RESEARCH ARTICLE OPEN ACCESS

Trajectory Pattern of Cognitive Decline in Cerebral Autosomal Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy

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Neurology® 2022;99:e1019-e1031. doi:10.1212/WNL.0000000000200805

Abstract

Background and Objectives

The course and pattern of cognitive decline in ischemic cerebral small vessel disease remain poorly characterized. We analyzed the trajectory pattern of cognitive decline from age 25 to 75 years in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL).

Methods

We applied latent process mixed models to data obtained from patients with CADASIL who were repeatedly scored during their follow-up using 16 selected clinical scales or cognitive tests.

Results

The modeled evolutions of these scores obtained from 1,243 observations in 265 patients recruited at the French National Referral Centre (50.1 years on average and 45.3% men) showed wide and heterogeneous variations in amplitude along the age-related progression of the disease. Although the Backward Digit Span remained essentially stable, a linear deterioration of scores obtained using the Symbol Digit Numbers or Number of Errors of Trail Making Test B was detected from 25 to 75 years. By contrast, the largest score changes were observed at midlife using the Digit Cancellation Task. All other tests related to executive functions, memory performances, or global cognitive efficiency showed a rate of change accelerating especially at the advanced stage of the disease. Male gender and the presence of gait disorders or of some disability at baseline were found to predict earlier or large changes of 4 scores (Index of Sensitivity to Cueing, Delayed Total Recall, Initiation/Perseveration, and Barthel Index) in a subgroup of individuals distinct from the rest of the sample.

Discussion

Cognitive alterations develop heterogeneously during the progression of CADASIL and vary largely according to the stage of the disease. These results suggest that not only the target population and study duration but also the stage of disease progression should be considered in preparing future clinical trials aimed at reducing cognitive decline in any such condition.

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The Article Processing Charge was funded by the authors.

Glossary

CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; **cSVD** = cerebral small vessel disease; **EQ VAS** = Visual Analog Scale of the 3-level EuroQol; **IQR** = interquartile range; **MDRS** = Mattis Dementia Rating Scale; **mRS** = modified Rankin scale; **NIHSS** = NIH Stroke Score; **OR** = odds ratio; **TMT** = Trail Making Test; **VADAS-Cog** = Vascular Dementia Assessment Scale cognitive subscale.

Cerebral small vessel diseases (cSVDs) are common in the general population and represent a major source of stroke events and cognitive impairment during aging.[1,2] However, despite their frequency, the natural history of cognitive decline in cSVD remains poorly understood. This is likely due to the limited duration of previous longitudinal studies and their focus on elderly individuals, in whom manifestations of vascular origin are extremely variable in severity and often intertwined with effects of cerebral aging and early neurodegenerative processes.[3]

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a monogenic form of cerebral small artery disease caused by stereotyped mutations of the *NOTCH3* gene.[4] It is a unique model of severe ischemic cSVD[5,6] that starts long before the effects of aging on cognition.[7] Previous studies have shown that CADASIL can be responsible for slower processing speed, impaired executive functions, attention, and memory performances and, at the advanced stage, dementia.[5,8,9] All these manifestations were shown to closely match those detected in sporadic forms of cSVD.[6] However, the exact kinetics of cognitive decline throughout the whole course of CADASIL has not yet been investigated.

In this study, we aimed to analyze the trajectory of various cognitive deficiencies in patients with CADASIL using a comprehensive battery of neuropsychological tests in parallel with assessments of motor disability, functional dependence, and quality of life.

Methods

Study Population

Between 2003 and 2017, a total of 366 patients were recruited at the French National Referral Centre for rare cerebrovascular diseases, as a large prospective cohort of patients with CADASIL.[10,11] Inclusion criteria were of age 18 years or older, documentation of a cysteine-related mutation in the *NOTCH3* gene, and willingness to be evaluated regularly.

Standard Protocol Approvals, Registrations, and Patient Consents

Informed consent was obtained from each subject or from a close relative if necessary. The study was approved by an independent ethics committee (CEEI-IRB-17/388).

Evaluation of Patients During the Follow-up

Patients were evaluated every 18 months (on average) during the follow-up using various scales for assessing different clinical and cognitive aspects of the disease.[10,11] In this study, 16 scores, determined by consensus among neurologists (N.A., D.H., and H.C.) and neuropsychologists (A.J., S.R., C.M., and C.R.) of the referral center, were selected for the analysis of global cognitive efficiency, memory performances, executive functions, focal deficits with disability, dependence, and quality of life. Ranges of the 16 scores selected for analysis in this sample are given in Table 1.

Global cognitive efficiency was analyzed using total scores obtained from 2 measures: (1) the Mattis Dementia Rating Scale (MDRS)[12,13] and (2) the Vascular Dementia Assessment Scale cognitive subscale (VADAS-Cog).[14] The MDRS (from 0 to 144 [best score]) includes 5 subscales related to Attention, Initiation/Perseveration, Construction, Conceptualization, and Memory.[15] The VADAS-Cog (from 0 [normal] to 90 [severe impairment]) is composed of 14 items related to memory and orientation, language, praxis abilities, attention, and executive functions.[14,16]

Memory performance was analyzed specifically using 3 different scores obtained from the Free and Cued Selective Reminding Test adapted from the Grober and Buschke procedure.[17] In this study, we analyzed the capacity of retrieval or storage of information, implying correct encoding, using (1) the Total Free Recall score (without cues over the course of three 16 word recall trials varying from 0 to 48 [best score]); (2) the Index of Sensitivity to Cueing, a measure of retrieval/storage ability that decreases when information storage is compromised and cues are not useful; and (3) the Delayed Total Recall (from 0 to 16 [normal]) with both free and cued recalls.[18]

Executive performance, including attention and working memory performance, was analyzed using 7 different scores. Three were obtained from the VADAS-Cog: (1) the Digit Cancellation Test (from 0 [no impairment] to 10 [serious impairment]),[14,19] (2) Symbol Digit Test (from 0 [no impairment] to 10 [serious impairment]), and (3) Backward Digit Span (from 0 [no impairment] to 5 [serious impairment]).[14,20] The 4 other scores included (4) the Initiation/Perseveration component score from the MDRS (from 0 [worst] to 37 [best]) and 3 scores obtained from the Trail Making Test (TMT) evaluating cognitive speed and mental flexibility based on (5) the time in seconds of TMT part A, (6) the time in seconds of TMT part B, and (7) the Number of Errors in TMT part B.[21,22]

Disability was assessed using the modified Rankin scale (mRS). The values of 6 (death) were excluded because death was not considered in the other test scores. The severity of

Table 1 Total Number of Observations for Each Score and Number of Observations per Patient

Variable	No. of observations	No. of observations per patient[a]
Total Free Recall (min: 0; max: 48[b])	933	4.0 (3.0–6.0)
Index of Sensitivity to Cueing (min: 1; max: 100[b])	933	4.0 (3.0–6.0)
Delayed Total Recall (min: 2; max: 16[b])	932	4.0 (3.0–6.0)
Digit Cancellation Test (min: 0[b]; max: 10)	847	4.0 (3.0–5.0)
Symbol Digit Test (min: 0[b]; max: 10)	846	4.0 (3.0–5.0)
Backward Digit Span (min: 0[b]; max: 5)	854	4.0 (3.0–5.0)
Initiation/Perseveration (min: 0; max: 37[b])	945	5.0 (3.0–6.0)
TMT A Time (min: 0[b]; max: -)	940	4.0 (3.0–6.0)
TMT B Errors (min: 0[b]; max: -)	911	4.0 (3.0–6.0)
TMT B Time (min: 0[b]; max: -)	912	4.0 (3.0–6.0)
MDRS Total score (min: 0; max: 144[b])	943	5.0 (3.0–6.0)
VADAS-Cog Total score (min: 0[b]; max: 125)	687	3.0 (2.0–4.0)
NIHSS (min: 0[b]; max: 42)	1,180	6.0 (4.0–8.0)
Barthel Index (min: 0; max: 100[b])	1,192	6.0 (4.0–8.0)
mRS (min: 0[b]; max: 6)	1,199	6.0 (4.0–8.0)
EQ VAS (min: 0; max: 100[b])	937	5.0 (3.0–6.0)

Abbreviations: EQ VAS = Visual Analog Scale of the 3-level EuroQol; MDRS = Mattis Dementia Rating Scale; mRS = modified Rankin scale; NIHSS = NIH Stroke Score; TMT = Trail Making Test; VADAS-Cog = Vascular Dementia Assessment Scale cognitive subscale.
[a] Median number of observations per patient and interquartile range are provided.
[b] Best possible value.

focal neurologic deficits accumulated over time was analyzed using the NIH Stroke Score (NIHSS).[23] Daily living activities and functional independence were evaluated globally using the Barthel Index.[24] Finally, quality of life was assessed using the Visual Analog Scale of the 3-level EuroQol (EQ VAS).[25]

Explanatory Variables

The following parameters obtained at baseline were initially considered as potential predictors of clinical worsening in CADASIL: age, sex, education, smoking, alcohol consumption, diabetes, hypertension, systolic blood pressure, diastolic blood pressure, homocysteine, previous stroke events, gait disturbances, balance problems, disability, and dementia. Education was determined according to the French Barbizet scale[26] split in high level (at least the final high school diploma) and low level otherwise. Alcohol consumption was a qualitative variable with 3 categories: never, <2 glasses of wine per day for a man (1 glass or equivalent for a woman), and over these thresholds. Disability was split in moderate or severe disability (mRS ≥3) and no or mild disability otherwise. Dementia was assessed according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition criteria.[27] Neuroimaging data were not considered in the present analysis.

Statistical Analysis

We selected from the cohort individuals having at least 1 measure for each of the 16 scores obtained during the follow-up and who were 25 years or older at inclusion and 75 years or younger during the follow-up, an age range chosen because of the small number of observations outside these 2 extremes. In cases where a subtest could not be performed because alterations were too severe, the most altered performance measure for this subtest was applied to the patient and used in the statistical analysis. In this study, only raw total scores were analyzed. Data at baseline were summarized using descriptive statistics, with frequencies and percentages for qualitative data and means and SDs for quantitative variables.

Latent process mixed models[28-30] were used to overcome common limitations encountered during the analysis of clinical scores, particularly the frequent lack of normality in the distribution of scores, potential floor or ceiling effects, and curvilinearity.[30,31] This method allowed modeling the trajectory of the 16 scores selected for analysis in a more efficient way than simpler linear mixed models.[30,32] Age available throughout the follow-up was considered as the time variable for delineating the trajectories of test scores. For computation purposes, the time scale was age minus 25 years per 10 years, where 25 years corresponds to the age of the youngest patient observed at baseline. Thus, the intercept represents the cognitive level at age 25 years, and the change in cognitive level is measured for a decade.

Information on the different steps followed to build the model is given in eMethods (links.lww.com/WNL/C131). The final model was adjusted for the education level for the 12 cognitive scores.[33,34] The interaction between education and time was systematically assessed using the likelihood ratio test. Because potential heterogeneity in clinical progression cannot be excluded in the study population, we also considered this possible factor in the trajectory modeling analysis.[28] Without a priori, the latent process mixed models allow fitting simultaneously several models with different evolutions. Each individual is then assigned to the most probable evolution.

Finally, in cases where the evolution of a score was heterogeneous, a logistic regression model using a stepwise selection process was used to understand what distinguishes patients between groups. Multiple imputations were performed to take into account for missing data. Independent variables with p values <0.20 in the univariate setting and less than 10% missing data were introduced in the multivariate model.

Table 2 Baseline Characteristics of Patients Included in the Analysis and Comparison With Cohort Individuals Who Were Not Included

Baseline characteristic	Included (n = 265)	Not included (n = 101)	*p* Value
Age, y	50.0 (42.1–58.6)	58.4 (51.0–66.5)	<0.001
Sex: male	120 (45.3)	49 (49.0)	0.525
Education: >high school diploma	127 (47.9)	30 (33.3)	0.016
Smoking			
Never	85 (37.9)	45 (57.0)	0.009
Former	87 (38.8)	18 (22.8)	
Current	52 (23.2)	16 (20.3)	
Alcohol consumption			
Never	77 (34.8)	33 (41.8)	0.295
<2 glasses of wine for a man	123 (55.7)	36 (45.6)	
>2 glasses of wine for a man	21 (9.5)	10 (12.7)	
Hypertension: yes	54 (24.1)	24 (30.0)	0.300
Diabetes: yes	12 (5.4)	7 (8.5)	0.307
Systolic blood pressure, mm Hg	126.0 (115.8–138.0)	131.0 (121.2–144.0)	0.018
Diastolic blood pressure, mm Hg	74.0 (68.0–82.0)	76.0 (69.0–82.0)	0.308
Homocysteine, μmol/L	10.7 (8.7–13.8)	11.6 (9.2–15.3)	0.197
Previous stroke events: yes	132 (49.8)	63 (64.3)	0.014
Gait disturbances: yes	43 (16.2)	60 (61.2)	<0.001
Balance problems: yes	54 (20.4)	51 (52.0)	<0.001
Disability: moderate or severe	13 (4.9)	46 (47.9)	<0.001
Dementia: yes	6 (2.3)	31 (32.0)	<0.001
MADRS	6.0 (3.0–12.0)	8.0 (2.0–17.2)	0.274
Total Free Recall	30.0 (24.0–35.0)	19.5 (12.0–28.0)	<0.001
Index of Sensitivity to Cueing	95.2 (84.6–100.0)	88.9 (79.3–94.7)	<0.001
Delayed Total Recall	16.0 (15.0–16.0)	16.0 (13.2–16.0)	0.001
Digit Cancellation Task (correct numbers crossed off)	4.0 (2.0–8.0)	9.0 (4.0–10.0)	<0.001
Symbol Digit Correct Numbers	3.0 (1.0–8.0)	9.0 (5.0–10.0)	<0.001
Backward Digit Span	3.0 (2.0–5.0)	5.0 (4.0–5.0)	<0.001
Initiation/Perseveration	37.0 (35.0–37.0)	26.0 (16.0–33.0)	<0.001
TMT A Time	35.0 (26.0–47.0)	82.5 (44.0–116.8)	<0.001
TMT B Errors	0.0 (0.0–1.0)	0.0 (0.0–2.0)	0.556
TMT B Time	84.5 (59.8–135.2)	130.0 (77.5–295.0)	0.001
MDRS Total score	142.0 (138.0–143.0)	122.0 (100.0–135.0)	<0.001
VADAS-Cog Total score	32.5 (22.0–45.0)	51.5 (35.2–68.8)	<0.001
NIHSS	0.0 (0.0–1.0)	1.0 (0.0–4.0)	<0.001

Continued

Table 2 Baseline Characteristics of Patients Included in the Analysis and Comparison With Cohort Individuals Who Were Not Included *(continued)*

Baseline characteristic	Included (n = 265)	Not included (n = 101)	*p* Value
Barthel Index	100.0 (100.0–100.0)	95.0 (51.2–100.0)	<0.001
mRS	0.0 (0.0–1.0)	2.0 (1.0–4.0)	<0.001
EQ VAS	80.0 (60.0–90.0)	70.0 (50.0–80.0)	0.023

Abbreviations: EQ VAS = Visual Analog Scale of the 3-level EuroQol; MDRS = Mattis Dementia Rating Scale; mRS = modified Rankin scale; NIHSS = NIH Stroke Score; TMT = Trail Making Test; VADAS-Cog = Vascular Dementia Assessment Scale cognitive subscale.
Median and interquartile range are provided for quantitative variables. Frequencies and percentages are given for qualitative variables. Groups were compared using the Pearson χ^2 test for qualitative variables and with a Wilcoxon rank sum test for quantitative variables.

Statistical tests were performed at a conventional 2-tailed type I error of 0.05. Data were analyzed using SAS software version 9.4 (SAS Institute Inc., Cary, NC) and R software version 3.6.1.[35] Latent process mixed models and latent class mixed models were estimated using the package "lcmm" version 1.8.1.[36]

Data Availability

Data not provided in the article because of space limitations may be shared (anonymized) at the request of any qualified investigator for purposes of replicating procedures and results.

Results

Main Characteristics

The study sample consisted of a total of 1,243 observations obtained from 265 patients across a median number of 4 visits per individual (interquartile range [IQR]: 2–7 and eTable1, links.lww.com/WNL/C131). The median number of observations per patient ranged from 3 for the VADAS-Cog Total score to 6 for the NIHSS, Barthel Index, and mRS scores (Table 1). The follow-up duration varied from 0 to 14 years, with a median follow-up interval of 17 months (IQR: 9–23).

The 265 patients included in the analysis were younger, more educated, and more frequently never-smokers than the cohort participants who were not included in the analysis (Table 2). In addition, patients included in the analysis were less severely affected than those who were not included in the analysis, presenting less frequently with a history of stroke events, gait disturbances, balance problems, disability, dementia at inclusion, and better scores in all tests and scales except for the number of near-zero TMT B Errors (Table 2).

Trajectories of Cognitive and Associated Clinical Scores

Using different link functions (eTable 2, links.lww.com/WNL/C131), we modeled the trajectory of the latent process underlying each score with a linear ($y = \beta_1 x + \beta_0$), quadratic ($\beta_2 x^2 + \beta_1 x + \beta_0$), or cubic ($y = \beta_3 x^3 + \beta_2 x^2 + \beta_1 x + \beta_0$) form. The best model is given in eTable 3. We then used the link function to convert predictions obtained in the latent process scale to trajectories of all scores in their natural scale. These trajectories are illustrated for the different tests in Figures 1 and 2 (the corresponding underlying raw data are not shown for readability).

Homogeneous Evolution of 12 Cognitive and Clinical Scores

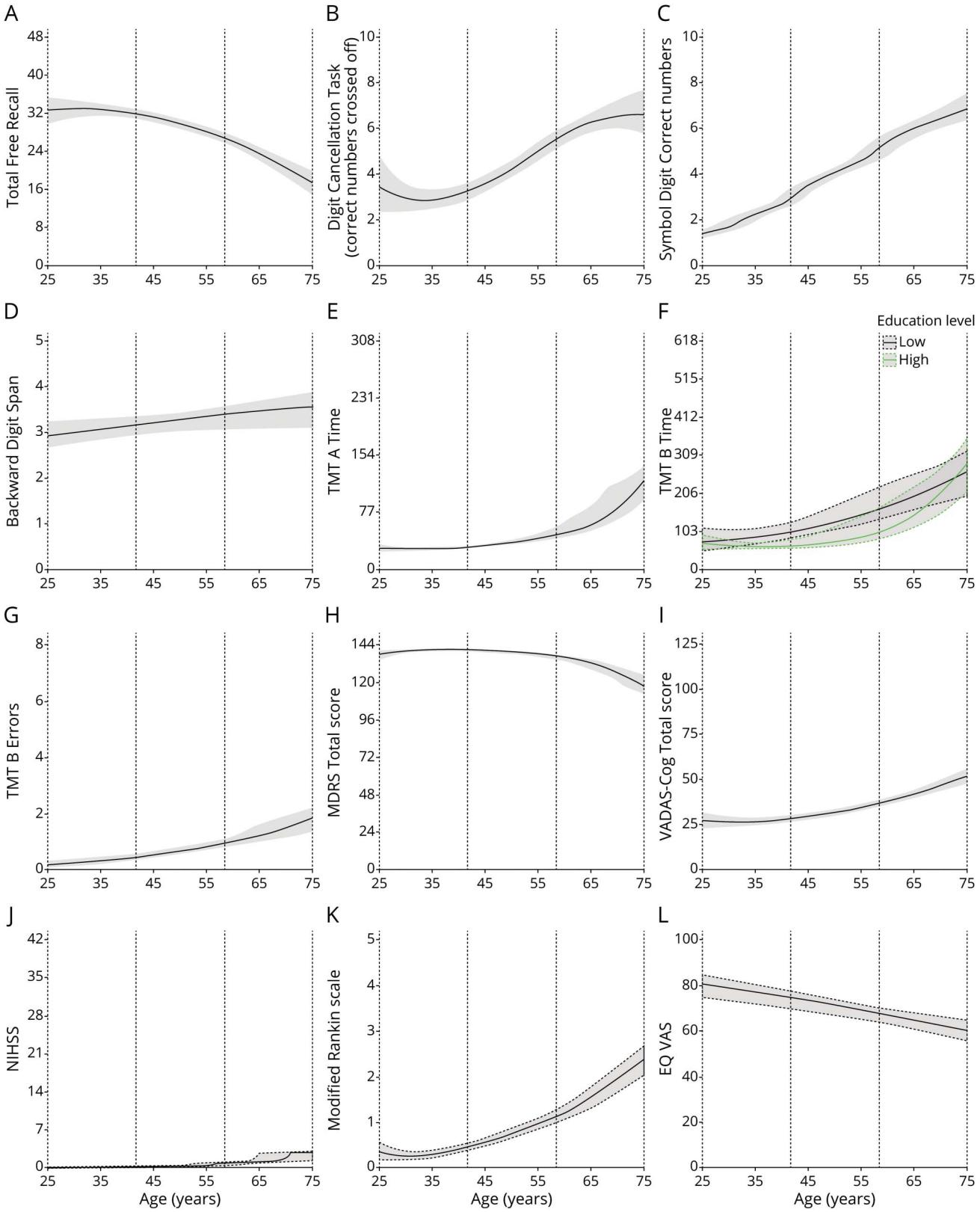
For 9 cognitive scores, the best latent process model selected included only a single latent class: Total Free Recall, Digit Cancellation Task (correct numbers crossed off), Symbol Digit Correct Numbers, Backward Digit Span, TMT A Time, TMT B Errors, TMT B Time, MDRS Total score, and VADAS-Cog Total score. The different trajectories obtained after adjustment for education are shown in Figure 1. In all corresponding models, no significant interaction was detected between education and time except for TMT B Time, for which a steeper and later progression was detected in patients with a high education level (Figure 1F). For 3 clinical scores (NIHSS, mRS, and EQ VAS), the best latent process model selected also included only a single latent class (Figure 1, J–L).

Heterogeneous Evolution of 4 Cognitive and Clinical Scores

For 3 cognitive scores—Index of Sensitivity to Cueing, Delayed Total Recall, and Initiation/Perseveration subscore of the MDRS—the best model for score changes included 2 latent classes (eAppendix1, links.lww.com/WNL/C131) with no significant interaction between education and time (Figure 2). The Index of Sensitivity to Cueing decreased early in 46 patients and late in 219 patients, whereas the Initiation/Perseveration subscore of the MDRS decreased early in 60 patients and late in 205 patients. By contrast, the Delayed Total Recall score decreased in 54 patients but remained stable in 211 patients. The Barthel Index was best modeled with 2 class-specific predicted trajectories with a strong early decrease in scores in 22 patients and a much later decrease in 243 patients.

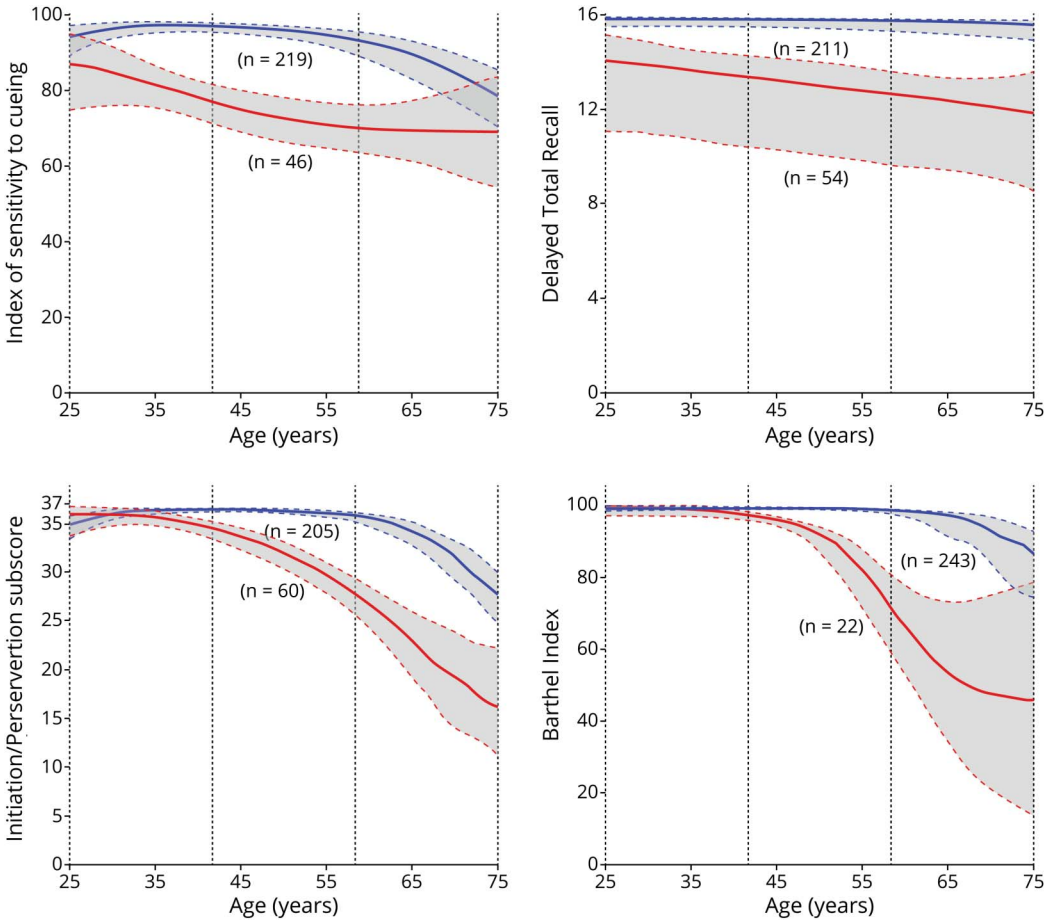
The variables associated with these different classes of evolution in univariate analysis are detailed in Table 3 and with the data after imputation of missing data (eTable 4, links.lww.com/WNL/C131). As the results were similar, multivariate models were performed with the data without imputation. The final multivariate model showed the following: (1) an earlier decline in the Index of Sensitivity to Cueing was only

Figure 1 Clinical and Cognitive Score Trajectories With Homogeneous Changes



Score trajectories showing homogeneous changes among patients from 25 to 75 years (according to the best latent process model with corresponding 95% confidence intervals (in gray) and after adjustment for the education level for all cognitive tests). The analysis of cognitive scores was performed after adjustment for the education level at baseline. No significant interaction was detected between education level and time for any score except TMT B Time, which increased later and more steeply after 55 years of age in patients with a high education level. Vertical lines indicate where data were calculated from the model at limits of 3 age-reference intervals.

Figure 2 Clinical and Cognitive Score Trajectories With Homogeneous Changes



Score trajectories delineated by the model showing a group of individuals with worst (or earlier) deterioration distinct from the rest of the population. Two groups were identified with modeling trajectories for the Index of Sensitivity to Cueing, Delayed Total Recall, Initiation/Perseveration subscore, and Barthel Index: a group with early or larger changes (in red), and a group with late or limited changes (in blue). The number of participants in each group is detailed for each score. The analysis of cognitive scores was performed after adjustment for the education level at baseline. Vertical lines indicate where results were obtained using the model at the limits of age tertiles.

associated with male sex (odds ratio [OR] 4.78, 95% CI 2.30–9.94, $p < 0.001$); (2) the decline in the Delayed Total Recall score was associated with male sex (OR 1.04, 95% CI 1.00–1.07, $p = 0.049$), age (OR 4.55 per additional year, 95% CI 2.22–9.34, $p < 0.001$), and the presence of gait disturbances (OR 3.50, 95% CI 1.55–7.92, $p = 0.003$) at inclusion, while highly educated participants were less likely to belong to this group (OR 0.45, 95% CI 0.22–0.93, $p = 0.030$); and (3) the earlier change in the Initiation/Perseveration subscore of the MDRS was independently related to male sex (OR 3.22, 95% CI 1.60–6.45, $p = 0.001$), moderate or severe disability (OR 15.68, 95% CI 3.10–79.33, $p = 0.001$), and higher MADRS scores (OR 1.06 per unit increase, 95% CI 1.02–1.11, $p = 0.007$) at inclusion; participants with a high level of education were also less likely to belong to this early decline group (OR 0.39, 95% CI 0.20–0.79, $p = 0.009$). For the Barthel Index, the multivariate analysis showed that participants with gait disturbances (OR 13.18, 95% CI 3.96–43.80, $p < 0.001$) and those with moderate or severe disability (OR 19.02, 95% CI 3.69–97.96, $p < 0.001$) at inclusion were more likely to belong to the earliest decline group.

Modeling Trajectories Revealed Early, Intermediate, and Late Score Changes in Variable Amplitude

To facilitate the translation of modeled trajectories to clinical practice, we also calculated the cognitive score changes during the follow-up depicted in Figures 1 and 2 using the latent process model at the age limits of 3 age-related reference intervals −25 to 41.7, 41.7 to 58.3, and 58.3–75 years of age-derived from the age range of the study sample (Tables 4 and 5). A significant score change was detected between each of the pairwise age groups for the Symbol Digit Correct Numbers. Most other cognitive performances significantly deteriorated over both the second and third age intervals with much larger changes over the interval of 58.3–75 years for Total Free Recall, TMT A Time, TMT B Time, MDRS Total score, VADAS-Cog Total score, Index of Sensitivity to Cueing (in group 2), and Initiation/Perseveration subscore of the MDRS (in groups 1 and 2) except for the Digit Cancellation

Table 3 Baseline Characteristics Predicting an Earlier or Larger Deterioration for 4 Scores (Index of Sensitivity to Cueing, Delayed Total Recall, Initiation/Perseveration Subscore, and Barthel Index) in a Subgroup of Patients (Univariate Logistic Regressions)

		Index of Sensitivity to Cueing		Delayed Total Recall		Initiation/Perseveration subscore		Barthel Index	
Baseline characteristic	**% NA**	**OR (95% CI)**	***p* Value**	**OR (95% CI)**	***p* Value**	**OR (95% CI)**	***p* Value**	**OR (95% CI)**	***p* Value**
Age, y	0.0	0.99 (0.96–1.02)	0.417	**1.05 (1.02–1.08)**	**0.001**	1.00 (0.98–1.03)	0.834	1.04 (1.00–1.08)	0.086
Sex: male	**0.0**	**4.38 (2.15–8.93)**	**<0.001**	**3.74 (1.96–7.13)**	**<0.001**	**2.59 (1.43–4.70)**	**0.002**	1.50 (0.62–3.60)	0.365
Education: >high school diploma	0.0	0.81 (0.42–1.53)	0.507	**0.38 (0.20–0.72)**	**0.003**	**0.31 (0.16–0.58)**	**<0.001**	**0.22 (0.07–0.66)**	**0.007**
Smoking									
Never	15.5	1.00	0.063	1.00	0.515	1.00	0.741	1.00	0.337
Former		0.68 (0.29–1.57)		0.72 (0.34–1.54)		1.11 (0.54–2.29)		0.59 (0.22–1.60)	
Current		1.89 (0.83–4.29)		1.16 (0.52–2.60)		1.37 (0.61–3.06)		0.41 (0.11–1.55)	
Alcohol consumption									
Never	16.6	1.00	0.208	1.00	0.146	1.00	0.307	**1.00**	**0.047**
<2 glasses of wine per day (male)		1.71 (0.77–3.79)		1.15 (0.55–2.37)		1.45 (0.71–2.95)		1.79 (0.55–5.84)	
>2 glasses of wine per day (male)		2.68 (0.84–8.52)		2.77 (0.97–7.95)		2.25 (0.77–6.60)		**5.70 (1.38–23.64)**	
Hypertension: yes	15.5	**2.13 (1.03–4.41)**	**0.042**	**2.43 (1.22–4.86)**	**0.012**	1.57 (0.79–3.13)	0.202	2.10 (0.82–5.38)	0.122
Diabetes: yes	15.5	1.58 (0.41–6.11)	0.510	1.31 (0.34–5.05)	0.695	0.67 (0.14–3.14)	0.607	2.03 (0.41–9.96)	0.382
Systolic blood pressure, mm Hg	1.9	1.00 (0.99–1.02)	0.684	1.01 (0.99–1.03)	0.190	1.01 (0.99–1.03)	0.194	**1.03 (1.00–1.05)**	**0.036**
Diastolic blood pressure, mm Hg	1.9	1.01 (0.98–1.04)	0.580	1.01 (0.99–1.04)	0.287	1.02 (1.00–1.05)	0.094	1.04 (0.99–1.08)	0.088
Homocysteine, μmol/L	16.2	1.04 (0.98–1.10)	0.186	**1.11 (1.04–1.19)**	**0.002**	1.04 (0.99–1.10)	0.122	1.02 (0.94–1.10)	0.646
Previous stroke events: yes	0.0	1.92 (1.00–3.70)	0.051	1.61 (0.88–2.96)	0.122	1.86 (1.03–3.35)	0.038	**2.92 (1.11–7.71)**	**0.031**
Gait disturbances: yes	0.0	1.32 (0.59–2.99)	0.500	**4.81 (2.38–9.70)**	**<0.001**	**3.49 (1.75–6.97)**	**<0.001**	**28.38 (9.67–83.30)**	**<0.001**
Balance problems: yes	0.0	0.94 (0.42–2.09)	0.880	1.70 (0.85–3.38)	0.133	1.60 (0.82–3.13)	0.171	**5.74 (2.33–14.16)**	**<0.001**
Disability: moderate or severe	0.4	2.28 (0.67–7.74)	0.188	**7.13 (2.23–22.80)**	**0.001**	**13.40 (3.56–50.51)**	**<0.001**	**66.37 (16.13–273.03)**	**<0.001**
Dementia: yes	0.0	2.44 (0.43–13.75)	0.311	4.08 (0.80–20.80)	0.091	**18.54 (2.12–162.03)**	**0.008**	**26.78 (4.59–156.21)**	**<0.001**
MADRS	1.9	1.01 (0.97–1.05)	0.586	1.02 (0.98–1.06)	0.352	**1.05 (1.01–1.09)**	**0.012**	1.04 (0.98–1.09)	0.184

Abbreviations: MDRS = Mattis Dementia Rating Scale; NA = number of missing data; OR = odds ratio.
The modeled probability is that of belonging to the most severely affected group of patients (worst or earlier deterioration of performances also in red in Figure 2).

Table 4 Variations Estimated by the Latent-Process Model at the Limits of Age Tertiles for Scores With Homogeneous Evolution

Parameters estimated by the model	Baseline value estimated at age 25 y	Variation estimated between 25 and 41.7 y	Variation estimated between 41.7 and 58.3 y	Variation estimated between 58.3 and 75 y
Total Free Recall	33	−1	**−5**	**−9**
Digit Cancellation Test	3.4	0	**+2**	**+1**
Symbol Digit Test	1.4	**+2**	**+2**	**+2**
Backward Digit Span	3	0	**0**	**0**
TMT A Time (s)	29	+1	**+16**	**+74**
TMT B Errors	0	0	**0**	**+1**
TMT B Time (s) and low education level	72	+30	**+61**	**+101**
TMT B Time (s) and high education level	72	−7	**+36**	**+188**
MDRS Total score	138	+3	**−4**	**−19**
VADAS-Cog Total score	27	+1	**+9**	**+15**
NIHSS	0	0	**+1**	**+2**
mRS	0	0	**+1**	**+1**
EQ VAS	81	−6	**−7**	**−8**

Abbreviations: EQ VAS = Visual Analog Scale of the 3-level EuroQol; MDRS = Mattis Dementia Rating Scale; mRS = modified Rankin scale; NIHSS = NIH Stroke Score; TMT = Trail Making Test; VADAS-Cog = Vascular Dementia Assessment Scale cognitive subscale.
The score values (rounded) estimated by the model at 25 years and their variations calculated at the limits of age tertiles are given. The variation over each age interval was considered significant (bold) when the scores estimated by the model at the boundaries of each age tertile were outside those estimated just at previous age (CIs are not shown).

Crossed Off Task, which showed much larger changes between 41.7 and 58.3 years (Tables 4 and 5).

Variable changes over time were also detected for other global clinical measures. Changes in the global disability assessed using the mRS, the NIHSS, and the Barthel Index (groups 1 and 2) were found mainly during intermediate-age and late-age intervals. Conversely, changes in the quality of life, measured by EQ VAS scores, occurred from the early stage of the disease onward.

Discussion

The results of this study show that cognitive decline not only develops gradually over several decades but also heterogeneously and depends on the cognitive ability evaluated and test used in CADASIL. Modeled evolution curves of different test scores vary widely in global amplitude and according to age. Although the Backward Digit Span remained essentially stable, a linear deterioration of scores obtained using the Symbol Digit Numbers or Number of Errors of TMT B was detected from 25 to 75 years. Conversely, changes observed using the Digit Cancellation Task show the largest variation occurring at midlife, with little or no significant change observed at the youngest or oldest ages. The progression of the other measures related to executive functions, memory performance, or global cognitive efficiency shows little or no variation at the onset of the disease, followed by an increase in changes that accelerates with aging.

Analysis of modeled curves allowed us to predict the potential extent of score changes over 3 age reference groups. Between 25 and 41.7 years, the first score to worsen is the Symbol Digit Number score, which primarily measures the speed of information processing.[37] In line, a trend toward an increase in TMT B Time by 30 seconds is also predicted over the same age interval in individuals with a low education level. The lack of significant results in highly educated patients might be related to the strong influence of education and practice effects on some aspects of cognitive processing speed.[38] Using a simple computer interface, we previously highlighted an increased reaction time for visual stimuli in patients with CADASIL for whom global cognitive abilities were preserved.[39] All these results converge on the hypothesis that cognitive processing can long exhibit an isolated and limited slowdown at the onset of the disease.

By contrast, between 41.7 and 58.3 years of age, the model predicts that Symbol Digit Number scores continue to deteriorate at the same rate but in combination with alterations of other cognitive skills. The large increase in time to completion of TMT A and B during this age interval is possibly related to the further increase of cognitive slowness.[22] The largest changes are detected using the Digit Cancellation Test

Table 5 Variations Estimated by the Latent-Process Model at the Limits of Age Tertiles for Scores With Heterogeneous Evolution (A Separate Group of Patients Presented With Earlier or Larger Score Changes [Group 1] Than the Rest of the Sample [Group 2])

	Baseline value estimated at age 25 y	Variation estimated between 25 and 41.7 y	Variation estimated between 41.7 and 58.3 y	Variation estimated between 58.3 and 75 y
Index of Sensitivity to Cueing				
Group 1	87	−10	**−7**	−1
Group 2	94	+3	**−4**	**−15**
Delayed Total Recall				
Group 1	14	−1	−1	−1
Group 2	16	0	0	0
Initiation/Perseveration subscore				
Group 1	36	−1	**−7**	**−12**
Group 2	35	+2	−1	**−8**
Barthel Index				
Group 1	100	−3	**−26**	**−25**
Group 2	99	0	−1	**−12**

The score values (rounded) estimated by the model at 25 years and their variations calculated at the limits of age tertiles are given in Table 4. The variation over each age interval was considered significant (bold) when the scores estimated by the model at the boundaries of each age tertile were outside those estimated just at previous age (CIs are not shown).

which evaluates both focused and selective attention.[19] This is observed in parallel with a reduction in the Initiation/Perseveration subscore, which mainly reflects a reduction in mental flexibility. These results are consistent because attentional control plays a key role in cognitive flexibility, defined as the ability to switch between different mental operations and strategies and to simultaneously override habitual responses.[38] The high effect of education on cognitive flexibility also explains the largest change in the Initiation/Perseveration subscore in our patients having the lowest education level.[40] In the same age interval, alterations in memory performance become detectable. The Total Free Recall is reduced, while the Index of Sensitivity to Cueing is only slightly decreased, and Delayed Total Recall is globally maintained. This indicates that memory retrieval of information is primarily affected, while the encoding of information remains largely preserved. Alterations in attention and mental flexibility might also be involved at this level.[41] Finally, at this stage, the decreases in VADAS-Cog and MDRS scores may simply result from all previous specific alterations leading to a global reduction in cognitive efficiency. This occurs when some motor disability and functional alterations are just appearing, but while most patients remain independent.

After the age of 57.3 years, the model shows a steep acceleration of cognitive decline and disability. All chronometric measures related to mental processing speed, attention, and executive dysfunction showed the greatest increase. Memory performances and global efficiency scores drop sharply. Significant changes in TMT B accuracy also occur at this stage, possibly reflecting severe frontal dysfunction.[42,43] Surprisingly, no significant change in the Backward Digit Span score is predicted by the model. This test has been previously linked to working memory and planning ability, as well as visual image processing.[44,45] Our results may indicate that the underlying cognitive processes are essentially preserved during disease progression, but a poor sensitivity of the test to moderate working memory changes cannot be excluded.

Four measures, the Initiation/Perseveration subscale, Index of Sensitivity to Cueing, Delayed Total Recall and Barthel Index, do not follow a homogeneous progression across the entire study sample. For these tests, a group of individuals present with an earlier or larger decline in performance compared with the others. Depending on the test, these groups are of variable size, ranging from 22 to 60 individuals, half of whom belonged to another group (data not shown). This separation into distinct groups is possibly related to some intrinsic properties of each corresponding measure. Thus, the difference detected between the heterogeneous course of the Initiation/Perseveration subscore of the MDRS compared with the homogeneous variation in the global MDRS score illustrates that some specific cognitive changes occurring early in a distinct group of patients might be masked by a more global measure. These results may also support that some individuals within the study population really have a different evolution profile and may worsen much more rapidly than the other participants on some specific clinical aspects.

The results of this study are important for designing future clinical trials in ischemic cSVD, and particularly in CADASIL. Because clinical trials can be performed over a limited time frame, most likely less than 2 or 3 years, the present results support the conclusion that outcome metrics for measuring cognitive or clinical changes should be carefully selected during such a limited period. Our study suggests that, during the first 2 decades overall after the age of 25 years, only measures highly sensitive to processing speed should be considered. At this stage, only white-matter lesions are usually detected on cerebral MRI in patients with CADASIL.[5,46,47] Their location within the forceps minor or along the thalamofrontal tracts might be responsible for cognitive slowdown.[48] In this study, only limited variations are detected using the Symbol Digit Test. Additional studies are thus needed to determine which tests should be used for capturing the limited changes in cognitive processing speed when white-matter lesions are just appearing or expand slowly. Later, over the next 2 decades, the choice of cognitive tests capable of capturing variations over 2–3 years seems easier. Our results suggest that measures sensitive to cognitive speed, attention, and executive dysfunction should be used. Chronometric measures showing the largest changes seem to be of particular interest. A combination of cognitive measures may also represent an alternative approach for capturing the larger spectrum of cognitive alterations. The VADAS-Cog Total score seems a promising approach.[14] An average variation of 9 points is predicted by our model over 17 years. Conversely, the modeled variation of the MDRS score, which is limited to 4 points over the same age interval, does not seem to be of sufficient amplitude to be recommended as a unique outcome. Finally, at the latest stage of the disease, the same tools, including the MDRS, could be proposed because their largest modifications are detected after the fifth decade.

Our results also suggest that some predictors may help identify patients with the highest risk of cognitive or clinical changes, particularly when memory performance, executive dysfunction, or functional dependence are targeted. Patients with some initial manifestations of disability or gait alterations might be at the highest risk of rapid cognitive decline, as previously reported in a 3-year longitudinal study.[11] In contrast to all other cognitive or clinical test measures, the EuroQol score decreases progressively and linearly from 25 years, which does not seem related to changes in disability or cognitive scores. The multidimensional nature of quality of life, which includes various psychological, social, cultural, and economic aspects in addition to health status, might explain this discrepancy.[25,49]

This study has a number of limitations. Our study sample does not represent the entire population of patients with CADASIL. Our cohort participants were selected from our National Referral Centre, which only includes volunteers who can travel. Moreover, only individuals who had at least 1 measure for each of the 16 scores during the follow-up were included in the analysis. Consequently, patients at the most severe clinical stage who could not be assessed repeatedly are most likely underrepresented. On the other hand, we think that our sample is conversely well representative of the individuals who might be included in future therapeutic trials. The exclusion of incomplete data from analysis represents another potential selection bias. However, our results did not differ after including all data collected and using multiple imputations for lacking results. Another potential limitation is that, as age was considered as the time scale, this study is unable to discriminate effects related to aging from those related to the disease itself as often reported in studies of long-term degenerative disorders. Unfortunately, age at clinical onset is also particularly difficult to determine in this condition which may start by attacks of migraine with aura which are inconsistent and unrelated to the clinical severity or by subtle cognitive impairment particularly difficult to identify.

The study also has multiple strengths. The amount of data is considerable, particularly for such a rare disease. The neuropsychological measures assessed through a large battery of tests were selected by consensus as those that best reflect the most salient cognitive features of the disease. Our data were also acquired in multiple individuals of different ages and at very different stages of the disease. Thus, their evaluation at multiple time points allows mimicking a continuous collection of information. Finally, latent process modeling used to delineate their trajectories is a robust method considering missing at random data.

Finally, we think that these long-term cognitive changes delineated in CADASIL may indicate that the tools used to assess cognitive decline in similar conditions must be chosen with extreme caution depending on the rate of progression of the underlying disease, the duration of the study, and the stage of disease progression.

Acknowledgment

The authors warmly thank the team in charge of formatting and cleaning the database using multiple information collected over 14 years from different sources and which made possible this study, particularly Prof. Sylvie Chevret and Mrs. Claire Pacheco (INSERM UMR1136). The authors thank very much Mr. Abbas Taleb responsible for collecting most of information along the cohort study, Mrs. Solange Hello who managed and organized the appointment of multiple family members involved in the study, Mrs. Jocelyne Ruffie, Mrs. Annie Kurtz, and Prof. M.G. Bousser who had a crucial role when we initiated the collection of these data. The authors also thank the CADASIL France Association for their help and permanent support.

Study Funding

This research was supported by the ANR grant: RHU TRT_cSVD (ANR:16-RHUS-0004) and also by the Association ARNEVA (Association de Recherche en Neurologie Vasculaire).

Disclosure

The authors report no relevant disclosures. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* January 3, 2022. Accepted in final form April 14, 2022. Submitted and externally peer reviewed. The handling editor was Linda Hershey, MD, PhD, FAAN.

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References

1. Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. *Lancet Neurol*. 2010;9(7):689-701.
2. Erkinjuntti T. Subcortical ischemic vascular disease and dementia. *Int Psychogeriatr*. 2003;15(suppl 1):23-26.
3. Akinyemi RO, Mukaetova-Ladinska EB, Attems J, Ihara M, Kalaria RN. Vascular risk factors and neurodegeneration in ageing related dementias: Alzheimer's disease and vascular dementia. *Curr Alzheimer Res*. 2013;10(6):642-653.
4. Joutel A, Corpechot C, Ducros A, et al. Notch3 mutations in CADASIL, a hereditary adult-onset condition causing stroke and dementia. *Nature*. 1996;383(6602):707-710.
5. Chabriat H, Joutel A, Tournier-Lasserve E, Bousser MG. CADASIL: yesterday, today, tomorrow. *Eur J Neurol*. 2020;27(8):1588-1595.
6. Charlton RA, Morris RG, Nitkunan A, Markus HS. The cognitive profiles of CADASIL and sporadic small vessel disease. *Neurology*. 2006;66(10):1523-1526.
7. Joutel A, Andreux F, Gaulis S, et al. The ectodomain of the Notch3 receptor accumulates within the cerebrovasculature of CADASIL patients. *J Clin Invest*. 2000;105(5):597-605.
8. Dichgans M, Mayer M, Uttner I, et al. The phenotypic spectrum of CADASIL: clinical findings in 102 cases. *Ann Neurol*. 1998;44(5):731-739.

9. Chabriat H, Vahedi K, Iba Zizen MT, et al. Clinical spectrum of CADASIL: a study of 7 families. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. *Lancet*. 1995;346(8980):939-939.
10. Viswanathan A, Guichard JP, Gschwendtner A, et al. Blood pressure and haemoglobin A1c are associated with microhaemorrhage in CADASIL: a two-centre cohort study. *Brain*. 2006;129(pt 9):2375-2383.
11. Chabriat H, Hervé D, Duering M, et al. Predictors of clinical worsening in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy: prospective cohort study. *Stroke*. 2016;47(1):4-11.
12. Shay KA, Duke LW, Conboy T, Harrell LE, Callaway R, Folks DG. The clinical validity of the Mattis Dementia Rating Scale in staging Alzheimer's dementia. *J Geriatr Psychiatry Neurol*. 1991;4(1):18-25.
13. Lucas JA, Ivnik RJ, Smith GE, et al. Normative data for the Mattis Dementia Rating Scale. *J Clin Exp Neuropsychol*. 1998;20(4):536-547.
14. Madureira S, Verdelho A, Ferro J, et al. Development of a neuropsychological battery for the Leukoaraiosis and Disability in the Elderly Study (LADIS): experience and baseline data. *Neuroepidemiology*. 2006;27(2):101-116.
15. Marson DC, Dymek MP, Duke LW, Harrell LE. Subscale validity of the Mattis Dementia Rating Scale. *Arch Clin Neuropsychol*. 1997;12:269-275.
16. Ferris SH. General measures of cognition. *Int Psychogeriatr*. 2003;15(suppl 1): 215-217.
17. Grober E, Lipton RB, Hall C, Crystal H. Memory impairment on free and cued selective reminding predicts dementia. *Neurology*. 2000;54(4):827-832.
18. Epelbaum S, Benisty S, Reyes S, et al. Verbal memory impairment in subcortical ischemic vascular disease: a descriptive analysis in CADASIL. *Neurobiol Aging*. 2011; 32(12):2172-2182.
19. Hatta T, Yoshizaki K, Mase M, Ito Y, Kabasawa H. Reliability and validity of the digit cancellation test, a brief screen of attention. *Psychologia*. 2012;55(4):246-256.
20. Peters N, Opherk C, Danek A, Ballard C, Herzog J, Dichgans M. The pattern of cognitive performance in CADASIL: a monogenic condition leading to subcortical ischemic vascular dementia. *Am J Psychiatry*. 2005;162(11):2078-2085.
21. Giovagnoli AR, Del Pesce M, Mascheroni S, Simoncelli M, Laiacona M, Capitani E. Trail making test: normative values from 287 normal adult controls. *Ital J Neurol Sci*. 1996;17(4):305-309.
22. Bowie CR, Harvey PD. Administration and interpretation of the Trail Making Test. *Nat Protoc*. 2006;1(5):2277-2281.
23. Adams HP, Davis PH, Leira EC, et al. Baseline NIH Stroke Scale score strongly predicts outcome after stroke: a report of the Trial of Org 10172 in Acute Stroke Treatment (TOAST). *Neurology*. 1999;53(1):126-131.
24. Granger CV, Dewis LS, Peters NC, Sherwood CC, Barrett JE. Stroke rehabilitation: analysis of repeated Barthel index measures. *Arch Phys Med Rehabil*. 1979;60(1): 14-17.
25. Naess H, Lunde L, Brogger J. The effects of fatigue, pain, and depression on quality of life in ischemic stroke patients: the Bergen Stroke Study. *Vasc Health Risk Manag*. 2012;8:407-413.
26. Barbizet J. *Human Memory and its Pathology*. Freeman, 1970.
27. American Psychological Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. APA, 1994.
28. Han J, Slate EH, Peña EA. Parametric latent class joint model for a longitudinal biomarker and recurrent events. *Stat Med*. 2007;26(29):5285-5302.
29. Proust-Lima C, Sene M, Taylor JM, Jacqmin-Gadda H. Joint latent class models for longitudinal and time-to-event data: a review. *Stat Methods Med Res*. 2014;23:74-90.
30. Proust C, Jacqmin-Gadda H, Taylor JM, Ganiayre J, Commenges D. A nonlinear model with latent process for cognitive evolution using multivariate longitudinal data. *Biometrics*. 2006;62(4):1014-1024.
31. Proust-Lima C, Dartigues JF, Jacqmin-Gadda H. Joint modeling of repeated multivariate cognitive measures and competing risks of dementia and death: a latent process and latent class approach. *Stat Med*. 2016;35(3):382-398.
32. Brice S, Jabouley A, Reyes S, et al. Modeling the cognitive trajectory in CADASIL. *J Alzheimers Dis*. 2020;77(1):291-300.
33. Jorm AF, Scott R, Henderson AS, Kay DW. Educational level differences on the Mini-Mental State: the role of test bias. *Psychol Med*. 1988;18(3):727-731.
34. Tombaugh T, McIntyre N. The mini-mental state examination: a comprehensive review. *J Am Geriatr Soc*. 1992;40:922-935.
35. R Core Team. *R: A Language and Environment for Statistical Computing*. Foundation for Statistical Computing, 2018.
36. Proust-Lima C, Philipps V, Liquet B. Estimation of extended mixed models using latent classes and latent processes: the R package lcmm. *J Stat Softw*. 2017;78(72):1-56.
37. Joy S, Fein D, Kaplan E. Decoding digit symbol: speed, memory, and visual scanning. *Assessment*. 2003;10(1):56-65.
38. MacPherson SE, Cox SR, Dickie DA, et al. Processing speed and the relationship between Trail Making Test-B performance, cortical thinning and white matter microstructure in older adults. *Cortex*. 2017;95:92-103.
39. Jouvent E, Reyes S, De Guio F, Chabriat H. Reaction time is a marker of early cognitive and behavioral alterations in pure cerebral small vessel disease. *J Alzheimers Dis*. 2015;47(2):413-419.
40. Delgado-Losada ML, Rubio-Valdehita S, Lopez-Higes R, et al. How cognitive reserve influences older adults' cognitive state, executive functions and language comprehension: a structural equation model. *Arch Gerontol Geriatr*. 2019;84:103891.
41. Madore KP, Khazenzon AM, Backes CW, et al. Memory failure predicted by attention lapsing and media multitasking. *Nature*. 2020;587(7832):87-91.
42. McCaffrey RJ, Krahula MM, Heimberg RG. An analysis of the significance of performance errors on the Trail Making Test in polysubstance users. *Arch Clin Neuropsychol*. 1989;4(4):393-398.
43. Christidi F, Kararizou E, Triantafyllou NI, Paraskevas GP, Zalonis I. Trail Making Test error analysis in classic motor neuron disease. *Neurol Sci*. 2013;34(8):1367-1374.
44. Gregoire J, Van Der Linden M. Effect of age on forward and backward digit spans. *Aging Neuropsychol Cogn*. 2007;4:140-149.
45. Hoshi Y, Oda I, Oda M, et al. Visuospatial imagery is a fruitful strategy for the digit span backward task: a study with near-infrared optical tomography. *Brain Res Cogn Brain Res*. 2000;9(3):339-342.
46. Chabriat H, Joutel A, Dichgans M, Tournier-Lasserve E, Bousser MG. Cadasil. *Lancet Neurol*. 2009;8(7):643-653.
47. Chabriat H, Levy C, Taillia H, et al. Patterns of MRI lesions in CADASIL. *Neurology*. 1998;51(2):452-457.
48. Duering M, Zieren N, Herve D, et al. Strategic role of frontal white matter tracts in vascular cognitive impairment: a voxel-based lesion-symptom mapping study in CADASIL. *Brain*. 2011;134(pt 8):2366-2375.
49. Gudex C, Dolan P, Kind P, Williams A. Health state valuations from the general public using the Visual Analogue Scale. *Qual Life Res*. 1996;5(6):521-531.

Trajectory Pattern of Cognitive Decline in Cerebral Autosomal Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy

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Neurology 2022;99;e1019-e1031 Published Online before print June 15, 2022
DOI 10.1212/WNL.0000000000200805