

# Dementia as a core clinical feature of a patient with aceruloplasminemia

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## Abstract

Aceruloplasminemia is an autosomal recessive disease, caused by systemic iron accumulation due to mutations in the Ceruloplasmin gene. We report two Iranian siblings who have diagnosed with aceruloplasminemia. Based on our researches, dementia hasn't been published as the first neurological feature while one of them was presented with pure dementia

## Introduction

Aceruloplasminemia was firstly defined in 1987 as a rare adult-onset, an autosomal recessive disorder which is caused by mutations in the ceruloplasmin gene. [1–3]

As a consequence of this mutation iron accumulates all over the body, mostly in brain, retina, pancreas, and liver, which causes neurologic disturbance (68%), retinal degeneration (76%), and diabetes (70%), as main features. [4, 5]

The iron deposition involves the dentate nuclei of the cerebellum, striatum, and thalamus, and is demonstrated in magnetic resonance imaging (MRI).[6]

The disease can start at different ages and by various features.[4] The patients may experience diabetes in the third to the fifth decade, the retinal disorder in the second decade, and neurological problems in the forth to the sixth decade of life. Neurological manifestation can be ataxia (71%), Parkinsonism (20%) cognitive dysfunction (60%) and involuntary movements (64%) like tremors, chorea and blepharospasm. The retinal disorder is early beginning macular degeneration rather than diabetic retinopathy. [5]

Aceruloplasminemia is detected with specific MRI findings, quite one amongst the above clinical manifestations and typical results on laboratory tests, such as microcytic anemia, lack of serum ceruloplasmin, low serum copper and transferrin saturation, and increased ferritin. [4, 7, 8]

In this paper, we describe a family with two affected siblings with aceruloplasminemia, which dementia was the sole clinical manifestation in one of them.

## Case report

### *Case 1:*

A 64-year-old woman was referred to our movement disorder clinic with four years history of bradykinesia and rigidity. She was born as a first child of consanguineous parents and has history of diabetes mellitus, myelodysplastic syndrome, and gout for 15 years.

On examination, she had generalized bradykinesia and rigidity without tremor, slow saccadic eye movements, limbs dysmetria and ataxic gait. Other neurological examination including, cognitive, sensory, and motor function were unremarkable.

On follow-up, after 2 years, she became wheelchair-bound due to severe gait freezing, cognitively declined (MOCA: 19), and tremor was added to her clinical manifestations. In addition, at that time she had severe aggression, agitation, and visual hallucination.

The evaluation showed microcytic anemia, low serum ceruloplasmin, copper and transferrin saturation, and increased ferritin. (Table 1) Brain MRI detected abnormal signal intensity of the cerebellum, basal ganglia, and midbrain. (Figure A, B) According to imaging findings and other laboratory assessments, the diagnosis of aceruloplasminemia was suspected. Genetic analysis was requested. The direct DNA Sequencing revealed homozygote pathogenic variant defined as (c.2425+1G>C) in splice region of exon 13 of CP gene. DNA was extracted from the patient sample using salting-out technique. PCR was used to intensify the indicated exons plus extra flanking intronic or other non-coding sequences. Subsequently cleaning of the PCR supplies, cycle sequencing was carried out using the ABI Big Dye Terminator v.3.0 kit. Products were resolved by electrophoresis on an ABI 3130 capillary sequencer. Sequencing was accomplished separately in both the forward and reverse directions.

### Case 2:

The 56-year-old sibling had had cognitive decline for 8 years, and Alzheimer's disease had been diagnosed. . He has a history of diabetes mellitus (DM) since the age of 28. On examination, he had mostly attention, concentration, memory, executive dysfunction, and his MOCA was 5. Other examinations including, cerebellar, pyramidal, extrapyramidal, eye movements, and sensory function were unremarkable.

According to his positive family history, more workup showed microcytic anemia, elevated ferritin, and low serum ceruloplasmin. (Table 1)

The brain MRI revealed low signal intensity on the T2/fluid attenuated inversion recovery weighted image. (Figure C, D)

After careful history taking, it was showed that the apart that case 1, other siblings have diabetes, plus the younger brother has a high ferritin level and mild cognitive dysfunction without other neurological findings.

The family history, laboratory and imaging results were leading to the diagnosis of aceruloplasminemia, therefore, the genetic study was asked and showed homozygote pathogenic variant defined as (c.2425+1G>C) in splice region of exon 13 of CP gene.

## Discussion

Ceruloplasmin which is mostly synthesized in liver cells has a crucial role within the iron metabolism by oxidation of Fe<sup>2+</sup> to Fe<sup>3+</sup>. [8] This protein's gene is positioned in chromosome 3q25, and according to human gene mutation databank more than 40 CP gene variant has been described; previous studies failed to show any correlations between the genotypes and, phenotypes.[9, 10] In our patients by direct DNA Sequencing we revealed a unique variant which is (c.2425+1G>C) in splice region of exon 13 of CP gene.

CP mutation causes iron to accumulate all over the body that provides free radicals and lipoperoxidation supplies that cause oxidative stress and eventually organ damage. [9]

According to prior researches, the initial neurological presentation varies in different races as an example in Japanese patients, the primary neurological manifestations mostly are movement disorders, and cognitive dysfunction will be added in several years. Although, in other races such as Caucasians around 50% of patients at first presented with cognitive disorders or psychiatric complaints such as depression, anxiety and apathy or a mixture of non-motor and motor manifestations.[11]. Based on these researches, dementia has not been published as the sole neurological feature while we reported a case which was presented with pure dementia without any other neurological findings which hitherto no other neurological symptoms have

been added. Forasmuch as there are the first Iranian cases of Aceruloplasminemia no previous research has been done.

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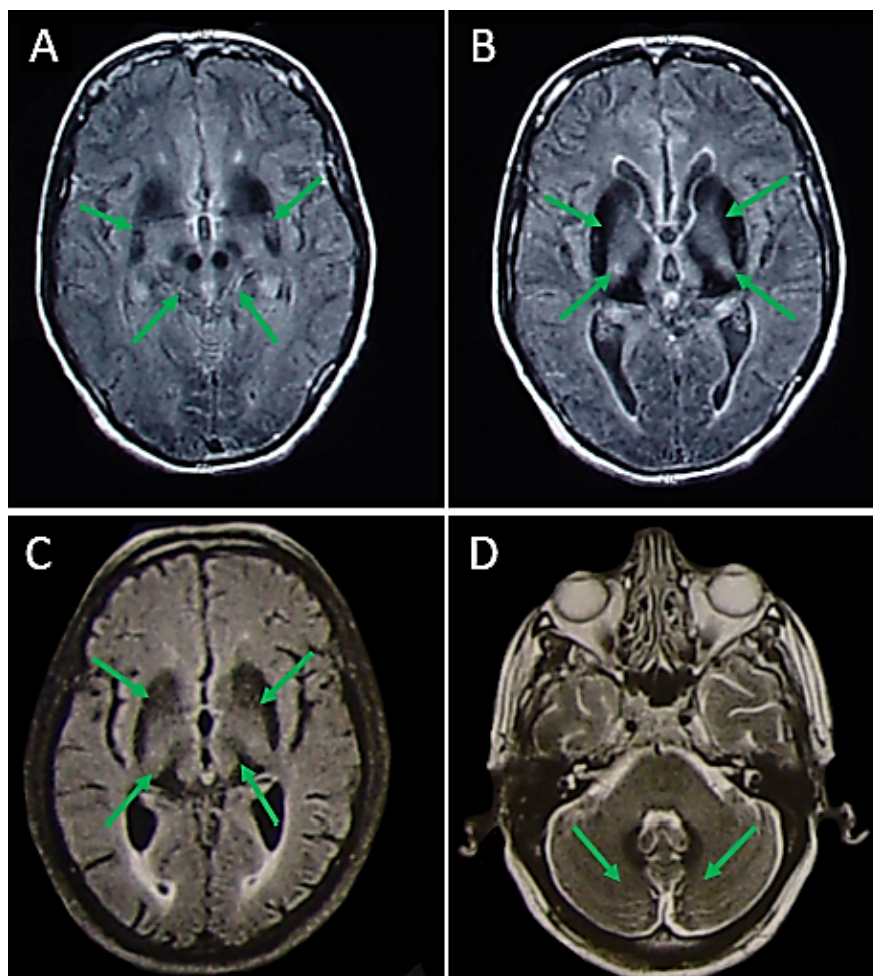
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|   | Case 1 | Case 2 | Normal Range |
|---|--------|--------|--------------|
| white blood cell (/uL)                        | 5900   | 7900   | 4000-10800   |
| red blood cell (×106/uL)                      | 4.64   | 5.11   | 3.8-5.2      |
| Hemoglobin (g/dL)                             | 10.6   | 11.90  | 11.5-16      |
| Hematocrit (%)                                | 34.5   | 38.80  | 32-46        |
| mean corpuscular volume (fL)                  | 74.4   | 75.90  | 80-96        |
| mean corpuscular hemoglobin (pg)              | 22.8   | 23.30  | 24-35        |
| Mean corpuscular hemoglobin concentration (%) | 30.7   | 30.70  | 28-38        |
| Red blood cell distribution width (%)         | 19     | 17.50  | <15          |
| erythrocyte sedimentation rate (mm/hr)        | 10     | 10     | 0-30         |
| Fasting Blood Sugar (mg/dL)                   | 90     | 307    | 70-115       |
| Urea (mg/dL)                                  | 21     | 29     | 15-45        |
| blood urea nitrogen (mg/dL)                   | 9.8    | 9.9    | 4-23         |
| Creatinine (mg/dL)                            | 0.8    | 0.8    | 0.5-1.3      |
| Serum copper (µg/dL)                          | 9      | 25     | 80-155       |
| Ceruloplasmin (mg/dL)                         | 6.4    | 6      | 15-60        |
| Ferritin (µg/L)                               | 1008.8 | 1460   | 5-73.3       |

## Table:

Laboratory Examinations

## Figure:



### Figure legend:

**Figure. A, B** Magnetic resonance imaging (FLAIR) of *case 1* : There were low-signal intensities in the bilateral lentiform nuclei, caudate nuclei, and thalamus.

**Figure. C, D** Magnetic resonance imaging (T2/FLAIR) of *case 2* : There were low-signal intensities in the bilateral lentiform nuclei, caudate nuclei, thalamus, and cerebellar dentate nuclei.

