

Central nervous system involvement in a rare genetic iron overload disorder

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ABSTRACT

In most genetic iron overload disorders the diagnosis can be rejected when transferrin saturation is low. We describe a patient and her family with hyperferritinaemia and low transferrin saturation with iron accumulation in the central nervous system (CNS) and liver due to hereditary aceruloplasminaemia. In this rare genetic iron overload disorder oxidation of iron is disturbed, resulting in storage of iron in the CNS and visceral organs.

KEYWORDS

Iron overload disorder, hereditary aceruloplasminaemia, hereditary haemochromatosis

What was known on this topic?

The diagnostic approach in patients suspected for hereditary haemochromatosis is focused on hyperferritinaemia and a high transferrin saturation due to the high frequency of HFE-related haemochromatosis.

What does this add?

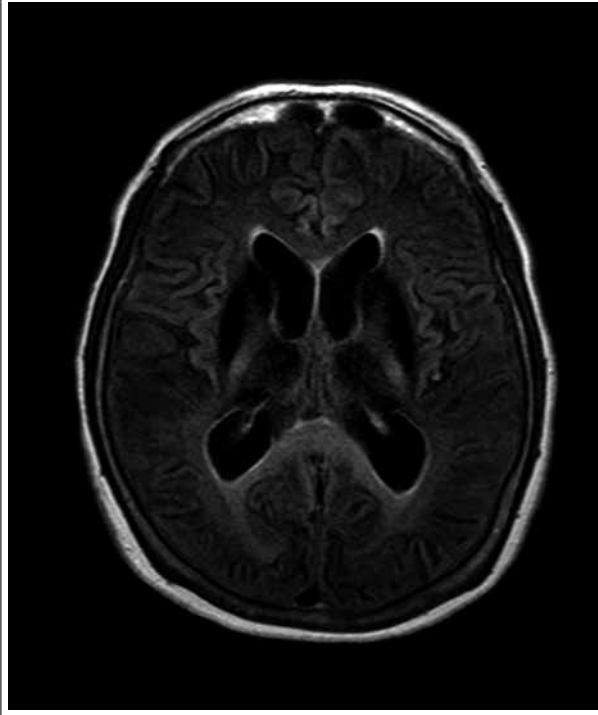
Hyperferritinaemia in combination with a low transferrin saturation does not always exclude an iron overload disorder. Particularly when neurological symptoms occur in the presence of persistent hyperferritinaemia, hereditary aceruloplasminaemia needs to be excluded.

CASE REPORT

A 59-year-old woman presented at the neurology department with ataxia, involuntary movements and mild cognitive impairment. Her medical history was notable for chronic obstructive pulmonary disease and long-lasting microcytic anaemia, intermittently treated with iron supplements. Brain magnetic resonance imaging (MRI) revealed global cortical atrophy and an abnormal signal of the basal ganglia suggestive for storage disease (*figure 1*). Laboratory results showed a haemoglobin of 7.1 mmol/l (normal 7.2 to 9.8 mmol/l), MCV 74 fl (normal 81 to 96 fl), ferritin 1320 µg/l (normal 14 to 150 µg/l) combined with low serum iron (3.0 µmol/l; normal 10 to 30 µmol/l) and decreased transferrin saturation (6.5%; normal 15 to 50%). Serum copper was low (<8 µmol/l; normal 13 to 24 µmol/l) with a normal urine excretion of copper. Retinal degeneration and Kayser-Fleischer rings were not present. Genetic analysis for Huntington's disease was negative. Iron

accumulation in the liver was proven with MRI, showing an iron concentration of 350 µmol/g (normal <36 µmol/g) according to the protocol of Gandon (University of Rennes, France) and liver biopsy (grade 4 iron accumulation). In conclusion, an iron overload disease in combination with low transferrin saturation was observed. Differential diagnostic considerations were dysmetabolic hyperferritinaemia, ferroportin disease or hereditary aceruloplasminaemia (*figure 2*). Ceruloplasmin concentration was markedly decreased (31 mg/l, normal 200 to 350 mg/l) and the diagnosis of hereditary aceruloplasminaemia was made. Additional genetic analysis showed a homozygote mutation (Gly650Arg) in the ceruloplasmin gene on chromosome 3. This mutation has not been previously reported in the literature. Family screening revealed that both children with a slightly decreased ceruloplasmin concentration (128 mg/l and 139 mg/l respectively) and normal serum ferritin were heterozygous for the mutation.

Figure 1. MRI brain showing a hypointense signal of the basal ganglia

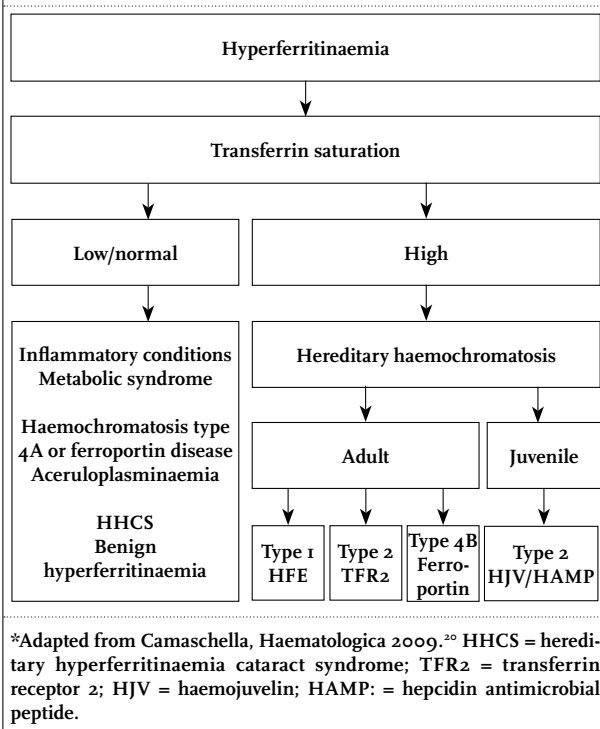


other sibling had normal laboratory results. In our patient treatment with phlebotomies was impossible because of the anaemia. Instead the patient received the oral iron chelator deferasirox, resulting in normalisation of the ferritin concentration without resolving the neurological symptoms. A few months later she developed diabetes mellitus.

DISCUSSION

Ninety percent of the cases with haemochromatosis are related to mutations of the HFE gene.¹ Furthermore, the prevalence of HFE gene mutation in the general population is high. Therefore, the diagnostic approach in patients suspected for haemochromatosis is focused on the classic HFE-related haemochromatosis. Hyperferritinaemia and increased transferrin saturation are used as discriminating tests. Normal or low transferrin saturation excludes the diagnosis of HFE-related haemochromatosis.² However, as illustrated in our case presentation, using these laboratory parameters, rare non-HFE-related genetic haemochromatosis such as hereditary aceruloplasminaemia can be missed.

Figure 2. Diagnostic diagram of hyperferritinaemia



Aceruloplasminaemia is a rare autosomal recessive iron overload disorder, due to mutations in the ceruloplasmin gene on chromosome 3q21-24.^{3,4} The disease has mainly been described in the Japanese, but is also rarely seen in whites.^{5,6} The incidence of aceruloplasminaemia in Japan is estimated to be approximately one per 2,000,000 in non-consanguineous marriages. There are no reliable data regarding incidence and prevalence in Western European countries.⁶ Forty mutations of the ceruloplasmin gene have been described,^{7,8} leading to failure to incorporate copper during synthesis, which causes secretion of an apoprotein without oxidase activity that diminishes rapidly.⁹ Ceruloplasmin plays a major role in iron mobilisation from the tissue stores. It catalyses oxidation of ferrous to ferric iron, which is essential for release to transferrin.^{10,11} Deficiency of ceruloplasmin results in iron deposition in liver, pancreas, basal ganglia and other organs.³ Aceruloplasminaemia is a lethal disease that typically presents in the fourth or fifth decade with neurological symptoms, retinal degeneration and diabetes mellitus. Brain involvement, particularly of the basal ganglia, thalamus and dentate nucleus, can present with various symptoms, such as cerebellar ataxia, involuntary movement, Parkinsonism, craniofacial dyskinesia and cognitive impairment.¹² Iron accumulation in the CNS is a unique finding among the classical iron overload syndromes.⁹

The patient's sister was also diagnosed with hereditary aceruloplasminaemia because of an iron overload disorder in combination with low transferrin saturation (8.3%) and low ceruloplasmin concentration (6 mg/l). The patient's

The diagnosis of aceruloplasminaemia can be made when there is an absence of serum ceruloplasmin, in

combination with low serum copper, low serum iron, high serum ferritin and increased hepatic iron concentration. Concomitantly a mild anaemia is also a constant finding in aceruloplasminaemia.^{13,14} The diagnosis is supported by characteristic findings on MRI that are compatible with iron accumulation in liver and brain.

Early recognition and intervention is essential to alter the fatal course of this disease. Because of the anaemia, the role for phlebotomies is limited. Iron chelation therapy can be used for treatment of aceruloplasminaemia.^{7,15-18} Normalisation of serum ferritin and decrease in hepatic iron overload have been described. However, its ability to remove iron from the CNS is doubted. Only one case described improvement of neurological symptoms while on the oral iron chelator deferasirox.¹⁹ Therefore, one should focus on early awareness and treatment of this rare disease with iron chelators to prevent devastating neurological damage in patients with aceruloplasminaemia. In patients with high serum ferritin and low transferrin saturation in the absence of inflammation, alcoholism or dysmetabolic syndrome, MRI of the liver and serum ceruloplasmin should be considered. However, additional tests in patients with high ferritin level and normal transferrin saturation are not routinely recommended.

CONCLUSION

It is important to consider the possibility of a genetic iron overload syndrome in patients with neurological symptoms and hyperferritinaemia, even in the presence of low transferrin saturation. Otherwise the rare genetic iron overload disorder aceruloplasminaemia can be missed. Early treatment with oral iron chelators may prevent progression of neurological symptoms in patients with iron overload due to aceruloplasminaemia.

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