Dementia as a core clinical feature of a patient with aceruloplasminemia

Farzad Ashrafi | Mehri Salari | Fatemeh Nouri | Fatemeh Shiravi

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 been diagnosed with aceruloplasminemia. Although dementia has not been published as the first neurological feature, one of our cases was presented with pure dementia.

KEYWORDS
aceruloplasminemia, ceruloplasmin, dementia, Iran, iron accumulation

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

As a consequence of this mutation, iron accumulates all over the body, mostly in the brain, retina, pancreas, and liver, which causes neurological 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, a retinal disorder in the second decade, and neurological problems in the fourth to the sixth decade of life.

Neurological manifestation can be ataxia (71%), Parkinsonism (20%) cognitive dysfunction (60%), and involuntary movements (64%) such as tremors, chorea, and blepharospasm. The retinal disorder is early beginning macular degeneration rather than diabetic retinopathy.5

Aceruloplasminemia is detected by specific MRI findings, quite one among the above clinical manifestations and typical results of laboratory tests, such as microcytic anemia, lack of serum ceruloplasmin, low serum copper, 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.

Fatemeh Nouri and Fatemeh Shiravi contributed equally to the study and share the corresponding authorship.
### CASE REPORT

#### 2.1 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 the first child of consanguineous parents and has a 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 examinations 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 1A,B). According to imaging findings and other laboratory assessments, the diagnosis of aceruloplasminemia was suspected. Genetic analysis was requested. The direct DNA Sequencing revealed a homozygote pathogenic variant defined as (c.2425+1G>C) in the splice region of exon 13 of the ceruloplasmin (CP) gene. DNA was extracted from the patient sample using the salting-out technique.

Polymerase chain reaction (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. The products were resolved by electrophoresis on an ABI 3130 capillary sequencer. Sequencing was accomplished separately in both the forward and the reverse directions.

#### 2.2 Case 2

The 56-year-old sibling had had a cognitive decline for 8 years, and Alzheimer's disease had been diagnosed. He has had a history of diabetes mellitus (DM) since the age of 28. On examination, he mainly had 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).

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### Table 1 Laboratory examinations

|                      | Case 1 | Case 2 | Normal range |
|----------------------|--------|--------|--------------|
| White blood cell (/Ul) | 5900   | 7900   | 4000–10,800  |
| Red blood cell (x106/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/h) | 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      |

The brain MRI revealed low-signal intensity on the T2/fluid-attenuated inversion recovery weighted image (Figure 1C,D).

After a careful history taking, it was shown that apart from 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 us to the diagnosis of aceruloplasminemia; therefore, the genetic study was asked and showed a homozygote pathogenic variant defined as (c.2425+1G>C) in the splice region of exon 13 of the CP gene.

### 3 DISCUSSION

Ceruloplasmin which is mostly synthesized in liver cells has a crucial role within the iron metabolism by oxidation of Fe2+ to Fe3+. 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. In our patients by direct DNA Sequencing, we revealed a unique variant which is (c.2425+1G>C) in the splice region of exon 13 of the 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 research, 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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CONFLICT OF INTEREST
The writers declared no conflicts of interests.

AUTHOR CONTRIBUTIONS
All authors have made substantial contributions to the conception, design, and acquisition of data and interpretation of data, and all of them have been involved in drafting the manuscript or revising it critically for important intellectual content. All the listed authors have given final approval of the version to be published. They all agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Farzad Ashrafi, MD: Conception, Organization; Mehr Salari, MD: Conception, Organization, Execution, Review, and Critique; Fatemeh Nouri: Writing of the first draft; Fatemeh Shiravi: Writing of the first draft.

ETHICAL APPROVAL
We hereby confirm that this study conforms to the ethical standards and guidelines of the journal and we also confirm that the approval of an institutional review board was not required for this work.
CONSENT
Written informed consent was obtained from the patient to publish this report in accordance with the journal’s patient consent policy.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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