Tumor necrosis factor-alpha -308G>A allelic variant modulates iron accumulation in patients with hereditary hemochromatosis

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BACKGROUND: In vitro and animal studies suggest that tumor necrosis factor alpha (TNF-alpha) modulates intestinal iron transport. We hypothesized that the effect of TNF-alpha might be particularly relevant if iron absorption is not effectively controlled by the HFE gene. METHODS: In patients with homozygous C282Y hemochromatosis, we investigated the influence of TNF-alpha -308G>A allelic variant on total body iron overload, determined in all patients by measuring iron removed during depletion therapy, and hepatic iron index and need for phlebotomy to prevent iron reaccumulation, measured in patient subgroups. RESULTS: Of 86 patients with hereditary hemochromatosis, 16 (19%) were heterozygous carriers and 1 (1%) was a homozygous carrier of the TNF-alpha promoter -308A allele. Mean (SD) total body iron overload was increased 2-fold in TNF-alpha -308A allele carriers [10.9 (7.6) g] compared with homozygous carriers of the G allele [5.6 (5.0) g, P<0.001]. Hepatic iron index differed markedly between TNF-alpha -308A allele carriers [5.6 (3.5) micromol/g/year] and homozygous G allele carriers [3.1 (2.2) micromol/g/year, P=0.040, n=30]. After iron depletion, the need for phlebotomy to prevent iron reaccumulation (maintenance therapy) was substantially higher in TNF-alpha -308A allele carriers than in homozygous G allele carriers (P=0.014, n=73). We used multiple regression analyses to exclude possible confounding effects of sex, age, family screening, body-mass index, and meat or alcohol intake. CONCLUSION: TNF-alpha -308G>A allelic variant modulates iron accumulation in patients with hereditary (homozygous C282Y) hemochromatosis, but the effect of the TNF-alpha -308A allele on clinical manifestations of hemochromatosis was less accentuated than expected from the increased iron load associated with this allele.

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