Effectiveness of Oral Iron Chelator Treatment with Deferasirox in an Aceruloplasminemia Patient with a Novel Ceruloplasmin Gene Mutation

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Abstract

A 59-year-old man presented with refractory anemia, choreoathetosis in the left upper extremity, an unsteady gait and cognitive dysfunction. The laboratory findings showed a marked decrease in ceruloplasmin. Magnetic resonance images revealed iron deposition in the brain and visceral organs. Iron accumulation was also observed in hepatocytes. Genetic analyses of the ceruloplasmin gene revealed a novel homozygous mutation of c.2185 delC in exon 12. The oral chelator deferasirox was effective in treating the left-side choreoathetosis and unsteady gait. Providing early treatment using deferasirox may be useful for preventing the progression of symptomatic neurological dysfunction.

Key words: aceruloplasminemia, ceruloplasmin, deferasirox

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Introduction

Aceruloplasminemia is a rare autosomal recessive disorder of iron metabolism. Ceruloplasmin (CP) mutations, which are encoded on chromosome 3, have been described by Harris et al. (1) and Yoshida et al. (2). In Japan, the incidence of aceruloplasminemia has been estimated to be approximately 1 per 2,000,000 cases of nonconsanguineous marriage (3). Miyajima et al. (4) reported the clinical manifestations of aceruloplasminemia in 45 Japanese patients. The neurological symptoms included ataxia, involuntary movements, parkinsonism and cognitive dysfunction in individuals ranging from age 25 to older than 60 years of age (4). CP carries 95% of plasma copper and functions as a ferroxidase that converts ferrous (Fe²⁺) to ferric iron (Fe³⁺). Ferroportin, a membrane-bound protein, transports intracellular ferrous iron (Fe²⁺) to transferrin via the oxidization of ferrous iron (Fe²⁺) to ferric iron (Fe³⁺) using the ferroxidase of ceruloplasmin. Therefore, ceruloplasmin plays a role in the mobilization and oxidation of iron from tissue stores associated with the subsequent incorporation of ferric iron into transferrin (5). The complete loss of CP ferroxidase activity due to CP gene mutations results in the accumulation of iron in the central nervous system, liver, pancreas and retina (6). Ultimately, this induces oxidative stress and the formation of reactive oxygen species (ROS), which triggers a cascade of pathological events that lead to neuronal death. Although aceruloplasminemia is usually fatal, patients have shown improvement when treated with the iron chelating agent desferrioxamine, oral zinc sulphate and fresh-frozen plasma (7-9). This report describes a case of aceruloplasminemia in a patient with a new mutation in the CP gene and provides information regarding the effectiveness of the use of the oral chelator deferasirox for the treatment of choreoathetosis and unsteady gait.

Case Report

A 59-year-old man presented for an evaluation of a six-year clinical history of mild cognitive dysfunction. Three years prior to his admission, the patient noted involuntary
movement of his left upper extremity. Due to the additional development of a tendency to fall down when walking, he was admitted to the hospital. No Kaiser-Fleischer rings were present in this case. The patient’s family history included a cousin marriage among his parents and mental retardation and liver dysfunction in his true younger sister. Although a neurological examination found grimacing in the patient, the remainder of the cranial nerve functions were intact. No motor or sensory disturbances were noted. The patient’s cognitive function was classified as subcortical dementia. Cerebellar testing detected slurred speech, as well as an ataxic gait, although the patient was able to walk unassisted. The involuntary movements were diagnosed as choreoathetosis and shown to originate from the left extremity in Barre’s position, with the patient being unable to voluntarily stop the movements. The laboratory findings revealed anemia (hemoglobin: 7.2 g/dL), in addition to very low levels of serum copper (13 μg/dL; reference range: 70-132 μg/dL), CP (1.2 mg/dL; reference range: 21-37 mg/dL) and serum iron (26 μg/dL; reference range: 54-181 μg/dL), along with an increased level of ferritin (817.5 ng/mL; reference range: 27-320 ng/mL). The patient was subsequently transferred to our hospital. An examination of the cerebrospinal fluid revealed increased levels of total protein (68.5 mg/dL; reference range: 10-40 mg/dL) and iron (8 μg/dL). A 75-g oral glucose tolerance test and the HbA1c level demonstrated no evidence of diabetes mellitus. Brain magnetic resonance imaging (MRI) revealed that the bilateral dentate nucleus of the cerebellum, nucleus ruber, basal ganglia, thalamus and subcortical white matter all exhibited low signals on T2-weighted images (Figure A). Abdominal MRI showed that the liver had a homogeneously abnormal low intensity on both the T1- and T2-weighted images (Figure B). A variegated pattern of distribution was noted in the liver tissue, with the Berlin blue staining showing deposition of iron in hepatocytes (Figure C).

After obtaining informed consent, DNA was isolated from the patient’s peripheral blood. The CP gene is listed in the Pubmed OMIM database as 117700. We performed a direct sequence analysis in accordance with a previously published procedure (1). The mutation is a homozygotic substitution of the stop codon in codon 749 caused by a new deletion of the CP gene. A-B. MRI of the brain and liver (A: T2, B-a: T1, B-b: T2), C. Histopathological findings of the liver. C-a: Hematoxylin and Eosin staining. C-b: Berlin blue stain. Bar=100 μm. D. Sequence analysis of CP gene exon 12. The arrow on the electropherogram of the patient indicates the deletion of c.2185 delC that resulted in the substitution of tgg (tryptophan) for ctg (leucine).
c.2185 delC in the CP gene exon 12, which subsequently produces a truncated protein within the CP gene (Figure D).

We attempted to treat the internal changes with daily administration of the oral iron chelator deferasirox (500 mg OD). Although this therapeutic approach caused both the serum ferritin level to decrease to 522.7 ng/mL and the disease progression to cease, there were no improvements in the patient’s cognitive dysfunction. However, the treatment did lead to the gradual disappearance of the involuntary movements causing twisting of the left upper extremity, which made it possible for the patient to voluntarily maintain his left hand in a forward position. While the patient spent a large part of the day in bed, 10 days after the start of the treatment, he was able to stand and walk for a few minutes without assistance. Unfortunately, two weeks later, a skin rash appeared over the patient’s entire body, which made it necessary to temporarily stop the treatment. Once the rash had disappeared, deferasirox was rechallenged with the minimum dose that did not contain a low dose of prednisolone. However, three months later, the patient suffered from aspiration pneumonia and died of respiratory failure.

**Discussion**

We herein described a case of aceruloplasminemia in a patient found to have a new gene mutation of the CP gene. This patient responded to the administration of the iron-chelating agent deferasirox, with both choreoathetosis of the left upper extremity and an unsteady gait improving after treatment. The mutation of the CP gene observed in this patient involved the stop codon in codon 749. The mutation was caused by a new deletion of c.2185 delC in the CP gene exon 12, which subsequently produced a truncated protein within the CP gene.

To date, approximately 40 aceruloplasminemia-causing mutations have been detected. The majority of these mutations are truncated mutations that lead to the formation of a premature stop codon. The ferroxidase activity of ceruloplasmin is dependent on the trinuclear copper cluster, the ligands for which are encoded by exon 18 (10). The identified truncated mutations are predicted to result in the formation of a protein that lacks copper cluster sites. These sites are presumed to be critical for the enzymatic function. Further studies must be undertaken to confirm the function of this site.

Deferoxamine is a high-affinity iron chelator that combines with a ferric iron molecule in a 1:1 molar ratio. After crossing the blood-brain barrier, deferoxamine has been shown to promote the excretion of excess iron in patients with inherited and acquired forms of iron overload (11). As detailed in a single case report (7), the administration of deferoxamine effectively reduced the hepatic iron overload and led to partial improvement of the patient’s neurological symptoms and the accumulation of iron in the brain. A previous study that administered oral deferasirox for iron chelation therapy resulted in no improvements in either neurological symptoms or the accumulation of iron in the brain, prior to the drug having to be discontinued due to anemia (12). In contrast, deferasirox therapy was reported to have led to mild improvement of clinical symptoms, including cognitive performance, gait and balance in an aceruloplasminemia patient who demonstrated no response to either deferoxamine or fresh-frozen plasma therapy (13). Although the effects of deferasirox remain controversial, a recent study that used an animal model to examine Friedreich’s ataxia suggested that the combined use of pyridoxal isonicotinoyl hydrazone and deferoxamine is an effective treatment that protects against iron accumulation in glial cells (14). Therefore, it is possible that the physiological role of CP may be more involved with iron uptake. No CP expression in the brain has been observed in any astrocytes; instead, CP is found in a unique subpopulation of glial cells that predominantly surround the microvasculature. Therefore, providing early treatment using the oral chelator deferasirox may prevent massive accumulation of iron within glial cells, thereby reducing the number of cell deaths. Why the involuntary movements of the present patient quickly improved following the administration of deferasirox is not clear. The half-life of deferasirox in the blood is very long (8 to 16 hours) compared with that of deferoxamine, which is very short (5 to 10 minutes). The differences in the pharmacological properties of deferasirox may modify the cell function and explain the improvements observed in the present patient’s clinical symptoms.

The adverse events associated with the administration of deferasirox primarily include mild-to-moderate gastrointestinal disturbances and skin rashes in patients with bone-marrow-failure syndromes (15). When administering deferasirox, it is important not only to monitor the levels of ferritin and hemoglobin and the liver and renal functions, but also clinical symptoms, particularly gastrointestinal and skin problems, when this agent is used over a long period of time.

Taken together, these results demonstrate that providing early treatments using the iron chelator deferasirox is useful for reducing deposition of iron in the central nervous system and preventing neurodegeneration. To definitively establish the efficacy of deferasirox, making an early diagnosis of aceruloplasminemia and conducting further detailed investigations is required in order to develop similar strategies for affected patients.

**The authors state that they have no Conflict of Interest (COI).**

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**References**


