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Border-Zone Cerebral Infarcts Associated with COVID-19 in CADASIL: A Report of 3 Cases and Literature Review

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Keywords
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy · COVID-19 · Ischemic stroke · Border-zone infarcts · Magnetic resonance imaging

Abstract
Introduction: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is the most common inherited cerebral small vessel disease and is a cause of early onset ischemic lacunar stroke. COVID-19 infection may lead, in addition to acute respiratory syndrome, to vascular complications including stroke. Herein, we report three CADASIL patients presenting with cerebral border-zone infarcts concomitant to COVID-19 infection and summarize similar cases previously published in literature. ***Methods:*** Clinical and radiological features of the 3 patients were collected and described. A narrative review of literature was performed in PubMed and Google Scholar by the end of 2022 using the "CADASIL" AND "COVID-19" AND "stroke" terms. ***Results:*** In our 3 patients, aged 40–58 years, stroke symptoms occurred one to 11 days after the first COVID-19 manifestations. Pulmonary symptoms were mild or absent. One patient presented with hemodynamic failure presumably related to acute cardiomyopathy. Brain magnetic resonance imaging revealed in all cases, ischemic lesions within border-zone areas in both cerebral hemispheres, lesions in the genu of the corpus callosum or in the medium cerebellar peduncles in two cases. The watershed pattern of ischemic lesions was detected in two cases despite any blood pressure drop or severe respiratory dysfunction. Seven CADASIL patients presenting with acute brain infarcts (multiple in 4/7) in context of SARS-CoV-2 infection were identified in literature, despite no fall in blood pressure except for one of them. ***Conclusion:*** Our observations, in line with previous reports, further suggest that COVID-19 infection may alter blood flow autoregulation in the deepest cerebral white matter in CADASIL patients. The thrombocytopathy and endotheliopathy developing during COVID-19 infection may participate to the underlying vascular processes.

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Introduction

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is the most common inherited cerebral small vessel disease. CADASIL is responsible for recurrent ischemic lesions accumulating in the deepest part of the brain and predominating in basal ganglia and the centrum semi-ovale. Accumulation of these lesions is presumably responsible for the development of cognitive and motor decline during the progression of the disease [1].

COVID-19 is associated with acute respiratory syndrome of various severities. Besides the lungs damage frequently detected during the infection, extrapulmonary manifestations are often observed [2]. Cardiovascular ischemic events including strokes have been repeatedly reported during the viral infection [3–5].

Herein, we describe 3 CADASIL cases who presented with cerebral ischemic lesions in supratentorial watershed areas concomitant to acute COVID-19 infection. We also performed a literature review to identify previously published CADASIL patients showing ischemic strokes in the context of COVID-19.

Methods

Clinical and paraclinical data of the 3 cases – all of them being followed at our department (French reference center for rare cerebrovascular diseases, Lariboisière, Paris, France) – were collected and summarized. A narrative review of literature was performed interrogating PubMed and Google Scholar, using the terms "CADASIL" AND "COVID-19" AND "stroke" before December 2022. The extracted articles were then manually sorted, and off-topic papers were removed.

Results

Clinical Description

Case 1

This 58-year-old woman was diagnosed with CADASIL in 2009 after the occurrence of a transient episode of sensory disturbances and dysarthria. She had no other significant comorbidity and no other vascular risk factor than current smoking. The diagnosis was confirmed after MRI investigation by a genetic test showing a typical cysteine mutation in exon 4 of the *NOTCH3* gene (p.Tyr150Cys). She was admitted at hospital on March 22, 2021, because of an unusual dyspnea revealing an acute dilated cardiomyopathy (systolic ejection function estimated at 30%) with healthy coronary arteries. This episode was complicated by a cardiogenic shock which required administration of vasopressive drugs for several days. Three days after hospital admission, she developed a cough and SARS-CoV-2 PCR returned positive. At the pulmonary level, COVID-19 infection was responsible for an isolated peak of fever and very mild lung damage on thoracic scan. The cardiomyopathy was attributed to COVID-19 after negative work-up. Her systolic blood pressure (BP) remained low at discharge, at 90 mm Hg. One day after discharge, the patient began to develop psychomotor slowdown and dizziness. A few days later, she presented with swallowing difficulties. Due to symptoms worsening, cerebral MRI was performed 11 days after discharge and showed on diffusion-weighted images recent bilateral deep border-zone ischemic lesions at the junction between anterior and middle cerebral artery territories within the centrum semi-ovale. These lesions were associated with lesions in the genu of the callosum corpus. She was transferred to a neurology department. BP at admission was at 100/54 mm Hg. Ultrasound examination of cervical arteries was normal. No cardioembolic cause of ischemic stroke was detected (sinusal rhythm recorded, no dilation of left atrium, and no cardiac thrombus seen on transthoracic electrocardiography [TTE]). Six months later, the patient still suffered from a persisting psychomotor slowdown.

Case 2

This 47-year-old man who had a family history of CADASIL suffered from repeated attacks of migraine with aura since young age. He was diagnosed as having CADASIL after a 3-week episode of paranoid delusion in February 2021 leading to an MRI examination that showed white matter hyperintensities extending in both external capsules and anterior temporal gyri. He had no vascular risk factor. The diagnosis was confirmed by a genetic test showing a typical cysteine mutation in exon 3 of the *NOTCH3* gene (p.Arg90Cys). On July 21, 2021, he developed asthenia, ageusia, anosmia. Five days later, he presented with fever during 48 h. Two days after onset of fever, he was somnolent and confused. There was no respiratory symptom. His BP was at 120/70 mm Hg. The SARS-CoV-2 PCR returned positive. The patient had not been vaccinated against COVID-19 before. The neurological examination showed a frontal syndrome with mutism associated with a right hemiparesis. The cerebral CT scan at admission was normal. The brain MRI obtained 5 days later, showed, on diffusion-weighted images,

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Table 1. Reported CADASIL patients with brain infarcts concomitant to COVID-19 infection proven by a positive SARS-CoV-2 PCR

Reference	Date of publication	Age, years	Gender	Vascular risk factors	Neurological symptoms	Acute ischemic lesions on brain MRI	COVID symptoms	Hemodynamics failure	Delay between first COVID manifestations and stroke symptoms	CADASIL mutation
Williams et al. [6]	2020	38	Woman	No	Dysarthria, followed 1 day later by increased dysarthria and transient right facial palsy concomitant to BP drop. Persistent deterioration 4 days later consisting in dysphagia, right hemiparesis, facial weakness, and deficit in the left upper limb (NIHSS 9)	Eleven lesions with a bilateral border-zone distribution on initial MRI. New acute infarcts in the same territory with a confluence of some lesions that had increased in size on control MRI performed after clinical deterioration	Fever, myalgia, anosmia, ageusia	Spontaneous BP drop from 119/66 to 89/47 mm Hg	7 days	p.Arg90Cys
Trifan et al. [7]	2020	37	Woman	Controlled high BP, smoking	Left leg weakness, dysarthria, and ataxia spontaneously resolving in a few hours	One small lesion in the right pons	Absent	Absent	na (absence of COVID symptoms) SARS-CoV-2 PCR positive on systematic screening at admission in hospital	p.Tyr1021Cys
Zhang et al. [8]	2020	Early 40s	Woman	Controlled high BP, dyslipidemia	Lethargia, dysphagia, dysarthria, and expressive aphasia	Multiple lesions in bilateral centrum semi-ovale	Headache, myalgia, fever, diffuse pulmonary rhonchi, and mild desaturation (92%)	Absent	11 days	na

Table 1 (continued)

Reference	Date of publication	Age, years	Gender	Vascular risk factors	Neurological symptoms	Acute ischemic lesions on brain MRI	COVID symptoms	Hemodynamics failure	Delay between first COVID manifestations and stroke symptoms	CADASIL mutation
Krol et al. [9]	2021	30	Woman	No	Right-sided pulsating headache, dysarthria, and psychomotor slowness, followed by deterioration of consciousness 3 days later	Multiple lesions in bilateral corona radiata and genu of the corpus callosum	Fever, anosmia, general weakness, small peripheral areas of ground glass opacities on chest-CT scan lungs (3% lung surface) but no respiratory symptoms	Absent	11 days	p.Cys440Trp
Rajendran et al. [10]	2021	45	Woman	Not mentioned	Dysarthria, followed by confusion 8 days later	Bilateral centrum semi-ovale (border-zone distribution) on initial MRI. New acute infarcts in the same distribution on control MRI performed after clinical deterioration	Fever, persistent cough, tiredness, and generalized myalgia, resolving after self-isolating for past 14 days	Not mentioned	≥14 days	na
Cruciani et al. [11]	2021	60	Woman	High BP	Aphasia, agraphia, and worsening of right upper limb chronic motor deficit	One small lesion in the corona radiata	Mild respiratory symptoms not requiring hospitalization or any specific treatment	Not mentioned	15 days	p.Arg332Cys (c.994C>T)
Giménez et al. [12]	2022	28	Man	No	Bradyphrenia, dysarthria, and dysphagia	Multiple subcortical lesions in bilateral centrum semi-ovale	Vomiting and diarrhea, absence of respiratory symptoms	Not mentioned	≤36 h	na

Table 1 (continued)

Reference	Date of publication	Age, years	Gender	Vascular risk factors	Neurological symptoms	Acute ischemic lesions on brain MRI	COVID symptoms	Hemodynamics failure	Delay between first COVID manifestations and stroke symptoms	CADASIL mutation
Aghetti et al. [present study]	2023	58	Woman	Smoking	Psychomotor slowdown and dysphagia	Patchy lesions in bilateral corona radiata and one in genu of corpus callosum	Isolated fever peak, cough, and dyspnea attributed to acute dilated cardiomyopathy related to COVID-19. Very mild lung damages on thoracic CT scan	Cardiogenic choc requiring a vasopressor support for several days	7 days	p.Tyr150Cys
Aghetti et al. [present study]	2023	47	Man	No	Confusion, somnolence, and aphasia	Multiple lesions in bilateral corona radiata, bilateral cerebellar peduncles, and genu of corpus callosum	Asthenia, anosmia, ageusia, fever, oxygen 1 L/min during 2 days, 10–25% of lung damages on thoracic CT scan	Absent	9 days	p.Arg90Cys
Aghetti et al. [present study]	2023	40	Man	No	Ataxia	Multiple lesions in bilateral corona radiata and medium cerebellar peduncles	Cough, ageusia	Absent	11 days	p.Cys108Arg

BP, blood pressure.

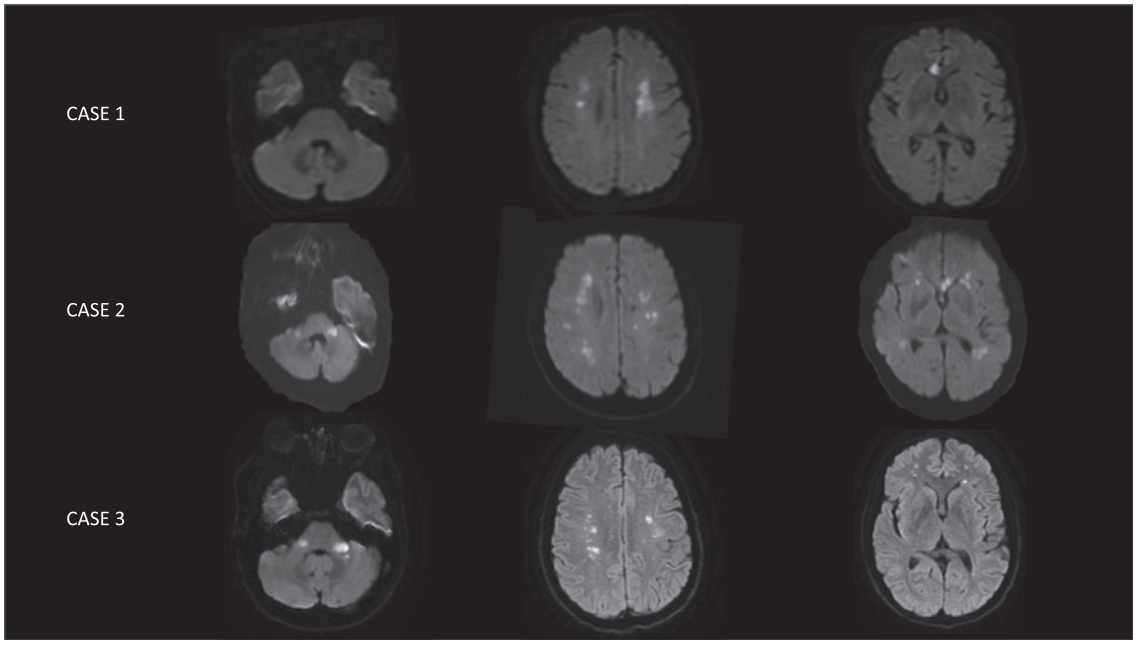

Fig. 1. Acute ischemic lesions observed in the 3 CADASIL patients (diffusion-weighted magnetic resonance imaging). Acute ischemic lesions are observed in bilateral deep watershed regions of cerebral hemispheres (cases 1–3, middle column), in bilateral medium cerebellar peduncles (cases 2 and 3, left column), and in genu of corpus callosum (cases 1 and 2, right column).

acute border-zone ischemic lesions in the deepest areas of both hemispheres at the junction between the anterior and middle cerebral arteries territories. Ischemic lesions were also present in the genu of the corpus callosum and in both cerebellar peduncles. A thoracic CT scan showed lesions affecting about 10% of lungs. A complete cerebrovascular work-up did not show any obvious cause of cardioembolism (sinusal rhythm, no dilation of left atrium, and no intracardiac thrombus on TTE), and angio-CT showed normal cervical and intracranial arteries. Blood coagulation tests were normal except for an isolated lupus anticoagulant and elevated D-dimers at 790 ng/mL. The patient needed a treatment of 1 L/min of oxygen during 2 days, and a new thoracic CT scan showed an increase of lungs damage at 25%. After this episode, the patient remained stable and did not require any respiratory help. Five months later, the patient was able to walk without any assistance and presented with persisting frontal symptoms.

Case 3

This 40-year-old man without any vascular risk factors, who had a history of stroke in his brother and his mother, was diagnosed for CADASIL in 2013 after the occurrence of a transient ischemic attack. His genetic test showed a typical cysteine mutation in exon 3 of the *NOTCH3* gene (p.Cys108Arg). On December 20, 2021, the patient had a cough and developed ageusia. He stopped his preventive treatment by aspirin started in 2013. Nine days after the onset of pulmonary symptoms, he was tested positive for SARS-CoV-2 despite a previous Comirnaty® full-dose vaccination, with the last injection performed 3 months earlier. Two days later, he developed gait difficulties. He was admitted to the emergency department 2 days after. His neurological examination showed a cerebellar ataxia. His brain MRI showed several subacute deep ischemic lesions involving border-zone areas in both hemispheres, at the junction between anterior and middle cerebral arteries, associated with lesions in both cerebellar peduncles. BP values and respiratory parameters were normal during the whole hospitalization. No respiratory symptom was detected. The cerebrovascular work-up was normal (sinusal rhythm, no dilation of left atrium, and no intracardiac thrombus on TTE). No stenosis of cervical or intracranial arteries was observed on the angio-CT scan. D-dimers were initially elevated (830 ng/mL at day 2) and decreased during the hospitalization. Four months later, the patient presented with slight walking difficulties with a moderate cognitive slowdown.

Literature Review

Seven reports of CADASIL patients showing an acute ischemic stroke in the context of COVID-19 were identified in the literature (Table 1) [6–12]. In 4 out of them, acute ischemic lesions were multiple, involving bilateral centrum semi-ovale with a pattern compatible with a watershed distribution [8–10, 12]. No hemodynamic failure was reported except in the patient described by Williams et al. [6], for whom a drop from 119/66 to 89/47 mm Hg in BP had been recorded. In the patient reported by Krol et al. [9], one acute infarct involved the corpus callosum. No lesion in the cerebellar peduncles was reported in these different cases.

Discussion

In this report, 3 CADASIL cases presented few days after contracting COVID-19, neurological manifestations related to bilateral deep ischemic lesions with a similar pattern in border-zone areas, i.e., at the junction of two main arterial territories in both cerebral hemispheres (shown in Fig. 1). In two of these cases, ischemic lesions were also detected in the genu of the corpus callosum and within both medium cerebellar peduncles. In all patients, steno-occlusive lesions of cervical or large intracranial arteries have been ruled out, as intracardiac thrombus. In all cases, respiratory manifestations of COVID-19 were moderate or absent. These findings contrast with the usual location of cerebral infarcts observed during COVID-19 infections in the general population that generally occurs at more severe stage of pulmonary infection and is mostly related to thrombosis of large intracranial arteries [5].

Ischemic lesions in these cases differ from those usually observed in CADASIL patients outside the context of infection. Small deep infarcts accumulate progressively during the course of the disease but most often occur in isolation [1]. Multiple acute ischemic lesions have already been reported in CADASIL [13, 14]. Basically, multiple infarcts in CADASIL are observed in the context of arterial hypotension or hemodynamic failure, mostly involving border-zone regions, but also corpus callosum and infratentorial regions in some patients [13]. There is accumulating evidence suggesting that the progressive loss of smooth muscle cells in the wall of cerebral arterioles might alter cerebral blood flow autoregulation during the course of the disease [15, 16]. This may promote the occurrence of multiple lesions in specific circumstances particularly with perfusion variations secondary to BP drop or dehydration.

Intriguingly, in our observations, multiple infarcts occurred in border-zone regions without any BP lowering in 2 cases (cases 2 and 3). In line, most stroke CADASIL cases reported at time of SARS-CoV-2 infection also presented with multiple infarcts in watershed cerebral areas without hemodynamic failure, hypotension, or severe respiratory deficiency or anoxia [8–10, 12] (Table 1). Altogether, these data suggest that some alterations occurring at the level of the cerebral microvasculature in CADASIL patients during SARS-CoV-2 infection may promote the occurrence of ischemic lesions without BP drop and regardless of the severity of pulmonary infection. In case 1, the development of cardiomyopathy prior to COVID-19 symptoms has led to variations of BP which may have contributed to the development of border-zone infarcts. Given the absence of risk factor and cardiac comorbidity, and the negative etiological work-up in this patient, the acute cardiomyopathy was presumably secondary to COVID-19 infection, as already described [2].

In our 3 cases, stroke events occurred after a median of 9 days after the onset of symptoms related to COVID-19 infection. This delay is in line with that reported in literature, most of cases showing a delay below 2 weeks (Table 1). Considering the similar delays between the first symptoms of COVID-19 and the occurrence of multiple infarcts in most patients, it seems reasonable to assume a causal relationship between COVID-19 and ischemic manifestations in our patients. Exact determinants of this vulnerability to ischemic cerebral lesions in CADASIL patients in the context of COVID-19 infection are still unknown. Alterations of endothelial cells (ECs) in the vascular wall induced by SARS-CoV-2 [5] might be involved. The penetration of SARS-CoV-2 in EC through the angiotensin-converting enzyme type 2 transmembrane protein promotes the release of pro-thrombotic molecules such as von Willebrand factor and fibrinogen resulting in the formation of microthrombi in the vascular network [17–19]. Changes of EC can also lead to dysregulation of vascular tone control, through alterations of the renin-angiotensin system and loss of vasorelaxation mediated by nitric oxide and bradykinin [19–21]. Impairment of the microvascular vasoreactivity resulting from COVID-19 has been already shown to promote a mismatch between tissue perfusion and local oxygen needs. This has been demonstrated in the lungs [22] but also in the brain with bilateral hypoperfusion in fronto-temporal regions in the current form of infection [23]. We presume that this SARS-CoV-2-mediated endotheliopathy may worsen the chronic microvascular dysfunction already present in CADASIL cases

and promote the occurrence of ischemic lesions in the most vulnerable cerebral areas even in mild forms of the viral infection.

Statement of Ethics

Included patients provided their written and informed consent for the use of their clinical, imaging, and genetic data for research purposes, and for the use of that information in a scientific publication. The study protocol was reviewed and approved by Inserm Ethic Committee (IRB00003888) under the approval number 17-088.

Conflict of Interest Statement

The authors declare that research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Author Contributions

A.A. and T.A. drafted the manuscript. S.G., D.H., and H.C. revised the manuscript. All authors approved the final version of the manuscript.

Data Availability Statement

The data that support this article are not publicly available due to containing information that could compromise the privacy of research participants but are available from S.G. upon reasonable request.

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