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Molecular basis of new disorders of iron metabolism in man

In the last few years there have been major advances in our understanding of the molecular control of cellular iron metabolism and of molecular genetics of disorders characterized by abnormal iron absorption.

A fundamental step has been the cloning of HFE, the gene of HLA-related genetic hemochromatosis.[1] HFE is an atypical HLA-class I-like gene, mapping approximately 4 Megabases telomeric to HLA-A. Since the first report it was considered as a strong candidate gene for hemochromatosis, as most patients were found to be homozygous for a missense mutation changing cysteine at position 282 to tyrosine (C282Y) while other patients were found to carry a second mutation that changes histidine at position 63 to aspartic acid (H63D). It is now well established that most patients with HLA-related genetic hemochromatosis are homozygous for the C282Y mutation. However, homozygosity for C282Y is found in more than 90% of North European patients[2] but in only 64% of severely iron-loaded Italian individuals.[3] This clearly indicates that various genetic iron overload syndromes exist in addition to the HFE-related one.[4] In fact, a recent study has shown that the juvenile genetic hemochromatosis locus maps to chromosome 1q.[5] The spectrum of iron overload syndromes[6] is further complicated by the observation that co-inheritance of the HFE mutant allele C282Y may play an additional role in the expression of iron loading anemias.[7]

Another fundamental step has been the recognition that the synthesis of transferrin receptor (TfR) and ferritin is regulated by cytoplasmic mRNA-binding proteins, now identified as the iron regulatory proteins (IRPs).[8,9] IRP1 and IRP2 control the expression of genes involved in iron metabolism whose transcripts contain RNA-stem-loop structures known as iron-responsive elements (IREs). Recently a new hereditary condition, characterized by the association of cataract with hyperferritinemia not related to iron overload, has been described.[10] The disorder, transmitted as an autosomal dominant condition, is due to point mutations or deletions within the IRE of the mRNA of ferritin L subunit. These mutations prevent the inhibition of ferritin synthesis which occurs when there is shortage of cellular iron. Since the severity of cataract appears to be related to the serum ferritin level, it is suggested that high ferritin levels in lens cells are responsible for cataract formation.

Although the prevalence of this new condition is presently unknown, it might not be extremely rare, since until recently it was not recognized as a distinct entity and all subjects with hyperferritinemia were generally diagnosed as having either iron overload, inflammation, liver disease or tumors. In this issue, in fact, two papers describe new cases of this condition.[11,12] The observation that a *de novo* mutation can be responsible for the hyperferritinemia-cataract syndrome appears particularly interesting, since it indicates that the disease should be searched for even in sporadic cases of early-onset cataract formation.

Knowledge of this new syndrome is important for the clinician. In fact, when hyperferritinemia was discovered in the first patients with the syndrome, one of them had a liver biopsy whereas venesection therapy was started in four subjects because a wrong diagnosis of genetic hemochromatosis had been established.[10] Later on these subjects developed iron deficiency anemia. Since the diagnosis of hemochromatosis was essentially based on the presence of high serum ferritin levels, an accurate differential diagnosis of hyperferritinemia conditions is mandatory in order to avoid unnecessary invasive diagnostic procedures and treatment related morbidity. A diagnosis of iron overload can be considered only when transferrin saturation is greater than 60% in men or 50% in women. Lower levels of transferrin saturation are not an indication for doing liver biopsies and/or starting venesection therapy. Main diagnostic problems may occour in patients with high serum ferritin and normal transferrin saturation. Such patients may have an occult malignancy, asymptomatic liver disease or hyperthyroidism in addition to the new hereditary hyperferritinemia syndrome. For these patients accurate personal and family histories for hyperferritinemia and/or cataract provide useful information for a correct diagnosis. When other reasons for the high serum ferritin are not apparent and the patient/family history is negative for cataract, a slit lamp examination of the lens might be useful to identify those patients with asymptomatic cataract associated with the mild form of hereditary hyperferritinaemia.

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