CADASIL with Cysteine-Sparing Notch-3 Mutation

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ABSTRACT: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an inherited vascular dementia. The mutations implicated in CADASIL are located on Chromosome 19 within the NOTCH3 gene, which encodes a transmembrane receptor that is primarily expressed in vascular smooth muscle cells. Over one hundred distinct mutations have been described which alter the number of cysteine residues in the extracellular region and result in a CADASIL phenotype. Cysteine-sparing mutations with CADASIL phenotype have been reported in two families. The patient is a 55-year-old Caucasian woman with five years of progressive cognitive impairment, chronic headaches, and gait instability. Prior to presenting at our clinic, she had been diagnosed with Alzheimer disease. Her neuropsychological testing (Table One) and MRI studies (Figure One), however, were more consistent with a subcortical vascular dementia. Her genetic CADASIL screen was “negative” although a missense mutation in NOTCH3 was identified. At the time of that test, no cysteine-sparing mutations causing CADASIL had been reported. Workup of other family members is ongoing. Elucidation of this case will provide corroboration of a cysteine-sparing CADASIL mutation, and will inform the discussion of whether this represents a distinct entity or a CADASIL subtype. With the field of neurogenetics rapidly evolving, interpretation of standard genetic tests may need to include literature review to ascertain the correct diagnosis.

CASE DESCRIPTION: A 55-year-old right handed divorced HS graduate, retired nursing assistant, presented with 5-year history of progressive cognitive decline characterized by inability to complete familiar work routines, falling behind in financial obligations, and loss of memory for extensive Shakespearean monologues from her theatrical background. Attention to ADLs had declined and she had fallen behind on housework. In contrast to her premorbid personality, she developed a “short fuse” and became prone to sudden angry outbursts. She also had fallen several times.

Medical History
• Longstanding migraines, worsening to chronic daily headache in the past two years
• Hypertension, easily controlled on lisinopril 10mg/day
• Subclavian venous thrombosis of unknown etiology
• Depression treated intermittently in the past 20 years, recently started on sertraline
• Glaucoma

Family History
• Mother (79 yo): Migraine, personality change, dementia, confined to nursing home
• Daughter (31 yo): Migraine, seizures, short-term memory loss, word-finding difficulties, depression.

Neurological Examination
• Mild right-sided pronator drift
• Bilateral paresthesia & biceps hyperreflexia
• Mildly positive Romberg

Medications
Sertraline 50 mg/day  Fexofenadine 60 mg BID
Lisinopril 10 mg/day  Tramadol 50 mg TID (back pain)
Donepezil 10 mg/day  Tizanidine 4 mg TID (back pain)

DIAGNOSTIC STUDIES
• Cerebral Angiography: 1.7 mm berry aneurysm left MCA at origin of anterior temporal, 1.5 mm berry aneurysm right posterior communicating artery origin
• Laboratory investigations for coagulopathies, leukodystrophies, vasculitides, demyelinating diseases, other causes of vascular dementia unrevealing
• Genetic testing for CADASIL “negative,” but with missense mutation in Notch3 (A1020P)

COGNITIVE STATUS
Attention
Diget Span = 5 F/ 4 B
Serial 7’s: 100 → 79 [could not proceed]
Auditory Vigilance: 2/35 errors of omission
Trails B: slow
Recall
5 objects: 1 trial to register; 2/5 spontaneous recall at 5 min; 3/5 with category cue, 5/5 from list
Needed daughter’s assistance to relate history in sequence
Language
Running speech WNL
Naming, repetition, auditory comprehension, oral reading intact
Verbal fluency: 25 “T”words in 1 minute
Praxis
Axial, gestural, tool-use praxis intact
Visual-Spatial
Clock Drawing: Self-corrected hand placement
Copy of cube: intact
Frontal-Executive
Go/no-go: 3/12 errors of commission
Luria 3-step: required verbal cues
Proverbs & similarities: WNL

CONCLUSION
Our case appears similar in both phenotype and mutation to that of 2 recently reported German kindreds.

The similarity of this case to the CADASIL phenotype (Table Two) argues that various NOTCH 3 mutations, even if cysteine-sparing, can result in the abnormal protein folding suspected in this syndrome.

REFERENCES

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