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SHORT COMMUNICATION

Vessel wall magnetic resonance imaging in COVID-19-associated cryptogenic ischemic stroke

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Abstract

Background and purpose: Acute ischemic stroke (AIS) is a common complication of coronavirus disease 2019 (COVID-19), but the underlying biological mechanisms remain unclear. We aimed to describe the prevalence of vessel wall alterations in patients with cryptogenic stroke through vessel wall magnetic resonance imaging (vwMRI).

Methods: All consecutive patients admitted for AIS and COVID-19 to a single neuro-COVID unit from 10 November to 31 December 2020 were prospectively evaluated and underwent a complete etiologic workup for AIS. In patients with cryptogenic stroke, the diagnostic workup was completed with vwMRI study.

Results: After the exclusion of four patients ineligible for MRI, a total of 10 patients were included (median age = 78 years, 50% males), of whom four (40%) had a cryptogenic stroke. vwMRI showed vascular changes consistent with inflammation of intracranial artery walls in three subjects (75%). Two patients had focal and one multifocal involvement.

Conclusions: vwMRI detected signs of vascular inflammation in the majority of patients with cryptogenic AIS, leading to an etiologic definition with potential therapeutical implications. Our findings are best interpreted as hypothesis-generating, suggesting the possibility of expanding the diagnostic workup of cryptogenic stroke with vessel wall imaging.

KEYWORDS
cerebrovascular, SARS-CoV-2, undetermined stroke, vasculitis, vwMRI

INTRODUCTION

Ischemic cerebrovascular events have been reported in up to 5.7% of patients with coronavirus disease 2019 (COVID-19) [1].

The pathophysiology and etiology of acute ischemic stroke (AIS) in COVID-19 patients remain poorly characterized, and a high frequency of cryptogenic events has been reported [2].

Several hypotheses have been proposed, including coagulopathy, acute hypoxemia, and endotheliopathy [3]. The latter could be induced by either cytokine storm or cerebral vessel endotheliitis caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. The hypothesis of vascular inflammation related to COVID-19 has been supported by evidence derived from pathology and imaging studies [4,5].

Vessel wall magnetic resonance imaging (vwMRI) is a promising technique that allows a noninvasive imaging study of arterial wall inflammation in vivo and is a useful tool in the diagnostic definition of cryptogenic stroke in patients without SARS-CoV-2 infection [6] and in patients with central nervous system (CNS) vasculitis [7–9]. Preliminary findings showed that vwMRI may provide useful information also in patients with COVID-19, but its added value in the investigation and etiological classification of AIS remains unclear [10,11].

The primary aim of this study was to investigate the role of vwMRI in the diagnostic workup of COVID-19 patients with cryptogenic AIS

and its ability to detect a possible underlying inflammatory process involving intracranial arteries.

MATERIALS AND METHODS

We conducted a single-center observational prospective study on AIS associated with COVID-19. We evaluated all consecutive patients admitted for AIS to a neuro-COVID ward, a nonintensive care setting, at IRCCS Mondino Foundation, Pavia, Italy, from 10 November to 31 December 2020. COVID-19 diagnosis was based in all cases on a positive real-time reverse transcription–polymerase chain reaction assay for SARS-CoV-2 RNA in nasopharyngeal swab samples.

All patients underwent a standardized etiologic workup for AIS, including 48-h electrocardiographic monitoring, epiaortic and intracranial vessel study with either computed tomographic angiography or MRI angiography, laboratory testing, and transthoracic or transesophageal echocardiography [12]. Stroke etiology was determined according to the TOAST classification [13].

In case of undetermined stroke etiology after a complete diagnostic workup, patients underwent vwMRI. All vwMRI studies were conducted with a 3-T Siemens Magnetom Skyra scanner. Our MRI protocol included standard diffusion-weighted imaging, two-dimensional (2D) axial fluid-attenuated inversion recovery, and T1, T2, and T2*sequences; in patients with cryptogenic stroke, black-blood sequences, before and after gadolinium administration, were performed. Black-blood sequences used in the study MRI protocol were T1 Turbo Spin Echo 2D sequences (echo time = 10 ms, repetition time = 523 ms; in-plane spatial resolution = 0.2 × 0.2 mm reconstructed, 0.4 × 0.4 mm acquired), oriented on axial and coronal planes, covering the circle of Willis.

MRI was evaluated independently by two experienced neuroradiologists, and discrepancies were adjudicated by consensus. All patients provided written informed consent to participate, and the study protocol was approved by the local ethics committee.

RESULTS

We screened 14 patients with AIS and COVID-19, of whom 10 were included in the study (four patients were excluded for the following reasons: two died before MRI and two could not undergo MRI due to medical instability and presence of a pacemaker, respectively). Of the remaining 10 patients, four were diagnosed with cardioembolic stroke, one with atherothrombotic stroke and one with lacunar stroke. Four of 10 patients (40%) who had cryptogenic stroke, three males and one female, median age = 57 years, underwent vwMRI. Clinical and radiological characteristics of the patients are summarized in Table 1.

Three of four patients with cryptogenic stroke (75%) presented concentric vessel wall enhancement, consistent with inflammatory alterations of arterial walls. Two of them had a focal concentric vessel wall enhancement in the artery feeding the territory of ischemic lesions, with associated arterial lumen stenosis, involving the A2 segment of an azygos anterior cerebral artery variant in one case (Figure 1a–c) and the M1–M2 segment of the right middle cerebral artery in the other case.

The third patient had bilateral and more widespread vessel wall enhancements in the intracranial anterior and posterior circulation (Figure 1d–f). This patient developed recurrent ischemic lesions in the following 2 months, with persistent vessel wall enhancement. Digital subtraction angiography revealed progressive multifocal intracranial artery stenosis, suggestive of CNS vasculitis. He was then treated with high-dose intravenous methylprednisolone. After treatment, at 6-month follow-up, he had no new ischemic lesion or stroke and vwMRI demonstrated the resolution of vessel wall contrast enhancement.

DISCUSSION

In this prospective, single-center study, we observed that the majority of AIS patients with an unclear etiology after a standard workup had pathological enhancement of cerebral arteries on vwMRI.

Our results are in line with a previous study reporting intracranial vessel wall abnormalities in patients with COVID-19-associated AIS [11]. Other studies have detected a high frequency of vascular abnormalities on MRI, although not related with clinically evident acute cerebrovascular events [10].

The inflammatory etiology of the arterial lesions detected by vwMRI cannot be definitively established with imaging features but was supported by laboratory findings, clinical features, and vascular risk factor profile. Furthermore, all patients underwent a complete and standardized etiological workup to rule out traditional causes of ischemic stroke and in particular intracranial atherosclerosis.

Specifically, our two patients with focal arterial lesions had only mild hypertension and did not have other significant intracranial stenosis, neither concomitant aortic arch and carotid artery atherosclerosis. In the third patient, the association of vwMRI abnormalities, digital subtraction angiography, and cerebrospinal fluid analysis findings associated with recurrent ischemic strokes yielded a very high diagnostic probability of CNS vasculitis [14].

Several biological mechanisms may explain our findings and the previously reported associations between COVID-19 and vessel wall inflammation. Focal cerebral arteriopathy may arise from endotheliitis resulting from direct viral infection, and this hypothesis is in line with a previous report of pediatric AIS with vwMRI suggestive of endothelial inflammation [15,16]. Another plausible hypothesis is the development of CNS angiitis, resulting either from direct vascular invasion from COVID-19 or indirectly from molecular mimicry similarly to other neurological complications of COVID-19 infection [17]. Finally, endotheliitis may be the consequence of massive cytokine release during the acute inflammatory phase of COVID-19 infection.

Our findings are best interpreted as hypothesis-generating, expanding the spectrum of the neurological manifestations of SARS-CoV-2. From a clinical point of view, the high prevalence of vessel wall abnormalities in patients with cryptogenic stroke suggests the need to expand the etiological workup of AIS associated with COVID-19, obtaining vwMRI images, especially in cases with an undetermined

TABLE 1 Clinical characteristics of patients with cryptogenic stroke

Characteristic	1	2	3	4
Age, years	67	56	58	56
Sex	Male	Male	Male	Female
Previous stroke/TIA	No	No	No	No
Diabetes	No	No	Yes	No
Hypertension	Yes	Yes	Yes	Yes
Atrial fibrillation	No	No	No	No
Carotid stenosis	No	No	No	No
Complicated aortic plaque	No	No	No	No
Obesity	No	No	No	No
NIHSS at admission	3	10	1	4
Acute stroke therapy	None	Endovenous thrombolysis and mechanical thrombectomy	None	None
Chest radiography	Normal	Bilateral interstitial pneumonia	Normal	Normal
COVID-19 severity	Asymptomatic	Pneumonia	Mild	Mild
Lymphopenia	Yes	Yes	No	No
C-reactive protein	Normal	1.5 mg/dL	1.1 mg/dL	Normal
D-Dimer	Normal	1341 ng/mL	Normal	Normal
Time from COVID-19 to AIS	Diagnosis at stroke onset	7 days	21 days	5 days
MRI	Bilateral acute ischemic lesions in anterior cerebral artery territory (azygos anterior cerebral artery)	Acute ischemic lesions in right middle cerebral artery territory; subacute left frontal ischemic lesion	Bilateral acute ischemic lesions; basal ganglia perivascular contrast enhancement	Single acute ischemic lesion located in right corona radiata
MRI/CT angiography	Severe A2 stenosis (azygos anterior cerebral artery)	Right M1 occlusion; recanalization after thrombectomy	Progressive multifocal stenosis of intracranial arteries	Mild diffuse atheromasia
vwMRI	Focal concentric enhancement, A2 segment of anterior cerebral artery	Focal concentric enhancement, M1–M2 right middle cerebral artery	Multifocal enhancement	Negative
CSF analysis	Normal	Not performed	Oligoclonal bands in CSF and serum, mirror pattern	Not performed
Modified Rankin Scale at 3 months	1	2	1	1

Abbreviations: AIS, acute ischemic stroke; CSF, cerebrospinal fluid; CT, computed tomographic; MRI, magnetic resonance imaging; NIHSS, National Institutes of Health stroke scale; TIA, transient ischemic attack; vwMRI, vessel wall MRI.

etiology after routine tests. Some limitations should be considered in the interpretation of our study. First, our results derive from a single-center study with a small sample size, requiring prospective confirmation. The generalizability of our findings is therefore limited, and the observed rates of cryptogenic stroke and vwMRI findings may not reflect real incidence and prevalence in the population.

Second, selection bias in favor of less severely affected patients may have occurred, as patients were enrolled in a nonintensive setting. Third, we did not include control AIS patients without COVID-19 and vwMRI was not performed in patients with AIS having a clear etiology. Finally, the presence of an association between vascular abnormalities and AIS does not necessarily imply causality. vwMRI findings alone cannot demonstrate an inflammatory etiology of vascular abnormalities, and imaging findings have to be supported by clinical and laboratory data. More research is also needed to better characterize the underlying pathophysiological mechanisms.

CONCLUSIONS

vwMRI provides additional diagnostic value in the etiological workup of cryptogenic stroke associated with COVID-19. Further studies are

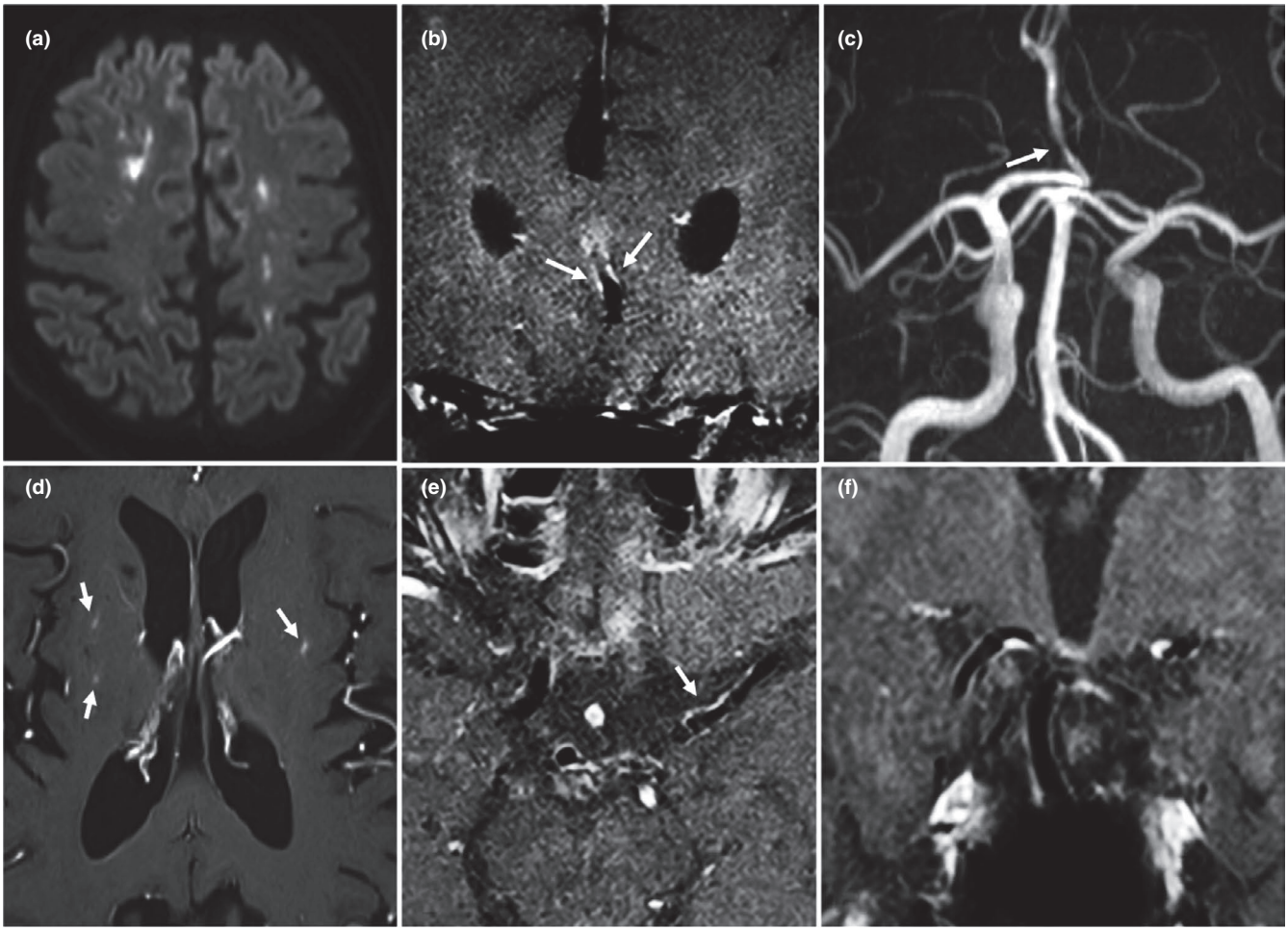

FIGURE 1 Imaging findings in two of the patients with cryptogenic ischemic stroke. Patient 1 presented with bilateral acute ischemic lesions in anterior cerebral artery territory (a); vessel wall magnetic resonance imaging revealed arterial wall contrast enhancement of the A2 tract of an azygos anterior cerebral artery variant (b) with associated stenosis documented by magnetic resonance angiography (c). Patient 3 had bilateral punctate perivascular contrast enhancement in basal ganglia (d), associated with multifocal vessel wall enhancement in both anterior (e) and posterior circulation (f)

needed to confirm our findings in larger sample sizes and to provide more insights into the underlying biological mechanisms and specific treatment for this condition.

CONFLICT OF INTEREST

None of the authors has any conflict of interest to disclose.

AUTHOR CONTRIBUTIONS

Federico Mazzacane: Conceptualization (lead), data curation (lead), investigation (equal), writing–original draft (lead), writing–review & editing (equal). **Antonio Zito:** Conceptualization (equal), writing–original draft (lead), writing–review & editing (equal). **Serena Magno:** Conceptualization (equal), writing–review & editing (equal). **Alessandra Persico:** Writing–review & editing (equal). **Valentina Mazzoleni:** Writing–original draft (equal), writing–review & editing (equal). **Carlo Asteggiano:** Investigation (equal), writing–review & editing (equal). **Elisa Rognone:** Conceptualization (equal), investigation (equal), writing–original draft (equal), writing–review & editing (equal). **Anna Pichiecchio:** Writing–review & editing (equal). **Alessandro Padovani:** Writing–review & editing (equal). **Anna Cavallini:** Conceptualization (lead), investigation (equal), supervision (equal), writing–review & editing (equal). **Andrea Morotti:** Conceptualization (lead), supervision (lead), writing–original draft (lead), writing–review & editing (equal).

ETHICAL APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

INFORMED CONSENT

Informed consent was obtained from all individual participants included in the study.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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