

The patient's two brothers, aged 56 years and 53 years, were investigated. Both were hypertensive and had mild hypercholesterolemia; one was on therapy with low-dose steroids for rheumatoid arthritis and had an increased fasting serum glucose level (211 mg/dL). Serum ferritin level (119 µg/L and 159 µg/L), serum iron level (120 µg/dL and 130 µg/dL) and transferrin saturation (42% and 43%) were normal in both cases. Lens abnormalities were excluded. At DNA analysis, one of them resulted to be heterozygous for the Cys282Tyr mutation in the HFE gene.

The proband does not meet the clinical diagnostic criteria for HH, and he does not carry the two known HH mutations in the HFE gene. Despite the genetic heterogeneity of HH in Italy,<sup>7,8</sup> the hypothesis that non-HFE related hemochromatosis could account for the isolated hyperferritinemia in this patient seems remote, given that the Cys282Tyr mutation was detectable in a proband's brother.

The recently described HHCS can also be ruled out in our case, as the IRE gene showed a normal sequence and no lens abnormalities were observed. Other factors that could induce hyperferritinemia with normal transferrin saturation<sup>9</sup> were reasonably excluded. The patient denied alcohol intake and biochemical markers related to alcohol abuse were absent. No neoplasia was detectable; in this respect, it should be noted that hyperferritinemia was already present one year before our observation and that the patient is still in good clinical condition after 18 months of follow up. Homozygosity for Gaucher's disease (type 1) seems to be excluded on clinical grounds. Because of the absence of clinical or biochemical stigmata of the disease, specific molecular and enzymatic investigations were not performed. Ceruloplasmin deficiency is highly improbable.

This patient with *unexplained* hyperferritinemia, normal transferrin saturation, mild iron overload and metabolic abnormalities resembles patients described by Moirand *et al.*,<sup>5</sup> although in Moirand's cases the mean serum ferritin value was lower and the LIC values were higher than in the present case. The French authors later reported that two thirds of patients with dysmetabolic iron overload syndrome were heterozygous for one HFE mutation.<sup>10</sup>

As the physiopathology of the association of iron overload with dysmetabolism is still unknown, the clinical features corresponding to this disorder are not clearly stated. Nonetheless, this disorder should be taken into account in the differential diagnosis of hyperferritinemic patients. The clinical evolution of this condition and the need for treatment with phlebotomy or iron-chelating agents are still to be defined.

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## Key words

Hyperferritinemia, metabolic disorders

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## The dysmetabolic iron overload syndrome is clinically and genetically distinct from HFE-related genetic hemochromatosis

Sir,

We describe two monozygotic twins who developed non-insulin-dependent diabetes mellitus and hyperferritinemia. They have no molecular lesions diagnostic of HLA-related genetic hemochromatosis or hyperferritinemia/cataract syndrome. The condition found in our patients closely resembles the dysmetabolic iron overload syndrome. The fact that these monozygotic twins have a combination of abnormal glucose metabolism and hyperferritinaemia suggests a genetic basis

for this dysmetabolic syndrome.

In 1997 Moirand *et al.*<sup>1</sup> described 65 patients with a non-HLA-linked iron overload syndrome characterized by normal transferrin saturation and elevated serum ferritin. These individuals were significantly older and had significantly less hepatic iron overload than individuals with HFE-related genetic hemochromatosis.<sup>2</sup> Almost all patients had concomitant metabolic disorder (obesity, hyperlipidemia, abnormal glucose metabolism, or hypertension). The French authors later studied the prevalence of HFE mutations in these patients.<sup>3</sup> They found that two-thirds of these individuals had at least one HFE mutation (C282Y and/or H63D, mainly the latter) and concluded that heterozygosity for one of these mutations is likely to be responsible for the expression of this dysmetabolic iron overload syndrome.

We studied two monozygotic twins referred to us because of hyperferritinemia. These HLA-identical 54-years-old men had had non-insulin-dependent diabetes mellitus since the age of 49. Their serum ferritin was found to be elevated during routine investigations (652 and 780 µg/L) and subsequent checks showed stable values in a range from 500 to 800 µg/L. Serum iron and transferrin saturation have always been normal. Since hyperferritinemia with normal to low serum iron is a typical pattern of inflammation,<sup>4</sup> studies for evaluation of acute phase reactants were performed. ESR, reactive protein C, α<sub>2</sub> globulins and fibrinogen were completely normal. Furthermore, the two patients had no evidence of congenital iron loading anemia.<sup>5</sup>

Some of the authors have recently described the so-called hereditary hyperferritinemia/cataract syndrome, a new genetic disorder inherited as an autosomal dominant trait and characterized by elevated serum ferritin not related to iron overload and congenital nuclear cataracts.<sup>6</sup> Several point mutations in the iron regulatory element (IRE) of ferritin light-chain mRNA have been found in the families described so far. These mutations have been shown to variably prevent binding of an inhibitory iron regulatory protein, thus leading to excessive L-ferritin synthesis. Although our twins had no evidence of cataract, we sequenced the 5' untranslated region of ferritin light-chain mRNA as previously described.<sup>6</sup> We found no mutation either in the IRE or in the surrounding regions (5' of the IRE to the end of the transcript and 50 nucleotides 3'), thus ruling out hereditary hyperferritinemia/cataract syndrome at the molecular level.

We then studied C282Y and H63D HFE mutations using a PCR-RFLP detection method.<sup>7</sup> The absence of any mutation excluded HFE-related genetic hemochromatosis. Liver function tests were completely normal and alcohol consumption was < 50 g/day in both cases. Both twins refused a liver biopsy. The condition found in our patients closely resembled that described by Moirand *et al.*<sup>1</sup> Although we could not evaluate liv-

er iron concentration,<sup>8</sup> we ruled out a genetic dysregulation in ferritin synthesis,<sup>6</sup> so that the hyperferritinemia probably reflects increased iron stores in these individuals. The fact that these monozygotic twins have a combination of abnormal glucose metabolism and hyperferritinemia suggests a genetic basis for this dysmetabolic syndrome. The absence of HFE mutations indicates that this condition is genetically distinct from HLA-related genetic hemochromatosis. These observations may help to overcome our ignorance about ferritin metabolism.<sup>9</sup>

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