

Case Report: Early onset Alzheimer's disease with a strong family history of dementia found to have a PSEN1 c.836A>T (p.Asn279Ile) variant



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BACKGROUND

Early onset Alzheimer's disease (AD) is significantly more likely to be caused by a single gene mutation. Increased genetic testing for possible autosomal dominant causes of early onset AD is leading to increased identification of potential pathogenic mutations.

CASE HISTORY

Brief HPI: A 48-year-old woman was seen in the Memory Disorders Clinic reporting approximately 18 months of initially mild word finding difficulty with progression to dementia. Cognitive symptoms included using less specific or portions of words and having frequent circumlocutions. She was admitted from clinic for an expedited rapidly progressive dementia work-up

Medical history:

- Past Medical/Surgical: asthma, migraine, cesarean x4
- Social: No tobacco, alcohol, or illicit drug use

Educational/baseline functional history:

- College Degree in Elementary Education

Positive Neurological Exam Findings:

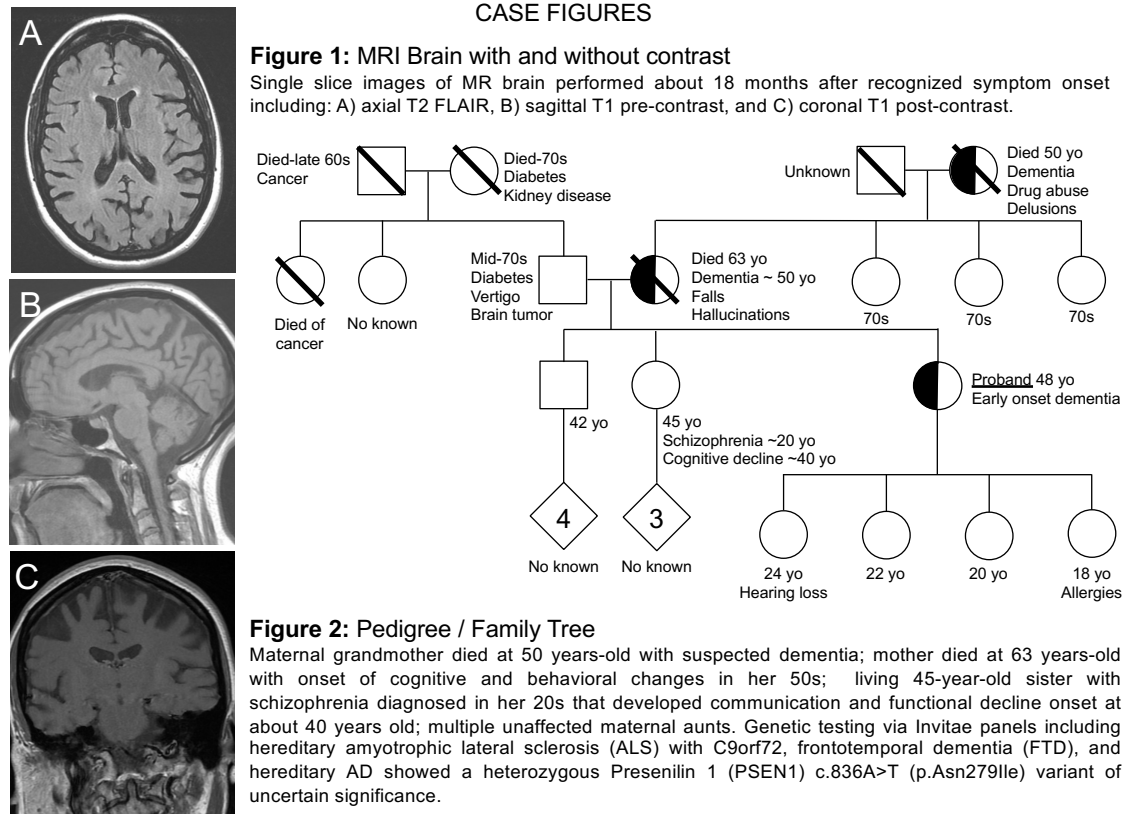
- Paratonia in L > R
- Slight parietal lobe list in the LUE
- No asymmetric cortical sensory deficit
- Fine and high frequency tremor BUE

Neurobehavioral Assessment:

- Orientation: Alert and oriented to person, place, and situation.
- Memory: Generally intact to recent and remote events (confirmed via collateral), but missing details and exact dates.
- Attention: Not distracted, attentive throughout visit.
- Language: Slowed spontaneous speech with circumlocutions, word-finding difficulty, frequent paraphasic errors (ex: "hunder" for "under"), and restricted phonemic loop with repetition; BNT 13/15.
- Executive/Planning: Difficulty with overlapping pentagons.
- Visuospatial: Overlapping and Navon figures intact.

Work-up:

- Blood labs unrevealing (TSH/T4, TG/TPO, vitamin B12, HIV, Treponema antibodies, ceruloplasmin, copper, heavy metals, ESR/CRP, serum Mayo AIE panel, ANA, RF, ANCA)
- MRI brain with/without contrast (Figure 1)
- EEG with continuous, symmetric, and composed of a well-organized mixture of beta and alpha frequencies in a normal anterior to posterior gradient
- Lumbar Puncture
 - 2 RBC, <3 WBC, 60 G, 30 TP, 0 OCBs
 - CSF Mayo AIE and Cytokine 13 panels negative
 - 14-3-3 4194 AU/mL (range <30-1999)
 - ADEVL CSF Abeta42 467 pg/mL (range >834)
 - ADEVL CSF p-tau181 22.5 pg/mL (range <=21.6)
 - ADEVL CSF total tau 183 pg/mL (range <=238)
- Genetic counseling and family history (Figure 2)
- Genetic testing performed with Invitae panels
 - Presenilin 1 (PSEN1) c.836A>T (p.Asn279Ile) variant



DISCUSSION / CONCLUSION

The PSEN1 c.836A>T (p.Asn279Ile) variant has not previously been reported as pathogenic. Given multiple generations of family members with reported cognitive decline and dementia, there is high suspicion that the PSEN1 c.836A>T (p.Asn279Ile) variant may be a pathogenic mutation for dominantly inherited AD. The resulting amino acid alteration is within the transmembrane domain 5 portion of the PSEN1 protein (1), which may impact gamma-secretase catalytic activity among other possible functions (2). Additional testing of other potentially affected and unaffected family members is needed, however has been difficult to coordinate in the setting of multiple social challenges (3).

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