To the Editor,

Aceruloplasminemia is a rare autosomal recessively inherited iron accumulation disease that can manifest itself with neurological findings in the forth and fifth decades, peripheral retinal degeneration, microcytic anemia, decrease in serum iron and increase in ferritin concentration, diabetes or abnormal glucose tolerance [1]. The incidence of this disorder is 1/2000000 in unrelated marriages in Japan. Aceruloplasminemia is the only known disease that involves both brain and systemic iron metabolism among the iron overload syndromes [2]. Here, a long-term undiagnosed case with microcytic anemia accompanied by high ferritin levels will be presented. A 34-year-old Turkish female patient followed by an external hospital with an undiagnosed iron metabolism disease applied to the hematology outpatient clinic. Anemia and high ferritin levels had been detected during the premarital screening test seven years ago. She had no
history of oral or parenteral iron replacement for the last three years. Bone marrow biopsy which had been reported as normocellular with an increase in depository iron, alpha thalassemia and HFE gene tests had been performed before admission. The genetic test result for alpha thalassemia had been negative, and HFE gene sequencing had revealed a heterozygous p.His63Asp mutation. Moderate iron accumulation had been observed in the liver on the T2-weighted Magnetic Resonance Imaging (MRI). She had refused the recommended liver biopsy. The patient whose ferritin level had been over 1000 µg/L had been administered an oral iron chelator for a while. However, the drug had been discontinued due to a grade 2-3 allergic reaction.

Her parents had a 4th-degree consanguinity. There were no individuals with neurological findings or similar blood test results in her family history. The liver was palpable at 1 cm below the right costal margin and the spleen was nonpalpable. She did not have any neurological findings. Her full blood count was as follows: WBC: 8160/mm³; RBC: 4.480.000/mm³; Hb: 10 g/dL; Htc: 33.2%; MCV: 74.1 fl; MCH: 22.3 pg; MCHC: 30.1 g/dl; RDW: 17.5 (11.6-16%). Serum iron level (33 µg/dl; 25 to 156 µg/dL) and total iron-binding capacity (317 µg/dL; 240 to 450 µg/dL) were normal. C-reactive protein (CRP) was slightly increased (9 mg/L; 0-5 mg/L). Transferrin saturation was low (%10; 15-50%). Serum ferritin level was high (681 µg/L; 10-204 µg/L). Liver function tests were within normal values. Inflammation markers were normal despite high ferritin levels persisted in our follow up. The liver size was increased and consistent with a moderate iron deposition, the parenchymal signal was diffusely decreased in the T2A weighted upper abdomen MRI (iron load 10.3 mg/g). Signal changes secondary to iron accumulation were detected in both kidneys. Due to lack of evidence of any inflammatory state we did not consider inflammation. Regarding the differential diagnosis of thalassemia peripheral smear and hemoglobin electrophoresis were performed but both were not consistent with thalassemia and the alpha thalassemia gene test had been negative. Although HFE gene analysis had been performed previously in another outpatient clinic, we did not suspect hemochromatosis due to low transferrin saturation.

After a comprehensive literature search for iron metabolism disorders, aceruloplasminemia was suspected based on the high ferritin levels, microcytic anemia, and iron accumulation in the liver and kidney. Her serum ceruloplasmin level (<0.023 g/L; 0.2-0.6 g/L) and copper level (57.7 µg/dl; 80-155 µg/l) were low, 24-hour urinary copper excretion was normal (6.65 µg/day; 0-52 µg/day). Signal loss secondary to paramagnetic material accumulation in the bilateral basal ganglia and dentate nucleus was observed in the Susceptibility Weighted Imaging (SWI) series of non-contrast brain MRI. In her ophthalmological examination, due to the borderline eye pressure and the increased cup/disc ratio (C/D) visual field investigation was planned. A CP gene sequence analysis was performed. DNA isolated from EDTA whole blood was amplified by the polymerase chain reaction (PCR) method with the primers specific to the exons interested. The purified PCR products were sequenced on ABI 3500 Genetic Analyzer (Applied Biosystems, Foster City, Ca, USA). A novel c.1712delA (p.Gln 571ArgfsTer4) homozygous pathogenic variant causing a frameshift and an early stop codon formation in exon 9 was detected in the CP gene (NM_000096) (Figure 1). Since the patient had a history of allergic reaction with deferasirox, iron chelation with deferasirox at the lowest dose of 15 mg/kg and oral zinc therapy were commenced. Her serum ferritin level decreased from 939 micrograms/L to 405 micrograms/L on the 13th day of treatment. We also planned to draw blood from her siblings and parents to check their hemogram and ferritin levels and perform a physical examination of them.
Ceruloplasmin has various functions such as copper transport, oxidation of biological amines and ferrous iron, and antioxidant activity by preventing the formation of free radicals in serum [3]. The ceruloplasmin is mostly secreted into plasma by hepatocytes [4]. It has been shown that an isoform plays a role in the cell surface stabilization of ferroportin in the astrocytes and bone marrow-derived macrophages. It is considered that iron accumulation in the brain and low serum iron levels in these patients may have developed secondary to the deterioration of iron export from these cells [5]. Aceruloplasminemia should be kept in mind in the case of microcytic anemia and increased serum ferritin levels. A transferrinemia, divalent metal transporter 1 deficiency, hemochromatosis, ferroportin disease also should be considered while approaching systemic hereditary iron overload disorders. Transferrin saturation and anemia status are very important in differential diagnosis [6]. Biochemical changes are usually the earliest manifestations of aceruloplasminemia and may appear decades before other clinical manifestations, especially neurological complications which are irreversible [7]. Therefore it is important for hematologists to consider aceruloplasminemia in the differential diagnosis of microcytic anemia and hyperferritinemia.

**Keywords:** Hyperferritinemia; ceruloplasmin; mutation; anemia

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**Informed Consent:** Informed consent was obtained from this patient.

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**References**

Chromatogram showing the novel pathogenic variant

**Figure 1.** Chromatogram showing the novel pathogenic homozygous c.1712delA (p.Gln571ArgfsTer4) variant in exon 9 of CP gene (NM_000096).