CADASIL
Do the Clinical and MRI Profiles Differ for Women and Men?

Philip B. Gorelick, MD, MPH, FACP

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In 1977, Sourander and Walinder1 described a family with neuropsychiatric disease, a relapsing course, and cognitive impairment. The disorder began in early adulthood, affected women and men, and lasted for 10 to 15 years. At brain necropsy, there were multiple small infarcts, particularly of the basal ganglia, thalamus, periventricular white matter, and pons. Vascular changes were prominent in small muscular arteries and in arterioles of the pia-arachnoid, basal ganglia, thalamus, mesencephalon, pons, and cerebellum and in small vessels of the cerebral and cerebellar white matter. The disorder was thought to be genetically transmitted by an autosomal-dominant mechanism and was called hereditary multi-infarct dementia. In 1993, the monogenic disorder, cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), was mapped to chromosome 19q12 by Tournier-Lasserve et al.2

Now, CADASIL is recognized as the most common hereditary cause of vascular cognitive impairment and may present clinically as migraine with aura, mood disturbance, recurrent strokes, cognitive impairment, and MRI-based extensive white matter lesions, lacunar infarcts, cerebral microbleeds, and brain atrophy.3–5 Most cases are caused by missense mutations of the Notch3 gene that create or eliminate cysteine residues.6 Characteristic ultrastructural changes in skin and muscle vessels include granular osmophilic material in the arteriolar media.

During the past several decades, our understanding of CADASIL has advanced. In relation to clinical manifestations, it has been suggested that: cardiovascular risk factors (eg, hypertension, smoking) may modulate clinical expression of CADASIL;7 migraine with atypical aura may be a distinguishing feature of the disorder;8 and, overall burden of lacunar infarcts may importantly impact on the occurrence of cognitive impairment and disability, whereas white matter lesions may not be predictive of these domains.9,10 In relation to structural brain changes elucidated by neuroimaging studies: diffusion tensor imaging may define microstructural tissue alterations in asymptomatic and symptomatic brain areas affected by CADASIL.11,12; brain parenchymal fraction may be predicted by volume of lacunar lesions and increase in mean cerebral apparent diffusion coefficient13; however, individual lacunar volume may not be related to other CADASIL neuroimaging lesions or vascular risk factors14; and there may be segmentation of lacunar infarcts.15 When neuropathological examination is taken into account, neuronal apoptosis may be associated with the burden of subcortical ischemic lesions.16 Furthermore, fibrotic thickening of arteriolar walls that supply the lenticular nucleus may occur without stenosis of the vessel lumen and differs from that of stenotic vessels supplying the white matter. Therefore, stenosis of vessels supplying the white matter and hemodynamic factors may be the basis of white matter lesions and lacunar infarcts, respectively.17 Finally, the following physiological parameters may be abnormal: endothelial-dependent vasodilation in resistance arteries and vasoconstrictor responses18,19; heart rate variability20; systemic blood pressure profile (lower than expected)21; and cerebrovascular CO2 reactivity.22

A recently published guidance statement recommends genetic testing for CADASIL as being reasonable in patients with progressive cognitive impairment, appropriate imaging findings, and a family history suggestive of autosomal-dominant inheritance (class IIa and level of evidence A), and it may be considered in sporadic patients with suggestive clinical and imaging findings (class IIb and level of evidence B).3 In this issue of Stroke, Gunda et al23 advance our knowledge of CADASIL by providing a comparison of clinical and neuroimaging features in women and men.

Methods

Study Design

The authors report the findings of a cross-sectional study of 313 CADASIL patients from Paris and Munich having a typical Notch3 gene mutation.23 All subjects had a detailed neurological history and examination, and MRI head study according to a systematic protocol for image processing and analysis.24 Key MRI variables of interest were global brain volume and volume of white matter hyperintensities and lacunar infarcts. Clinical characteristics, cognitive scores, and MRI parameters were then compared between women (n=172) and men (n=141).

Results

With the exception of alcohol consumption, which was more frequent among men (79.1% versus 49.7%; P<0.001), the frequency of the remainder of the demographic and cardiovascular risk factors was comparable between women and men.23 Migraine with aura was more common among women (44.2% versus 31.2%; P=0.02), whereas stroke (74.5%
versus 57.6%; \( P=0.003 \)) and apathy (57.1% versus 26.1%; \( P=0.0001 \)) were more common among men. When analyzed by age strata, the findings were statistically significant for migraine with aura (women more than men) and stroke events (men more than women), respectively, in patients younger than 51 years, and the frequency of apathy (men more than women) was significant in those younger and older than age 51 years. Other variables that did not differ between the 2 groups included frequency of dementia, psychiatric symptoms, seizures, gait and balance disturbances, hearing loss, and urinary incontinence.

There were distinctive differences in the frequencies of migraine with aura between the 2 groups.\(^23\) Migraine with aura began at an earlier age in women (younger than 30 years in most migraine patients; 63.2% versus 34.1%; \( P=0.008 \)), and women more commonly experienced visual (94.7% versus 79.6%; \( P=0.01 \)) and aphasic (71.1% versus 52.3%; \( P=0.04 \)) migraine auras. Other aura or related features such as sensory and motor auras, frequency of migraine events, duration of aura and of headache, and the presence of triggering factors did not differ between the 2 groups.

In relation to clinical scores, men had higher modified Rankin Scale scores (1.24 versus 0.91; \( P=0.02 \)) and National Institutes of Health Stroke Scale scores (1.70 versus 0.82; \( P=0.002 \)) and lower Mattis Initiation scores (31.9 versus 33.4; \( P=0.04 \)).\(^\text{23} \) There were no statistically significant differences on the Mini-Mental State examination or Mattis Dementia Rating Scale. Changes in the modified Rankin Scale score, National Institutes of Health Stroke Scale score, and Mattis Initiation test were significantly worse for men older than age 51 years but not for those younger than age 51 years.

Finally, mean brain parenchymal fraction was consistent with more atrophy among men (83.6 versus 86.7; \( P<0.0001 \)), a finding independent of age strata, and the volume of lacunar infarcts was 50% larger in men, but this finding did not reach statistical significance (\( P=0.08 \)).\(^\text{23} \) Volume of white matter hyperintensities and number of cerebral microbleeds did not differ by group.

### Interpretation of Study Results

The findings of this study suggest that women and men with CADASIL may have different clinical profiles and MRI features. Specifically, women with CADASIL may more frequently have migraine with aura and less frequently have stroke before the usual age of menopause, with the difference vanishing after the fifth decade of life, whereas men may more frequently have apathy, a higher degree of cerebral atrophy, and a larger volume of subcortical infarcts (borderline statistical significance). In addition, after the age of 51 years, men with CADASIL may have more executive dysfunction, disability, neurological impairment, and brain atrophy.

The main findings\(^2\)\(^2\)\(^3\) are plausible because previous studies have suggested that the burden of lacunar infarcts may be an important predictor of cognitive impairment and disability,\(^9\),\(^10\) and brain atrophy, a predictor of cognitive impairment, may be predicted by volume of lacunar lesions.\(^13\) The presence and volume of lacunar infarcts, therefore, seem to be important in relation to outcome in CADASIL. Furthermore, the Notch3 gene mutation may enhance spreading depression susceptibility, implicating the neurovascular unit in the development of migraine with aura.\(^25\)

How, then, might the phenotypic differences for women and men with CADASIL be explained? Sex hormones could play a key role.\(^26\) Gunda et al\(^2\)\(^2\)\(^3\) argue that migraine with aura may be associated with high levels of circulating estrogen, and ovarian hormones may increase cortical excitability that promotes spreading depression responsible for symptoms of aura. Furthermore, the less frequent occurrence of stroke in women might be explained by the beneficial effects of estrogens, such as increase in cerebral blood flow and vasoreactivity, and anti-inflammatory, antioxidant, and antiapoptotic effects.\(^26\) A more favorable hemodynamic environment and the other aforementioned factors, therefore, are hypothesized to protect women with CADASIL from lacunar infarcts.

As the authors point out, the study has certain limitations, including a relatively small sample size, lack of validation of menopausal status, possible recall bias in relation to certain key study variables, general pitfalls of a cross-sectional study design, and lack of data on specific hormonal evaluation.\(^2\)\(^3\) Although there are potential study limitations, the research provides important knowledge about the clinical and MRI profile of CADASIL in women and men and insights into possible hormonal explanations of this disorder. The authors wisely caution against extrapolation of the study findings to administration of hormonal replacement therapy in CADASIL patients based on previous failed trials of hormonal replacement therapy in women.

Gunda et al\(^2\)\(^3\) are to be congratulated for clarifying potential differences in the clinical and MRI profiles of women and men with CADASIL. Persons with CADASIL, their family members, and health care professionals who diagnose and treat CADASIL are in substantial need of new information and explanations about the disorder as a prelude to prevention and treatment.\(^2\)\(^8\) Continued exploration of hemodynamic alterations associated with CADASIL\(^1\)\(^7\)\(^\text{–}\)\(^2\)\(^2\) is desirable because it could lead to development of, at least, a short-term treatment to possibly prevent lacunar infarcts or other CADASIL-associated brain damage. Some practitioners routinely treat CADASIL patients with a calcium channel-blocking agent or other blood pressure-lowering medication with vessel wall-protective properties. It is not clear, however, if the latter strategy to protect the vessel wall is an effective practice in light of possible blood pressure-lowering effects when taking into account the hemodynamic hypothesis of lacunar infarct generation in CADASIL patients. Finally, it is tempting to consider whether hormonal therapy administered at an opportune time might be administered to prevent the occurrence of lacunar infarcts in women with CADASIL.

### Disclosures

None.

### References


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