with heart failure in an Israeli cohort.[4] Interestingly, in a study from Brazil of 319 patients with cardiomyopathy of different etiologies, a higher incidence of C282Y mutations was found in the group of patients with ischemic cardiomyopathy than in patients with nonischemic cardiomyopathy.[5] This poor penetrance of the clinical manifestations of hemochromatosis is obviously a limitation in screening for the presence of the disease and may be a confounding factor in population-based studies.

Disclosures

None.

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Response

In our study of 9174 individuals from the Danish general population, the Copenhagen City Heart Study, none of the 23 C282Y/C282Y individuals developed clinically overt hemochromatosis[1]; however, most C282Y/C282Y individuals slowly developed increased levels of transferrin saturation and ferritin with age (from 25 to 85 years), reaching only modest iron overload. Goland and Malnick propose that such lack of penetrance of classic hemochromatosis in C282Y/C282Y individuals represents a limitation and could be a confounder in screening for disease in population-based studies.

The aim of our latest study was to determine whether hereditary hemochromatosis genotypes were risk factors for ischemic heart disease and myocardial infarction in the general population, which they were not.[2] This is a different question from estimating risk of these diseases in patients with clinically manifest hereditary hemochromatosis. Therefore, our study cannot exclude that among patients with manifest hereditary hemochromatosis, there might be an increased risk of ischemic heart disease and myocardial infarction. However, because we not only studied the general population but also a case-control group that consisted of 2441 patients with both ischemic heart disease and coronary atherosclerosis documented on coronary angiography versus 8080 controls, we can exclude that C282Y/wild-type and C282Y/C282Y individuals have an increased risk of ischemic heart disease of 1.3-fold and 3.6-fold or greater, respectively.

Thus, in our study, we examined the effect of genotype on ischemic heart disease and not the effect of manifest hereditary hemochromatosis on ischemic heart disease. We thank Goland and Malnick for pointing this out. Although studies of effect of manifest hereditary hemochromatosis on ischemic heart disease are very difficult to perform in the general population because of the enormous sample size needed, the effect of genotype on ischemic heart disease ideally should be examined in population-based studies like ours.[2]

Disclosures

None.

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