Beyond the Usual Suspects: Aceruloplasminemia as a Hidden Cause of Cognitive Impairment and Parkinsonism

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Background

Aceruloplasminemia is a rare genetic disease caused by mutations in the ceruloplasmin gene, resulting in systemic and brain iron accumulation [1]. Diagnosis is based on the combination of clinical and biochemical findings such as microcytic anaemia, low transferrin saturation, high serum ferritin and undetectable or very low serum ceruloplasmin [2]. MRI may show iron deposit in the basal ganglia and other brain regions [3].

Case description

We highlight the diagnostic complexity of a 66-year-old woman reporting recurrent falls and subtle cognitive deficits for about 18 months. The patient's family history was notable for several cases of cancer and one instance of late-onset memory decline. Her medical history included a probable diagnosis of latent autoimmune diabetes in adults (LADA) and chronic iron-deficiency anaemia, which was managed with iron supplementation, resulting in an increase in ferritin levels. Neurological examination revealed parkinsonian features, including a forward-leaning posture, reduced arm-swing, narrow base-of-support, positive pull-test, mild plastic limbs rigidity, bradykinesia and dysdiadochokinesia.

Results

The patient underwent different examinations to deepen the suspect of neurodegenerative disease:

- Neuropsychological assessment: MMSE and MoCA scores were 24/30 and 12/30 respectively; deficits involved executive, visuospatial, praxis and mnemonic functions.
- Brain MRI: in both FLAIR and SWI sequences demonstrated bilateral hypo-intensity in basal ganglia (caudate and lenticular nuclei) and cerebellar dentate nuclei (figure 1).
- Brain 18FDG-PET: showed asymmetric uptake in putamen's region without evident pathological hypometabolism (figure 1).
- Lumbar puncture: CSF levels of t-tau (879,0pg/mL), p-tau 181 (112,4pg/mL) and NfL (3445,0pg/mL) were increased. CSF levels of Aβ and the Aβ 42/40 ratio were normal instead, in contrast with the diagnosis of Alzheimer's disease.

Additionally, other examinations were performed:

- Liver ultrasound revealed mild hepatic steatosis with preserved liver enzymes levels.
- Blood tests showed increased ferritin (1460 mcg/L), reduced serum iron (33 mcg/dL) and low transferrin saturation (13%). Ceruloplasmin and copper were both undetectable.
- Thorax-abdomen MRI showed myocardial and hepatic iron accumulation.
- Ophthalmological evaluation excluded signs of retinopathy.
- Genetic analysis ruled out the differential diagnosis of hereditary hemochromatosis since it was negative for the presence of mutations of genes HFE, TFR2, SLC40A1. A homozygous mutation in the CP gene was identified: an in-frame deletion/insertion, c.330_338del p.(Lys110_Ala113delinsAsn).

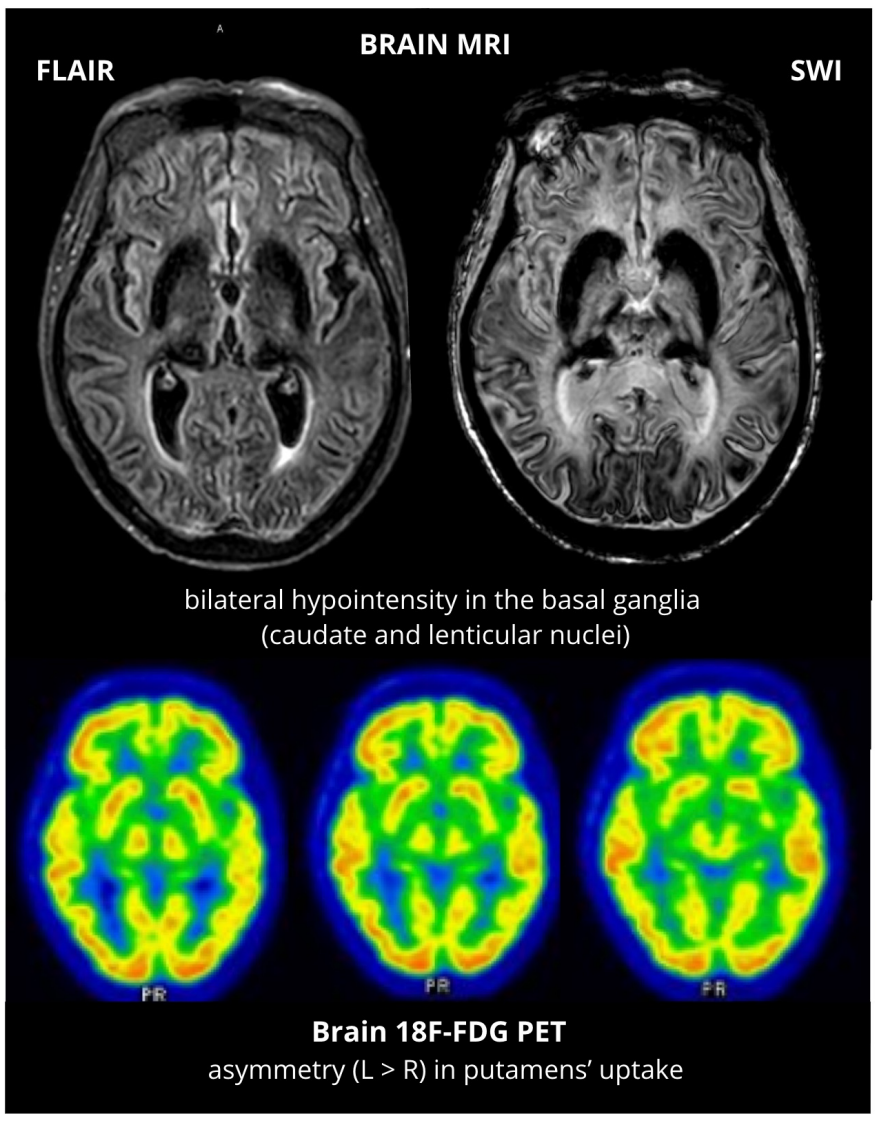

Figure 1. Brain MRI and brain 18F-FDG PET findings.

Discussion

Clinical presentation, neuroimaging and biochemical findings are strongly suggestive of aceruloplasminemia, a neurodegeneration with brain iron accumulation (NBIA). Differential diagnosis such as Wilson's Disease were deemed unlikely due to the MRI pattern [4]. Current treatment consists in the use of iron-chelating agent (for example, deferasirox).

This clinical case highlights how cognitive impairment and parkinsonism warrant a thorough workup to uncover rare but potentially treatable causes for patients and their offspring.

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