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# 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<sup>1,2</sup>. 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 four times. Two German kindreds were recently described with a CADASIL-like phenotype associated with a cysteine-sparing NOTCH3 mutation. We present another such case in a third family, with the same point mutation described in the German 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 patellar & biceps hyperreflexia
- Mildly positive Romberg

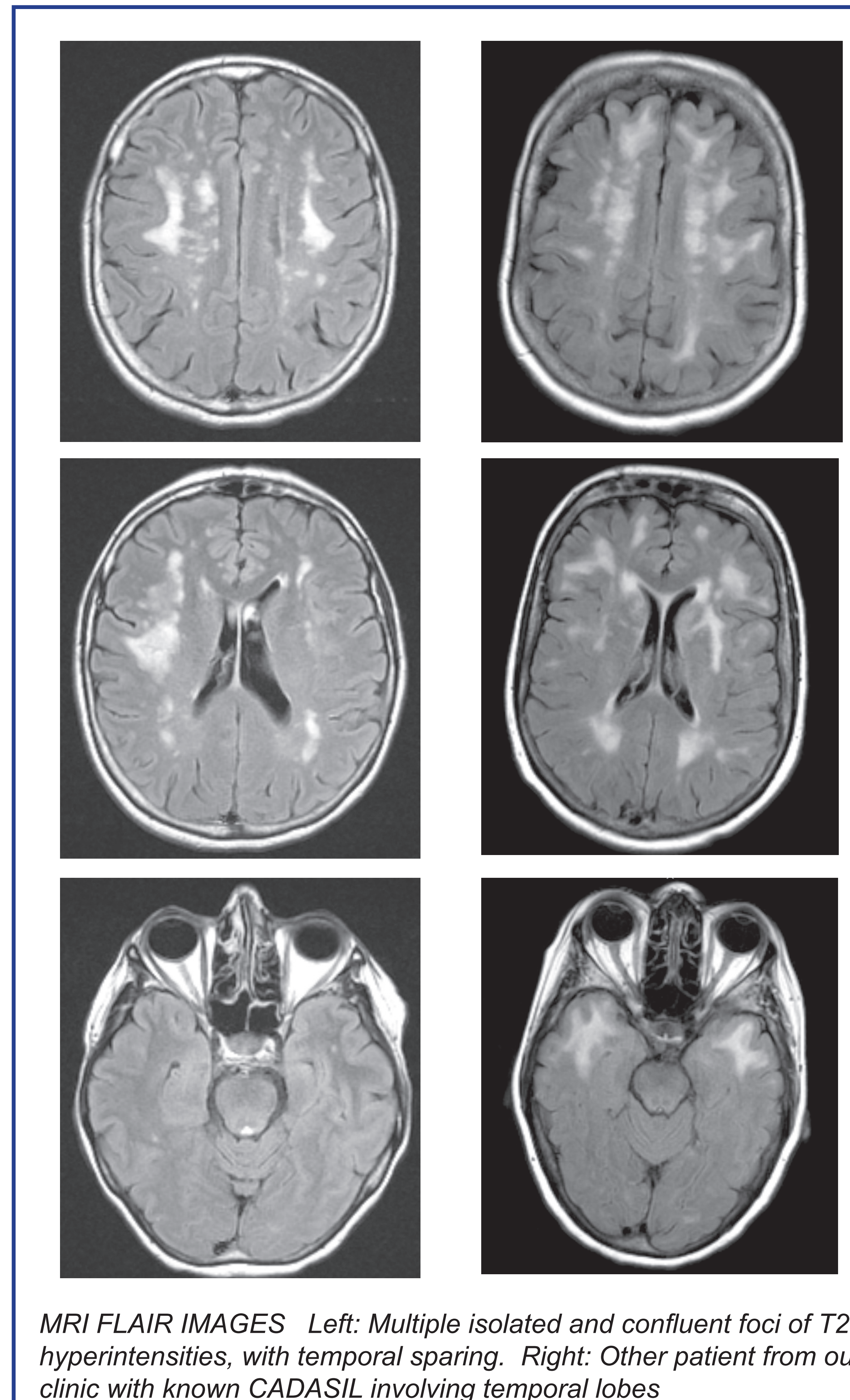
#### Medications

- |                      |                                 |
|----------------------|---------------------------------|
| 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)

**FIGURE ONE: MRI OF PATIENT vs KNOWN CADASIL**



#### COGNITIVE STATUS

##### Attention

Digit 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 “f” 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

**TABLE ONE: NEUROPSYCHOLOGICAL FINDINGS**

WAIS III VIQ 118	PIQ 111	FSIQ 116
IMPAIRMENTS:		
Complex figure copy, immediate & delayed recall	WCS learning efficiency	
Controlled oral word association	Trails B	
Animal naming	D-KEFS concept formation verbal response	

**TABLE TWO: COMMON FEATURES OF CADASIL<sup>1</sup>**

71% Recurrent ischemic episodes (TIA, Stroke)	28% Dementia (90% gait disturbance; 86% urinary incontinence; 52% pseudobulbar palsy)
48% Cognitive deficits	
38% Migraine (87% with aura)	10% Seizures
30% Psychiatric disturbance	

#### DISCUSSION:

Review of this patient's history and symptoms revealed a presentation inconsistent with her previous diagnosis of Alzheimer Disease. Likewise, her hypertension was not severe or prolonged enough to be a likely cause of her symptoms, or the striking imaging findings (Figure One). Although the relative sparing of the temporal lobes is not typical for CADASIL, we investigated this possibility further, given her Notch3 mutation. Review of the literature revealed a recent case report of similar presentation and an identical mutation in two German kindreds<sup>3</sup>. This mutation had previously been reported as a known allele without clinical significance.

The postulated CADASIL mechanism is alteration of Notch3 receptor function in vascular smooth muscle. The molecular mechanism has been thought to depend on gain or loss of a cysteine residue, which disrupts folding in the extracellular portion of the protein<sup>1,2</sup>. In this case, however, the number of cysteine residues is conserved, with substitution of a proline for an alanine (A1020P). Proline may have a cysteine-like role in protein folding, causing a CADASIL-like phenotype<sup>3</sup>. As in the previous case report, this patient's MRI showed relative sparing of the temporal lobes, compared to that of a “typical” CADASIL patient (Figure Two). Although the details are not yet understood, different CADASIL genotypes may result in different phenotypes. If the current case can be considered a CADASIL variant, it would lend support to this hypothesis.

#### CONCLUSION

**Our case appears similar in both phenotype and mutation to that of 2 recently reported German kindreds<sup>3</sup>.**

**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.**

**Standard gene testing may need to be supplemented by review of recent literature to ascertain correct diagnoses.**

#### REFERENCES

1. Dichgans M et al, The phenotypic spectrum of CADASIL: Clinical findings in 102 cases, Ann Neurol 44 (1998) 731-739.
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