Haematologica
Journal of Hematology
volume 84 – number 2 – February 1999

Haematologica 1999; 84:97-98

editorial, comments and views

Gilbert's syndrome

Over the last few years the genetic basis of Gilbert's syndrome has been clarified. This issue of the journal contains four papers on this condition. One paper describes a novel molecular mechanism responsible for decreased bilirubin-UDP-glucuronosyltransferase activity, while two articles evaluate the interaction between Gilbert's syndrome and hematologic disorders associated with increase bilirubin production. Finally, a review article analyzes our present knowledge of the molecular pathogenesis of this condition.

Why publish papers on Gilbert's syndrome in a hematology journal? There are several reasons. First, Haematologica aims to be a journal of hematologic medicine in a broad sense: borderline subjects that may be of interest to our readers are therefore welcome. Second, Gilbert's syndrome is borderline subject. This condition is characterized by mild unconjugated hyperbilirubinemia in the absence of overt hemolysis or evidence of liver disease. However, several studies have shown that red cell lifespan is shorter than normal in half the cases of Gilbert's syndrome, suggesting a mild, compensated hemolytic state. Third, being a common condition, Gilbert's syndrome frequently coexists and may interact with hematologic disorders that involve unconjugated hyperbilirubinemia, *per se*.

Dysmetabolic iron overload syndrome

A new iron overload syndrome, characterized by hyperferritinemia and increased liver iron concentration in the presence of a normal transferrin saturation, was recently described by Deugnier *et al*.[1] Patients with similar characteristics have also been described in Italy but it was hypothesized that they represented a subgroup of subjects with genetic hemochromatosis (GH).[2]

From the start it was observed that hyperlipidemia, glucose intolerance, increased body mass index and hypertension were frequently present in subjects with this unusual presentation of iron overload. More recently analysis of the mutations of the HFE gene, the gene associated with GH,[3] showed that in this population the frequency of mutations was significantly higher than in normal controls.[4] The French group, however, observed no difference in the degree of iron overload in patients carrying either one or no mutation. Similarly, they did not find any relation between the degree of iron overload, liver histology and HFE mutations. The authors, therefore, concluded that HFE mutations may lead to overexpression of the dysmetabolic iron overload syndrome together with yet unknown factors.[5]

In the last few years another disease in which iron appears to have a role has become more important: this disease, called non-alcoholic steatohepatitis (NASH), was originally described in middle aged overweight and often diabetic women, but more recently has been identified in larger series of patients, often of male sex. The pathognomonic feature of NASH is the finding in the liver biopsy of steatosis associated with cellular inflammation in the presence or absence of fibrosis.[6,7]

Recently a large spectrum of pathologies including fat alone, steatohepatitis and fibrosis have been considered to be different stages of NASH. Unexpectedly, more than 50% of patients in the different series studied had hyperferritinemia whereas increased transferrin saturation was found in a much lower proportion of patients.[8,9]

In the present issue of Hematologica two scientific letters on the relation between increased ferritin and dysmetabolism draw attention to this subject. The first, from Orlandi *et al.*,[10] reports the case of a patient with increased ferritin, normal transferrin saturation and a very slight increase in liver iron, negative for the mutations of the HFE gene as well as for point mutations in the iron-regulatory element, recently described in the hyperferritinemia-cataract syndrome. The patient, who had denied alcohol intake, was overweight and had non-insulin-dependent diabetes mellitus. He had only a monoclonal gammopathy and a bone marrow biopsy showed 8% of plasma cells. He also had hepatomegaly and a liver biopsy showed mild focal iron deposition in hepatocytes with steatosis and mild portal fibrosis.

In the second letter, from Rovati *et al.*,[11] two monozygotic twins who came to medical attention because of hyperferritinemia with non-insulin-dependent diabetes mellitus are described. Both twins consumed less than 50 g alcohol/day, both had a transferrin saturation within the normal range and increased ferritin as an acute phase protein was ruled out by appropriate investigations. No association with HFE mutations and no point mutation of IRE was found. Both patients refused liver biopsy.

Both letters conclude that there is a link between

altered metabolism and iron overload but that the dysmetabolic iron overload syndrome is genetically distinct from GH.[12-14]

These two interesting letters on such a poorly defined topic stimulate several questions. Was the diabetes responsible for the hyperferritinemia? Were these patients hypersensitive to modest alcohol consumption? Did the patients have NASH? Would the ferritin values also have been stable after a correct diet?

The patients described in the two letters had diabetes. In a recent paper by Turnbull *et al*.,[15] increased values of ferritin were found in several patients with diabetes. When liver biopsy was performed, in the hypothesis that they had GH, only one patient was found to have liver iron overload whereas all the others had steatosis. Thus, a major subject of discussion is whether steatosis, by itself, can cause hyperferritinemia. But if it does, why don't all patients with steatosis have increased values of ferritin?

It is well known that induction of ferritin synthesis occurs during alcohol abuse, which in susceptible patients causes at least liver steatosis. Generally, complete alcohol abstinence from alcohol as well as gradual weight loss, is followed by normalization of ferritin levels. One of the patients described in this issue of Haematologica denied alcohol abuse, while the two brothers consumed less than 50 g alcohol/day. Did hyperferritinemia reflect their particular susceptibilty to small amounts of alcohol? However, the patient for whom a liver biopsy was available had a mildly increased liver iron concentration, indicating that the increased ferritin reflected not only an induction by alcohol but, at least in part, increased iron stores.

Could hepatic triglyceride accumulation interfere with intrahepatocyte iron movement with reduced iron mobilization from ferritin, causing on the one hand increased ferritin synthesis and on the other hand a low transferrin saturation? Increased tryglicerides in the liver provide increased substrate for lipid peroxidation with consequent generation of potentially reactive and cytotoxic intermediates. An imbalance of hepatic oxidant and antioxidant mechanisms could occur and interfere with iron mobilization from ferritin. This imbalance could become even more evident if subjects with fatty liver have mildly increased liver iron stores as may occur in heterozygotes for GH. Thus, the coexistence of fatty liver and heterozygosis for GH could exert a synergistic effect on ferritin synthesis. Recently, in iron overloaded mice, induction of hepatic genes involved in lipid metabolism was shown.[16] Is this the link between iron overload and the metabolic abnormalities found in the dysmetabolic iron overload syndrome? The dysmetabolic iron overload syndrome has, however, also been described in the absence of HFE mutations.[10,11] Thus, with no evidence of heterozygosis for GH, what is the trigger mechanism for iron overload?

It is clear that this extremely interesting subject is far from being understood and it is to be hoped that in the near feature that the relation between metabolic abnormalities and liver iron overload will be elucidated.

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