



Severity grading of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy

James F. Meschia

Department of Neurology, Mayo Clinic, Jacksonville, Florida, United States

To the Editors

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an inherited small-vessel disease caused by various mutations in the *NOTCH3* gene, typically resulting in an unpaired cysteine [1]. Pathologically, patients develop granular osmiophilic deposits in small blood vessels. Patients often present with migraines, later developing lacunar strokes, vascular cognitive impairment, and dementia. The phenotypic expression of the disease is highly variable, and depends in part on the precise nature of the *NOTCH3* gene mutation [2].

However, as with other inherited disorders [3], knowledge of the genetic mutation alone is insufficient to characterise CADASIL patients. The presence of vascular risk factors such as hypertension and tobacco smoking strongly influences phenotypic expression [4]. Current pharmacotherapy is limited to non-disease modifying drugs for treating migraine and cognitive symptoms.

As better understanding of the pathophysiology of the disease accrues and gene therapy technology evolves, consideration is being given to future disease-modifying trials [5]. However, one obstacle to developing therapies for CADASIL is

its rarity. Powering randomised trials poses a challenge, even when the intervention has a major effect. This challenge is familiar to physicians studying new therapies for uncommon cancers. In oncological trials, it is commonplace to grade the severity of the disease and to restrict enrollment in such trials to individuals of a specific grade or grades. This results in a less heterogeneous patient population at trial entry, reducing imbalances in treatment groups in the trial itself. Progress in developing rational therapies for CADASIL might be accelerated by the adoption of a simple grading system, analogous to the Hoehn and Yahr scale for Parkinson's Disease [6].

The CADASIL grading system here being proposed is informed by more than two decades of clinical experience and previous CADASIL cohort studies describing the natural history of the disease (Table 1). In a cohort of 300 patients, the onset of migraines was found to occur at a median age of 28 years, and median age at onset of lacunar stroke was 48 [7]. In a separate cohort of 411 patients, median age at first stroke was 50.7 years in men and 52.5 in women; median age at time of onset of assistance with walking was 58.9 years in men and 62.1 in women; and median age at time of becoming bedridden was 62.1 years for men and 66.5 for women [8]. A consecutive series of 147 CADASIL patients demonstrated that the lacunar

Table 1. CADASIL Clinical Grading System

Grade	Description
0: Asymptomatic	Patient free of neurological symptoms referable to CADASIL
1: Migraine only	Patient has suffered at least one migraine-like headache with or without aura
2: Stroke or MCI	Patient has had at least one stroke or transient ischaemic attack with brain imaging confirming the presence of a symptomatic infarct, and/or mild cognitive impairment with brain imaging showing signs of small vessel disease
3: Gait assistance or dementia	Patient requires assistance from another person or from devices like a cane or walker for walking due to neurological gait disorder and/or requires assistance in daily activities due to dementia but is not confined to bed
4: Bedbound	Patient is confined to bed for most of day

CADASIL — cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; MCI — mild cognitive impairment

Address for correspondence: James Meschia MD, Mayo Clinic, Jacksonville, FL 32224, USA; e-mail: meschia.james@mayo.edu

Received: 3.02.2022 Accepted: 3.02.2022 Early publication date: 15.02.2022

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lesion burden is proportional to the severity of the cognitive impairment [9].

The proposed CADASIL Grading System would only apply to patients known to have a pathogenic *NOTCH3* mutation, a brain MRI showing characteristic ischaemic lesions, or a skin biopsy showing characteristic intravascular deposits. An asymptomatic relative of a patient with CADASIL would be considered to have Grade 0 disease only if there was evidence that the patient was an asymptomatic carrier of a pathogenic mutation. Grading a patient requires only a neurological assessment and clinically indicated brain imaging.

Patients are to be scored by the highest category for which they qualify. For example, a patient who presents with migraines and requires a walking stick because of a non-orthopaedic gait disorder would be considered to have Grade 3 disease. Not every patient will progress linearly through each grade, and so it would not be appropriate to refer to the grades as 'stages'. For example, some patients go on to have a stroke and ultimately become bedridden without ever having had a migraine. Nonetheless, the proposed grading system is intended to reflect progressively more severe small vessel disease.

The CADASIL Grading System is not intended to act as a substitute for standardised testing to characterise the cognitive burden of disease, or to take the place of standardised assessments of functional capacity. Other features of CADASIL such as encephalopathy, apathy, and mood disorders have not been included in the proposed Grading System because of suspected poor sensitivity and reliability of diagnosing these conditions in the absence of extensive testing dedicated to screening for them.

In conclusion, a simple grading system for CADASIL is proposed, with higher grades intended to reflect more severe small vessel disease. It is hoped that grading will allow for more homogeneous patient populations in future CADASIL clinical trials, and more consistent descriptions of patient populations in observational studies. Although this proposed system would appear to be valid, future studies will be needed to test its reliability in diverse patient populations.

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