

[ CASE REPORT ]

## Deferasirox Might Be Effective for Microcytic Anemia and Neurological Symptoms Associated with Aceruloplasminemia: A Case Report and Review of the Literature

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### Abstract:

The patient was a 64-year-old man presented with difficulty in walking, articulation, and swallowing, as well as cognitive impairment. He had refractory microcytic anemia and diabetes mellitus. His serum levels of iron, copper, and ceruloplasmin were low. Magnetic resonance imaging suggested iron deposition in the basal ganglia, thalami, cerebellar dentate nuclei, and cerebral and cerebellar cortices. He was diagnosed with aceruloplasminemia after a ceruloplasmin gene analysis. Iron chelation therapy with deferasirox improved his anemia and cerebellar symptoms, which included dysarthria and limb ataxia. The present study and previous reports indicate that cerebellar symptoms with aceruloplasminemia might respond to deferasirox in less than one year.

**Key words:** aceruloplasminemia, microcytic anemia, cerebellar symptom, chorea, W1,017X mutation, iron chelation therapy

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### Introduction

Aceruloplasminemia is an autosomal recessive disorder of iron homeostasis due to loss-of-function mutations in the ceruloplasmin gene (1). Patients with aceruloplasminemia may develop anemia, diabetes mellitus, peripheral retinal degeneration, and various neurological symptoms, such as cognitive dysfunction, dysarthria, chorea, dystonia, rigidity, and cerebellar ataxia, due to iron deposition in multiple organs, including the brain. Laboratory data demonstrate decreased serum iron, copper, and ceruloplasmin and elevated ferritin (2). Aceruloplasminemia is an intractable disease. The most common treatment is iron chelation therapy with the intravenous administration of deferoxamine or an oral iron chelating agent such as deferoxamine, deferasirox, or deferiprone (1, 3). These drugs have been shown to be effective in reducing serum ferritin and iron accumulation in the

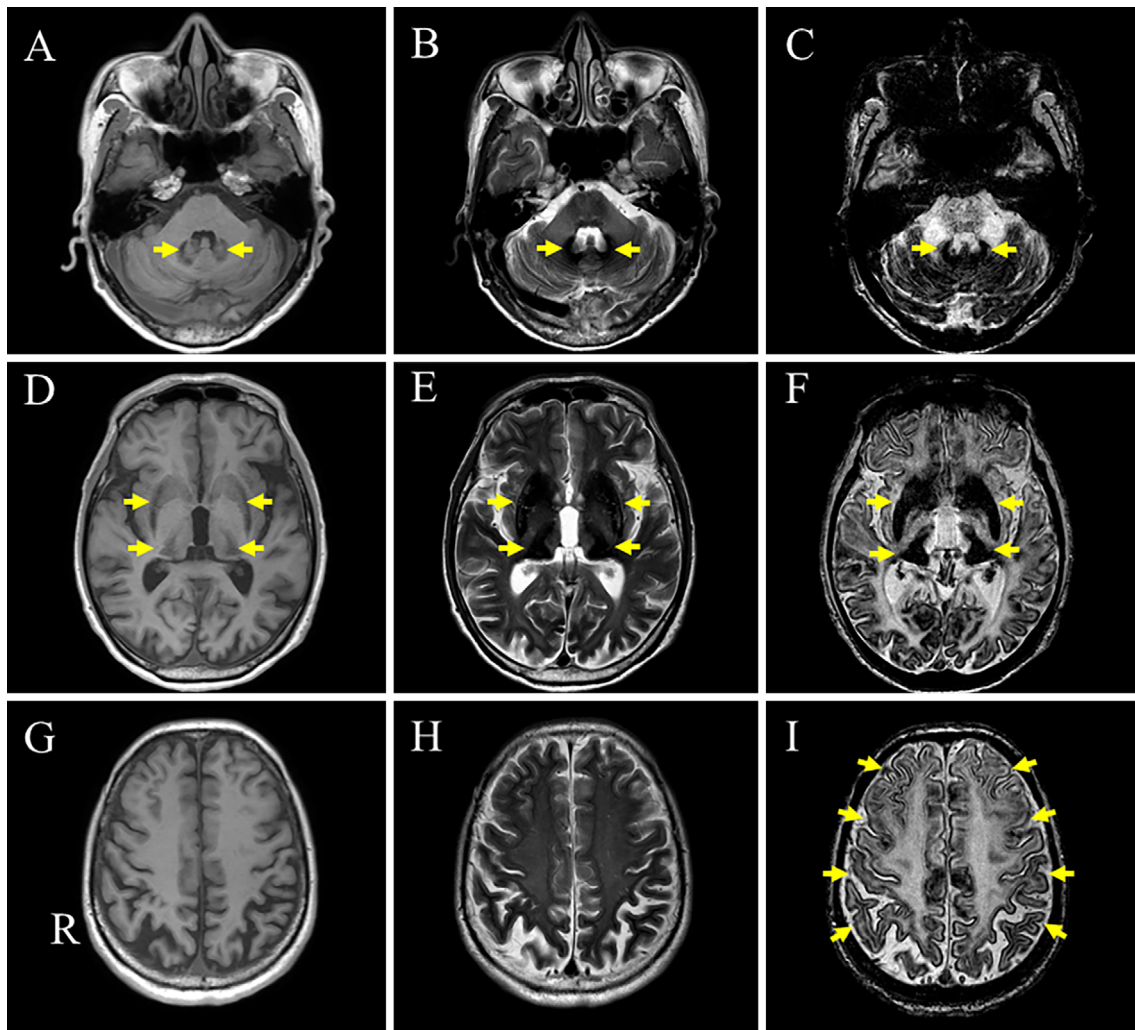
liver, though their efficacy for brain iron accumulation and neurological symptoms is controversial (3). In general, an early diagnosis and early treatment of patients before the appearance of neurological symptoms are thought to be important.

We herein report a case of aceruloplasminemia in which the patient's neurological symptoms were successfully treated with deferasirox.

### Case Report

A 64-year-old man visited our hospital with complaints of progressive difficulty in walking, articulation, and swallowing, as well as cognitive impairment. He had an approximately 30-year history of ulcerative colitis with repeated bleeding and had been treated by subtotal colectomy at 51 years of age. Even after that radical surgery, he suffered from chronic anemia. He was diagnosed with iron-

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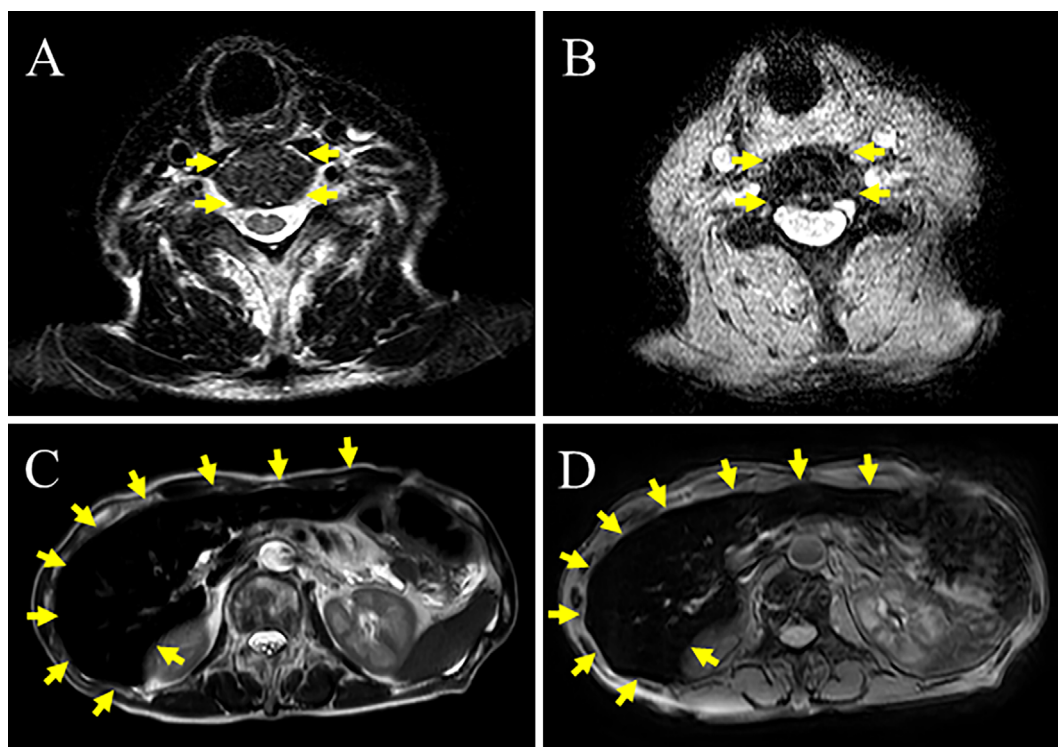
**Figure 1.** T1-, T2-, and susceptibility-weighted magnetic resonance images of the head. (A, D, G) T1-weighted images showed hypointense lesions in the bilateral cerebral and cerebellar cortex, basal ganglia, thalami, and cerebellar dentate nuclei (arrows). (B, E, H) On T2-weighted images, the hypointensity observed on T1-weighted images was more prominent (arrows). (C, F, I) Susceptibility-weighted images also showed hypointense areas in the bilateral cerebral white matter and basal ganglia (arrows).

deficiency anemia and took iron supplements and iron-containing foods, but with no effect. The patient was also diagnosed with type 2 diabetes mellitus at 38 years of age and started insulin treatment 6 years after the diagnosis. At 61 years of age, he had difficulty listening to what others said, and then developed the abovementioned neurological symptoms. He consulted a neurosurgeon and underwent cranial magnetic resonance imaging (MRI), which showed decreased T2\*-weighted signal intensities of dentate nuclei at the cerebellum, lentiform nuclei, and cerebral cortices. He was suspected of having superficial siderosis and was admitted to our hospital about one year after the emergence of the neurological symptoms.

The patient had a history of drinking 350 mL of beer per day. His father, older brother, and aunt had been diagnosed with diabetes mellitus. On admission, he had a blood pressure of 97/51 mmHg, a pulse rate of 77/min, a body temperature of 36.4°C, percutaneous oxygen saturation of 96%,

and a height and weight of 172 cm and 50 kg, respectively. The general physical examination revealed conjunctival anemia. The patient was alert and conscious, though the dementia scale revealed markedly impaired recent memory. An ophthalmologic examination revealed choroidal atrophy and mild pigmentation in the fundus in both eyes, and an electroretinogram showed reduced amplitudes and changes, including retinitis pigmentosa. He had lateral gaze-evoked nystagmus, sensory hearing loss on the right side, and decreased pharyngeal reflex. He had no muscle weakness or atrophy in any limb, no pathological reflexes, normal tendon reflexes in the upper extremities without laterality, exaggerated patellar tendon reflexes, and attenuated Achilles tendon reflexes. The patient exhibited no sensory disturbance. Cerebellar testing revealed scanning speech, left-dominant limb dysmetria and decomposition, and ataxic gait with assistance.

Blood tests revealed microcytic anemia (hemoglobin, 7.3



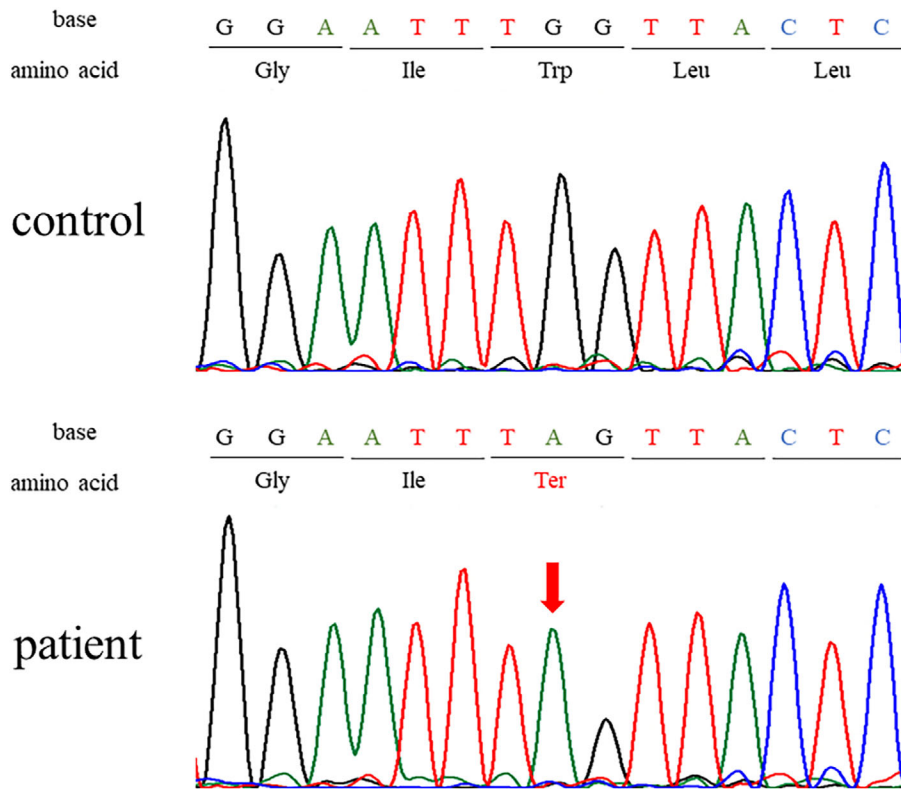
**Figure 2.** T2- and T2\*-weighted magnetic resonance images of the cervical spine (C6 level) (A, B) and the upper abdomen (C, D). (A, C) T2-weighted images showed hypointense lesions in the bone marrow and liver (arrows). (B, D) On T2\*-weighted images, hypointensity was found in the bone marrow and the liver (arrows).

g/dL; mean corpuscular volume, 76.1 fL, and mean corpuscular hemoglobin concentration, 28.3%), abnormal coagulation and fibrinolytic systems [activated partial thromboplastin time, 40.0 sec (control, 27.6 sec); prothrombin time, 13.9 sec (77.4%); fibrinogen, 616.0 mg/dL; and D-dimer (2.8 mcg/mL)], and impaired glucose tolerance (casual blood glucose 204 mg/dL and hemoglobin A1c 6.8%). The serum levels of iron and copper were low (13  $\mu$ g/dL and 12  $\mu$ g/dL, respectively), while that of ferritin was high (1,474 ng/mL). The serum ceruloplasmin level was below the limit of detection (<2.0 mg/dL). Immunoglobulin G and A were both high (3,280 mg/dL and 637 mg/dL, respectively). A cerebrospinal fluid analysis revealed normocytosis with an increased protein concentration of 144 mg/dL (normal range <40 mg/dL). MRI of the head revealed atrophy of the bilateral parietal lobes and hypointense bilateral lesions in the basal ganglia, thalami, cerebellar dentate nuclei, and cerebral and cerebellar cortices on T1-, T2-, and susceptibility-weighted imaging (Fig. 1).  $^{123}$ I-N-isopropyl-pioidoamphetamine single-photon emission computed tomography (SPECT) showed slightly decreased accumulation in the basal ganglia, in the temporal, parietal, and occipital lobes, and in the cerebellar hemispheres. Dopamine transporter SPECT revealed slightly reduced  $^{123}$ I ioflupane binding in the bilateral dorsal side of the striatum. Cervical spine MRI revealed heterogeneous low signals of the bone marrow on T2- and T2\*-weighted imaging (Fig. 2A, B). Abdominal computed tomography showed atrophy and marked fat infil-

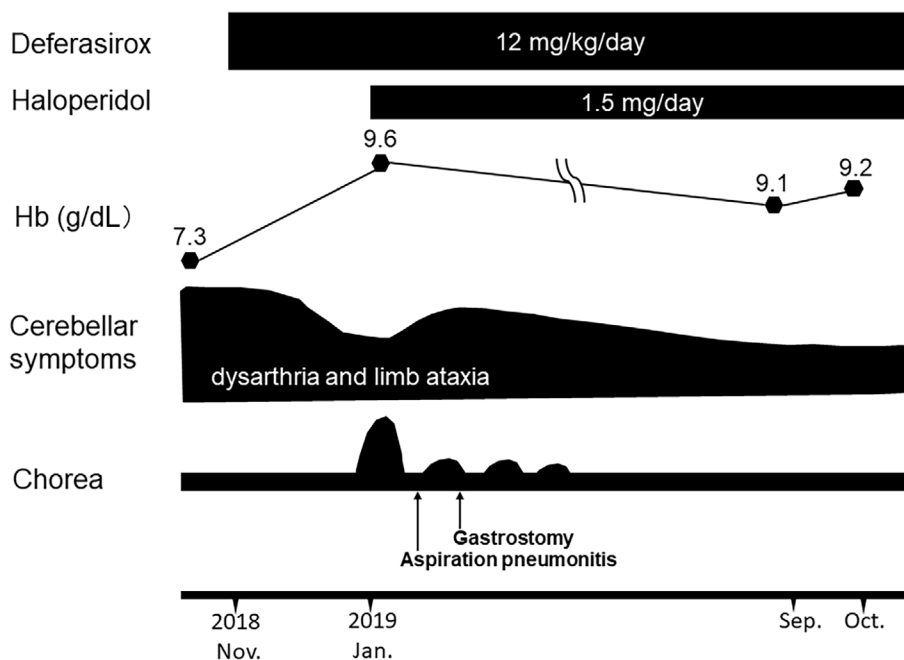
tration in the pancreas (not shown), and abdominal MRI revealed diffuse hypointensity in the liver and a mildly low signal on T2\*-weighted imaging (Fig. 2C, D). These data suggested iron deposition in multiple organs, including the central nervous system.

Based on the results of the blood tests and MRI, aceruloplasminemia was suspected as the cause of the patient's anemia and neurological symptoms. A ceruloplasmin gene analysis was performed at Shinshu University after the patient gave his informed consent. The identified mutation was homozygotic substitution of the 3,107th guanine to adenine in exon 18 (c. 3,107G<A), which resulted in the substitution of tryptophan for the stop codon at the 1,017th amino acid (p. W1,017X); a disease-causing mutation that was reported in 2010 (Fig. 3) (4).

The patient started taking an oral ironchelation drug, deferasirox (12 mg/kg/day), after his diagnosis. Unexpectedly, his anemia, glucose tolerance, and ataxic gait gradually improved. About two months after the administration of deferasirox, the patient's hemoglobin rose to 9.6 g/dL, his HbA1c improved to 6.2% without increasing insulin, and his dysarthria, limb ataxia, and ataxic gait improved. His Modified Rankin Scale (MRS) also improved from 4 to 2 (Fig. 4). In contrast, chorea became gradually apparent, and after the administration of haloperidol, the chorea improved. Aspiration pneumonia occurred, and gastrostomy was performed. At approximately 12 months after the administration of deferasirox, the patient's hemoglobin was 9.2 g/dL, his



**Figure 3.** The analysis of the ceruloplasmin gene. A homozygotic substitution of the 3,107th guanine to adenine in exon 18 (c. 3,107 G<A) was identified (red arrow).



**Figure 4.** The clinical course after iron chelation therapy.

serum level of ferritin was 815 ng/mL, and the improvement of both dysarthria and limb ataxia was maintained (Fig. 4). On the other hand, there was no change in the iron deposition in the brain or liver on MRI at 1 year after the start of treatment with deferasirox.

The patient and his family provided their written informed consent for the publication of the clinical data. The

presented data are anonymized, and the risk of identification is minimal.

## Discussion

We herein report a very interesting case of aceruloplasminemia in which the patient's symptoms were unexpectedly

**Table. Comparison of the Characteristics of Other Aceruloplasminemia Cases with Those of Our Case after Iron Chelation Therapy.**

Reference	Age	Sex	Neurological symptoms	Hb g/dL	DM	Mutation of ceruloplasmin gene	Period from neurological onset to treatment	Duration of ICT	Neurological symptoms after ICT
(6)	55	M	Psychosis Depression Dementia Parkinsonism	11.9	+	NA	NA	288 months	Progression
(7)	43	F	None	7.1	+	c. 2122G>A	None	12 months	None
	39	M	None	8.1	+	c. 2122G>A	None	12 months	None
	24	M	None	7.9	+	c. 2122G>A	None	12 months	None
(8)	28	M	None	NA	-	NA	None	72 months	None
(9)	58	F	Dystonia	9.9	-	NA	3 years	120 months	No change
(10)	20	M	None	13.7	-	NA	None	18 months	None
(11)	39	M	None	NA	+	c. 1211_1212dupTG	None	24 months	None
(12)	35	M	None	9.5	+	p. G873E	None	11 months	None
(13)	59	M	Dementia Choreoathetosis Grimacing Slurred speech Ataxic gait	7.2	-	c. 2185delC	6 years	3 months	Improvement (choreoathetosis, ataxic gait)
(14)	52	F	Dementia Hand tremor Cervical Dystonia	9.7	+	c. 848G>C	6 years	48 months	Progression
(15)	57	F	Psychosis Depression	10.7	+	NA	1 year	10 months	Improvement (psychosis)
(16)	47	M	Intention tremor Slurred speech Ataxic gait	13.1	+	c. 2554+1G>T	3-4 years	3 months	No change
(17)	54	F	Dementia Psychosis Chorea Gait instability	7.0	-	NA	3-4 years	3 months	Improvement (dementia, gait instability)
(18)	40	F	None	10.6	-	p. F198S	None	8 months	None
(19)	62	F	Chorea	11.2	+	p. Y632X	3 years	12 months	No change
(20)	63	F	Blepharospasm Grimacing Cogwheel rigidity Scanning speech	9.0	+	NA	10 years	10 months	Improvement (blepharospasm, grimacing, cogwheel rigidity)
Present case	64	M	Dementia Chorea Ataxic gait Scanning speech	7.3	+	c. 3107G>A	3 years	12 months	Improvement (dysarthria, limb ataxia, ataxic gait)

Hb: hemoglobin, DM: diabetes mellitus, ICT: iron chelation therapy, NA: not available

relieved by iron chelation therapy. A ceruloplasmin gene analysis revealed a homogeneous nonsense point mutation in exon 18 (c. 3,107G>A), which produced truncated ceruloplasmin proteins with deficiency in endoplasmic reticulum to Golgi tracking (4).

According to the review of 55 cases of aceruloplasminemia by Vroegindeweyj et al., 90% of the patients developed diabetes mellitus or anemia an average of 12.5 years before the appearance of neurological symptoms (5). Therefore, the key to an early diagnosis is to consider aceruloplasminemia as one of the differential diagnoses when examining patients with uncontrolled diabetes mellitus and/or anemia. However,

since aceruloplasminemia is a very rare disease, its early diagnosis is in fact extremely difficult, and in many cases, like ours, the diagnosis was made after the appearance of neurological symptoms. In the present case, the administration of deferasirox resulted in continuous improvements in dysarthria and limb ataxia, microcytic anemia, and impaired glucose tolerance in spite of the long time from the onset to the diagnosis.

We compared the present case with previous ones, limited to those referring to iron chelation therapy (Table) (6-20). Neurological symptoms were improved in 5 of 10 cases (50%), including ours. In the cases in which neurological

symptoms did not appear at the time of the diagnosis, none of the patients developed neurological manifestations after the administration of iron chelators, indicating that iron chelation therapy could prevent the appearance of neurological symptoms by blocking iron deposition in the brain. Indeed, the previous report by Pan et al. using a T2\*-weighted gradient echo sequence on a 3.0-T MR scanner suggested that iron chelation therapy could reduce iron accumulation in brain regions such as the putamen and substantia nigra (14). Regarding the cases with any neurological symptoms, no fixed trend could be found between the period from the onset of neurological symptoms to the start of treatment and the therapeutic effect. Therefore, it could not be said that treating patients with aceruloplasminemia as early as possible after the appearance of neurological symptoms may affect their neurological prognosis. On the other hand, iron chelation therapy might be more effective for improving cerebellar ataxia than involuntary movements such as dystonia, chorea, and tremor. The reason for this theory is that iron deposition in the cerebellar cortex is milder than that in the basal ganglia and cerebellar dentate nucleus. Previous imaging and pathological studies indicated that iron deposition in the basal ganglia and dentate nucleus of the cerebellum is conspicuous from the early stage of aceruloplasminemia, whereas iron accumulation in the cerebellar and cerebral cortices is not obvious until the advanced stage (1, 21). In the present study, the appearance of chorea in spite of iron chelation therapy might be consistent with the above considerations. Furthermore, the effect of iron chelators may also depend on differences in the blood-brain barrier permeability of iron chelators in each area in the central nervous system. Furthermore, in cases in which any neurological improvements were noted, the effects appeared within 10 months at the latest from the start of iron chelation therapy. This probably suggests that iron chelation therapy may have the potential to improve the neuronal function within 10 months if the iron-deposited neurons have not entered the irreversible degeneration stage.

In conclusion, iron chelation therapy could improve some neurological symptoms, especially cerebellar ataxia, in patients with aceruloplasminemia, though it took a long time from the onset to the diagnosis, as in the present case, and neurological improvement within 12 months after the initiation of therapy may be an indicator of the neurological prognosis. Further studies are needed to clarify the long-term therapeutic effects of iron chelation therapy on neurological symptoms.

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

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