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## Cerebral vasculitis of medium-sized vessels as a possible mechanism of brain damage in COVID-19 patients

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### **Authors contributions:**

Name	Location	Role	Contribution
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François LERSY, MD	University hospital of Strasbourg	Author	Design and conceptualized study; analyzed the data; drafted the manuscript for intellectual content
Mathieu ANHEIM, MD, PhD	University hospital of Strasbourg	Author	Analyzed the data; drafting and revision of manuscript
Thibault WILLAUME, MD	University hospital of Strasbourg	Author	Analyzed the data; drafting and revision of manuscript
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Stéphane KREMER, MD, PhD	University hospital of Strasbourg	Author	Design and conceptualized study; analyzed the data; drafted the manuscript for intellectual content

# **Cerebral vasculitis of medium-sized vessels as a possible mechanism of brain damage in COVID-19 patients**

## **Abstract:**

### **Background and Purpose**

Cerebral complications related to COVID-19 were recently reported, and the underlying mechanisms of brain damage remain uncertain, probably multifactorial. Among various hypotheses suggested, a possible vasculitis was issued but never confirmed. Herein, we aimed to describe brain MRIs focused on the intracranial vessel wall in a population of COVID-19 patients with neurologic manifestations.

### **Materials and Methods**

Between March 1 and May 31, 2020, 69 consecutive COVID-19 patients with neurologic manifestations underwent a brain MRI allowing the study of the intracranial vessel wall at Strasbourg University hospitals and were retrospectively included. During the same period, 25 consecutive patients, without suspicion of SARS-CoV-2 infection, underwent a brain MRI urgently, with the same imaging protocols. A vasculitis seemed likely when imaging demonstrated vessel wall thickening with homogeneous and concentric enhancement.

### **Results**

Among the 69 COVID-19 patients included, 11 (16%) presented arterial vessel wall thickening with homogeneous and concentric enhancement, compatible with cerebral vasculitis. These neuroimaging findings were not found among the 25 patients without SARS-CoV-2 infection, and the difference was statistically significant ( $p=0.03$ ). Middle cerebral arteries, basilar artery, and posterior cerebral arteries were the most frequent vessels involved. For nine of them, imaging demonstrated ischemic or hemorrhagic complications.

### **Conclusion**

Cerebral vasculitis of medium-sized vessels seems to be one of the mechanisms at the origin of brain damage related to COVID-19.

## **Abbreviations:**

RT-PCR: reverse transcriptase-polymerase chain reaction

VZV: varicella-zoster virus

# **Cerebral vasculitis of medium-sized vessels as a possible mechanism of brain damage in COVID-19 patients**

## **Introduction**

In recent weeks, some cerebral complications related to COVID-19 were documented by brain MRIs (1-5). Nevertheless, the underlying mechanisms of brain damage remain unclear, probably multifactorial. Among various hypotheses suggested, a possible vasculitis was issued but never confirmed (1-5). A recent pathologic study (6) has shown evidence of direct viral infection of the endothelial cells with endotheliitis. Herein, we aimed to describe brain MRIs focused on the intracranial vessel wall in a population of COVID-19 patients with neurologic manifestations.

## **Materials & Methods**

The study was approved by the ethical committee of Strasbourg University Hospital (CE-2020-37) and was in accordance with the 1964 Helsinki Declaration and its later amendments. Due to the emergency in the context of COVID-19 pandemic responsible for acute respiratory and neurological manifestations, the requirement for patients' written informed consent was waived.

### *Patient cohort and brain MRI protocols*

During the COVID-19 outbreak between March 1 and May 31, 2020, 112 consecutive COVID-19 patients with neurologic manifestations underwent a brain MRI at Strasbourg University hospitals. The diagnosis of COVID-19 was confirmed by the detection of SARS-CoV-2 by reverse transcriptase-polymerase chain reaction (RT-PCR) assays on the nasopharyngeal, throat, or lower respiratory tract swabs. Of these 112 patients, 69 patients were retrospectively included, based on the MRI sequences acquired: unenhanced and contrast-enhanced three-dimensional T1-weighted spin-echo MR imaging with a slice thickness of 1mm or 1.2mm (due to its black blood effect, the latter sequence allows the study of the intracranial vessel wall) (7), time-of-flight MR angiography, diffusion weighted-imaging, axial susceptibility-weighted MR and FLAIR sequences. All subjects underwent MR imaging with a 3T MR unit.

During the same period, 25 consecutive patients, without suspicion of SARS-CoV-2 infection underwent a brain MRI in an emergency context, for neurologic disorders, with the same imaging protocols, and with similar 3T MR units.

Clinical and laboratory data were extracted from the patients' electronic medical records in the Hospital Information System.

### *MRI interpretation*

Two neuroradiologists (S.K and F.L with 20 and 9 years of experience in neuroradiology, respectively) blinded to all patient data (SARS-CoV-2 infection or not), independently reviewed all brain MRIs, and reached a final agreement concerning the diagnosis of cerebral vasculitis. According to expert consensus recommendations (7), a vasculitis occurs likely when imaging demonstrates vessel wall thickening with homogeneous and concentric enhancement (7,8). Nonconcentric vessel wall enhancements were considered to be possibly related to atherosclerotic plaque (7,8). This latter pathological condition may also be associated with the development of vasa vasorum, which can mimic vasculitis. Due to the potential pitfall secondary to the development of intracranial vasa vasorum, concentric enhancements localized in the intracranial segments of the internal carotid and vertebral arteries have not been considered (7,8).

### *Statistical analysis*

As atherosclerosis may also be associated with concentric enhancements, we described and compared the distribution of the vascular disease risk factors in the two groups (with and without confirmed SARS-CoV-2 infection) to avoid a bias related to their presence. In a second step, in the COVID-19 group, by the same reasoning, the patients with suspected cerebral vasculitis were compared to those with normal vessel wall imaging.

Data were described using frequency and proportion (n, %) for categorical variables, using median and range for quantitative data. Categorical data were compared using Fisher exact test.

Quantitative data were compared using Student's t-test. A p-value lower than 0.05 was considered significant.

## Results

The characteristics of the two populations are summarized in table 1.

Among the 69 COVID-19 patients included, 11 (16%), ten men and one woman, with a median age of 69 years (range: 64-79 years) presented arterial vessel wall thickening with homogeneous and concentric enhancement, compatible with cerebral vasculitis (Figure 1). These neuroimaging findings were not found among the 25 patients without SARS-CoV-2 infection, and the difference was statistically significant ( $p=0.03$ ). They were more men in the group with SARS-CoV-2 infection ( $p=0.004$ ), without statistical differences concerning the other cardiovascular risk factors (table 1).

Among these 11 patients, the vascular involvement was unifocal in 3 (27%) cases and multifocal in 8 (73%) cases. Middle cerebral arteries (9 cases), basilar artery (8 cases), and posterior cerebral arteries (4 cases) were the most frequent vessels involved. Six patients (55%) demonstrated extensive white matter microhemorrhages, 3 (27%) subarachnoid hemorrhage, 4 (36%) acute ischemic stroke (especially watershed cerebral infarctions in three cases, the last patient demonstrated a small vessel infarct), and 2 (18%) brain parenchymal signal abnormalities (Table 2). Only two patients (18%) showed intracranial arterial narrowing (Figure 1).

Of these 11 patients, 6 underwent a lumbar puncture (the median between the onset symptoms of COVID-19, mostly respiratory, to lumbar puncture was 28 days, range 8-44 days), which presented increased inflammation markers for three of them, but SARS-CoV-2 RNA was never detected.

These patients' demographic and clinical characteristics, their neuroimaging findings, and cerebrospinal fluid analysis are summarized in Table 2.

As previously mentioned, the presence of vasa vasorum can mimic vasculitis, that is why the intracranial segments of the internal carotid and vertebral arteries have not been taken into account. Vasa vasorum may develop with pathologic conditions such as intracranial atherosclerotic plaques. As above-mentioned, to avoid a bias related to the presence of vascular disease risk factors, among the COVID-19 patients, the two populations, with and without suspicion of cerebral vasculitis, were compared (table 3). The COVID-19 patients with normal vessel wall imaging were younger ( $p=0.003$ ) without differences concerning stroke history or other risk factors for vascular disease.

## Discussion

Our study reinforces the assumption of cerebral vasculitis as one of the mechanisms at the origin of brain damage related to COVID-19. This seems possible, as angiotensin-converting enzyme 2 (ACE2), the main receptor for SARS-CoV-2, is expressed, among others, by endothelial cells (6). A recent pathologic study has shown for the first time that SARS-CoV-2 can infect endothelial cells with diffuse endothelial inflammation (6). This may recall what was previously described with the varicella-zoster virus (VZV), which is associated with a direct viral vascular involvement and cerebral vasculitis, either following a primary infection (varicella) or viral reactivation (herpes zoster) (9-10). Indeed, its DNA and antigens were detected in cerebral arteries from patients with VZV vasculopathy (9). Nine of our eleven COVID-19 patients suspected to have cerebral vasculitis

demonstrated common cerebral vasculitis complications, such as acute ischemic stroke, subarachnoid or cerebral hemorrhages. Six of them showed extensive white matter microhemorrhages with an atypical involvement of the corpus callosum. This pattern was recently described on brain MRIs in critically ill COVID-19 patients (1,2). However, the underlying pathophysiological mechanisms leading to diffuse microbleeds in the COVID-19 pandemic context remain unknown, and several hypotheses were proposed, notably those concerning the potential role of hypoxemia or vasculitis (1,2). Only two of our eleven COVID-19 patients suspected of cerebral vasculitis showed evidence of intracranial arterial narrowing, probably because small arteries injury could not be studied so easily as for medium-sized vessels. Moreover, although the presence of angiographic abnormalities (including vascular irregularities, stenoses, aneurysms, and occlusions) is helpful in diagnosing cerebral vasculitis, these are usually described if larger vessels are involved, and a normal angiography does not rule out the diagnosis of vasculitis (11). Concerning the cerebrospinal fluid analysis, only six patients suspected of cerebral vasculitis had a lumbar puncture, and SARS-CoV-2 RNA was never detected by RT-PCR, nevertheless, its absence does not exclude the diagnosis. First, it should be kept in mind that the lumbar punctures were performed late after SARS-CoV-2 infection (median of 28 days after the onset of respiratory symptoms). This long delay could explain our samples' negativity since the viral clearance was already significant at this time. Second, in VZV vasculopathy, search for VZV DNA in cerebrospinal fluid is frequently negative (9), and the detection of VZV antibody seems to be more sensitive (9). Unfortunately, search for SARS-CoV-2 antibodies in cerebrospinal fluid was not done in our study. Third, the mechanism leading to cerebral blood vessels inflammation is not necessarily a direct viral infection but may involve other phenomena, such as immune-mediated disorders.

Of the six patients who had a lumbar puncture, five displayed identical oligoclonal bands in cerebrospinal fluid and serum (type IV), in agreement with previous reports (12,13). In this context, they were probably secondary to the systemic infection with passive diffusion into the cerebrospinal fluid (14).

Our study's main limitation is the lack of neuropathological confirmation since none of our patients had a brain biopsy. Nevertheless, even if cerebral vasculitis related to COVID-19 has never been highlighted, clinical and histologic evidence of vasculitis has also been demonstrated in other organs, especially in the skin (15-17). Moreover, during the COVID-19 outbreak, the high incidence of Kawasaki disease (18,19), an example of vasculitis affecting medium and small-sized vessels (20), seems to bolster this hypothesis.

## **Conclusion**

Cerebral vasculitis of medium-sized vessels seems to be one of the mechanisms at the origin of brain damage related to COVID-19.

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**Key words:** vasculitis / COVID-19 / Magnetic Resonance Imaging (MRI)

**Subject terms:** Magnetic Resonance Imaging (MRI) / Vascular Disease

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**Figure:**

Figure 1: 69-year old man with pathological wakefulness after sedation. Axial unenhanced T1-weighted spin-echo (A), axial (B, E), and coronal (C, D) contrast-enhanced T1-weighted spin-echo, 3D TOF MR angiography (F). Basilar artery wall enhancement (B, C). Left middle cerebral artery (D), and right posterior cerebral artery (E) with concentric wall enhancement. Posterior cerebral arteries narrowing (F).

Table 1: Characteristics of the two populations

	<b>COVID-19 patients (N=69)</b>	<b>Patients without SARS-CoV-2 infection (N=25)</b>	<i>p-values</i>
<b>Sex</b>	46 men / 23 women	8 men / 17 women	<b>0.004</b>
<b>Age (median, range) (years)</b>	65 (21-86)	65 (27-91)	0.66
<b>History of stroke</b>	4 (6%)	4 (16%)	0.2
<b>Diabetes</b>	17 (25%)	6 (24%)	1
<b>High blood pressure</b>	33 (48%)	7 (28%)	0.1
<b>Hyperlipidemia</b>	25 (43%)	7 (28%)	0.62
<b>Smoking</b>	6 (9%)	4 (16%)	0.47
<b>Obesity</b>	24 (35%)	7 (28%)	0.62
<b>Vessel wall imaging compatible with cerebral vasculitis</b>	11 (16%)	0	<b>0.03</b>

Table 2: Description of the patients with suspected cerebral vasculitis

	Sex	Age	Days from COVID-19 respiratory symptom onset to brain MRI	Neurological history	Risk factors for vascular diseases	Neurological manifestations	Localization of vessel wall enhancement	Other neuroimaging findings	CSF analysis
1	M	69	34	-	High blood pressure / Type 2 diabetes mellitus / Hyperlipidemia / Obesity	Pathological wakefulness after sedation	Basilar artery / Left MCA / Bilateral PCA	AIS in anterior choroidal artery territory / extensive WM microhemorrhages	NR
2	M	70	36	-	-	Pathological wakefulness after sedation / Right pyramidal syndrome	Left MCA	Extensive WM microhemorrhages / Subarachnoid hemorrhages	10 cells/mm3 ↑ Total protein: 0.75g/L ↑ Immunoglobulin G: 123mg/L Oligoclonal bands identical in CSF and serum. SARS-CoV-2 ARN -
3	M	79	40	-	Hyperlipidemia	Pathological wakefulness after sedation	Basilar artery / Bilateral MCA	Extensive WM microhemorrhages / Subarachnoid hemorrhages	3 cells/mm3 Total protein: 0.4g/L ↑ Immunoglobulin G: 47mg/L Oligoclonal bands identical in CSF and serum. SARS-CoV-2 ARN -
4	M	75	36	-	-	Pathological wakefulness after sedation / Right clonic seizures	Basilar artery / Left MCA	Extensive WM microhemorrhages	NR
5	M	61	34	-	Hyperlipidemia / Smoking	Pathological wakefulness after sedation	Basilar artery / Bilateral MCA	Extensive WM microhemorrhages	0 cell/mm3 Total protein: 0.4g/L Immunoglobulin G: 27mg/L Oligoclonal bands identical in CSF and serum. SARS-CoV-2 ARN -
6	M	66	12	-	Hyperlipidemia / High blood pressure / Obesity	Confusion / Agitation	Basilar artery	-	0 cell/mm3 ↑ Total protein: 0.6g/L ↑ Immunoglobulin G: 51mg/L SARS-CoV-2 ARN -
7	M	67	34	Transient ischemic attack	High blood pressure / Hyperlipidemia	Impaired consciousness / Agitation	Basilar artery / Bilateral MCA / Bilateral PCA	-	NR
8	M	64	21	-	High blood pressure / Type 2 diabetes mellitus	Bilateral pyramidal syndrome / Aphasia / Confusion	Basilar artery / Bilateral MCA	AIS ( left ACA-MCA watershed cerebral infarction) / FLAIR hyperintense lesions involving both middle cerebellar peduncles	0 cell/mm3 ↑ Total protein: 0.71g/L ↑ Immunoglobulin G: 60mg/L Oligoclonal bands identical in CSF and serum. SARS-CoV-2 ARN -
9	W	71	32	-	High blood pressure / Type 2 diabetes mellitus / Hyperlipidemia / Obesity	Pathological wakefulness after sedation	Bilateral MCA / Bilateral PCA	Subarachnoid hemorrhages / Extensive and confluent supratentorial white matter FLAIR hyperintensities	2 cells/mm3 Total protein: 0.3g/L ↑ Immunoglobulin G: 42mg/L Oligoclonal bands identical in CSF and serum. SARS-CoV-2 ARN -
10	M	65	22	Transient ischemic attack	High blood pressure / Type 2 diabetes mellitus	Pathological wakefulness after sedation	Basilar artery	AIS (bilateral ACA-MCA and MCA-PCA watershed cerebral infarction)	NR

	Sex	Age	Days from COVID-19 respiratory symptom onset to brain MRI	Neurological history	Risk factors for vascular diseases	Neurological manifestations	Localization of vessel wall enhancement	Other neuroimaging findings	CSF analysis
11	M	73	37	-	-	Pathological wakefulness after sedation / Bilateral pyramidal syndrome	Bilateral MCA / Bilateral PCA	AIS (bilateral ACA-MCA and MCA-PCA watershed cerebral infarction) / Extensive white matter microhemorrhages	NR

ACA= anterior cerebral artery

AIS= acute ischemic stroke

CSF= cerebrospinal fluid

M= man

MCA= middle cerebral artery

NR= not realized

PCA= posterior cerebral artery

W= woman

WM= white matter

Table 3: Characteristics of the COVID-19 patients with and without suspicion of cerebral vasculitis

	COVID-19 patients suspect of cerebral vasculitis (N=11)	COVID-19 patients without suspicion of cerebral vasculitis (N=58)	<i>p-values</i>
<b>Sex</b>	10 men / 1 woman	36 men / 22 women	<i>0.08</i>
<b>Age (median, range) (years)</b>	69 (64-79)	65 (21-86)	<b><i>0.003</i></b>
<b>History of stroke</b>	2 (18%)	2 (3%)	<i>0.11</i>
<b>Diabetes</b>	4 (36%)	13 (22%)	<i>0.44</i>
<b>High blood pressure</b>	6 (55%)	27 (47%)	<i>0.74</i>
<b>Hyperlipidemia</b>	6 (55%)	19 (33%)	<i>0.18</i>
<b>Smoking</b>	1 (9%)	5 (9%)	<i>1</i>
<b>Obesity</b>	3 (27%)	21 (36%)	<i>0.73</i>

