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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. 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-sparring mutations with CADASIL phenotype have been reported four times. Two German kindreds were recently described with a CADASIL-like phenotype associated with a cysteine-sparring 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-sparring 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 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-sparring 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.

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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. 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. 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. 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.

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


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