Down the Wrong Rabbit Hole: Unraveling Alzheimer's Disease when Encephalopathy is Suspected

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Background

- Alzheimer's disease (AD) is the most common cause of dementia worldwide.
- Progressive cognitive decline with memory impairment is the most common initial symptom of AD.
- Hashimoto's encephalopathy (HE) is an autoimmune disorder that presents with altered mental status, hallucinations, and seizures.
- HE is often associated with elevated anti-thyroid antibodies and usually responsive to glucocorticoid therapy.
- Although these diagnoses seem easily distinguishable, we present a case of AD that was initially diagnosed and treated as HE, operating on the assumption of rapid memory decline.

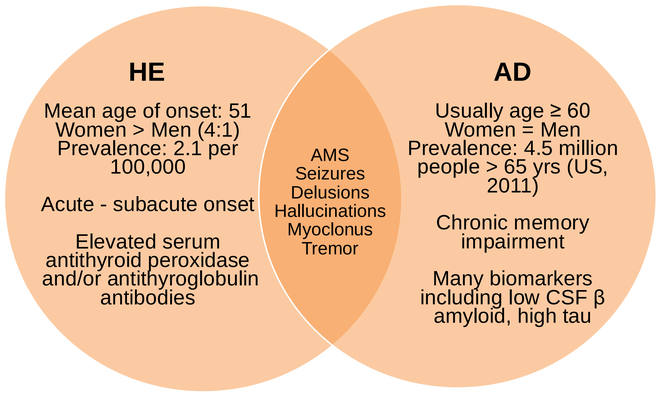

Figure 1. While HE and AD have clinically significant differences in presentation, there is symptomatic overlap that may challenge accurate diagnosis.

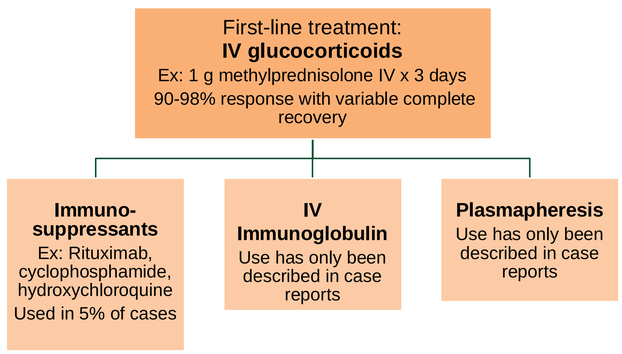

Figure 2. Because HE is uncommon, treatment is not fully understood. Although most patients respond to glucocorticoids, a small number require second-line treatment options.

A 75-year-old Caucasian female with hypothyroidism, HTN, and HLD initially presented to clinic with a history of rapid cognitive decline.

5 years*

- *Historical records were obtained after initial diagnostic workup.
- Patient's daughter describes concerns regarding her mother pertaining to memory, concentration, and cognitive deficits for about 5 years
- Rapid decline + long-term memory concerns suggest an **acute-on-chronic clinical picture** with multiple conditions.

2 years

- Patient presented to the ED with **sudden-onset expressive aphasia and altered mental status**. Patient was given IV tPA.
- CT brain without contrast, CT perfusion study, and CTA neck were unremarkable. TIA or stroke unlikely.
- MRI brain without contrast showed mild ischemic leukomalacia in the cerebral white matter, most notably in the posterior right parietal lobe.
- Aphasia resolved spontaneously in 24 hours.
- Patient experienced a few episodes of altered mental status without recollection.

1 year

- Patient subsequently experienced **rapid cognitive decline** and increasing difficulty in managing independent activities of daily life.
- Upon evaluation by neurology, **MoCA (24/30) showed deficits** in delayed recall and executive function.
- Patient had **a positive β-amyloid 42/40 ratio** and slightly elevated T-tau.
- Brain MRI demonstrated **hippocampal atrophy**.
- Family history revealed a brother with REM sleep behavior disorder.
- Neuropsychological testing was significant for impaired performance on tasks of working memory, verbal learning, and most executive type tasks.
- Patient was given a diagnosis of mild cognitive impairment and started on donepezil 5 mg PO daily.
- Patient's confusion continued to worsen significantly.

6 months

- Patient was hospitalized for seizure-like activity with **left facial twitching** that progressed to **left arm jerking**.
- She was given lorazepam 1 mg IV and started on levetiracetam 500 mg PO BID and lacosamide 50 mg PO BID.
- EEG showed showed lateralizing period discharges on the right, but no seizures.
- **Brain MRI was negative** for acute changes.
- CSF analysis, viral studies, and paraneoplastic and inflammatory markers were within normal limits.

5 months

- After discharge, **thyroglobulin antibodies** were found to be elevated to 34.1. Patient was given **a diagnosis of HE**.
- She received 5 days of inpatient **solumedrol 1 g IV without improvement**.
- Repeat brain MRI showed mildly increased T2 signal in the hippocampus.
- She was started on **5 days of IV immunoglobulin** (IVIG) 2g/kg with **mild improvement**.
- **Repeat MoCA declined** to 19/30. She began receiving home cognitive therapy services.
- Levetiracetam was discontinued, lacosamide was increased to 100 mg BID for seizures,

2 months

- Quetiapine 12.5 mg PO QHS, mycophenolate 250 mg QD started for agitation and sleep.
- Patient was readmitted due to **acute mental status changes** associated with headache, nausea, and left arm shaking.
- Repeat MRI (Figure 3) showed juxtacortical FLAIR hyperintensities (R>L) and asymmetry of hippocampi.
- She exhibited **signs of psychosis** including visual (resolved in 3 days) and auditory hallucinations (resolved in 2 weeks). Due to delusions, euphoria, pressured speech, and restlessness, she was started on haloperidol 1 mg BID.
- Patient received **IVIG** for HE with **more significant improvement.**

Patient's HE is now well-managed with IVIG and Rituximab 500 mg IV. Continuing cognitive defects with behavioral disturbances is likely AD, managed with donepezil 10 mg QHS.

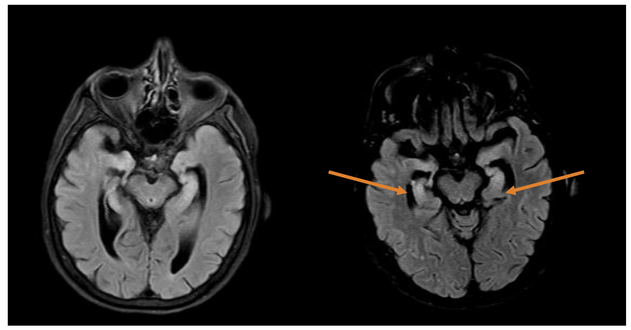

Figure 3. Brain MRI without contrast demonstrated persistent bilaterally hippocampal FLAIR hyperintensity (orange arrows) with worsening atrophy of the medial temporal lobes.

Discussion & Conclusions

- This case reflects a rare subset of HE that is non-responsive to IV glucocorticoids. The patient's response to IVIG is one of few documented cases of this treatment's success in HE after first-line treatment failure.
- Although this patient's acute cognitive decline was consistent with HE, her chronic clinical profile aligns more closely with AD based on the onset and progression of cognitive decline, along with the results of cognitive testing, brain MRI, and positive AD blood biomarkers.
- While AD remains a primary consideration in older adults presenting with insidiously-onset, progressive memory decline, AD must also be considered in patients with seemingly unusual presentations of cognitive impairment.
- Although clinicians often seek unifying diagnoses, the presence of multiple concurrent conditions should also remain a consideration.
- It is crucial to conduct a comprehensive clinical assessment and elicit a clear timeline to rule in and rule out other potential conditions.
- Providers must consider the differential diagnosis carefully to ensure accurate diagnosis and management of patients presenting with cognitive decline.

References & Disclosures

- Please scan the QR code for a complete list of references.
- The authors have no conflicts of interest to disclose.