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Original Article

Elderly CADASIL Patients with Intact Neurological Status

Ruiting Zhang,[a,b] Elisa Ouin,[c] Lina Grosset,[a,d] Karine Ighilkrim,[e] Jessica Lebenberg,[a,d] Stéphanie Guey,[a,d] Véronique François,[e] Elisabeth Tournier-Lasserve,[a,f] Eric Jouvent,[a,d] Hugues Chabriat[a,d]

[a]Paris-Cité University, Inserm U1141 NeuroDiderot, Paris, France
[b]Department of Radiology, the Second Affiliated Hospital of Zhejiang University, School of Medicine, Hangzhou, China
[c]Department of Neurology, Amiens University Hospital, Laboratory of Functional Neurosciences1,6 (UR UPJV 4559), Jules Verne Picardy University, Amiens, France
[d]Lariboisière University Hospital, APHP, Translational Neurovascular Centre and Department of Neurology, Reference Center for Rare Vascular Diseases of the Central Nervous System and the Retina (CERVCO), FHU NeuroVasc, Paris, France
[e]Department of Geriatrics, Lariboisière University Hospital, APHP, Paris, France
[f]Department of Neurovascular Molecular Genetics, Saint-Louis Hospital, APHP, Paris, France

Background and Purpose Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is one of the most devastating cerebral small vessel diseases. However, despite its progression with aging, some patients remain neurologically intact (N_{int}) even when they get older. Their main characteristics are poorly known. We aimed to delineate their clinical, imaging, and molecular features.

Methods Individuals aged over 65 years were selected from a cohort of 472 CADASIL patients. Subjects who had no focal deficit, cognitive impairment, or disability were considered N_{int}. Their demographic, genetic, clinical, and imaging features were compared to those with permanent neurological symptoms (N_{ps}).

Results Among 129 patients, 23 (17.8%) individuals were considered N_{int}. The frequency of vascular risk factors and *NOTCH3* cysteine mutations in epidermal growth factor-like repeat (EGFr) domains 7-34 did not differ between N_{int} and N_{ps} patients but N_{int} patients had less stroke events and were more likely to have migraine with aura. The number of lacunes and microbleeds and degree of brain atrophy were lower in the N_{int} group, but the volume of white matter hyperintensities did not differ between the two groups.

Conclusions Nearly one in five CADASIL patients can remain N_{int} after the age of 65 years. Their clinical and imaging profile differed from that of other age-matched CADASIL patients. The location of *NOTCH3* mutation inside or outside EGFr domains 1-6 cannot fully explain this discrepancy. The factors involved in their relative preservation of brain tissue from severe damage despite aging remain to be determined.

Keywords CADASIL; Cerebral small vessel diseases; Magnetic resonance imaging; Aging; Mutation

Correspondence: Hugues Chabriat
Centre NeuroVasculaire Translationnel, Hôpital Lariboisière, 2 rue Ambroise Paré, 75010 Paris, France
Tel: +33-1-49952593
Fax: +33-1-49952596
E-mail: hugues.chabriat@aphp.fr
https://orcid.org/0000-0001-8436-6074

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Introduction

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is the most common inherited cerebral small vessel disease (cSVD).[1] Although the spectrum of clinical manifestations appears very broad and their severity highly varies over decades of disease progression, motor disability and cognitive decline develop inexorably in most older patients with a confirmed diagnosis of CADASIL. In one of the largest samples reported so far, more than 90% of patients aged more than 65 years already experienced one or more strokes and half were severely demented and bedridden.[2] The median life expectancy was estimated around 65 years in men and 71 years in women.[2] Similar findings have been reported in multiple large cohorts of symptomatic patients.[3,4] Thus, although its rate of clinical progression appears highly variable over decades, CADASIL is mainly considered to be one of the most devastating cSVDs that, ultimately, always converges to severe disability with increasing age.[1]

In addition to age, different factors have been identified as potentially modulating the disease progression along aging. The ε2 allele of apolipoprotein E was found associated with a larger volume of white matter hyperintensities (WMHs),[5] male sex with a higher risk of cognitive decline and more lacunes and cerebral atrophy,[6] smoking with earlier and more incident stroke events,[7] higher blood pressure with an increased risk of cognitive decline.[8] More recently, after typical *NOTCH3* mutations in domains 7-34 were discovered at an unexpectedly high frequency in the general population, the location of cysteine mutations in epidermal growth factor-like repeat (EGFr) domains 1-6 versus 7-34 was also shown to have a strong detrimental effect on this clinical variability.[9] Some elderly individuals having mutations in EGFr domains 7-34 were even found to present with very limited cerebral lesions.[10] This does not rule out that patients with variants located in EGFr domain 1-6 cannot remain neurologically intact (N_{int}) or stable.[11]

In parallel, during the recent decade and with the spread of genetic testing, diagnosis of CADASIL has been broadened to include patients with more atypical symptoms or much less severe clinical picture. Moreover, the sensitivity of genetic testing in daily practice has been improved by allowing the search of cysteine mutations in all exons encoding for EGFr domains whereas the diagnostic test was initially limited to only few exons. Thus, the number of elderly patients diagnosed with the disease has increased, not only because of the aging of patients diagnosed many years ago but also because of the increased diagnostic rate in the elderly even in presence of transient or benign neurological manifestations or after incidental discovery of white matter signal changes.

Specific analysis of cases who remain neurologically normal despite the significant advancement in age may provide insight into the different sources of clinical variability in the presence of *NOTCH3* gene mutations. The demographics, clinical, imaging, and genotype characteristics of this population remain however poorly understood. In the present study, we aimed to better delineate these features by comparing elderly CADASIL patients with intact neurological status to the other patients of identical age but with some permanent symptoms.

Methods

Patients

All patients over 65 years of age at their last follow-up visits were selected for the present study from a long-term prospective cohort of 472 CADASIL patients. These patients were recruited at the National Referral Center for Rare Cerebrovascular disorders in France (CERVCO, www.cervco.fr) from September 2003 up to November 2021. All of them harbored a typical cysteine mutation within the *NOTCH3* gene and gave their written consent for collecting their biological, clinical, and imaging data according to a detailed predefined protocol[12] during their follow-up.[13] This study was approved by an independent ethics committee (updated agreement CEEI-IRB-17/388) and conducted in accordance with the Declaration of Helsinki and guidelines for Good Clinical Practice and General Data Protection Regulation (GDPR) in Europa.

Clinical parameters

All clinical and demographic data were collected at study entry and updated during follow-up. They included age, sex, years of education, and vascular risk factors. History of hypertension was defined as a previous diagnosis of hypertension (blood pressure >140/90 mm Hg) or use of antihypertensive treatment for control of blood pressure. Blood pressure was also measured at baseline and at follow-up visits. "Current smoking" was defined as active smoker at baseline, while "ever smoker" was defined as active smoker or past smoker. A history of transient ischemic attacks (TIAs) or stroke, and dementia defined according to Diagnostic and Statistical Manual of Mental Disorders (5th edition), were obtained at baseline and at follow-up visits. Subjects were regularly interviewed and evaluated for cognitive impairments. They also underwent a detailed neurological and neuropsychological examination at each follow-up visit. Any focal neurological deficit was systematically recorded, and the National Institutes of Health Stroke Scale (NIHSS) was assessed at each visit. Disability was measured using the

modified Rankin Scale (mRS) by experienced neurologists. Patients with disabilities due to other causes were not included in the study. Global cognitive function was evaluated by a neuropsychologist with over 10-year experience using the Mattis Dementia Rating Scale (MDRS) and Mini-Mental State Examination (MMSE). The cognitive evaluation included the Trail Making Test Part A (TMT A) and Part B (TMT B) tests as a measure of executive function.[14] The cut-off values for normality of each cognitive test were determined according to the patients' education level and age respectively. These values were for the MDRS scores, if <12 years of education, ≥122, ≥120, ≥118, and ≥114 at age <78, 78–80, 81–83, and 84–86 years; if ≥12 years, ≥133, ≥132, ≥131, ≥130, ≥129, and ≥128, at age <72, 72–74, 75–77, 78–80, 81–83, and 84–86 years; for the MMSE scores, if <9 years of education, ≥25; if 9–13 years, ≥27 and if >13 years, ≥28; for the TMT A time, if <6 years of education, ≤54, ≤60, and ≤90s at age <70, 70–79, and ≥80 years; if 6–11 years, ≤48 and ≤76s at age <80 and ≥80 years; if ≥12 years, ≤44 and ≤64s at age <80 and ≥80 years; for the TMT B time, if <6 years of education, ≤186, ≤196, and ≤212s; if 6–11 years, ≤133, ≤187, and ≤212s and; if ≥12 years, ≤129, ≤136, and ≤189s, always at age <70, 70–79, and ≥80 years.

Magnetic resonance imaging data

Details of the magnetic resonance imaging (MRI) protocol and sequences used in this study have been previously detailed extensively.[15,16] In brief, the MRI examination included three-dimensional millimetric T1-weighted (3D-T1), fluid-attenuated inversion recovery (FLAIR), diffusion weighted images (DWI), and T2*-weighted gradient-echo images or susceptibility weighted (SW) images. In the present study, cerebral lesions were systematically assessed by an experienced neuroradiologist blinded to the clinical characteristics of the patients and according to the STandards for ReportIng Vascular changes on nEuroimaging (STRIVE) criteria.[17]

Lacunes were identified on 3D-T1 images by two expert neurologists (H.C., L.G.) or a neuroradiologist (R.Z.) as round or ovoid, subcortical, fluid-filled cavities (with a signal similar to that of CSF) of diameter from 3 to 15 mm. A special attention was given to differentiate these lesions from enlarged perivascular spaces according to their size, shape, and rim. Recent small subcortical infarcts were sought on DWI images obtained at last visit as an hyperintense lesion located in the territory of a perforating artery and less than 20 mm in its maximum diameter. The number of microbleeds was determined after reading T2* or SW images after counting focal, small, rounded or circular, hypointense lesions within the brain parenchyma with clear margins and ranging from 2 to 10 mm in diameter.

The volume of WMHs was finally calculated in each subject using the Brain Intensity AbNormality Classification Algorithm (BIANCA, https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/)[18] segmentation tool, a fully automated, non-parametric, learning supervised method based on the k-nearest neighbor algorithm which was previously adapted to CADASIL patients.[16] The total volume of WMHs was normalized to the intracranial cavity (ICC) in each patient [normalized WMHs volume = (WMHs volume / ICC volume) × 100%].

The Fazekas scale was used separately for rating WMHs visually in different locations. Periventricular WMHs were graded as absent (grade 0), caps (grade 1), smooth halos (grade 2), or irregular and extending into the subcortical white matter (grade 3). Deep WMHs were graded as absent (grade 0), punctate foci (grade 1), early-confluent (grade 2), or confluent (grade 3).[19] WMHs in the temporal poles were assessed separately also using this latter grading.

Finally, brain atrophy was assessed after the segmentation of the whole brain tissue and of the ICC as previously reported.[20] This allowed to calculate the brain parenchymal fraction as the ratio of the brain tissue volume to the ICC volume.

Statistical analysis

All patients over 65 years of age at their last follow-up visit were dichotomized in two groups according to their clinical status. They were considered as N_{int} group if they fulfilled all the following criteria: (1) no focal deficit at neurological examination and NIHSS at 0; (2) lack of any significant disability and mRS ≤1; (3) no cognitive impairment and normal MDRS score according to age and education level or normal scores for both MMSE, TMT A time and TMT B time when the MDRS score was not available.[21] Patients with transient and benign manifestations such as migraine with aura or mood changes were included in the N_{int} group. All other patients older than 65 years belonging to the cohort were considered to present some permanent neurological symptoms (N_{ps}) or signs of the disease and grouped separately.

Fisher's exact test was used to compare the dichotomous variables between groups, while Mann-Whitney U test (for data with non-normal distributions) and Student's t-test (for data with normal distributions) was used for the continuous variables. All analyses were performed blinded to the participant identifying information. Statistical significance was set at a probability value of <0.05. All statistical analysis was performed with an SPSS package version 22.0 for Windows (IBM Co., Armonk, NY, USA).

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Results

One hundred and twenty-nine patients whose age was higher than 65 years at their last follow-up visit were selected from the entire cohort. Among them, 60.5% were women. The mean age at last visit was 72±5 years (median age, 72; interquartile range, 68 to 74). Eighty-nine patients (69.0%) were identified as the first family case at inclusion.

Among the 129 elderly selected CADASIL patients, 23 (17.8%) individuals were considered as N_{int}. Their main characteristics are summarized in Table 1. Thirteen of them were diagnosed after MRI evaluation of attacks of migraine with aura, one after the occurrence of repeated isolated auras, three had stroke and one had TIA, three had an MRI after a depressive episode associated in one case with chronic headache, and one patient had syncope-like episodes. Only in one patient, MRI and genetic testing were performed after the diagnosis of CADASIL in her brother who had a recent ischemic stroke. Vascular risk factors were present in 65% of N_{int} subjects, hypertension was diagnosed in 26% of them.

The comparison between N_{int} and N_{ps} patients is detailed in Table 2. The results showed that age, the sex ratio, and frequency of vascular risk factors did not differ between the two groups. Migraine with aura were significantly more frequent in the N_{int} than in the N_{ps} group. Notably, N_{int} patients had significantly less stroke than the N_{ps} patients. Transient episode of mood disturbance, such as episodes of anxiety or depression that needed a medical treatment, in the N_{int} group were significantly less frequent than in the N_{ps} group. Also, the different clinical scores (mRS, Barthel index, NIHSS, MMSE, and MDRS) obtained in each group confirmed the large clinical integrity of N_{int} patients compared to the N_{ps} group. The same differences were observed from inclusion in the study when only baseline data were considered in the analysis (Supplementary Table 1).

The analysis of MRI parameters detailed in Table 3 showed that the volume of WMHs did not differ between the N_{int} and N_{ps} group, nor did the Fazekas scores obtained separately for the periventricular and deep WMHs. Conversely, the load of lacunes and microbleeds largely differ between the two groups.

Table 1. Characteristics of the N_{int} patients

N_{int} patients	Age (yr)	Sex	First symptom	Stroke history	Exon	Protein	EGFr	Vascular risk factors
1	70	M	Migraine with aura	No	4	R133C	3	No
2	76	F	Migraine with aura	No	4	R133C	3	HT, smoking
3	68	F	Migraine with aura	No	4	R133C	3	No
4	68	F	MRI after stroke in her 38 years old brother	No	4	R133C	3	No
5	72	F	Migraine with aura	Yes	4	R133C	3	Smoking
6	65	M	Depression episode	Yes	4	R133C	3	HT, diabetes, HChol
7	70	M	Migraine with aura	Yes	4	C222G	5	HT, HChol
8	72	F	Migraine with aura	No	4	R182C	4	HT, diabetes, HChol
9	71	F	Depression episode	No	3	R90C	2	Smoking, alcohol
10	72	F	Transient ischemic attack	Yes	5	C251R	6	HChol, alcohol
11	73	M	Isolated auras	No	4	R182C	4	HChol
12	70	F	Migraine with aura	Yes	10	C522S	13	HT, HChol
13	77	F	Migraine with aura	Yes	11	R607C	15	Alcohol
14	76	M	Stroke	Yes	11	R558C	14	HChol, alcohol
15	75	F	Stroke	Yes	11	R592C	15	Alcohol
16	66	F	Syncope-like episodes	Yes	11	R558C	14	No
17	72	M	Migraine with aura	No	6	C338S	8	HT, HChol, alcohol
18	66	F	Migraine with aura	No	20	C1099Y	28	No
19	70	F	Chronic headache and depression	No	11	R578C	14	No
20	74	F	Migraine with aura	Yes	18	R985C	25	HChol
21	66	M	Migraine with aura	No	11	R607C	15	No
22	66	F	Migraine with aura	No	22	R1201C	30	HChol
23	71	M	Stroke	Yes	24	C1315Y	33	No

N_{int}, neurologically intact; EGFr, epidermal growth factor-like repeat; HT, hypertension; MRI, magnetic resonance imaging; HChol, hypercholesterolemia.

Table 2. Comparison of the main demographic, clinical and genetic features between N_{int} and N_{ps} patients

	N_{int} patients (n=23)	N_{ps} patients (n=106)	*P*
Age at inclusion (yr)	63 (60–69)	67 (61–70)	0.127
Age at last visit (yr)	71 (68–73)	72 (68–74)	0.362
Female sex	15 (65.2)	63 (59.4)	0.647
Education (yr)	12 (9–17)	9 (6–12)	0.014
Systolic blood pressure (mm Hg)	128 (112–149)	132 (119–142)	0.678
Diastolic blood pressure (mm Hg)	77 (67–89)	75 (69–84)	0.907
Vascular risk factors			
Hypertension	6 (26.1)	30 (28.3)	1.000
Diabetes mellitus	2 (8.7)	11 (10.4)	1.000
Hypercholesterolemia	10 (43.5)	56 (52.8)	0.493
Current smoking	3 (13.0)	5 (4.7)	0.151
Ever smoker	11 (47.8)	37 (34.9)	0.341
Alcohol consumption	6 (26.1)	46 (43.4)	0.374
Clinical manifestations			
Migraine with aura	13 (56.5)	34 (32.1)	0.033
Migraine without aura	7 (30.4)	22 (20.8)	0.408
Positive history of stroke	11 (47.8)	75 (70.8)	0.050
Number of stroke episodes	0 (0–1)	1 (0–2)	0.003
Any cognitive impairments	0 (0)	67 (63.2)	< 0.001
Dementia	0 (0)	17 (16.0)	0.041
Transient episode of mood disturbance	4 (17.4)	47 (44.3)	0.019
Seizures	0 (0)	14 (13.2)	0.073
Clinical scales			
Severe disability preventing cognitive testing	0 (0)	15 (14.2)	0.071
mRS	1 (1–1)	3 (2–4)	<0.001
Barthel index	100 (100–100)	95 (55–100)	<0.001
NIHSS	0 (0–0)	1 (0–3)	<0.001
MMSE	29 (28–30)	24 (20–27)	<0.001
MDRS	141 (139–142)	126 (105–138)	<0.001
EGFr domain 1-6	11 (47.8)	53 (50.0)	1.000

Values are presented as median (interquartile range) or number (%).
N_{int}, neurologically intact; N_{ps}, with permanent neurological symptoms; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; MMSE, Mini-Mental State Examination; MDRS, Mattis Dementia Rating Scale; EGFr, epidermal growth factor-like repeat.

Table 3. Comparison of MRI data between N_{int} and N_{ps} patients

	N_{int} patients (n=23)	N_{ps} patients (n=96)	*P*
Brain parenchymal fraction (%)	80.0 (77.9–83.0)	76.4 (73.7–79.6)	<0.001
WMHs volume (mL)	97.6 (56.1–124.3)	99.4 (57.9–155.1)	0.340
Normalized WMHs (%)	6.5 (4.0–8.9)	6.7 (4.2–11.6)	0.354
Fazekas periventricular WMHs score	3 (3–3)	3 (3–3)	0.221
Fazekas deep WMHs score	3 (3–3)	3 (3–3)	0.312
Score of WMHs in temporal poles	2 (1–3)	3 (1–3)	0.109
Presence of lacune	17 (73.9)	87 (90.6)	0.073
Total lacune number	3 (0–9)	10 (4–16)	0.001
Presence of microbleeds	12 (52.2)	73 (76.0)	0.038
Total microbleeds number	1 (0–7)	5 (1–24)	0.016
Presence of RSSI	0 (0)	20 (20.8)	0.012

Values are presented as median (interquartile range) or number (%). In 10 patients of the N_{ps} group imaging data could not be assessed (two patients did not have MRI at day of clinical examination, in seven cases imaging data were of poor quality, in another case errors were detected using the Brain Intensity Ab-Normality Classification Algorithm [BIANCA] processing).
MRI, magnetic resonance imaging; N_{int}, neurologically intact; N_{ps}, with permanent neurological symptoms; WMH, white matter hyperintensity; RSSI, recent small subcortical infarct.

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N_{int} patient also present with a higher normalized brain volume than N_{ps} patients. These results did not differ when only patients from distinct families were considered in the analysis (comparison restricted to only the first family members participating to the cohort study and considered as "index" patients, see Supplementary Tables 2 and 3).

The main imaging findings in the 23 N_{int} patients are summarized using FLAIR images on Figures 1 and 2. These data clearly confirmed the large variability in the load of WMHs in N_{int} patients whose normalized WMHs volume was ranging from 1.0% to 13.3%. Eleven patients harbored a variant located in EGFr domains 1-6, while 12 patients harbored a variant located in EGFr domains 7-34. The figures showed that patients with variants in EGFr domain 1-6 had a higher load of

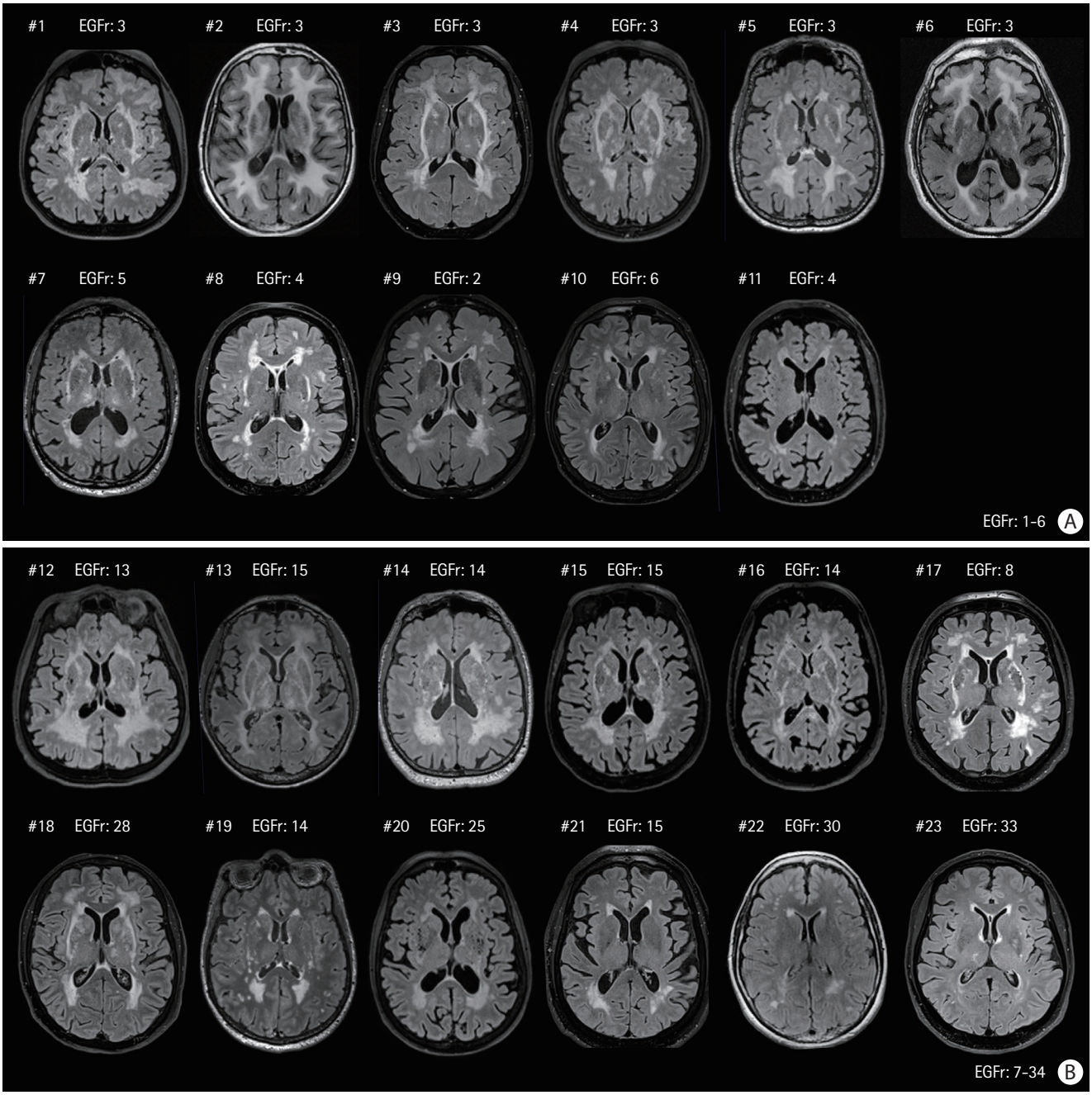

Figure 1. Magnetic resonance fluid-attenuated inversion recovery images of the 23 elderly neurologically intact (N_{int}) patients at the level of basal ganglia. (A) Eleven patients had their cysteine mutation in epidermal growth factor-like repeat (EGFr) domain 1-6 (Patient #1 to #11), (B) 12 others in EGFr domain 7-34 (Patient #12 to #23). Only three patients (Patient #1, #2, and #5) were from the same family. The patients were sorted according to their white matter hyperintensities load (from the highest to the lowest) in the two EGFr groups, respectively.

WMHs than patients with variants in EGFr domain 7-34 (normalized WMHs volume, 8.9% vs. 5.2%, *P*=0.027), especially in the temporal poles (WMHs score, 3 vs. 1, *P*=0.023). In the entire group (including both N_{int} and N_{ps} individuals), patients with variants in EGFr domain 1-6 also had a higher load of WMHs in the temporal poles than the others with variants in EGFr domain 7-34 (WMHs score, 3 vs. 2, *P*<0.001), but the total lesion load did not differ between the two groups (normalized WMHs volume, 8.0% vs. 6.3%, *P*=0.234). The results did not change when only the subgroup of N_{int} patients who never had a stroke (n=12) was compared to all other patients older than 65 years (n=117, see Supplementary Tables 4 and 5).

Discussion

In this large prospective cohort of patients diagnosed with CADASIL, we observed that 17.8% of individuals can remain N_{int} despite their age extending beyond 65 and up to 76 years. Only anecdotal elderly cases up to 86 years have been previously described in the literature as "minimally symptomatic," "pauci-symptomatic," or "with no history of stroke or vascular cognitive decline."[9,22-30] In the present study, the drastic selection of N_{int} cases from a large sample of consecutive elderly patients allows, for the first time, to delineate the spectrum of imaging and genetic characteristics associated with neurological preservation despite aging in CADASIL.

In the N_{int} group, 14 individuals already suffered attacks of

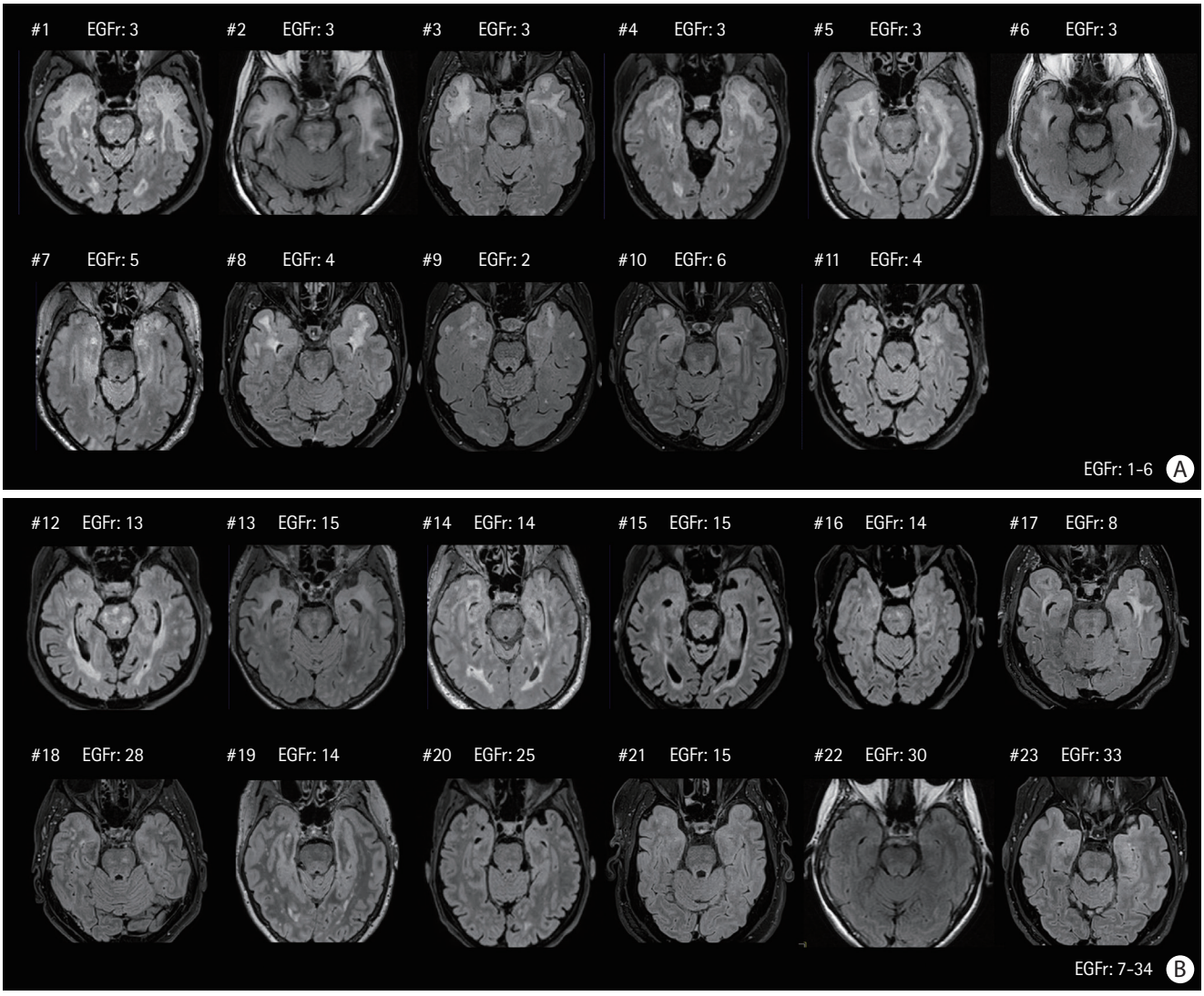

Figure 2. Magnetic resonance fluid-attenuated inversion recovery images of the neurologically intact (N_{int}) patients already presented in Figure 1 (same order) at the level of temporal pole. (A) Eleven patients had their cysteine mutation in epidermal growth factor-like repeat (EGFr) domain 1-6 (Patient #1 to #11), (B) 12 others in EGFr domain 7-34 (Patient #12 to #23).

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migraine with aura or isolated auras. This frequency is twice that observed in the N_{ps} group and much higher than the average frequency of 40% usually reported in cohorts of symptomatic CADASIL patients.[31,32] This is possibly related to our selection of N_{int} patients among cases recruited in a clinical center, who were mostly symptomatic and thus diagnosed after mild or transient clinical manifestations. Also, this high prevalence of migraine with aura in N_{int} elderly individuals further supports the absence of link between migraine with aura and clinical disability or cognitive decline in CADASIL.[31,33] Other transient clinical manifestations were depression episodes in two N_{int} cases, possibly favoured by the presence of confluent white matter abnormalities.[34] Interesting, only a single N_{int} woman was totally asymptomatic and diagnosed after her brother had a stroke at young age, which led to genetic testing. The results did not change when only "index" patients were considered in the analysis (supplementary data). Finally, we did not observe a significant difference in the frequency of cardiovascular risk factors between the N_{ps} and N_{int} groups, suggesting that these factors are not involved in this clinical contrast. Conversely, N_{int} patients were more educated than N_{ps} patients, thus whether additional protective factors related to differences in the level of regular exercise, diet, behavior, access to care, health awareness or to the environment cannot be ruled out.[35]

As expected, N_{int} elderly patients had much less lacunes and microbleeds as well as less cerebral atrophy than N_{ps} patients. These imaging markers are strongly related to the development of disability and dementia in CADASIL patients.[13,36] In contrast, the global amount of WMHs did not differ between the N_{int} and N_{ps} groups. This discrepancy suggests that although the disease has visible effects in the white matter, the development of lacunes and loss of cerebral tissue along aging does not occur or remains limited in most N_{int} patients. In line, accumulating data support that some WMHs in CADASIL may result more from water accumulation than from myelin or axonal loss as observed in ischemic cerebral tissue.[37,38]

The location of *NOTCH3* mutation in different EGFr domains might be involved in this relative preservation despite aging. About half of N_{int} CADASIL patients harbored cysteine mutations within EGFr domain 7-34. This is higher than the average frequency of such mutations in European cohorts of symptomatic diagnosed cases.[3] Since a selection bias related to the inclusion of only survivors aged more than 65 years cannot be excluded in our cohort, this proportion might be even underestimated. Recent pathology study of skin biopsies suggested that patients with an EGFr 7-34 variant might have less NOTCH3 extracellular domains accumulation in the wall of their brain vessels than patients with an EGFr 1-6 variant.[39] This would explain the higher prevalence of these mutations in the general population with a much larger number of silent or mild forms of the disease.[3,40] In the present study, the location of NOTCH3 variants within EGFr domains did not differ between N_{int} and N_{ps} patients. Therefore, if the impact of mutation location on the level of NOTCH3 accumulation is actually proven at cerebral vascular level, other additional factors are obviously involved. Various protection mechanisms may contribute to this relative preservation at multiple level, such as, genetic or hormonal modulation of brain tissue susceptibility to chronic hypoperfusion, anatomical or physiological characteristics of the cerebral microvascular network or processes involved in the triggering and adaptation of cerebral blood flow autoregulation at tissue level.

Obviously, among elderly N_{int} patients, a large amount of WMHs involving both temporal lobes was observed in most cases having a mutation in EGFr domain 1-6 while the extent of WMHs appeared much less and the temporal poles largely spared in presence of a mutation in EGFr domain 7-34. At the opposite extreme, very beginning and limited WMHs were detected in a 66-year-old patient having a cysteine mutation in EGFr domain 30 (case 22) but such beginning WMHs were also detected in a 73-year-old patient who had a mutation in EGFr domain 4 (case 11). Altogether, these results suggest that the location of *NOTCH3* mutation might modulate the mechanisms involved in the development of WMHs, especially in the white matter adjacent to the cortex as within the temporal poles. The factors needed to delay by several decades the appearance of WMHs in some individuals remain also unknown.

The strengths of this study are multiple. The selected sample of elderly CADASIL patients is large. Each case was extensively investigated. Both clinical results, MRI data and the location of their mutation in the *NOTCH3* gene were analyzed in detail. The collection of data was obtained by experienced clinicians over 15 years and always using the same imaging and clinical parameters. The study has also some limitations. It is based on data driven from the hospital, consequently, in the N_{int} group, totally asymptomatic individuals are probably largely underestimated. On the opposite side, in the N_{ps} group, elderly cases who were severely disabled or dependent are also most likely underrepresented. They have more difficulties to participate in research activities and to travel to the referral center. The most severe CADASIL cases who died before the age of 65 years are also not accounted in such a comparison study. Besides, due to the very long duration of the disease, we didn't analyze all treatments that may have been used over decades in all individuals. In addition, subtle psychiatric disturbances might have not been taken into account when defining "intact" neurologi-

cal status. Finally, the interpretation of our data based on imaging data, particularly in N_{int} patients should remain cautious in the absence of pathological examination.

Conclusions

We found that nearly one in five CADASIL patients can remain N_{int} after the age of 65 years. Their different clinical and imaging profile cannot be fully explained by the location of *NOTCH3* mutation inside or outside EGFr domains 1-6. In some N_{int} individuals, severe ischemic lesions do not develop conversely to WMHs that can become extensive. In others, all types of cerebral lesions, including WMHs appear extremely limited and might be delayed by several decades for unknown reasons. The factors involved in this relative cerebral tissue preservation along aging remain to be determined.

Supplementary materials

Supplementary materials related to this article can be found online at https://doi.org/10.5853/jos.2022.01578.

Disclosure

The authors have no financial conflicts of interest.

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Supplementary Table 1. Comparison of baseline characteristics between N_{int} and N_{ps} patients

Characteristic	N_{int} patients (n=23)	N_{ps} patients (n=106)	*P*
Age at inclusion (yr)	63 (60–69)	67 (61–70)	0.127
Weight (kg)	71.8±15.7	72.5±13.8	0.836
Systolic blood pressure (mm Hg)	132 (120–143)	132 (120–144)	0.971
Diastolic blood pressure (mm Hg)	73 (66–86)	75 (69–82)	0.579
Clinical manifestations			
Migraine with aura	8 (34.8)	26 (24.5)	0.309
Migraine without aura	3 (13.0)	18 (17.0)	0.765
Stroke	7 (30.4)	65 (61.3)	0.010
Any cognitive impairments	0 (0)	66 (62.3)	<0.001
Dementia	0 (0)	18 (17.0)	0.042
Transient episode of mood disturbance	4 (17.4)	48 (45.3)	0.018
Seizures	0 (0)	17 (16.0)	0.041
Clinical scales			
mRS	0 (0–1)	1 (0–3)	0.001
Barthel index	100 (100–100)	100 (95–100)	0.011
NIHSS	0 (0–0)	1 (0–2)	<0.001
MMSE	29 (28–29)	27 (22–28)	<0.001
MDRS	141 (139–142)	134 (117–141)	0.001
Laboratory results			
Total cholesterol (mmol/L)	5.0±1.5	5.3±1.5	0.412
LDL (mmol/L)	3.1±1.0	3.3±1.1	0.412
HDL (mmol/L)	1.6±0.6	1.4±0.4	0.229
HbA1c (%)	5.7±0.3	5.8±0.6	0.799
Blood glucose (mmol/L)	5.3±1.0	5.6±1.0	0.196
Homocysteine (μmol/L)	11.5±3.3	13.0±4.9	0.234

Values are presented as median (interquartile range), mean±standard deviation, or number (%).
N_{int}, neurologically intact; N_{ps}, with permanent neurological symptoms; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; MMSE, Mini-Mental State Examination; MDRS, Mattis Dementia Rating Scale; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HbA1c, hemoglobin A1c.

Supplementary Table 2. Comparison of demographic and clinical data between "index" N_{int} and N_{ps} patients

Characteristic	N_{int} patients (n=13)	N_{ps} patients (n=76)	*P*
Age at inclusion (yr)	64 (61–70)	66 (61–71)	0.611
Age at last visit (yr)	70 (67–74)	71 (68–75)	0.448
Female sex	10 (76.9)	47 (61.8)	0.363
Education (yr)	12 (9–17)	9 (6–12)	0.066
Vascular risk factors			
Hypertension	3 (23.1)	25 (32.9)	0.747
Diabetes mellitus	1 (7.7)	5 (6.6)	1.000
Hypercholesterolemia	5 (38.5)	40 (52.6)	0.384
Current smoking	0 (0)	4 (5.3)	1.000
Ever smoker	7 (53.9)	29 (38.2)	0.363
Alcohol consumption	4 (30.8)	36 (47.4)	0.611
Clinical manifestations			
Migraine with aura	7 (53.9)	26 (34.2)	0.219
Migraine without aura	4 (30.8)	15 (19.7)	0.463
Stroke	6 (46.2)	55 (72.4)	0.102
Number of strokes	0 (0–1)	1 (0–2)	0.028
Any cognitive complaints	0 (0)	45 (59.2)	<0.001
Dementia	0 (0)	12 (15.8)	0.201
Transient episode of mood disturbance	2 (15.4)	36 (47.4)	0.037
Seizures	0 (0)	9 (11.8)	0.346
Clinical scales			
Severely disability preventing cognitive testing	0 (0)	10 (13.2)	0.347
mRS	1 (1–1)	3 (2–3)	<0.001
Barthel	100 (100–100)	95 (55–100)	<0.001
NIHSS	0 (0–0)	1 (0–4)	<0.001
MMSE	29 (27–30)	24 (20–28)	<0.001
MDRS	140 (139–143)	128 (108–139)	0.001
EGFr domain 1-6	3 (23.1)	34 (44.7)	0.224

Values are presented as median (interquartile range) or number (%).
N_{int}, neurologically intact; N_{ps}, with permanent neurological symptoms; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; MMSE, Mini-Mental State Examination; MDRS, Mattis Dementia Rating Scale; EGFr, epidermal growth factor-like repeat.

Supplementary Table 3. Comparison of imaging data between "index" N_{int} and N_{ps} patients

Variable	N_{int} patients (n=13)	N_{ps} patients (n=70)	*P*
Brain parenchymal fraction (%)	81.4 (78.6–83.4)	76.1 (73.5–79.3)	<0.001
WMHs volume (mL)	98.4 (57.3–120.7)	85.9 (59.8–144.2)	0.633
Normalized WMHs (%)	6.5 (4.4–8.8)	6.3 (4.4–11.3)	0.706
Fazekas score-periventricular	3 (3–3)	3 (3–3)	0.245
Fazekas score-deep	3 (3–3)	3 (3–3)	0.109
WMHs score-temporal pole	1 (1–3)	2 (1–3)	0.316
Presence of lacune	9 (69.2)	63 (90.0)	0.065
Total lacune number	2 (0–9)	10 (4–15)	0.003
Presence of microbleeds	7 (53.9)	55 (78.6)	0.082
Total microbleeds number	3 (0–12)	6 (1–24)	0.160
Presence of RSSI	0 (0)	15 (21.4)	0.112

Values are presented as median (interquartile range) or number (%). In six patients of the N_{ps} group imaging data could not be assessed (one patient did not have MRI at day of clinical examination, in five cases imaging data were of poor quality).
N_{int}, neurologically intact; N_{ps}, with permanent neurological symptoms; WMH, white matter hyperintensity; RSSI, recent small subcortical infarct.

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Supplementary Table 4. Comparison of demographic and clinical data between N_{int} patients who never had a stroke and the other patients

Variable	N_{int} patients who never had a stroke (n=12)	The other patients (n=117)	*P*
Age at inclusion (yr)	64 (60–68)	66 (61–70)	0.305
Age at last visit (yr)	70 (67–72)	72 (68–75)	0.154
Female sex	8 (66.7)	70 (59.8)	0.763
Education (yr)	12 (9–17)	9 (6–12)	0.056
Vascular risk factors			
Hypertension	3 (25)	33 (28.2)	0.557
Diabetes mellitus	1 (8.3)	12 (10.3)	1.000
Hypercholesterolemia	4 (33.3)	62 (53.0)	0.160
Smoking	2 (16.7)	6 (5.1)	0.162
Alcohol consumption	2 (16.7)	50 (42.7)	0.210
Clinical manifestations			
Migraine with aura	8 (66.7)	39 (33.3)	0.030
Migraine without aura	6 (50.0)	23 (19.7)	0.027
Stroke	0 (0)	86 (73.5)	<0.001
Any cognitive complaints	0 (0)	67 (57.3)	<0.001
Dementia	0 (0)	17 (14.5)	0.365
Transient episode of mood disturbance	3 (25.0)	48 (41.0)	0.362
Seizures	0 (0)	14 (12.0)	0.360
Clinical scales			
Severe disability preventing cognitive testing	0 (0)	15 (12.8)	0.360
mRS	1 (1–1)	2 (1–3)	<0.001
Barthel index	100 (100–100)	95 (60–100)	0.001
NIHSS	0 (0–0)	1 (0–3)	<0.001
MMSE	29 (27–30)	25 (20–28)	<0.001
MDRS	142 (139–143)	130 (109–138)	<0.001
EGFr domain 1-6	7 (58.3)	57 (48.7)	0.560

Values are presented as median (interquartile range) or number (%).
N_{int}, neurologically intact; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; MMSE, Mini-Mental State Examination; MDRS, Mattis Dementia Rating Scale; EGFr, epidermal growth factor-like repeat.

Supplementary Table 5. Comparison of imaging data between N_{int} patients who never had a stroke and the other patients

	N_{int} patients who never had a stroke (n=12)	The other patients (n=107)	*P*
Brain parenchymal fraction (%)	81.9 (78.4–83.5)	77.1 (73.9–79.7)	<0.001
WMHs volume (mL)	112.6 (57.7–162.8)	97.6 (57.5–149.2)	0.881
Normalized WMHs (%)	7.8 (3.8–11.5)	6.4 (4.2–11.2)	0.832
Fazekas periventricular WMHs score	3 (3–3)	3 (3–3)	1.000
Fazekas deep WMHs score	3 (3–3)	3 (3–3)	0.596
Score of WMHs in temporal poles	2 (1–3)	3 (1–3)	0.384
Presence of lacune	7 (58.3)	97 (90.7)	0.008
Total lacune number	1 (0–3)	10 (4–16)	<0.001
Presence of microbleeds	2 (16.7)	83 (77.6)	<0.001
Total microbleeds number	0 (0–0)	5 (1–23)	<0.001
Presence of RSSI	0 (0)	20 (18.7)	0.214

Values are presented as median (interquartile range) or number (%). In 10 patients of the N_{ps} group imaging data could not be assessed (two patients did not have magnetic resonance imaging at day of clinical examination, in seven cases imaging data were of poor quality, in another case errors were detected using the Brain Intensity AbNormality Classification Algorithm [BIANCA] processing).
N_{int}, neurologically intact; WMH, white matter hyperintensity; RSSI, recent small subcortical infarct; N_{ps}, with permanent neurological symptoms.