

Aceruloplasminemia: a rare disease – diagnosis and treatment of two cases

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Aceruloplasminemia is a rare autosomal recessive disease in which a mutation leads to the absence or dysfunction of ceruloplasmin. Deficiency of this enzyme leads to the accumulation of iron in various organs; aceruloplasminemia is usually characterized by diabetes, retinal degeneration and neurological disorders. Diagnosis is suspected by the presence of elevated levels of ferritin, anemia, decreased serum copper and absence of ceruloplasmin in serum. Treatment of aceruloplasminemia is mainly based on the control of iron overload.

Keywords: Ceruloplasmin/deficiency; Ceruloplasmin/genetics; Cognition disorders/etiology; Iron metabolism disorders; Case reports

Introduction

Aceruloplasminemia is a rare autosomal recessive disease, in which there is a mutation that leads to the absence or dysfunction of ceruloplasmin.⁽¹⁾ Ceruloplasmin is a plasma ferroxidase, which contains copper and is related to the oxidation of Fe²⁺ to Fe³⁺, allowing it to be transported by transferrin.⁽¹⁾ Its deficiency leads to an accumulation of iron in organs, mainly in the pancreas, liver and nervous tissue, causing symptoms of the disease. The triad that usually characterizes aceruloplasminemia is diabetes, retinal degeneration and neurological disorders such as cerebellar ataxia, and dementia.⁽²⁾ Another manifestation is sideropenic anemia.⁽¹⁾

Diagnosis is suspected by the presence of elevated levels of ferritin, anemia, decreased serum copper and absence of ceruloplasmin in serum;⁽²⁾ this disease may exhibit some similarities to Wilson's disease.⁽³⁾

Because clinical manifestations are related to iron deposits in tissues, treatment is mainly based on controlling the overload of this ion through iron chelation therapy. Among possible drugs, deferasirox is an oral chelator taken daily that has already demonstrated good results in the treatment of transfusional overload of iron.⁽⁴⁾

This paper reports on two Brazilian cases from one family who were diagnosed with aceruloplasminemia and effectively treated with deferasirox.

Case Report

In December 2007, a 57-year-old female patient was attended in the clinic with alterations in behavior, lack of self-control, depression and anxiety. These symptoms had appeared 12 months previously. The patient, had already been evaluated in a psychiatric institution, had been diagnosed as having a mood disorder.

On clinical examination she was apathetic and little collaborative with pale skin. On abdominal palpation there was no evidence of visceromegalies. Her medical history included type 2 diabetes mellitus diagnosed in 2000 and controlled with oral hypoglycemic agents. Laboratory findings are shown in Table 1.

A percutaneous needle liver biopsy to measure liver copper showed no accumulation of this element but showed marked iron overload; urinary copper excretion in 24 hours was normal. Hereditary hemochromatosis related to the HFE gene was ruled out because of the absence of the C282Y/H63D mutation.

Brain magnetic resonance imaging (MRI) showed bilateral low signal on T2 at the basal ganglia probably due to iron deposits; similarly, MRI of the liver showed a significant iron deposit in the parenchyma.

When the diagnosis of hereditary aceruloplasminemia was established, treatment was initiated with 20 mg/kg/day deferasirox for 10 months, during which time there was an

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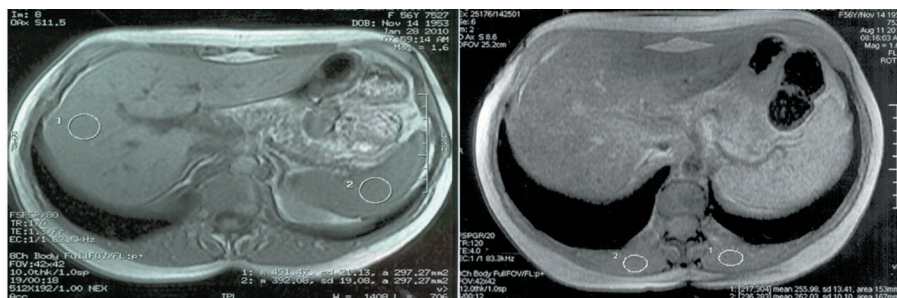


Figure 1 – Comparative study of upper abdomen MRI shows liver parenchyma with an increased signal in the left image due to increases in iron. On the right, after six months of treatment with deferasirox, a reduction in iron was observed by the MRI signal attenuation

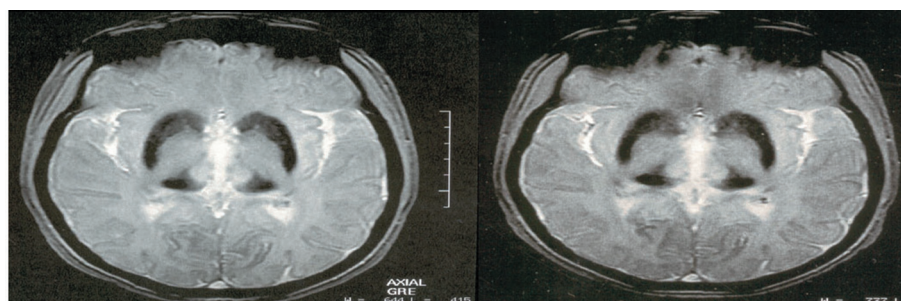


Figure 2 – Comparative study of brain MRI before (left) and six months after starting treatment with deferasirox (right) shows no change in the signal of basal ganglia structures

Table 1 - Laboratory findings

Variables	Patient 1	Patient 2
Hemoglobin (12 - 17 g/dL)	10.7 g/dL	10.5 g/dL
Serum Iron (60 - 150 mcg/dL)	31 mcg/dL	37 mcg/dL
Serum Ferritin (10 - 150 ng/mL)	1114 ng/mL	891 ng/mL
Percent Transferrin Saturation (30 - 40%)	5.7%	11%
Ceruloplasmin (22 - 58 mg/dL)	< 2 mg/dL	< 2 mg/dL
Serum Copper (85 - 155 mcg/dL)	50 mcg/dL	40 mcg/dL

improvement in the psychotic symptoms and a significant reduction in ferritin levels (from 1114 ng/mL to 457 ng/mL). The dose of deferasirox was reduced to 10 mg/kg/day and after six months the ferritin level had dropped to 107 ng/mL. A liver MRI in that period showed a reduction in iron deposits (Figure 1). However, the brain MRI showed that the iron deposit in the basal ganglia remained almost unchanged compared to the first MRI performed before the initiation of treatment. Currently the patient is asymptomatic but taking 5 mg/kg deferasirox daily.

The second case, the 61-year-old sister of the previous patient was asymptomatic until that age and was also attended in the clinic for hematological screening.

On clinical examination, she reported suffering from cardiac arrhythmia and hypertension, both compensated and treated with amiodarone and valsartan, respectively.

Abdominal palpation did not identify visceromegalies. Her laboratory findings are shown in Table 1.

A percutaneous needle liver biopsy to measure liver copper showed no accumulation of this element however it revealed marked iron overload. The urinary 24-hour copper excretion was normal. The brain and liver MRIs were similar to those of the first patient.

After diagnosis of aceruloplasminemia, treatment was initiated with 20 mg/kg/day deferasirox for 3 months with a notable decrease in ferritin levels (891 ng/mL to 410 ng/mL). The dose of deferasirox was reduced to 10 mg/kg/day for 6 months with further decreases in ferritin. Current treatment is with 5 mg/kg/day of deferasirox and the ferritin level is at 118 ng/mL. A liver MRI in this period, as opposed to the brain MRI (Figure 2), showed reductions in iron deposits.

Fasting glucose remained at 100 mg/dL throughout the follow-up and the patient is so far asymptomatic.

Discussion

For over 30 years, it has been postulated that ceruloplasmin is a ferroxidase which converts highly toxic iron (Fe^{2+}) to a non-toxic form (Fe^{3+}).⁽⁵⁾

This protein is mainly synthesized in hepatocytes. However, recent studies show that its anchored form - by glycosylphosphatidylinositol - is also expressed by astrocytes in the central nervous system of mammals, while the secreted form, expressed by the liver, is found in serum.⁽⁶⁾

Hereditary aceruloplasminemia leads to clinical manifestations resulting from the accumulation of iron in the body especially in organs such as the brain, liver and pancreas. The clinical changes resulting from this accumulation are classically characterized by neurological disorders, retinal degeneration and diabetes. Additionally, iron deficiency anemia is a common finding.

In our study, while one of the patients had only anemia, the other had neurological disorders, diabetes and sideropenic anemia. Hereditary retinal degeneration, diagnosed by fundoscopy, was not detected in either of the patients during the follow-up. This degeneration is a relatively frequent finding though it does not often compromise the visual acuity.⁽²⁾

Besides clinical and laboratory findings, brain MRI supports the diagnosis of aceruloplasminemia as it is common to observe uniform involvement of the basal ganglia and thalamus in this disease, but without cavities in the brain parenchyma.⁽⁷⁾

Another point is the phenotypic variation observed in individuals of some families affected by hereditary aceruloplasminemia as in this case. Fasano et al. reported the cases of brothers with different clinical manifestations and outcomes.⁽¹⁾

It is possible that genetic and environment factors are involved in the phenotypic expression of patients affected by the disease. The brother of these two patients has normal levels of ceruloplasmin, a situation also reported in the literature.⁽¹⁾

Low levels of ceruloplasmin are not specific for hereditary aceruloplasminemia. This enzyme is also deficient in Wilson's disease a disorder that has some similarities with Aceruloplasminemia. However, different from hereditary aceruloplasminemia, serum and urinary copper levels are elevated in Wilson's disease.⁽²⁾

Iron removal by phlebotomy is the preferred treatment for most cases of iron overload; it has been demonstrated that this technique prevents and even reverses some complications of iron overload.⁽⁸⁾ However, due to the inconvenience and discomfort arising from the procedure, the difficulty of guaranteeing venous access, and because of anemia, phlebotomy becomes unfavorable over time.⁽⁹⁾

More recent works show that only one in three patients with hereditary hemochromatosis undergo phlebotomy.⁽¹⁾ In specific cases of aceruloplasminemia, phlebotomy is contraindicated because of anemia.⁽⁸⁾ In these two cases, both patients had anemia. Thus an oral iron chelator (deferasirox) was chosen.⁽⁹⁾

Deferasirox was approved by the US Food and Drugs Administration in 2005 when it represented a significant advance in the treatment of patients with iron overload. It is an oral liposoluble iron chelator with a plasma half-life of about 12 hours which makes it ideal for once daily dosing.⁽¹⁰⁾

There are studies supporting the hypothesis that deferasirox is the most effective drug to prevent neurological symptoms related to aceruloplasminemia.⁽¹¹⁾ However, some studies have shown that deferasirox reduced serum ferritin and liver iron concentrations without altering neurological manifestations.⁽¹²⁾

Our experience has shown that the medication significantly reduced the deposition of hepatic iron and serum ferritin levels. On the other hand, the deposition of iron in basal ganglia remained unchanged, despite total remission of neurologic symptoms.

Special attention should be given to the side effects that may arise with the continued use of deferasirox including renal alterations.⁽⁷⁾ Other serious adverse effects such as agranulocytosis and thrombocytopenia have also been described⁽¹³⁾ but those were not observed in our patients.

Prior to the use of this medication, both patients had a creatinine clearance estimated at 60 mL/min. Eighteen months after continuous use of deferasirox, even after decreasing the doses, the creatinine clearance has dropped to 50 mL/min.

Although the most recent multicenter studies confirm the safety of deferasirox in the renal and hepatic profile of patients,⁽¹⁴⁾ we believe that the decrease in creatinine clearance in both cases may be related to the use of this medication because the second patient did not present blood glucose levels compatible with glucose intolerance during the study period.

It is known that in advanced stages of glomerulosclerosis, diabetic nephropathy progresses with an estimated decrease in creatinine clearance in the order of 12 mL/min per year, although there is great individual variation. Diabetic retinopathy is also present in 60% of diabetic individuals at this stage, to the extent that the absence of retinal involvement should lead to an investigation of other causes that are present with glomerulopathy.⁽¹⁵⁾

Therefore, deferasirox appears to be a promising drug in the treatment of iron metabolism disorders and the harmful effects of iron overload. However, deferasirox should be used with caution, observing the clinical variables of each patient.

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