Letter to the Editor

Novel ceruloplasmin mutation causing aceruloplasminemia with hepatic iron overload and diabetes without neurological symptoms

To the Editor:
We report a 39-year-old man from India with severe hepatic iron overload (grade 3–4) without signs of inflammation or fibrosis on liver biopsy (Fig. 1a), as well as recently diagnosed insulin-dependent diabetes mellitus. He had no risk factors for chronic liver disease. His older brother (44 years) was diagnosed with insulin-dependent diabetes 7 years ago.

Laboratory findings showed mild hypochromic anemia with reduced serum iron concentration (34 μg/dl, normal 59–158 μg/dl), high ferritin level (1273 ng/ml, normal 30–400 ng/dl) but low transferrin saturation (11%, normal 16–45%), and complete absence of serum copper and ceruloplasmin (CP). The biochemical liver function tests were normal. Genetic testing for hemochromatosis showed wild-type p.C282Y alleles and the heterozygous p.H63D variant in the HFE gene. Abdominal ultrasound revealed no signs of cirrhosis. The suspected diagnosis of aceruloplasminemia was confirmed by sequencing the coding region and exon/intron boundaries of the CP gene. We identified the novel homozygous mutation c.1211_1212dupTG at the boundary of intron 6 and exon 7. Reverse transcription-polymerase chain reaction (RT-PCR) demonstrated that the duplication of the two bases in the complementary DNA (cDNA) leads to an early termination of translation (Fig. 1b). Although cerebral magnetic resonance imaging (MRI) showed signs of iron accumulation in the basal ganglia, the thalamus and the dentate nucleus, there were no cerebellar pathology (especially no tremor) or other neurologic deficits, and the patient displayed no signs of retinal degeneration (Fig. 1c–d).

Fig. 1. (a) Prussion blue staining indicating predominant hepatocyte cell iron overload (x200). (b) Duplication of a TG dinucleotide at the intron 6 to exon 7 boundaries (vertical bars). mt, mutated sequence of patient; wt, wild-type sequence; letters in red indicate insertion (TG duplication). (c) Cerebral magnetic resonance (MR) imaging studies [susceptibility weighted imaging (SWI) sequences] highlighting iron overload in the basal ganglia, the thalamus as well as (d) in the dentate nucleus.
The genetic analysis of the brother detected the same mutation as in the index patient. Except for diabetes, he displayed no other symptoms, in particular no tremor.

To treat iron overload, an oral therapy of the index patient with the new iron chelator deferasirox has been initiated. At a dose of 500 mg daily, serum ferritin concentrations are below 350 ng/ml. There are no signs of neurological progress on follow-up now after 2 years of therapy.

Aceruloplasminemia presents typically in adult life with neurological and retinal degeneration as well as diabetes. Its natural course is lethal because of progressive neurodegeneration, secondary to cerebral iron deposition, which was shown to induce oxidative stress predominantly in astrocytes constituting part of the blood–brain barrier (1). Treatment options for symptomatic patients are limited; iron chelation has been reported to slow or even prevent the neurodegenerative process (2, 3).

Our case illustrates that rare genetic causes of iron overload such as aceruloplasminemia might be missed if only routine laboratory parameters and imaging studies are performed. As more than 40 CP mutations have been reported as yet, mutation detection is often difficult to accomplish in routine clinical practice. Up to now, there is no evidence for clear-cut genotype–phenotype associations, and phenotypic variability has been described in siblings carrying the same mutation (4).

Although aceruloplasminemia typically manifests in the fourth to fifth decade with predominant neurological symptoms, there are few reports of individuals in which diabetes preceded clinical onset of neurological symptoms (5, 6). In a systematic review on 45 Japanese aceruloplasminemia patients 89% of patients suffered from diabetes with a peak in the fourth decade (40%) (7). Therefore, it appears that diabetes may manifest prior to neurodegeneration, although a clinical diagnosis of aceruloplasminemia is uncommonly entertained at this stage. Likewise, it cannot be excluded that without therapy, our patient would develop neurodegeneration later in the disease course. Of interest, in a report on two siblings with identical CP mutational status, the untreated individual developed neurological disease at the age of 48 but the other sibling was free of clinical neurodegeneration at the age of 54 while on chelation treatment (4). We conclude that early recognition of aceruloplasminemia and treatment with iron chelators are critical in order to prevent disease progression in homozygous mutation carriers.

References

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