Multiple simultaneous acute infarcts in CADASIL: a retrospective cohort study and systematic review

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Abstract

Background:

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is the most common monogenic cause of stroke and typically presents with single lacunar infarcts. However, multiple simultaneous acute infarcts have increasingly been reported.

Methods:

We retrospectively reviewed a prospectively recruited CADASIL registry from a British National Referral Clinic to identify cases with multiple simultaneous acute infarcts. We combined this with data from a systematic review on MEDLINE, Embase, Web of Science, and Cochrane Library from inception to 16th February 2026. Multiple simultaneous infarcts were defined as multiple diffusion-restricted lesions on brain MRI.

Results:

Eight cases (5 male) were identified from 612 symptomatic CADASIL patients, corresponding to 1.3% of the cohort (95% CI 0.6–2.6%). Mean (SD) age 49.6±13.1 compared with 49.5±9.8 for 291 stroke patients with single lacunar infarct. All had a recent infection (COVID-19 3, unspecified respiratory tract infections 4, and Campylobacter infection 1), occurring 2–14 days before symptom onset. The systematic review identified an additional 36 cases (total n=44). Mean age was 48.3±10.2 years and 26 were male. Preceding events were identified in 31 cases, most commonly infection

(n=25), followed by surgery (n=4), trauma (n=1), and severe anaemia (n=1). Most patients had infarcts involving bilateral internal watershed regions (90.9%).

Conclusions:

Multiple simultaneous acute infarcts are a rare but important CADASIL presentation, typically involving bilateral watershed regions and frequently preceded by acute systemic stressors, most commonly infection, but also surgery and hypotension. This pattern may reflect increased cerebral microvascular vulnerability in CADASIL patients and warrants further investigation.

Key Messages

What is already known on this topic

Multiple simultaneous acute infarcts in CADASIL have been increasingly reported and potentially link to recent infections.

What this study adds

Multiple simultaneous acute infarcts had been experienced by 1.3% of patients in a symptomatic UK CADASIL cohort. Pooled cases were commonly associated with recent infection, showed predominantly bilateral internal watershed infarcts, and most occurred in patients with High-Risk EGFr mutations.

How this study might affect research, practice or policy

These findings highlight infection as a frequently observed preceding event to multiple simultaneous acute infarcts in CADASIL patients and support further research into the effects of systemic stressors on cerebral small vessel disease.

Introduction

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is the most common monogenic cause of cerebral small vessel disease. It is caused by pathogenic variants in the *NOTCH3* gene, leading to a systemic arteriopathy characterised by the deposition of granular osmiophilic material (GOM) within the basement membrane of vascular smooth muscle cells. This results in progressive damage to the small penetrating arteries and arterioles.[1] The common clinical manifestations include stroke, migraine with aura and vascular cognitive impairment progressing to dementia.[2]

The typical stroke in CADASIL is an ischaemic lacunar stroke, and these are usually single infarcts on neuroimaging. However, multiple simultaneous acute infarcts have been increasingly reported in recent years, particularly following the COVID-19 pandemic.[3] Despite these observations, data on the prevalence, clinical characteristics, and risk factors of multiple simultaneous acute infarcts in CADASIL remain limited.

To better understand this manifestation, we identified cases from a prospectively recruited CADASIL registry to estimate the prevalence of multiple simultaneous acute infarcts and to describe their clinical and radiological features. We also conducted a systematic review of the literature to identify previously reported cases. We then combined our case series with published cases to analyse clinical characteristics, risk factors, and outcomes associated with this phenotype.

Methods

Retrospective Cohort Analysis

We performed a retrospective review of a prospectively recruited CADASIL register from the UK CADASIL National Referral clinic based in London (2001-2013) and in Cambridge (2013-2025) and from the UK Familial Small Vessel Disease Study, a prospective register of CADASIL cases from 6 centres in the UK between 2016 and December 2025. The study was approved by the East of England Cambridge Central Research Ethics Committee (16/EE/0118). Informed consent was obtained from all participants before enrolment. Patients' data were collected at the first study encounter and during follow-up visits using standardized forms. All CADASIL patients were diagnosed with a typical cysteine-changing mutation in the *NOTCH3* gene.

Multiple simultaneous acute infarcts were defined as the presence of multiple spatially distinct acute diffusion-restricted lesions on diffusion-weighted imaging (DWI) magnetic resonance imaging (MRI), occurring in the context of an acute neurological syndrome.

Systematic Review

Search strategy

The study protocol was pre-registered in PROSPERO (CRD420251053590). We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement guidelines, 2020.[4] PubMed (MEDLINE), Embase, Web of Science, and Cochrane Library were searched to identify articles published from inception until 16

February 2026. The search strategy was as follows: ("CADASIL" OR "cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy") AND ("multiple infarcts" OR "multifactorial" OR "multifocal Infarcts" OR "bilateral infarcts" OR "simultaneous infarcts" OR "border zone" OR "watershed*" OR "hypoperfusion" OR "junctional").

Study selection and eligibility criteria

The following inclusion criteria were used: (1) adults 18 years of age or older diagnosed with CADASIL who had multiple acute infarcts on DWI confirmed on brain MRI. CADASIL diagnosed according to previous diagnosis criteria;[5] (2) articles published in English. Case reports, case series, and all observational studies with available data on multiple acute infarcts in CADASIL patients were included. Reference lists from selected publications were manually screened to identify additional relevant studies. Quality and risk of bias were assessed using the Joanna Briggs Institute (JBI) critical appraisal checklists.[6,7] (Table S1 and S2)

Data extraction and analysis

The studies searched were imported into Rayyan for screening, and de-duplication. Titles and abstracts were independently screened by two reviewers (JB and LC). Full texts of potentially eligible studies were then reviewed to determine final inclusion. Disagreements during screening were resolved by consensus and, where necessary, through discussion with a third reviewer (HSM). Data extraction was performed by one

reviewer (JB) using a predefined extraction form and was cross-checked by a second reviewer (LC). Any discrepancies in extracted data were resolved by consensus, with involvement of a third reviewer (HSM) where required.

The following data were extracted: (1) study characteristics (author, year of publication, country of residence of the cases); (2) demographic data (age, sex); (3) CADASIL-related history, including mutation details, history of any CADASIL symptoms, radiographical changes due to CADASIL; (4) medical history and vascular risk factors; (5) potential triggers; (6) complications; (7) prognosis; (8) clinical presentations and radiological characteristics of multiple acute infarcts.

Statistical Analysis

The estimated proportion of patients who had experienced multiple simultaneous acute infarcts was calculated in percentage (%) within the prospective CADASIL cohort, with 95% confidence interval estimated using the exact binomial method. The cases from the systematic review were pooled with our case series for combined analysis. Continuous variables were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR), while categorical variables were presented as count and percentage (%). All analyses were performed using R software (version 4.3.3).

Results

Retrospective Cohort Analysis

There was a total of 650 patients in the CADASIL register as of December 2025. Among these, 613 were symptomatic while 37 patients who were asymptomatic and diagnosed on predictive testing. One was homozygous and was excluded, and the other 612 symptomatic cases with heterozygous cysteine-altering mutations were included in the analysis.

Among the 612 patients, eight had experienced multiple simultaneous acute infarcts, corresponding to 1.3% of the cohort (8/612; exact binomial 95% CI 0.6–2.6%). Baseline information, clinical and radiological features and potential trigger events in these 8 patients are summarized in Table 1. Mean age at presentation was 49.6 ± 13.1 years, and 5 were male. It was the first clinical manifestation of CADASIL in 2 patients. Seven patients carried a pathogenic variant in epidermal growth factor repeat (EGFr) domains 1–6 of *NOTCH3* compared with 472/604 remaining registry patients. All eight carried mutations classified as High-Risk EGFr mutations.[8]

All 8 patients had a history of recent infection prior to the presentation. The infection was COVID-19 in 3 cases, unspecified respiratory tract infections in 4, and *Campylobacter* infection in 1. The interval between infection and stroke onset was within two weeks in all cases ranging from 2 days to 14 days. No cases had preceding hypotension or surgical procedures. No extra or intra cranial large artery stenosis or cardioembolic sources were found. The acute lesions involved internal watershed regions in all 8 patients with additional lesions in cerebellar peduncle or corpus callosum in 4 cases as shown in Figure 1.

Six of 8 patients achieved a good recovery, with a modified Rankin Scale (mRS) score of 1 at follow-up (median follow-up, 20 months). One patient had persistent symptoms

affecting mobility, while another remained significantly disabled (mRS 4). Only one patient (Case 6) experienced a recurrent lacunar stroke almost a decade later, and no deaths occurred during the follow-up period.

Systematic Review

The search identified 310 records across four databases. After removing 129 duplicates, 181 records remained. Following title and abstract screening, and with an additional 12 records identified through citation searching, 40 studies were selected for full-text review. Of these, 11 were excluded based on the predefined inclusion criteria. 29 studies met the eligibility criteria and were included. The PRISMA flowchart diagram is shown in Figure 2.

Among the included studies, 25 were case reports and 4 were case series, comprising a total of 36 CADASIL patients with multiple acute simultaneous infarcts (Table 2 and 3).

Combined Analysis of Case Series and Systematic Review

A total of 44 CADASIL patients were included in the pooled analysis. Forty-one patients were diagnosed with CADASIL based on the presence of a *NOTCH3* mutation, among whom 5 had additional GOM confirmed by skin biopsy. Three patients from the same study did not specify the diagnostic method. Specific mutations were recorded for 32 patients.

The characteristics of all 44 patients are summarized in Table 4. The mean age at the time of multiple acute infarcts was 48.3 ± 10.2 years and 26 were male. The

presentation was the initial manifestation of CADASIL in more than half of the cases. Among the 32 patients with available mutation data, 22/32 (68.8%) carried mutations in EGFr domains 1–6, and 28/32 (87.5%) had mutations in High-Risk EGFr domains.

Among patients with available trigger data, infection was the most frequently reported preceding event (25/31, 80.6%). Reported infections were heterogeneous, including COVID-19 (15/25, 60.0%), influenza A (2/25, 8.0%), Campylobacter infection (1/25, 4.0%), and unspecified infections (7/25, 28.0%). Most patients with preceding infection remained ambulatory before the onset of neurological symptoms (21/25, 84.0%), while 4/25 (16.0%) had more severe systemic illness or physiological compromise requiring medical attention. These included severe COVID-19 pneumonitis, COVID-19 associated cardiomyopathy,[3] and two cases with prominent gastrointestinal symptoms and severe dehydration.[9]

A recent surgical procedure was the most common non-infectious trigger, identified in 4 patients,[10–13] followed by trauma[14] and severe anaemia[15], each reported in 1 patient. The clinical presentations were within 2 weeks from the trigger events in all cases with a median of 7 days. Hypotensive status was available for 31 patients. Fourteen had a documented hypotensive episode, defined as blood pressure lower than 100/60 mmHg, while 17 had documented blood pressure measurements without hypotension. Hypotension status was not reported for the remaining 13 patients.

Among 26 cases with both EGFr and preceding event information available, 20 had a preceding infection and 6 had a non-infectious preceding event. EGFr 1–6 and High-Risk variants were present in 18/20 (90.0%) and 20/20 (100%) respectively among those with

preceding infection, compared with 2/6 (33.3%) and 3/6(50.0%) among those with non-infectious preceding events.

All patients demonstrated bilateral acute infarcts on MRI. In 40 of the 44 patients (90.9%), the lesions involved the internal watershed or border zone areas. Among these, 18 patients had infarcts confined exclusively to the internal watershed regions, whereas 22 patients had additional lesions in other areas, including the cerebellar peduncles and the corpus callosum.

Discussion

In this study, we identified multiple simultaneous acute infarcts in 8 of 612 patients from a large, prospectively recruited CADASIL cohort. Combined with cases identified through a systematic review, a total of 44 cases were analysed. Overall, the age at onset of this manifestation appears to be similar to that reported in cohorts of typical lacunar stroke,[16] but it can also occur in younger individuals, including those in their 20s. These events were frequently preceded by acute systemic triggers, including infection, surgery and hypotension. Notably, over 90% of infarcts involved the internal watershed territories.

Although this clinical presentation of CADASIL has been previously described, little is known about its prevalence within CADASIL cohorts. We identified 8 cases from a prospectively recruited cohort of 612 symptomatic CADASIL registry patients, corresponding to 1.3% of the cohort (95% CI 0.6–2.6%). Compared with typical lacunar stroke, which 47.5% of the same cohort had experienced, this represents a much rarer

presentation. However, it is comparable to that of intracerebral haemorrhage (ICH) reported in European CADASIL cohorts ranging from 0.5% to 2.7%.[17]

A recent study reported that multiple simultaneous acute infarcts were more frequent in CADASIL-related acute ischaemic stroke than in matched controls, with a prevalence of 35.7%.[18] The lower prevalence in our cohort may reflect differences in denominator, as our estimate was based on a symptomatic CADASIL registry irrespective of stroke history. However, this does not fully explain the discrepancy, as the prevalence remained low even when restricted to patients with a history of stroke in our cohort, at 2.7%. Population differences may also contribute, as Asian and European CADASIL cohorts differ in mutation distribution and clinical phenotype. A similarly marked population difference has previously been observed for ICH in CADASIL, which has been reported to occur almost nine times more frequently in Asian than in European cohorts.[17]

The exact mechanism of such a presentation is not clear. No embolic source was identified in any of the eight patients in our cohort. In the systematic review, only one case with a patent foramen ovale (PFO), which subsequently underwent closure, was reported.[19] Notably, the infarct pattern in this case involved bilateral cortical territories, in contrast to the predominantly watershed distribution observed in the remaining cases. In our study, 90.9% of infarcts involved the internal watershed territories, with additional lesions mainly affecting the corpus callosum and cerebellar peduncles. This pattern aligns with the known distribution of small vessel pathology in CADASIL and supports a microvascular rather than embolic mechanism.

It is well established that cerebral small blood vessels in CADASIL patients have impaired autoregulation and therefore could potentially be vulnerable to acute hypotension.[20] The involvement of the internal watershed territories in vast majority of the cases further supports this theory. The different preceding systemic stressors could therefore converge on a common haemodynamic pathway. Infection may lead to fever, dehydration and reduced circulating volume. Surgery may involve anaesthesia and perioperative haemodynamic instability. And transient hypotensive episodes can directly reduce cerebral perfusion, which were recorded in fourteen patients.

However, many patients only had mild or even asymptomatic infection with no documented hypotension, suggesting that alternative mechanisms are possible. One potential explanation is acute inflammation mediated endothelial dysfunction. Experimental studies have suggested that endothelial cells actively regulate vasodilation by transmitting signals from arterial type smooth muscle cells (SMCs) through a caveolae-dependent pathway.[21] Systemic infections, including COVID-19, have been shown to cause widespread endothelial injury.[22,23] Given that vascular SMCs are extensively damaged in CADASIL, additional acute endothelial dysfunction during systemic infection could further compromise microvascular regulation and eventually lead to multiple infarcts across watershed regions. Infection can also be associated with hypercoagulability, which could play an additive role.

However, how specific the role of preceding infection is in such presentation should be interpreted cautiously. Acute infection, including COVID-19, is a recognised trigger for ischaemic stroke and vascular events in the general population, and is not specific to CADASIL.[24] Moreover, with current data we cannot determine whether infection is

specifically associated with this phenotype or represents a more general trigger for CADASIL-related stroke. CADASIL may represent one setting of severe diffuse small-vessel vulnerability, in which infection or other physiological stressors could precipitate multifocal infarction. These findings suggest that avoiding or promptly addressing systemic stressors may be clinically important in CADASIL.

Previous studies have stratified NOTCH3 cysteine-altering variants by EGFr location, using either the conventional EGFr 1–6 versus EGFr 7–34 classification or a newer high-, medium-, and low-risk system.[8,25] In our cohort, 7/8 cases had EGFr 1–6 variants and all were in High-Risk EGFr domains with a similar pattern in pooled cases with available mutation data. It is worth noting that EGFr 1–6 and High-Risk variants were also more common in our overall registry cohort (479/612, 78.3%; and 520/612, 85.0%, respectively), and denominator mutation data were unavailable for published cases. Additionally, EGFr 1–6 and High-Risk variants were more frequently observed in infection associated cases than in those with non-infectious preceding events. However, given the very small number of non-infectious cases, these findings are descriptive and should be interpreted with caution.

This study has several strengths. The cases were identified from a large, prospectively recruited CADASIL cohort, allowing us to estimate the proportion of this presentation. Furthermore, by combining our cases with those reported in the literature, we were able to characterise the range of potential triggers associated with this presentation. There are also limitations. The CADASIL cohort included only patients presenting to the UK National CADASIL Clinic and other specialist stroke services, which may introduce referral bias and enrichment for symptomatic or more severely affected individuals.

Published case-level data were also incomplete, with variable reporting of genetic mutation, trigger factors, hypotension, vascular risk factors, and prognosis. These descriptive findings should therefore be interpreted cautiously. Lastly the small total number of cases limited our ability to reliably identify risk factors or assess prognosis for this presentation.

In conclusion, multiple simultaneous infarcts are a rare but clinically important manifestation of CADASIL, observed in approximately 1.3% of patients in a symptomatic UK CADASIL cohort. They typically involve bilateral internal watershed regions and are frequently preceded by acute systemic stressors, most commonly infections. The findings may reflect increased cerebral microvascular vulnerability during systemic physiological stress and highlight the importance of preventing and managing systemic stressors, including established preventive measures against seasonal infections, appropriate management of acute illness, and avoidance of haemodynamic instability.

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Ethics statement

All patients gave written informed consent for their data to be used for research. Ethical approval of the UK Familial Small Vessel Disease study was obtained from the East of England Cambridge Central Research Ethics Committee (16/EE/0118).

Competing interests

The authors declare that there is no conflict of interest.

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Data sharing

The anonymised data are available from the corresponding author upon reasonable request.

Contributorship Statement

JB and LC contributed equally to this paper. JB and LC conceived and designed the study, performed the systematic review and data analysis, interpreted the findings, and drafted the manuscript.

NO managed the dataset and critically reviewed and revised the manuscript.

HSM contributed to study conception and design, secured funding, acted as the third reviewer, interpreted the findings, and critically reviewed and revised the manuscript.

All authors reviewed and approved the final manuscript. LC is the guarantor and accepts full responsibility for the work, had access to the data, and controlled the decision to publish.

Supplemental Material:

Table S1-2

Nonstandard Abbreviations and Acronyms

CADASIL	cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
EGFr	epidermal growth factor repeat
GOM	granular osmiophilic material
DWI	diffusion-weighted imaging
MRI	magnetic resonance imaging
mRS	modified Rankin Scale (mRS)

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Tables:

Table 1. Demographic, clinical and radiological characteristics of 8 cases with multiple acute infarcts from the CADASIL registry

Characteristics	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Gender	Female	Male	Female	Male	Male	Male	Female	Male
Age at stroke	60s	40s	60s	30s	60s	20s	50s	40s
BMI	27.6	23.2	25.0	28.9	26.9	26.8	26.3	30.6
Smoking status	Ex-smoker	Never smoke	Ex-smoker	Never smoke	Never smoke	Never smoke	Never smoke	Never smoke
Hypertension	No	No	Yes	No	No	No	No	No
Hypercholesterolemia	Yes	No	Yes	Yes	Yes	No	Yes	Yes
Age at CADASIL diagnosis	60s	40s	50s	30s	60s	30s	50s	40s
Previous CADASIL features	MWA, encephalopathy and psychiatric syndrome	MWA	MWA, psychiatric syndrome	MWA, encephalopathy with seizure	Psychiatric syndrome	Migraine without aura, psychiatric syndrome	None	None
Gene mutation	c.421C>T, p.Arg141Cys	c.505C>T, p.Arg169Cys	c.421C>T, p.Arg141Cys	c.268C>T, p.Arg90Cys	c.1364G>T, p.Cys455Phe	c.431G>C, p.Cys144Ser	c.505C>T, p.Arg169Cys	c.544C>T, p.Arg182Cys
EGFr domains	3	4	3	2	11	3	4	4
Multiple acute infarcts information								
First stroke of CADASIL	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Preceding event	Respiratory infection	COVID-19	Respiratory infection	Respiratory infection	COVID-19	Campylobacter sp. isolate	COVID-19	Respiratory infection
Preceding event details	Respiratory infection required oral antibiotics	Erythematous rash over neck and chest	Fever and severe cough.	Common cold symptoms.	Severe COVID pneumonitis required intubation and ventilation.	Very unwell with severe diarrhea, dehydrated	Asthenia	Fever and significant cough
WHO clinical progression scale	Mild disease	Mild disease	Mild disease	Mild disease	Severe disease	Moderate disease	Mild disease	Mild disease

Trigger–stroke interval	14 days	3 days	3 days	7 days	2 days	9 days	3 days	8 days
Clinical presentation	Ataxia and dysarthria	Drowsy and confusion	Speech disturbance	Progressive confusion and uncontrollable movements	Confusion and severe COVID pneumonitis	Dysarthria, left-sided weakness	Dysarthria and confusion	Dysarthria and confusion
Infarct Location	Bilateral centrum semiovale and right cerebellar peduncle	Bilateral corona radiata, centrum semiovale and genu of the corpus callosum	Bilateral corona radiata and centrum semiovale	Bilateral corona radiata and centrum semiovale	Bilateral corona radiata and centrum semiovale	Bilateral corona radiata and centrum semiovale	Bilateral centrum semiovale, splenium of the corpus callosum, and right cerebellar peduncle	Bilateral centrum semiovale, corona radiata, and right cerebellar peduncle
Prognosis								
mRS before current stroke	0	0	1	0	0	0	0	0
mRS at follow up	2	1	1	1	4	1	1	1
Follow-up duration, month	25	14	4	10	54	132	59	10

Abbreviation: CADASIL = Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy, MWA = Migraine with aura, BMI = Body Mass Index, mRS = modified Rankin Scale

Table 2. Summary of patient characteristics of 36 cases in 29 studies included in the systematic review

Study	**Age/Sex**	**Clinical presentation**	**Infarct locations**	***NOTCH3* mutation/ EGFr domain**

Aghetti A et al.[3]	58F	Psychomotor slowdown, dizziness, swallowing difficulties	Bilateral centrum semiovale and genu of the corpus callosum	p.Tyr150Cys/ 3
Aghetti A et al.[3]	47M	Confusion, somnolence, and mutism with hemiparesis	Bilateral centrum semiovale, cerebellar peduncles, and genu of the corpus callosum	p.Arg90Cys/ 2
Aghetti A et al.[3]	40M	Ataxia	Bilateral centrum semiovale, bilateral cerebellar peduncles	p.Cys108Arg/ 2
Ando T et al.[26]	37M	Dysarthria and gait difficulties	Bilateral corona radiata	p.Cys329Tyr/ 8
Au K et al.[27]	46M	Abrupt cognitive decline, emotional lability and a mild gait ataxia	Bilateral corona radiata and cerebellar peduncles	N/A
Caba S et al.[28]	51M	Malaise, confusion, apathy, anorexia, expression aphasia and right arm weakness	Bilateral corona radiata, centrum semiovale, right cerebellar peduncle, and splenium of the corpus callosum	Heterozygous missense mutation
Güngor Doğan et al.[29]	58M	Seizure, acute speech, and gait disturbances	Bilateral corona radiata, centrum semiovale, cerebellar peduncle, and corpus callosum	p.Arg207Cys/ 5
Giménez MV et al.[30]	28M	Bradyphrenia, severe dysarthria, and dysphagia	Bilateral centrum semiovale	Heterozygous missense mutation
Gobron C et al.[31]	44M	Transient right-sided face, arm and leg weakness and dysarthria	Left pontine and right occipitoparietal infarcts	N/A
Gobron C et al.[31]	51M	Left sided weakness and speech difficulties	Left caudate and right corona radiata	N/A
Gobron C et al.[31]	54F	Right facial paraesthesia	Right periventricular and the left corona radiata	N/A
GÖKÇAL E et al.[32]	35M	Dysarthria	Bilateral corona radiata	N/A
González Mingot C et al.[10]	38M	Dysarthria, left dysmetria, severe bradypsychia	Corpus callosum and left cerebellar peduncle	p.Cys379Tyr/ 9
Gordhan A et al.[33]	48F	Acute short-term memory loss and word finding difficulty	Bilateral corona radiata and centrum semiovale	N/A
Hsiao CT et al.[11]	69M	Confusion, right hemiparesis and dysarthria	Bilateral corona radiata and centrum semiovale	p.Arg544Cys/ 13-14
Huang H et al.[15]	44F	right-sided weakness and slurred speech	Bilateral corona radiata, centrum semiovale, and corpus callosum	p.Cys222Tyr/ 5
Huang H et al.[15]	49F	Cognitive impairment and behavioural abnormality	Bilateral corona radiata, centrum semiovale, cerebellar peduncles and corpus callosum	p.Arg182Cys/ 4
Huang H et al.[15]	39M	Cognitive impairment and an acute loss of ambulation	Bilateral corona radiata, centrum semiovale	p.Arg182Cys/ 4
Huang H et al.[15]	58F	Dizziness and slurred speech	Bilateral corona radiata, centrum semiovale	p.Arg54Cys/ 1
Król ZJ et al.[34]	30F	Right-sided pulsating headache, dysarthria, fatigue and psychomotor slowness	Bilateral corona radiata and centrum semiovale and genu of the corpus callosum	p.Cys440Trp/ 11
Liu W et al.[12]	52F	Speech impairment with left limb dysfunction	Bilateral corona radiata, centrum semiovale and genu of the corpus callosum	p.Cys484Tyr/ 12
Menounos S et al.[9]	51F	Dysarthria and ataxia	Bilateral cerebellar peduncles, splenium of the corpus callosum, and right temporal subcortical region	p.Arg141Cys/ 3
Mitsutake A et al.[35]	59M	Dysarthria and gait disturbance	Bilateral corona radiata and cerebellar peduncles	p.Arg169Cys/ 4
Mizuno T et al.[36]	64F	Dysarthria, dysphagia and dizziness	Bilateral corona radiata, centrum semiovale and right cerebellar peduncle	p.Arg141Cys/ 3
Mizutani K et al.[13]	41F	Acute disturbance of consciousness	Bilateral corona radiata, centrum semiovale and the corpus callosum	p.Arg54Cys/ 1

Pescini F et al.[19]	57M	Severe dysarthria	Bilateral cortical areas on right parietal lobe and occipital lobe	p.Arg1006Cys/ 26
Pettersen J A et al.[14]	61M	Quadriplegia and unresponsiveness	Bilateral corona radiata, centrum semiovale, cerebellar peduncles	p.Arg332Cys/ 8
Rackimuthu S et al.[37]	48F	Acute-onset loss of speech and ambulation	Bilateral corona radiata, genu and body of the corpus callosum	p.Cys49Trp/ 1
Rajendran I et al.[38]	45F	Dysarthria and confusion	Bilateral corona radiata and centrum semiovale	Heterozygous missense mutation
Rosenblum JS et al.[39]	64M	Dysarthria	Bilateral corona radiata and left frontal and parietal lobe	N/A
Saito S et al.[40]	42M	Mild abulia and cognitive impairment	Bilateral corona radiata and centrum semiovale and genu of the corpus callosum	p.Arg169Cys/ 4
Sweeney B J et al.[41]	47M	Dysarthria	Bilateral centrum semiovale and right cerebellar peduncle	p.Cys395Gly/ 10
Taieb G et al.[42]	48M	Acute dysarthria and bradyphrenia	Bilateral corona radiata and centrum semiovale	N/A
Tojima M et al.[43]	47M	Cortical motor aphasia and right hemiplegia	Bilateral corona radiata, centrum semiovale	p.Cys323Trp/ 8
Williams OH et al.[44]	38F	Dysarthria, right hemiparesis and facial weakness	Bilateral corona radiata and centrum semiovale	p.Arg90Cys/ 2
Zhang T et al.[45]	early 40sF	Dysphagia, dysarthria, and encephalopathy	Bilateral corona radiata	Heterozygous missense mutation

Table 3. Summary of preceding event and prognosis of 36 cases in 29 studies included in the systematic review

Study	Trigger event	Trigger details	WHO clinical progression scale	Interval	Hypotension episode	Prognosis

Aghetti A et al.[3]	COVID-19	Fever, mild lung damage and cardiomyopathy requiring admission	Moderate disease	9 days	Yes	Persisting psychomotor slowing at 6 months
Aghetti A et al.[3]	COVID-19	Asthenia, ageusia, anosmia and fever	Mild disease	7 days	N/A	Independent walking with persisting frontal symptoms at 5 months
Aghetti A et al.[3]	COVID-19	cough and ageusia	Mild disease	11 days	N/A	Slight walking difficulties and moderate cognitive slowing at 4 months
Ando T et al.[26]	N/A	N/A	N/A	N/A	N/A	Marked improvement and returned to work at 3 months
Au K et al.[27]	N/A	N/A	N/A	N/A	N/A	N/A
Caba S et al.[28]	COVID-19	No typical COVID19 manifestations	Mild disease	3 days	N/A	Limited in instrumental activities and unable to return to work at 10 months
Güngor Doğan et al.[29]	COVID-19	High fever	Mild disease	6 days	N/A	Ongoing cognitive impairment at 3 months
Giménez MV et al.[30]	COVID-19	Diarrhoea and vomiting but no respiratory symptoms	Mild disease	2 days	N/A	mRS 1 at 3 months
Gobron C et al.[31]	N/A	N/A	N/A	N/A	Yes	N/A
Gobron C et al.[31]	N/A	N/A	N/A	N/A	Yes	N/A
Gobron C et al.[31]	N/A	N/A	N/A	N/A	No	N/A
GÖKÇAL E et al.[32]	N/A	N/A	N/A	N/A	No	Improved in 3 weeks
González Mingot C et al.[10]	Drainage of perineal abscess under general anaesthetic	No procedure complication	N/A	5 days	Yes	mRS 3 at 12 months with moderate cognitive impairment
Gordhan A et al.[33]	N/A	N/A	N/A	N/A	No	N/A
Hsiao CT et al.[11]	Surgical revision for a knee prosthetic	No procedure complications	N/A	4 days	N/A	Consciousness and mentality recovered within 3 days
Huang H et al.[15]	N/A	N/A	N/A	N/A	Yes	Complete recovery at discharge
Huang H et al.[15]	Menorrhagia and severe anaemia (62 g/L)	N/A	N/A	N/A	Yes	Dramatic recovery at 4 weeks
Huang H et al.[15]	N/A	N/A	N/A	N/A	Yes	Gradual recovery of gait and cognition
Huang H et al.[15]	Fever	5-day history of fever with excessive sweating	Mild disease	5 days	Yes	Gradual improvement
Król ZJ et al.[34]	COVID-19	Swollen tongue, anosmia and general weakness.	Mild disease	11days	No	Persistent mild impairments in attention, memory, and executive function at 1–6 months follow-up

Liu W et al.[12]	Disc herniation surgery	No procedure complications	N/A	14 days	Yes	Complete recovery at discharge
Menounos S et al.[9]	Influenza A	Reduced oral intake, nausea, fevers, chills, generalized weakness and syncope.	Mild disease	14 days	No	Significant neurological recovery
Mitsutake A et al.[35]	COVID-19	Fever and sore throat	Mild disease	4 days	N/A	Walking independently at 3 months
Mizuno T et al.[36]	Renal biopsy	No procedure complications	N/A	N/A	No	Preserved cognitive function
Mizutani K et al.[13]	Influenza A	High fever and cough	Mild disease	4 days	Yes	Regained consciousness and could move independently at discharge
Pescini F et al.[19]	N/A	N/A	N/A	N/A	N/A	Patent foramen ovale with severe right-left shunt. Underwent PFO closure. Goof recovery.
Pettersen J A et al.[14]	Trauma and hypotension	Open femoral fracture and shock, requiring intubation and ventilation	N/A	0 day	Yes	Died 5 weeks post trauma
Rackimuthu S et al.[37]	A self-limiting fever episode	A self-limiting fever episode	Mild disease	7 days	N/A	Independent daily activities with mild persistent cognitive impairment
Rajendran I et al.[38]	COVID-19	Fever, persistent cough, tiredness and generalised myalgia	Mild disease	14 days	N/A	Symptoms improved at discharge
Rosenblum JS et al.[39]	COVID-19	3-day history of flulike symptoms	Mild disease	3 days	N/A	Mild improvement at discharge
Saito S et al.[40]	Respiratory infection	Cold and decreased oral intake	Mild disease	7 days	Yes	N/A
Sweeney B J et al.[41]	N/A	N/A	N/A	N/A	No	N/A
Taieb G et al.[42]	N/A	N/A	N/A	N/A	No	N/A
Tojima M et al.[43]	N/A	N/A	N/A	N/A	Yes	Aphasia and hemiplegia disappeared within 1 month
Williams OH et al.[44]	COVID-19	Fever, myalgia, anosmia and ageusia.	Mild disease	7 days	Yes	mRS was 2 at discharge
Zhang T et al.[45]	COVID-19	Fever, headache and myalgia	Mild disease	11days	No	Returned to work and driving at 8 weeks

Hypotension defined as recorded BP ≤ 100/60 mmHg. Abbreviation: CADASIL = Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy, mRS = Modified Rankin Scale, N/A = Not Available.

Table 4. Summary of characteristics of all 44 CADASIL patients with multiple acute infarcts, including cases from our cohort

Characteristics		**All cases (n=44)**
Age at current presentation		48.3 ± 10.2
Age at CADASIL diagnosis		46.4 ± 10.4
Male, n (%)		26 (59.1%)
Study site		
Asia		13/44 (29.5%)
Europe		23/44 (52.3%)
North America		5/44 (11.4%)
South America		2/44 (4.5%)
Oceania		1/44 (2.3%)
CADASIL features prior to current event		
Current presentation as the first manifestation		25/44 (56.8%)
Stroke		8/44 (18.2%)
Migraine		11/44 (25.0%)
Cognitive impairment		5/44 (11.4%)
Encephalopathy		3/44 (6.8%)
Seizure		1/44 (2.3%)
Psychiatric syndrome		5/44 (11.4%)
Traditional vascular risk factors		
Hypertension	Yes	5/44 (11.4%)
	No	29/44 (65.9%)
	NR	10/44 (22.7%)
Diabetes mellitus	Yes	0/44 (0.0%)
	No	34/44 (77.3%)
	NR	10/44 (22.7%)
Hyperlipidaemia	Yes	11/44 (25.0%)
	No	23/44 (52.3%)
	NR	10/44 (22.7%)
History of smoking	Yes	7/44 (15.9%)
	No	28/44 (63.6%)
	NR	9/44 (20.5%)
No above risk factor reported	Yes	17/44 (38.6%)
	No	17/44 (38.6%)

	NR	10/44 (22.7%)
***NOTCH3* EGFr Group**		
Available data		32/44 (72.7%)
Not reported/Unknown		12/44 (27.3%)
EGFr 1-6		22/32 (68.8%)
EGFr 7-34		10/32 (31.3%)
HR-EGFr domains (1–6, 8, 11, 26)		28/32 (87.5%)
MR-EGFr domains (9, 10, 12–15, 17, 25, 27, 32)		4/32 (12.5%)
LR-EGFr domains (16, 18–20, 23, 24, 28–31, 33)		0/32 (0.0%)
Preceding event and interval		
Available data		31/44 (70.5%)
Not reported/Unknown		13/44 (29.5%)
Infection:		25/31 (80.6%)
COVID-19		15/25 (60.0%)
Influenza A		2/25 (8.0%)
Campylobacter sp. isolate		1/25 (4.0%)
Unspecified infection		7/25 (28.0%)
Surgical procedure		4/31 (12.9%)
Trauma		1/31 (3.2%)
Severe anaemia		1/31 (3.2%)
Interval, days (median, min-max)		7 (0-14)
Hypotensive episodes		
Available BP data		31/44 (70.5%)
Not reported/Unknown		13/44 (29.5%)
Documented BP without hypotension		17/31 (54.8%)
Hypotension		14/31 (45.2%)
90/60 mmHg < BP ⩽100/60 mmHg		10/14 (71.4%)
BP ⩽ 90/60 mmHg		4/14 (28.6%)
Acute infarct lesion distribution		
Internal watershed regions:		40/44 (90.9%)
Confined to internal watershed only		18/44 (40.9%)
Internal watershed with other regions:		22/44 (50.0%)
+ Cerebellar peduncle		8/22 (36.4%)
+ Corpus callosum		8/22 (36.4%)

+ Cerebellar peduncle and corpus callosum	6/22 (27.3%)
Other watershed regions (corpus callosum/cerebellar peduncle)	2/44 (4.5%)
Non-watershed regions	2/44 (4.5%)
Multiple cortical regions only	1/44 (2.3%)

CADASIL = Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy; NR = Not Reported; EGFr = Epidermal Growth Factor-like Repeat; HR = High Risk; MR = Moderate Risk; LR = Low Risk; BP = Blood Pressure.