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Letter to the Editor

Parkinsonism in Cerebral Autosomal Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy: Clinical Features and Biomarkers

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Dear Sir:

Cerebral small vessel disease (SVD) encompasses a spectrum of neurological manifestations, including stroke, cognitive decline, and progressive gait difficulty.[1] The associated gait abnormalities are commonly characterized by slowed and shuffling gait, resembling vascular parkinsonism. Lesions associated with parkinsonism generally affect the striatal and related motor pathways, while SVD neuroimaging marker burden can predict the risk of parkinsonism.[2,3] Genetic forms of SVD, such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), also commonly present with parkinsonism.[4] Gait difficulties are common in advanced CADASIL; however, the prevalence and characteristics of parkinsonism remain underexplored.[5]

The present study aimed to comprehensively evaluate the motor features of parkinsonism in patients with CADASIL, assess their prevalence, and identify potential clinical and neuroimaging markers. We hypothesized that the pathophysiology of parkinsonism is primarily vascular, distinct from the α-synucleinopathy seen in idiopathic Parkinson's disease (PD).

Patients from the Taiwan CADASIL Registry and patients with idiopathic PD from the same hospital were evaluated and compared (Supplementary Figure 1). In patients with CADASIL, parkinsonism was diagnosed based on gait impairment, bradykinesia, or rigidity, excluding stroke-related paresis.[3,6] The severity of parkinsonism motor symptoms was assessed by two movement disorder specialists using the Unified Parkinson's Disease Rating Scale part III (UPDRS-III), and items in the UPDRS-III were further categorized into four domains: tremor, rigidity, bradykinesia, and postural instability. Overall disability was determined using the Hoehn-Yahr (H-Y) stage. Gait speed was examined using the 4-meter walking test. Magnetic resonance imaging (MRI) features were analyzed visually and quantitatively. Plasma α-synuclein levels were measured using an immunomagnetic reduction method. The first part of the analysis identified factors associated with parkinsonism in CADASIL, and the second part compared the phenotypes and severity of Parkinsonism between patients with CADASIL and those with PD. Detailed methods are provided in the Supplementary Methods.

Among the 75 CADASIL patients enrolled (median age 64 years, interquartile range [IQR] 57–72 years, 52% male), 55 (73%) exhibited parkinsonism features, with the prevalence increasing with age (Supplementary Figure 2). The median UPDRS-III score was 9 (IQR, 3–23), median H-Y stage was 1 (1–2), and median gait speed was 0.83 m/s (0.57–1.09 m/s). The neuroimaging markers are shown in Table 1.

Of the 55 patients with parkinsonism, 19 reported subjective

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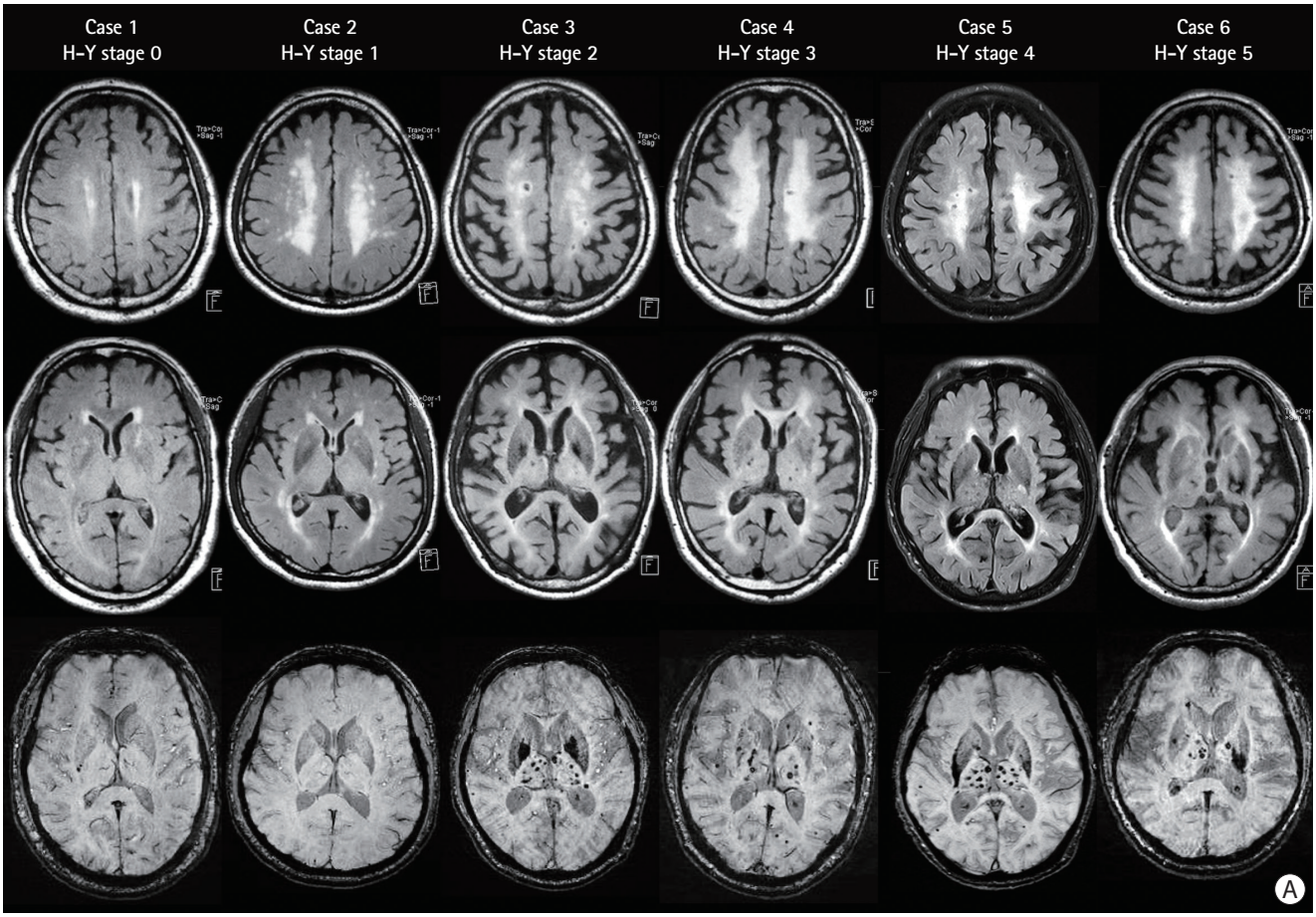
Table 1. Clinical and neuroimaging features of patients with CADASIL with and without parkinsonism

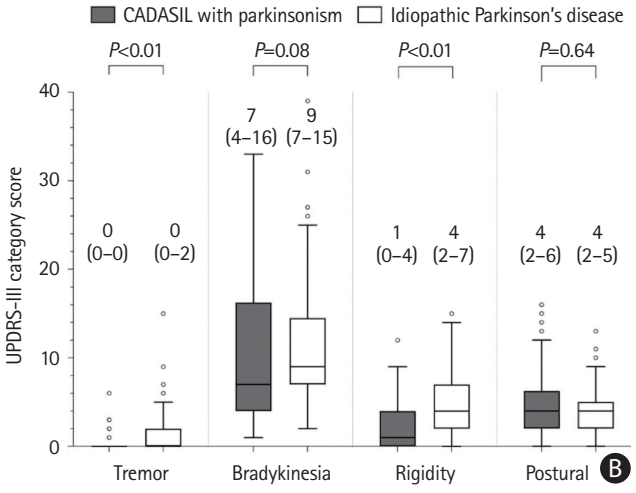
	All CADASIL (n=75)	Without parkinsonism (n=20)	With parkinsonism (n=55)	Unadjusted		Age- and sex-adjusted		Multivariate adjusted	
				OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Age (yr)	64 (57–72)	57 (53–62)	67 (60–73)	1.10 (1.04–1.18)	<0.01	1.10 (1.04–1.18)	<0.01	1.07 (0.997–1.15)	0.06
Male sex	39 (52.0)	8 (40.0)	31 (56.4)	1.94 (0.69–5.67)	0.21	1.80 (0.59–5.79)	0.31	-	-
UPDRS part III	9 (3–23)	0	12 (7–26)	-	-	-	-	-	-
H-Y stage	1 (1–2)	0	2 (1–3)	-	-	-	-	-	-
Gait speed (m/s)	0.83 (0.57–1.09)	0.75 (0.56–1.00)	1.06 (0.96–1.26)	-	-	-	-	-	-
Hypertension	46 (61.3)	10 (50.0)	36 (65.5)	1.90 (0.67–5.42)	0.23	1.66 (0.53–5.17)	0.38	-	-
Diabetes mellitus	18 (24.0)	2 (10.0)	16 (29.1)	3.69 (0.92–24.93)	0.07	3.36 (0.74–24.30)	0.12	-	-
Dyslipidemia	37 (49.3)	10 (50.0)	27 (49.1)	0.96 (0.34–2.71)	0.94	0.91 (0.30–2.78)	0.86	-	-
Smoking	18 (24.0)	0 (0.0)	18 (32.7)	-	-	-	-	-	-
Stroke history	45 (60.0)	9 (45.0)	36 (65.5)	2.32 (0.82–6.72)	0.11	2.41 (0.77–7.85)	0.13	-	-
Onset age of stroke (yr)	60 (52–64)	55 (52–63)	60 (53–64)	-	-	-	-	-	-
Modified Rankin Scale score	1 (0–3)	0 (0–0)	1 (0–3)	-	-	-	-	-	-
α-Synuclein (pg/mL)*	0.09 (0.07–0.14)	0.12 (0.07–0.18)	0.08 (0.07–0.13)	0.52 (0.16–1.63)	0.26	0.85 (0.22–3.22)	0.81	-	-
Cortical thickness (mm)	2.37 (2.25–2.41)	2.39 (2.36–2.46)	2.35 (2.23–2.39)	0.39 (0.15–0.88)	0.02	0.70 (0.23–1.91)	0.50	-	-
WMH volume (mL)	41.5 (23.3–56.7)	20.2 (7.9–40.1)	47.3 (31.0–60.3)	1.05 (1.02–1.09)	<0.01	1.04 (1.01–1.07)	0.01	1.04 (1.003–1.07)	0.03
Fazekas scale									
Periventricular	3 (2–3)	3 (2–3)	2 (1–3)	3.26 (1.56–7.52)	<0.01	2.85 (1.23–7.50)	0.01	-	-
Subcortical	3 (2–3)	2 (2–3)	3 (3–3)	3.04 (1.45–6.99)	<0.01	2.30 (0.98–5.82)	0.06	-	-
Total	6 (5–6)	5 (3–6)	6 (5–6)	1.92 (1.29–3.03)	<0.01	1.72 (1.09–2.90)	0.02	-	-
Basal ganglia dilated PVS	3 (2–3)	3 (2–3)	3 (2–3)	1.27 (0.66–2.50)	0.47	0.61 (0.24–1.42)	0.26	-	-
Lacune number	5 (2–11)	3 (2–9)	7 (3–12)	1.08 (0.98–1.21)	0.13	1.04 (0.93–1.16)	0.49	-	-
Any BG lacune	39 (52.0)	6 (30.0)	33 (60.0)	3.50 (1.17–10.49)	0.03	3.43 (0.98–12.02)	0.05	2.23 (0.61–8.07)	0.22
BG lacune number	1 (0–2)	0 (0–1)	1 (0–2)	1.67 (0.97–2.87)	0.07	1.57 (0.87–2.84)	0.13	-	-
CMB number	15 (3–58)	11 (1–23)	21 (4–61)	1.02 (1.00–1.04)	0.04	1.01 (1.00–1.04)	0.20	-	-
Any BG CMB	43 (57.3)	8 (40.0)	35 (63.6)	2.63 (0.92–7.50)	0.07	1.65 (0.52–5.25)	0.40	-	-
BG CMB number	1 (0–5)	0 (0–4)	1 (0–5)	1.12 (0.92–1.35)	0.26	1.07 (0.89–1.28)	0.50	-	-

Values are presented as median (interquartile range) or n (%) unless otherwise indicated.
CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; OR, odds ratio; CI, confidence interval; UPDRS, Unified Parkinson's Disease Rating Scale; H-Y, Hoehn-Yahr; WMH, white matter hyperintensity; PVS, perivascular spaces; CMB, cerebral microbleed; BG, basal ganglia.
*Log transformed in regression models.

motor symptoms, while others were identified during examination. The median age at parkinsonism onset was 66 years (IQR, 62–70 years). Twenty-two patients (40%) received levodopa at a median levodopa-equivalent daily dose of 225 mg (100–400 mg).

Among the 32 patients who underwent ^{99m}Tc-TRODAT-1 SPECT (single-photon emission computed tomography), 31 (97%) showed decreased dopamine uptake, which was graded as mild (75%), moderate (16%), or severe (6%). A decrease in asymmetrical up-





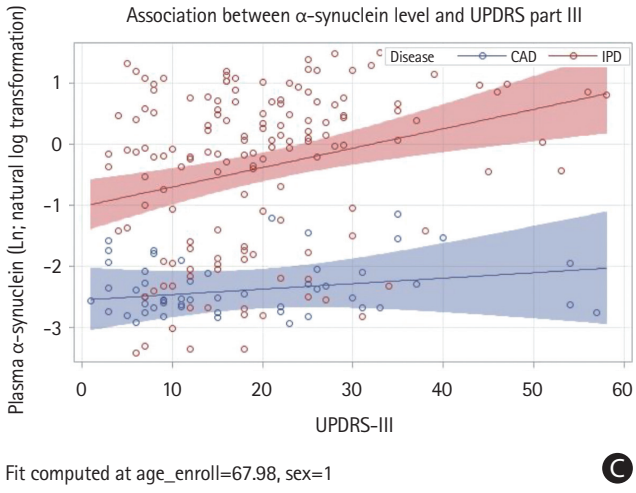


Figure 1. Clinical features and biomarkers of parkinsonism in CADASIL patients. (A) Exemplar brain MRI results in CADASIL patients with parkinsonism at different H-Y stages. Comparisons between CADASIL patients with parkinsonism (CAD) and idiopathic Parkinson's disease patients (IPD). (B) UPDRS-III category score. (C) Alpha-synuclein level at different H-Y stages. MRI, magnetic resonance imaging; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; H-Y, Hoehn-Yahr; UPDRS-III, Unified Parkinson's Disease Rating Scale part III.

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take was observed in 24 (77%) patients.

CADASIL patients with parkinsonism were older (median age 67 vs. 57) than those without parkinsonism, though no significant differences were noted in vascular risk factors, stroke history, or plasma α-synuclein levels (Table 1). Neuroimaging findings revealed that CADASIL patients with parkinsonism had thinner cortices (median 2.35 vs. 2.39 mm), larger white matter hyperintensity (WMH) volumes (47.3 vs. 20.2 mL), and a higher prevalence of basal ganglia lacunes (60% vs. 30%). Patients with higher H-Y stages also had larger WMH volumes, thinner cortices, and a trend toward more lacunes and microbleeds (Supplementary Table 1). Figure 1A shows examples of brain MRI scans in patients with CADASIL at different H-Y stages.

In the age- and sex-adjusted logistic regression models, age, WMH volume, Fazekas scale score, and basal ganglia lacunes were associated with parkinsonism (Table 1). In multivariate analysis, only the WMH volume remained statistically significant (odds ratio [OR], 1.04; 95% confidence interval [CI], 1.003–1.07). Among patients with parkinsonism, thinner cortical thickness was associated with higher UPDRS-III scores (adjusted beta -5.48, 95% CI -9.98 to -0.99) and advanced H-Y stages (OR 0.30, 95% CI 0.07–1.00) (Supplementary Table 2).

Compared to 158 patients with idiopathic PD (median age, 70 years; 51% male), CADASIL patients with parkinsonism had lower UPDRS-III scores (median, 12 vs. 18) but similar H-Y stages (2 vs. 2) (Table 2). Patients with CADASIL had significantly lower tremor (0 vs. 0) and rigidity scores (1 vs. 4), with borderline lower bradykinesia (7 vs. 9), but no differences in postural instability (4 vs. 4) (Figure 1B). Plasma α-synuclein levels were significantly lower in CADASIL patients with parkinsonism (0.08 vs. 0.95 pg/mL) compared with patients with PD. Plasma α-synuclein levels correlated with UPDRS-III scores in PD patients (beta 2.13, 95% CI 0.83–3.43), but not in CADASIL patients (beta 5.27, 95% CI -2.21–12.75) (Supplementary Table 3 and Figure 1C). Neuroimaging comparisons revealed that CADASIL patients with parkinsonism had thinner cortices (median 2.35 vs. 2.44 mm), higher Fazekas scores (6 vs. 2), and more lacunes (7 vs. 0) and microbleeds (21 vs. 0) than PD patients.

In summary, we found that over 70% of symptomatic patients with CADASIL exhibited parkinsonism, a higher prevalence than previously reported. Prior studies have reported parkinsonism in 11% of 45 Italian patients and 33% of 157 Korean patients.[4,5] These discrepancies may be due to the older age of our cohort, differences in *NOTCH3* variants, and more thorough motor examinations. Motor symptoms in CADASIL, characterized by postural instability and bradykinesia with less rigidity and tremor, resemble "lower-body" type of vascular parkinsonism.

Our study suggests that WMH volume contributes to the development of parkinsonism in CADASIL, while cortical thinning correlates with motor symptom severity. These findings are consistent with existing evidence showing that the severity of SVD features, such as WMH volume and cortical thinning, may serve as surrogate markers of parkinsonism. For example, a cross-sectional study in sporadic SVD patients found that the total SVD burden was associated with mild parkinsonism features.[7] Similarly, in sporadic SVD patients without parkinsonism at baseline, a high WMH volume and number of lacunes were associated with the incident parkinsonism over five years.[2] Furthermore, in PD patients, WMH was associated with worsening axial motor performance, independent of nigrostriatal dopaminergic denervation,[8] while cortical thinning was linked to advanced motor stage.[9] In CADASIL, a diffuse SVD, the cumulative WMH burden could potentially damage the cortico-basal ganglia-thalamus interconnecting fibers, and secondary neurodegeneration, such as cortical thinning, may occur.

Table 2. Comparisons of patients with CADASIL with parkinsonism and those with Parkinson's disease

	CADASIL with parkinsonism (n=55)	Parkinson' disease (n=158)	*P*
Age (yr)	67 (60–73)	70 (62–76)	0.17
Male sex	31 (56.4)	80 (50.6)	0.53
UPDRS part III	12 (7–26)	18 (12–25)	0.05
Tremor	0 (0–0)	0 (0–2)	<0.01
Bradykinesia	7 (4–16)	9 (7–15)	0.08
Rigidity	1 (0–4)	4 (2–7)	<0.01
Postural instability	4 (2–6)	4 (2–5)	0.64
H-Y stage	2 (1–3)	2 (1–3)	0.26
α-Synuclein (pg/mL)	0.08 (0.07–0.13)	0.95 (0.24–1.99)	<0.01
Cortical thickness (mm)	2.35 (2.23–2.39)	2.44 (2.36–2.53)	<0.01
Fazekas scale			
Periventricular	3 (2–3)	1 (0–1)	<0.01
Subcortical	2 (2–3)	1 (0–1)	<0.01
Total	6 (5–6)	2 (1–3)	<0.01
Basal ganglia dilated PVS	3 (2–3)	1 (1–2)	<0.01
Lacune number	7 (3–12)	0 (0–0)	<0.01
Any BG lacune	33 (60.0)	7 (4.4)	<0.01
BG lacune number	1 (0–2)	0 (0–0)	<0.01
CMB number	21 (4–61)	0 (0–0)	<0.01
Any BG CMB	35 (63.6)	3 (1.9)	<0.01
BG CMB number	1 (0–5)	0 (0–0)	<0.01

Values are presented as median (interquartile range) or n (%) unless otherwise indicated.
CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; UPDRS, Unified Parkinson's Disease Rating Scale; H-Y, Hoehn-Yahr; PVS, perivascular spaces; CMB, cerebral microbleed; BG, basal ganglia.

We speculate that the association of cortical thinning, but not WMH, with motor severity could be linked to the ceiling effect of large WMH volumes in patients with CADASIL; however, secondary cortical thinning, reflecting brain atrophy, is more closely related to the severity of clinical symptoms. This is consistent with findings that brain atrophy is strongly associated with cognitive score, disability scales, and predicting clinical deterioration in CADASIL.[10] The significantly lower plasma α-synuclein levels in CADASIL patients, which did not correlate with motor symptoms, indicate that α-synucleinopathy is not the underlying pathology of parkinsonism in CADASIL.

While parkinsonism can occur in sporadic SVD or in individuals with brain frailty, CADASIL is a genetically driven subtype with a more severe vascular pathology, particularly in the cortico-basal ganglia-thalamic circuits. Some of our CADASIL cases were initially diagnosed with vascular parkinsonism, only later receiving a genetic diagnosis due to neuroimaging features such as disproportionately severe WMH, multiple lacunes, and microbleeds. We propose that clinicians review brain MRI scans carefully in cases of vascular parkinsonism and be aware that genetic SVD can also result in such a phenotype.

Our study has several limitations. First, a selection bias may exist because severe cases were excluded, and minor cases might have been missing. Second, the study enrolled CADASIL patients with the predominant *NOTCH3* p.R544C variant; therefore, the results might not be generalizable to populations with different *NOTCH3* variants. Third, *NOTCH3* was not tested in patients with PD. Finally, we did not compare the differences between CADASIL patients with parkinsonism and those with non-genetic vascular parkinsonism.

In conclusion, we found that parkinsonism is common in patients with CADASIL. The burden of cerebral SVD, particularly WMH volume and cortical thinning, may contribute to its development and severity.

Supplementary materials

Supplementary materials related to this article can be found online at https://doi.org/10.5853/jos.2024.03944.

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Conflicts of interest

The authors have no financial conflicts of interest.

Author contribution

Conceptualization: CHC, SCT. Study design: CHL, SCT. Methodology: CHC. Data collection: CHC, TWW, YWC, YTC, MFC, YFC. Investigation: CHC, YWC, SCT. Statistical analysis: CHC, TWW. Writing—orinignal draft CHC, TWW. Writing—review & editing: YWC, YTC, MFC, YFC, CHL, SCT. Funding acquisition: CHC, SCT. Approval of final manuscript: all authors.

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Supplementary Methods

Standard protocol approvals, registrations, and patient consent

This study was approved by the Ethics Committee of the National Taiwan University Hospital (NTUH-REC No. 202006173MINB), and was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants and/or their relatives.

Study design and study population

This study comprised a cross-sectional analysis of an ongoing cohort study enrolling patients with CADASIL (Taiwan CADASIL registry).[1] Patients with symptomatic CADASIL who presented with either stroke, cognitive impairment, gait disturbance, psychiatric symptoms, or headache, and were genetically confirmed to have a *NOTCH3* mutation, were included. Presymptomatic *NOTCH3* mutation carriers were excluded from this study.

Patients with idiopathic Parkinson's disease (PD) were recruited from the movement disorder clinic of the same hospital for comparison. The diagnosis of PD was based on the clinical diagnostic criteria of the United Kingdom PD Society Brain Bank.[2] Patients were excluded if they had any contraindications to magnetic resonance imaging (MRI) examinations or severe medical illnesses that would predispose them to significant morbidity or mortality.

Clinical assessment

Demographic and clinical information of patients with CADASIL, including age, sex, medication history, vascular risk factors (hypertension, diabetes mellitus, dyslipidemia, and coronary artery disease), smoking history, and the number of first-degree relatives with stroke, were recorded.

Patients were evaluated for parkinsonism features, and assessed to see whether these features could be attributed to or disproportionate to post-stroke hemiparesis. We referred to the diagnostic criteria for vascular parkinsonism proposed by Zijlmans et al.[3] The age at onset, if available, was retrieved by reviewing the baseline CADASIL questionnaire or medical chart. The severity of parkinsonism motor symptoms was assessed using the Unified Parkinson's Disease Rating Scale part III (UPDRS-III) by two movement disorder specialists (YTC and CHL).[4] Items in the UPDRS-III were further categorized into four domains, namely tremor (items 3.15–3.18), rigidity (item 3.3), bradykinesia (items 3.1, 3.2, 3.4–3.8, and 3.14), and posture instability (items 3.9–3.13). The average scores for each domain were subsequently calculated. If stroke-related weakness prevented the proper assessment of UPDRS motor symptoms, the limb was not scored. Overall functional disability was assessed based on the modified Rankin Scale and Hoehn-Yahr (H-Y) stage.[5] Gait speed (m/s) was examined using a 4-meter walking test.[6] In our center, ^{99m}Tc-TRODAT-1 SPECT (single-photon emission computed tomography) was applied for dopaminergic transporter imaging. However, whether the patients underwent this imaging examination was optional.

Brain magnetic resonance imaging

All patients underwent at least one brain MRI examination at enrollment and follow-up examinations, usually every 2 years. We selected the MRI study closest to the parkinsonism evaluation, with an interval of less than six months.

Brain MRI was performed using a standard 1.5-T scanner. Sequences included high-resolution T1-weighted volumetric scan, T2, fluid-attenuated inversion recovery (FLAIR), and susceptibility-weighted imaging. Visual analyses of small vessel disease (SVD) markers, including white matter hyperintensity (WMH), lacunes, enlarged perivascular spaces (PVS), and cerebral microbleeds (CMB), were assessed according to the Standards for Reporting Vascular Changes on Neuroimaging 2 criteria.[7] The severity of WMH was scored using the Fazekas scale.[8] Enlarged PVS were scored using the Wardlaw scale.[9]

Quantitative analyses of MRI lesions included measurement of the WMH volume (mL) and mean cortical thickness (mm). WMH volumes were segmented on FLAIR imaging using a lesion growth algorithm implemented in the Lesion Segmentation Tool toolbox version 3.0.0[10] and confirmed later by visual screening. The mean cortical thickness was quantified on T1-weighted structural MRI scans using the FreeSurfer software version 7.2.0.[11]

Plasma biomarkers

Plasma α-synuclein levels in patients with CADASIL or PD were measured using the immunomagnetic reduction method (MF-ASC-0060; MagQu, Taiwan), as previously described.[12]

Statistical analysis

Continuous and categorical data are expressed as the median (interquartile range) and number (percentage), respectively. Differences between groups were compared using the Kruskal-Wallis one-way analysis of variance or Fisher's exact test. The first part of the analysis involved searching for factors associated with parkinsonism in patients with CADASIL. We subsequently compared clinical variables, UPDRS-III, H-Y stage, plasma α-synuclein, and MRI markers between patients with CADASIL with and without features of parkinsonism. We then applied univariate, age- and sex-adjusted, and multivariate logistic regression models to explore independent factors associated with the presence of par-

kinsonism in patients with CADASIL. The multivariate model was further adjusted for variables that reached statistical significance in the age- and sex-adjusted models. Additionally, in CADASIL patients with parkinsonism, we further conducted analyses using linear regression models for the associations between biomarkers (both plasma and neuroimaging) and UPDRS-III scores, as well as logistic regression models for associations with advanced H-Y stage (H-Y stage ≥3); these analyses were adjusted for age and sex. Plasma α-synuclein levels were log-transformed before entering the regression models.

The second part of the analysis aimed to compare the phenotypes and severity of parkinsonism between patients with CADASIL and those with PD. Only patients with CADASIL exhibiting parkinsonism features were included in this analysis, which involved comparison of total UPDRS-III scores and the average scores of the four domains, H-Y stage, plasma α-synuclein levels, and MRI markers. Finally, we investigated whether the burden of synucleinopathy contributed to parkinsonism features by analyzing the effects of plasma α-synuclein levels (log-transformed) on UPDRS-III scores and advanced motor stage (H-Y stage ≥3) in CADASIL patients with parkinsonism and PD patients, respectively. Given the exploratory nature of this study, multiple comparisons were not controlled for. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). The level of statistical significance was set at $P<0.05$.

Supplementary References

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Supplementary Table 1. Clinical and neuroimaging features of CADASIL patients in different H-Y stages

	H-Y stage 0 (n=20)	H-Y stage 1–2 (n=40)	H-Y stage 3–5 (n=15)	*P*
Age (yr)	57.0 (53.0–61.5)	65.0 (58.0–69.5)	74.0 (71.0–80.0)	<0.01
Male sex	8 (40.0)	20 (50.0)	11 (73.3)	0.14
UPDRS part III	0 (0–0)	9 (6.5–14.5)	31 (26–40)	<0.01
H-Y stage	0 (0–0)	1 (1–2)	3 (3–4)	<0.01
Hypertension	10 (50.0)	25 (62.5)	11 (73.3)	0.39
Diabetes mellitus	2 (10.0)	14 (35.0)	2 (13.3)	0.07
Dyslipidemia	10 (50.0)	21 (52.5)	6 (40.0)	0.75
Smoking	0 (0.0)	13 (32.5)	5 (33.3)	<0.01
Stroke	9 (45.0)	25 (62.5)	11 (73.3)	0.25
α-synuclein (pg/mL)	0.12 (0.07–0.18)	0.08 (0.07–0.13)	0.09 (0.07– 0.13)	0.64
Gait speed (m/s)	1.06 (0.96–1.26)	0.78 (0.66–1.06)	0.33 (0.13–0.57)	<0.01
Cortical thickness (mm)	2.39 (2.36–2.46)	2.37 (2.29–2.44)	2.19 (2.13–2.31)	<0.01
WMH volume (mL)	20.2 (7.9–40.1)	42.0 (25.1–57.7)	56.0 (42.1–65.7)	<0.01
Fazekas scale				
Periventricular	2 (1–3)	3 (2–3)	3 (2–3)	0.02
Subcortical	3 (3–3)	3 (2–3)	3 (3–3)	<0.01
Total	6 (5–6)	6 (5–6)	6 (5–6)	<0.01
Basal ganglia dilated PVS	3 (2–3)	3 (2–3)	3 (2–4)	0.20
Lacune number	3 (2–9)	5 (2.5–11)	10 (5–15)	0.05
Any BG lacune	6 (30.0)	23 (57.5)	10 (66.7)	0.07
BG lacune number	0 (0–1)	1 (0–2)	1 (0–3)	0.11
CMB number	11 (1–23)	12 (3–58)	39 (9–76)	0.06
Any BG CMB	8 (40.0)	23 (57.5)	12 (80.0)	0.07
BG CMB number	0 (0–4)	0 (1–4.5)	2 (1–5)	0.33

Values are presented as median (interquartile range) or n (%) unless otherwise indicated.
CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; UPDRS, Unified Parkinson's Disease Rating Scale; H-Y, Hoehn-Yahr; WMH, white matter hyperintensity; PVS, perivascular spaces; CMB, cerebral microbleeds; BG, basal ganglia.

Supplementary Table 2. Factors associated with UPDRS-III scores and advanced Hoehn-and-Yahr stages in CADASIL patients with parkinsonism (n=55)

	UPDRS-III score		Hoehn-Yahr stage ≥3	
	Beta* (95% CI)	*P*	OR* (95% CI)	*P*
Log α-synuclein (pg/mL)	5.27 (-2.21 to 12.75)	0.16	1.61 (0.28 to 10.60)	0.60
Cortical thickness (mm)	-5.48 (-9.98 to -0.99)	0.02	0.30 (0.07 to 1.00)	0.049
WMH volume (mL)	0.13 (-0.03 to 0.29)	0.12	1.05 (1.00 to 1.11)	0.06
Fazekas scale				
Periventricular	-0.55 (-7.06 to 5.97)	0.87	1.59 (0.33 to 9.13)	0.58
Subcortical	1.48 (-4.78 to 7.74)	0.64	4.97 (0.72 to 107.50)	0.12
Total	0.30 (-3.20 to 3.80)	0.86	1.90 (0.71 to 6.91)	0.23
Basal ganglia dilated PVS	-4.03 (-8.57 to 0.50)	0.08	1.02 (0.38 to 2.68)	0.97
Lacune number	0.20 (-0.41 to 0.81)	0.51	1.08 (0.95 to 1.25)	0.23
Any BG lacune	0.10 (-7.37 to 7.57)	0.98	1.67 (0.32 to 8.62)	0.54
BG lacune number	0.47 (-1.94 to 2.87)	0.70	1.27 (0.78 to 2.09)	0.34
CMB number	0.04 (-0.02 to 0.11)	0.18	1.01 (0.99 to 1.02)	0.41
Any BG CMB	2.48 (-4.56 to 9.52)	0.48	2.70 (0.50 to 14.59)	0.25
BG CMB number	0.32 (-0.35 to 0.99)	0.34	1.08 (0.95 to 1.24)	0.24

UPDRS-III, Unified Parkinson's Disease Rating Scale part III; OR, odds ratio; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CI, confidence interval; WMH, white matter hyperintensity; PVS, perivascular space; CMB, cerebral microbleeds; BG, basal ganglia.
*Age- and sex-adjusted.

Supplementary Table 3. Effects of plasma α-synuclein on motor severity in patients with CADASIL or idiopathic Parkinson's disease

	CADASIL with parkinsonism (n=55)		Idiopathic Parkinson's disease (n=158)	
UPDRS-III score	Beta* (95% CI)	*P*	Beta* (95% CI)	*P*
Log α-synuclein	5.27 (-2.21 to 12.75)	0.16	2.13 (0.83 to 3.43)	<0.01
H-Y stage ≥3	OR* (95% CI)	*P*	OR* (95% CI)	*P*
Log α-synuclein	1.61 (0.28 to 10.60)	0.60	1.57 (1.12 to 2.21)	0.01

CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; UPDRS-III, Unified Parkinson's Disease Rating Scale part III; OR, odds ratio; CI, confidence interval; H-Y, Hoehn-Yahr.
*Age and sex adjusted.

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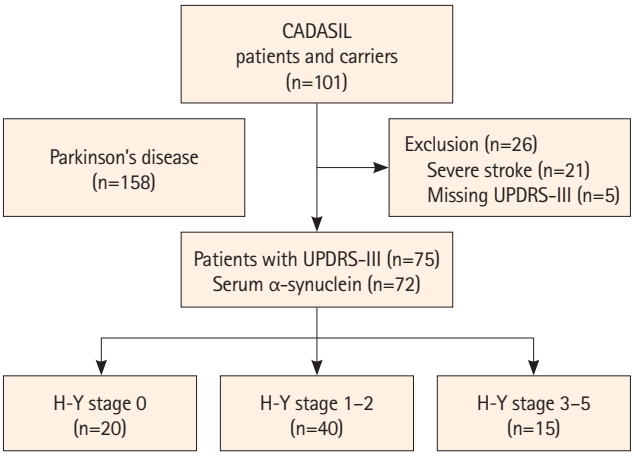
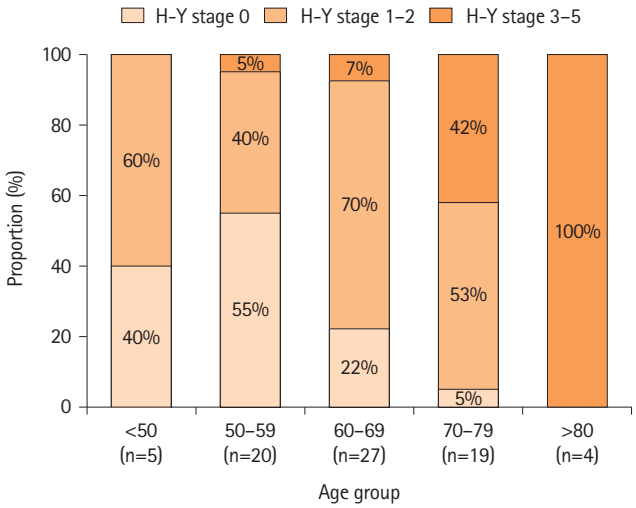


Supplementary Figure 1. Study flowchart. CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; UPDRS-III, Unified Parkinson's Disease Rating Scale part III; H-Y, Hoehn-Yahr.



Supplementary Figure 2. Distribution of the Hoehn-and-Yahr stage among patients with CADASIL in different age groups. CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; H-Y, Hoehn-Yahr.