ACERULOPLASMINEMIA PRESENTING AS NEUROPSYCHIATRIC SYNDROME: A RARE NBIA VARIANT

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PRESENTATION

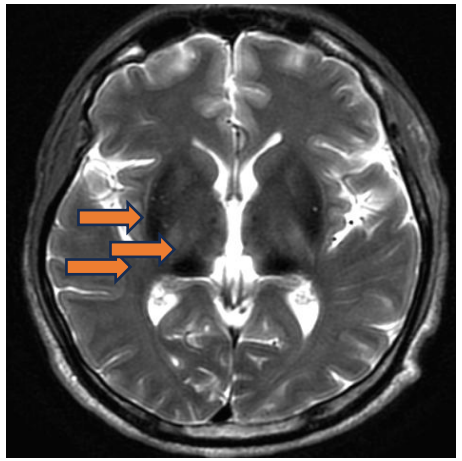
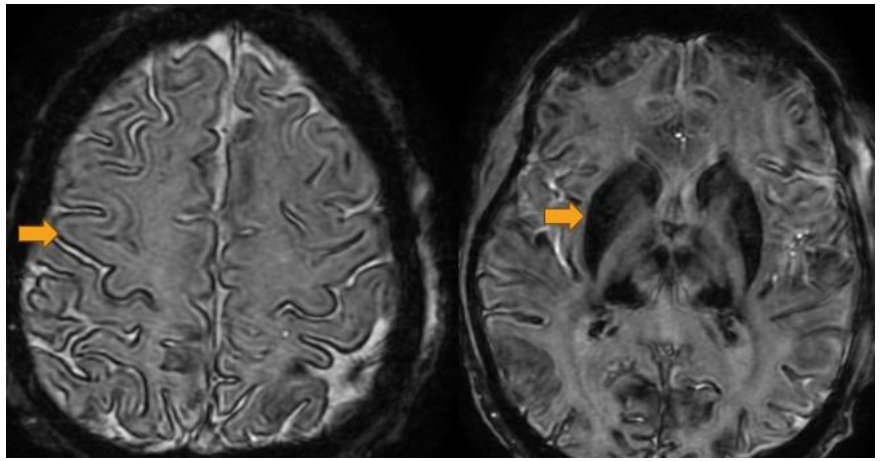
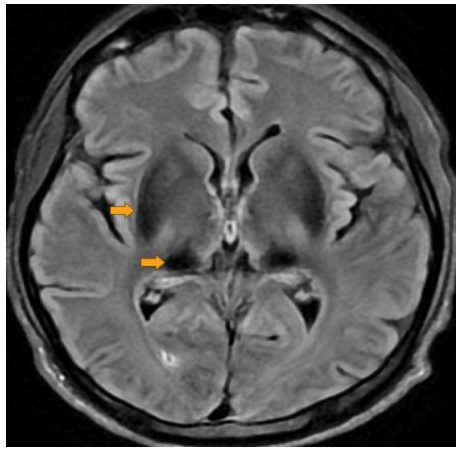
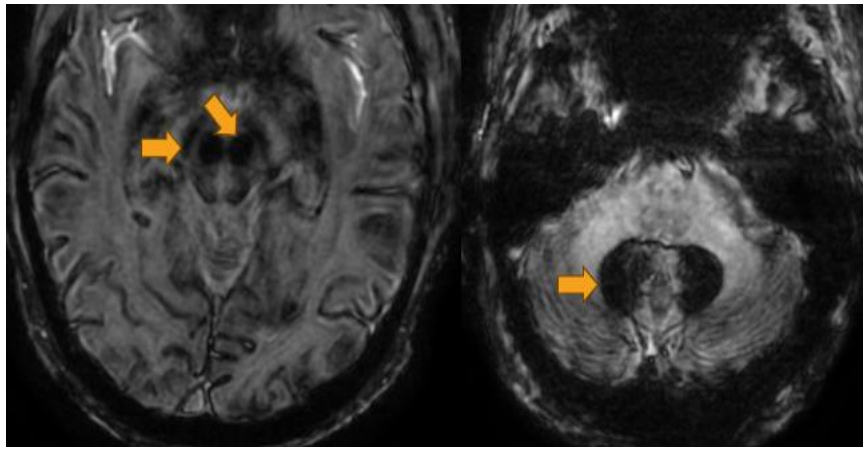
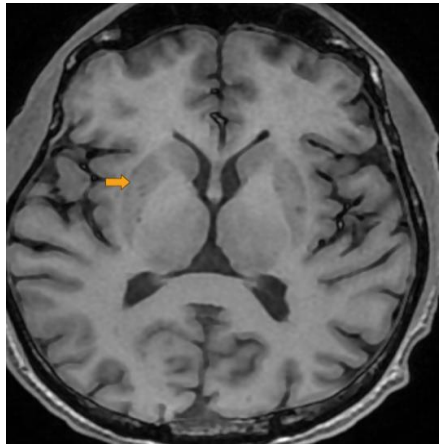
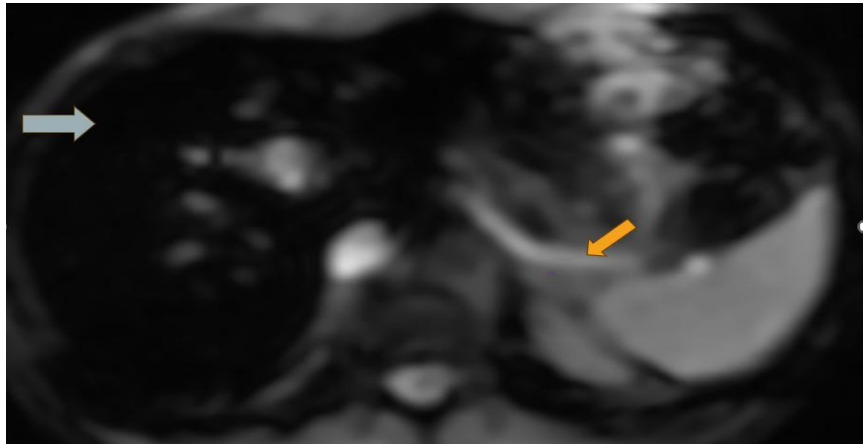
- 50-year-old man with **young-onset type 2 diabetes (diagnosed at 38 yrs)**, insulin-dependent with recurrent hypoglycemia-hyperglycaemia.
- **Behavioral changes** (since 5 yrs): aggression, irritability, reckless spending, grandiose ideas.
- **Cognitive decline** (since 4 yrs): forgetfulness, misplacing objects, difficulty with transactions, poor concentration, repetitive questioning.
- Presented to ER with hypoglycaemia.
- Previous medications: Insulin and OHAs

EXAMINATION

- ACE-3 score showed mild memory impairement.
- FAB-14/18 (conflicting instructions and inhibitory control)
- No KF Ring was noted.
- EPS: mild cervical dystonia (laterocollis-left) on examination.
- No Other clinical signs noted.

COURSE IN HOSPITAL

- Cognitive Impairement, psychiatric disturbances with dystonia lead to evaluation of organic etiology.
- Routine evlaution showed microcytic hypochromic anaemia with low iron stores and elevated Ferretin.
- MRI brain that revealed extensive iron deposition in the cerebral cortex, cerebellar cortex, basal ganglia, thalamus and dentate nucleus .
- Hence, NBIA was suspected. Ceruloplasmin levels were undetectable with high ferretin levels. MRI abdomen showed extensive iron deposition in liver with pancreatic atrophy.
- Diagnosis of Aceruloplasminaemia was done, genetics were sent. Whole exome sequencing identified two likely pathogenic compound heterozygous variants in the *CP* gene: a frameshift variant (c.2274del; p.Leu758PhefsTer11) and a splice-site variant (c.1349-1G>T), confirming aceruloplasminemia.
- Patient was started on Deferasirox and patient was followed up.
- Serial follow up at 3 and 6 months showed significant improvement in neuropsychiatric symptoms, paving the way for tapering of anti-psychotic medications.

MRI

MRI Brain: Diffuse mineralization in cortex, basal nuclei, substantia nigra, red nuclei, dentate nuclei.

MR Abdomen: Liver shows T2 hypointense and T1 Hyperintense- s/o haemochromatosis
Pancreas shows diffuse fatty atrophy

NBIA

- **Ceruloplasmin: Protein**: Single-chain glycoprotein (1,046 amino acids), binds up to **six copper atoms**. **Gene associated**: CP gene on **chromosome 3q24–q25**; inheritance is **autosomal recessive**[1]. **Function**: Major plasma copper-carrying protein (~95% of circulating copper). Acts as a **ferroxidase**: converts Fe^{2+} → Fe^{3+}, enabling binding to transferrin. Facilitates systemic iron export from liver, astrocytes, pancreas, and retinal cells. **Deficiency of ceruloplasmin** leads to Loss of ferroxidase activity → **intracellular iron accumulation** with paradoxical **low serum iron + high ferritin** → ineffective erythropoiesis[2].
- **Aceruloplasminemia has Systemic triad (classically described)[1] :**
  - Neurological manifestations (60–70%) → movement disorders (ataxia, dystonia, parkinsonism, chorea), psychiatric symptoms, cognitive impairment.
  - Retinal degeneration (~75%).
  - Diabetes mellitus (~70%), usually pancreatic in origin.
  - **Other common features: Microcytic hypochromic anemia** (≈80%) despite iron overload. Systemic iron deposition in **liver, pancreas**, occasionally myocardium.
- **Neuroimaging[3]:**
  MRI shows **widespread brain iron deposition**: cerebral & cerebellar cortex, basal ganglia, thalamus, substantia nigra, dentate nucleus.
- **Natural history:**
  Males often present with diabetes in late 30s; neuropsychiatric symptoms appear after 50 yrs.
  Progressive, multisystem disorder; early recognition critical for management.
- **Management:** Mainstay – **Iron chelation therapy with supportive measures**. Deferiprone (preferred for brain iron) ± other chelators (deferasirox/desferrioxamine) — oral deferiprone crosses BBB and is used to mobilize cerebral iron; deferasirox/desferrioxamine remove visceral iron better; **combination strategies (chelator ± phlebotomy or dual-chelation)** are used case-by-case with strict hematologic/biochemical monitoring. Recombinant ceruloplasmin/enzyme-replacement and gene therapy are experimental but promising. Recurrent FFP transfusion have been attempted in early disease for ceruloplasmin replacement, but has short half with significant logistic issues for long term therapy.

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