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Novel grading system for CADASIL severity: A multicenter cross-sectional study

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ABSTRACT

Background: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an inherited progressive cerebral microangiopathy with considerable phenotypic variability. The purpose of this study was to describe the generalizability of a recently proposed grading system of CADASIL across multiple centers in the United States.

Methods: Electronic medical records (EMR) of an initial neurological assessment of adult patients with confirmed CADASIL were reviewed across 5 tertiary referral medical centers with expertise in CADASIL. Demographic, vascular risk factors, and neuroimaging data were abstracted from EMR. Patients were categorized into groups according to the proposed CADASIL grading system: Grade 0 (asymptomatic), Grade 1 (migraine only), Grade 2 (stroke, TIA, or MCI), Grade 3 (gait assistance or dementia), and Grade 4 (bedbound or end-stage). Inter-rater reliability (IRR) of grading was tested in a subset of cases.

Results: We identified 138 patients with a mean age of 50.9 ± 13.1 years, and 57.2% were female. The IRR was acceptable over 33 cases (κ=0.855, SD 0.078, $p<0.001$) with 81.8% being concordant. There were 15 patients (10.9%) with Grade 0, 50 (36.2%) with Grade 1, 61 (44.2%) with Grade 2, 12 (8.7%) with Grade 3, and none with Grade 4. Patients with a lower severity grade (grade 0 vs 3) tended to be younger (49.5 vs. 61.9 years) and had a lower prevalence of hypertension (50% vs. 20%, $p = 0.027$) and diabetes mellitus (0% vs. 25%, $p = 0.018$). A higher severity grade was associated with an increased number of vascular risk factors ($p = 0.02$) and independently associated with hypertension and diabetes ($p<0.05$). Comparing Grade 0 vs. 3, cortical thickness tended to be greater (2.06 vs. 1.87 mm; $p = 0.06$) and white matter hyperintensity volume tended to be lower (54.7 vs. 72.5 ml; $p = 0.73$), but the differences did not reach significance.

Conclusion: The CADASIL severity grading system is a pragmatic, reliable system for characterizing CADASIL phenotype that does not require testing beyond that done in standard clinical practice. Higher severity grades tended to have a higher vascular risk factor burden. This system offers a simple method of categorizing CADASIL patients which may help to describe populations in observational and interventional studies.

Abbreviations: CADASIL, Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CMB, Cerebral microbleed; EMR, Electronic medical record; ICHD-3, International Classification of Headache Disorders, version 3; IRR, Inter-rater reliability; MRI, Magnetic resonance imaging; SVD, Small vessel disease; WMH, White matter hyperintensities.

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Introduction

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), a rare hereditary small-vessel disease (SVD) caused by mutations in the NOTCH3 gene, is characterized classically by five main symptoms that can change with duration of the disease: migraine with aura, subcortical ischemic infarcts, ambulatory dependency, neuropsychiatric changes, and cognitive impairment leading to dementia and death. [1,2] A relationship between phenotypic and genotypic variability has been noted in European [3,4] and Asian populations. [5] Phenotypic variability is also influenced by vascular risk factors, including chronic arterial hypertension, [6,7] diabetes mellitus, [8] and tobacco smoking history [9].

A clinical grading system for CADASIL was recently proposed to characterize patients at various stages of severity of the disease. [10] It was designed for simplicity of use in the clinical setting, with the intent of improving the description of populations and defining eligibility criteria in prospective studies to reduce between-group baseline differences. This system consists of 5 grades of clinical severity based on the presence or absence of migraine with aura, ischemic cerebrovascular symptoms, cognitive impairment, and physical disability. Other features of CADASIL, such as psychiatric disorders, seizures, and vision problems have not been included in the proposed grading system because of concerns regarding the need for dedicated screening tests. The purpose of this study was to validate the CADASIL Severity Score in a multicenter cohort of CADASIL patients at the time of their initial presentation to neurology clinics. We hypothesize that the CADASIL severity score will allow for the categorization of individuals with good inter-rater reliability.

Methods

Patient selection and methodology

We performed a multicenter, retrospective, cross-sectional study with data between January 2002 and January 2022. The CADASIL Severity Grading Scale was introduced at five academic medical centers with CADASIL expertise: Mayo Clinic Florida (MCF), Mayo Clinic Rochester (MCR), the Warren Alpert Medical School of Brown University (BrownU), University of California San Francisco (UCSF), and University of Virginia (UVA). Cases were consecutive patients diagnosed with CADASIL by neurologists based on a skin biopsy showing characteristic intravascular deposits, detection of a pathogenic NOTCH3 mutation, or a brain MRI revealing distinctive ischemic lesions with appropriate family history. Neurologist investigators at each site were familiarized with the use of the Severity Grading Scale before applying it to record review.

CADASIL severity grading system

The CADASIL Severity Grading System consists of 5 ordinal grades, ranging from 0 to 4. [10] Grade 0 is a patient with a known pathogenic mutation in the NOTCH3 gene, skin biopsy findings diagnostic of CADASIL, or with characteristic brain MRI small vessel disease features and a positive family history of CADASIL who is free of neurological symptoms referrable to CADASIL. Grade 1 is a patient who has developed at least one migraine-like headache with or without aura based on International Classification of Headache Disorders-3 (ICHD-3) diagnostic criteria [11]. Grade 2 is a patient who has suffered at least one stroke (ischemic or hemorrhagic) identified by CT or MR brain imaging or a transient ischemic attack, and/or has mild cognitive impairment with brain imaging showing hallmarks of CADASIL. Patients were considered to have mild cognitive impairment if they had evidence on examination of cognitive impairment that is not severe enough to interfere with independence in everyday activities. Grade 3 is a patient who requires ambulatory assistance from another person or device and/or requires assistance in daily activities due to dementia but is not confined to bed. Grade 4 is a patient with end-stage symptoms resulting in being bedbound most of the day. Patients meeting criteria for more than one grade are assigned to the highest category for which they qualify (e.g., a patient with migraines and a stroke, would be Grade 2).

Reviewers at these medical centers were familiarized with the grading system and rated the severity of each case based on their initial clinical presentation to a neurology outpatient clinic. All cases were reviewed by a single author, except for the inter-rater reliability phase of the study. A subset of 33 cases from Mayo Clinic Florida were independently reviewed by two clinicians (AS and MKB). Each reviewer was blinded to the grade given by the other. The grades assigned by reviewers to each patient were subsequently analyzed for testing of interrater reliability (IRR).

Clinical characteristics

Five vascular risk factors were abstracted from the medical records: arterial hypertension; diabetes mellitus; history of tobacco cigarette smoking; coronary artery disease; and atrial fibrillation. Hypertension was defined by a physician's diagnosis or as systolic blood pressure (SBP) $\geq$140 mmHg, diastolic blood pressure (DBP) $\geq$ 90 mmHg, or by the use of antihypertensive medication, as recommended. [12,13] Diabetes mellitus was defined according to the guidelines of the American Diabetes Association. [14] Coronary artery disease and atrial fibrillation were identified according to the clinical documentation. Cigarette smoking history was considered positive in cases of current or past smoking status regardless of duration or quantity. The number of vascular risk factors (0–5) was assigned to each patient.

Radiographic characteristics

Magnetic resonance imaging (MRI) brain images were collected from 58 patients from Mayo Clinic sites (MCR and MCF). These images were on 1.5 or 3 Tesla as available clinically with standard sequences. Those with an uninterpretable brain MRI due to movement or other technical factors were excluded.

The Standards for Reporting Vascular Changes on Neuroimaging (STRIVE) definition criteria were used to define the WMH. [15] The WMH volume (ml) on T2- fluid-attenuated inversion recovery (FLAIR) images were quantified using the Lesion Growth Algorithm (LGA) in the Lesion Segmentation Toolbox 2.0.1.5 (LST, http://www.statistical-modeling.de/lst.html) with the suggested threshold of 0.3 within Statistical Parametric Mapping-12 (SPM12) (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/, version 6225) using Matrix Laboratory (MATLAB) (R2016b; MathWorks, Natick, MA, USA). [16] This provided the lesion probability maps and calculated WMH volume by quantifying the spatial dimensions of the voxels in each MRI slice.

The process of cortical thickness extraction has been described. [17] To gather the cortical thickness data of all participants, we processed T1-weighted MRI Brain images using the computational anatomy toolbox 12 (CAT12) toolbox (http://www.neuro.uni-jena.de/cat/, version r1109) within SPM12 using MATLAB to generate a cortical surface that provided cortical thickness measurement. The mean global cortical thickness was extracted from all participants in millimeters.

Statistical analysis

Descriptive analysis was done with continuous variables represented as means with standard deviation (SD). Categorical variables were represented by frequencies. The study population was categorized into 5 grades ranging from 0 to 4 based on the symptoms and severity of the disease. We have dichotomized into early and late stages based on the grades. The early stage includes patients with Grades 0 and 1, and the late-stage included patients with grades 2 and 3. The rationale for this categorization was implemented to address the potential of obtaining

misleading outcomes due to the limited number of patients within certain severity grades (example, Grade 3, $n = 3$). The association between the CADASIL grades and the demographics, clinical, and radiographic findings were tested using the chi-squared ($\chi 2$) test for categorical variables. One-way analysis of variance (ANOVA) and the Kruskal-Wallis rank sum test were used for parametric and for non-parametric continuous variables respectively, as appropriate.

The interrater reliability was assessed using the unweighted Cohen's kappa coefficient (κ) with SD between the reviewers. P-values < 0.05 were considered statistically significant and all statistical tests were two-sided. All the statistical analysis was performed using Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) version 28 (https://www.ibm.com/products/spss-statistics)

Results

Main findings

We identified 138 patients that met our inclusion criteria. Of these patients, 108 (78.3%) were confirmed to have CADASIL with results of NOTCH3 clinical testing available in the primary electronic medical record (EMR) and the remaining cases 30 (21.7%) were referred cases with EMR evidence that the diagnosis of CADASIL was confirmed at the referring medical center. Fig. 1 shows a flow diagram of the contribution of patients from each center to various cohorts in this study. Table 1 shows the demographic and clinical characteristics of the combined cohort. No patient had Grade 4 severity at presentation. In the cohort, 47.1% (65/138) were early stage (Grades 0 to 1), with the remainder being in advanced stage (Grades 2 to 3)

There were far more women (43/50, 86%) than men with Grade 1 CADASIL. Severity distributions did not differ amongst the different centers. Diabetes mellitus and chronic arterial hypertension were more prevalent at higher grades. Further, the number of vascular risk factors increased significantly with higher grades.

Inter-rater reliability

IRR was strong with a κ of 0.855 (SD.078, $p<0.001$), with an unadjusted agreement rate of 81.81% (27/33), indicating a strong degree of agreement. [18] In the considered subset of 33 patients, Grade 2 of the disease was the most represented grade (45.5%). The mean age was 52.76 ± 12.46 and 17 patients (51.5%) were female. The single-center cohort involved in the reliability study did not differ significantly in demographic or clinical characteristics from the cohort from the four remaining clinical centers (**Supplemental Table 1**).

Radiographic characteristics

Table 2 provides an overview of the radiographic findings observed in CADASIL patients from two clinical centers. The mean volume of white matter hyperintensities (WMH) for the entire cohort was determined to be 54.72 ± 33.8 ml. WMH volumes observed in patients with late-stage severity grades were not significantly higher than for patients with early-stage disease (58.35 ± 34.75 ml vs. 50.84 ± 32.93 ml, respectively; $p = 0.402$). Additionally, the average global cortical thickness across the entire cohort was found to be 2.06 ± 0.25 mm. An inclination towards thinner cortices was observed in patients with advanced severity grades, as early-stage patients had an average global cortical thickness of 2.07 ± 0.23 mm, while late-stage patients had 2.06 ± 0.26 mm ($p = 0.830$). Furthermore, the demographic and clinical characteristics of the two-center cohort involved in the imaging study did not significantly differ from those of the cohort derived from the remaining three clinical centers (**Supplemental** Table 2).

Discussion

In this multicenter, retrospective cross-sectional study, we describe the first preliminary experience with a CADASIL severity grading system applied to the first neurological evaluations at referral centers. This grading scale showed strong inter-rater reliability and was able to easily categorize individuals. At the initial clinical assessment, more than half of the patients belonged to grade 1 or 2 severity groups (111/138, 80.4%). Our cohort of patients is similar to that of a large German series, where ischemic episodes (TIA or stroke) were also the most frequent presentation. [19]

In our cohort, grade 3 (gait assistance or dementia) patients had a mean age of 61.9 years and were older than patients with grade 2 (stroke or TIA or MCI) and grade 1 (migraine only) severity, who had a mean age of 53.4 years and 45.6 years, respectively. In a retrospective study reporting 411 patients, the median age of onset of required walking assistance was 58.9 years in men and 62.1 in women, while the median age at a first stroke was 50.7 years in men and 52.5 in women. [20] In accordance with the literature, grade 1 patients (migraine only) were predominantly females (86.0%) while grade 2 patients (stroke or TIA or

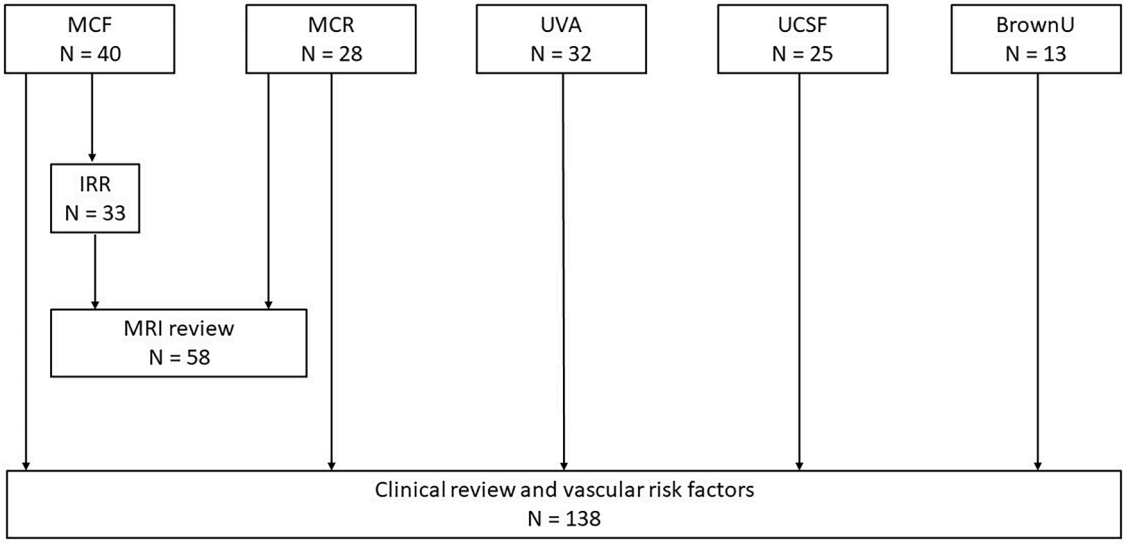

Fig. 1. Flow diagram showing the patient cohort: the patient contribution from each center, the patients included in the reliability test, and those with Brain MRI imaging.

Table 1
Baseline and clinical characteristics across the 5 centers.

n (%)	Overall	CADASIL Grade				p-value
		0	1	2	3	
	138 (100)	15 (10.9)	50 (36.2)	61 (44.2)	12 (8.7)	
Site - n (%)						0.278 *
MCF	40	8 (20)	11 (27.5)	19 (47.5)	2 (5)	
MCR	28	2 (10.4)	12 (38.7)	12 (45.3)	2 (5.7)	
UVA	32	4 (12.5)	9 (28.1)	13 (40.6)	6 (18.8)	
UCSF	25	1 (4)	12 (48)	11 (44)	1 (4)	
BrownU	13	0 (0)	6 (46.2)	6 (46.2)	1 (7.7)	
Age of initial assessment years - mean (SD)	50.89 ± 13.1	49.5 ± 9.2	45.6 ± 13.6	53.4 ± 12.1	61.9 ± 10.6	0.231 †
Sex – n (%)						< 0.001 *
Male	59 (42.8)	12 (80)	7 (14)	35 (57.4)	5 (41.7)	
Female	79 (57.2)	3 (20)	43 (86)	26 (42.6)	7 (58.3)	
Vascular Risk Factors – n (%)						
Hypertension	32 (23.2)	3 (20)	6 (12)	17 (27.9)	6 (50)	0.027 *
Diabetes mellitus	12 (9.5)	0 (0)	1 (2)	9 (14.8)	3 (25)	0.018 *
Smoking History	45 (33.3)	4 (26.7)	15 (31.3)	31 (35)	5 (41.7)	0.839 *
Coronary artery disease	1 (0.7)	0 (0)	0 (0)	1 (1.7)	0 (0)	0.739 *
Atrial fibrillation	1 (0.8)	0 (0)	0 (0)	1 (1.7)	0 (0)	0.738 *
No. of Vascular Risk Factors - n (%)						0.020 *
0	42 (30.4)	6 (40)	23 (46)	13 (21.3)	0 (0)	
1	55 (39.9)	5 (33.3)	18 (36)	27 (44.3)	5 (41.7)	
2	29 (21.0)	4 (26.7)	9 (18)	12 (19.7)	4 (33.3)	
3	9 (6.5)	0 (0)	0 (0)	7 (11.5)	2 (16.7)	
4–5	3 (2.2)	0 (0)	0 (0)	2 (3.3)	1 (8.3)	

Note:.
BrownU Brown University; CADASIL Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; MCF Mayo Clinic Florida; MCR Mayo Clinic Rochester; UCSF University of California San Francisco; UVA University of Virginia.
* Chi-Square Test.
† ANOVA Test
# No subject had a CADASIL grade 4.

MCI) were predominantly males (57.4%). Interestingly, we found a female predominance (58.3%) also in the grade 3 group (gait assistance or dementia). This unexpected sex disparity may be due to the lower sample size. Overall, sex, but not age, distribution differed across grades of severity ($p < 0.01$). Recent data show that the disease can remain neurologically silent at an advanced age in some patients [21] while cardiovascular risk factors have a key role in exacerbating the clinical progression and modulating the severity of the disease. [6,22] Future studies in independent cohorts should explore the relationship between sex and CADASIL severity grade.

We found that those patients with a higher grade of CADASIL disease

Table 2
Radiographic findings between CADASIL stages.

	Overall	CADASIL Grade		p-value
		Early stage	Late stage	
White matter hyperintensity vol. ml, mean (SD)	54.72 (33.8)	50.84 (32.93)	58.35 (34.75)	0.402 *
Global Cortical Thickness mm, mean (SD)	2.06 (0.25)	2.07 (0.23)	2.06 (0.26)	0.830 *

Note:.
CADASIL Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy.
* ANOVA test was used
Early stage includes Grade 0–1
Late stage includes Grade 2–3.

are likely to have more vascular risk factors ($p = 0.02$). In terms of individual risk factors, we found that the severity of CADASIL was significantly associated with hypertension ($p = 0.03$) and diabetes ($p = 0.02$). Different studies concluded that hypertension is a strong vascular risk factor associated with the occurrence of ischemic manifestations in deep gray structures and subcortical white matter, cerebral microbleeds (CMBs) and intracranial hemorrhage (ICH), with consequent functional disability, and dementia [4,6,22-26] Diabetes, in turn, is considered a risk factor for both strokes [22,27] and CMBs. [23] Regarding other risk factors, we have also observed a positive trend between tobacco smoking history and higher severity of disease ($p = 0.8$). Mixed results are found in the literature, with some studies showing no association between smoking and disability/dementia in CADASIL patients [4] and other studies showing a strong association with the phenotypic severity and the occurrence of lacunes, WMHs, and CMBs. [6,22,25,28]

Neither quantitative imaging trait that we studied significantly correlated with severity grade, but we found that the mean global cortical thickness was the greatest in Grade 0 patients (2.21 ± 0.27 mm) and the lowest in grade 3 patients (1.87 ± 0.25 mm). Larger studies would be needed to clarify the imaging-severity relationship. Our experience supports the clinical relevance of severity grading that cannot be substituted by imaging parameters. While clinical grades are easily assigned and require no new testing, imaging produces numerous small vessel parameters, for which there is no accepted standard for generating an easily interpretable severity grade for this population. The presence and extension of these MRI findings can vary based on the specific NOTCH3 mutation and the vascular risk factors. [25] For example, hypertension may contribute to reduced cerebral blood flow to cortical and subcortical structures, which associates with higher WMH volume and reduced cortical thickness in older adults. [29,30] Small vessel disease markers like WMHs, CMBs, lacunes, enlarged perivascular spaces, and cortical atrophy can be found in 70% of CADASIL patients over 65 years old. The presence of WMHs in the anterior temporal lobes and the external capsule is the principal neuroimaging feature of CADASIL and can be detected early in the progression of the disease. However, recent studies suggest that only the WMHs localized in the periventricular space seem associated with clinical disability and dementia, as well as CMBs, lacunes, and brain atrophy. Although our findings suggest that these radiographic features may be associated with the severity of the disease, the knowledge of the imaging alone is not sufficient to characterize CADASIL patients and clinical assessment remains crucial in assessing severity. We do not recommend relying exclusively on imaging features but do recognize the value of imaging in displaying the evolution of tissue damage even earlier than clinical deterioration, especially with the advancing of imaging modalities with higher sensitivity. [31]

Limitations

Our study has several limitations. The retrospective design forced us

to focus on variables obtained in routine clinical practice. Additionally, the study population is vulnerable to referral bias. Patients were often referred by other medical centers, so the initial assessment performed at our study centers did not always correspond to the first center where the diagnosis of CADASIL was secured. Importantly, since patients were usually seen only after the occurrence of neurological manifestations, the number of asymptomatic subjects (Grade 0) was low. Relying on clinical interviews or information documented in medical records for the assessment of cognitive status rather than formal cognitive testing may underestimate the prevalence and severity of cognitive impairment. At the same time, focusing on the initial evaluation of patients likely skewed our sample to lower CADASIL grades. In our cohort, no patient was classified as grade 4 of severity (bedbound), so it was not possible to characterize these patients and investigate their association with vascular risk factors and radiographic findings. Another limitation is that, depending on the patient's age, disease history, and clinical and neuroimaging characteristics, the clinical suspicion of CADASIL may vary.

Finally, radiological data were available only for a subgroup of patients, limiting statistical power, and MR imaging protocols varied because we relied on clinical imaging.

Conclusion and future directions

Our study shows that the simple CADASIL severity grading system is pragmatic (requires no testing for research purposes) and reliably applied to patients in clinical practice. This scale can help to describe CADASIL patients and classify them into more homogeneous groups by using only a neurological assessment and clinically obtained brain imaging. Higher grades of severity correlated with a greater number of risk factors in particular hypertension, diabetes mellitus, and smoking history, and future studies can evaluate the casual association behind this observation. Control of vascular risk factors might in turn influence the progression of the disease. Positive trends, although non-significant, were also observed between the clinical severity and the degree of WMH and cortical thickness. This system can be useful for characterizing CADASIL cohorts in future prospective and retrospective observational studies and interventional trials. Severity grading may help in meta-analyses of CADASIL cohorts by allowing adjustment or stratification by baseline severity.

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Declaration of Competing Interest

None.

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None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cccb.2023.100170.

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