

Large vessel stroke in six patients following SARS-CoV-2 infection: a retrospective case study series of acute thrombotic complications on stable underlying atherosclerotic disease

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Background and purpose: Ischaemic stroke has been described in association with COVID-19. Several pathophysiological mechanisms have been suggested, i.e. prothrombotic state, cardiac injury etc. It was sought to assess the potential association between ischaemic stroke associated with SARS-CoV-2 infection and underlying atherosclerotic lesions.

Methods: A retrospective analysis of stroke related to large vessel occlusion was conducted amongst patients with SARS-CoV-2 infection and underlying mild atherosclerotic disease, between 19 March and 19 April 2020 in six different stroke centers in the Île-de France area, France.

Results: The median age was 52 years, median body mass index was 29.5 kg/m². All patients displayed previous vascular risk factors such as high blood pressure, diabetes, dyslipidemia or body mass index > 25. The delay between the first respiratory symptoms of COVID-19 and stroke was 11.5 days. At baseline, all had tandem occlusions, i.e. intracerebral and extracerebral thrombus assessed with computed tomography or magnetic resonance imaging. Cases displayed a large thrombus in the cervical carotid artery with underlying mild non-stenosing atheroma, after an etiological workup based on angio-computed tomography or magnetic resonance imaging and/or cervical echography.

Conclusion: Our study should alert clinicians to scrutinize any new onset of ischaemic stroke during COVID-19 infection, mainly in patients with vascular risk factors or underlying atherosclerotic lesions.

Introduction

The pandemic outbreak of coronavirus disease 19 (COVID-19) was first described as a flu-like syndrome with respiratory symptoms [1]. However, neurological symptoms have been reported in 31% of cases, with 6% of cerebrovascular disease [2]. A limited number of strokes associated with COVID-19 have been

described, either occurring in young patients ($n = 5$) or associated with antiphospholipid antibodies or hypercoagulability ($n = 9$) [3–5]. The cause of stroke was suggested to be related to the coagulopathy induced by COVID-19 infection and the associated inflammation [6].

Here, healthcare providers are warned about the catastrophic association of stable atherosclerotic disease and COVID-19 infection which may precipitate acute stroke.

Accordingly, six cases of patients with SARS-CoV-2 infection who developed large vessel ischaemic stroke, all with large intraluminal thrombus and mildly, stable, underlying atherosclerotic lesions are reported here.

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The demographic, clinical, radiological and laboratory characteristics of six consecutive patients admitted for ischaemic stroke associated with SARS-CoV-2 infection are described.

The study was performed in accordance with the principles of the Declaration of Helsinki and was approved by the Research Ethics Committee of Foch Hospital. Oral consent was obtained from patients or next of kin.

Results

A retrospective analysis of stroke related to large vessel occlusion was conducted amongst patients with SARS-CoV-2 infection and underlying mild atherosclerotic disease.

Six cases of large vessel occlusion on mild atherosclerotic lesions were admitted during the study period between 19 March and 19 April 2020 in six different stroke centers in the Île-de-France area, France.

The median age was 52 years, median body mass index (BMI) was 29.5 kg/m². All patients displayed previous vascular risk factors such as high blood pressure, diabetes, dyslipidemia or BMI > 25.

The delay between the first respiratory symptoms of COVID-19 and stroke was 11.5 days. The diagnosis of SARS-CoV-2 infection was asserted by polymerase chain reaction or thoracic computed tomography (CT) scan for all patients. Four of the six reported cases displayed no/mild respiratory symptoms. All the patients showed an increase in inflammatory markers and a hypercoagulability state (elevation of D-dimer or C-reactive protein).

At baseline, all had tandem occlusions, i.e. intracerebral and extracerebral thrombi assessed by CT or magnetic resonance imaging. All cases except one (patient 1) displayed a large thrombus in the cervical carotid artery with underlying mild non-stenosing atheroma, after an etiological workup based on angio-CT or magnetic resonance imaging and/or cervical echography. They were classified as stroke of undetermined etiology according to the TOAST classification. Although no underlying atherosclerotic lesion was found, patient 1 displayed BMI = 33, high blood pressure and diabetes in his medical history. The rest of the etiological workup was negative for these patients (Fig. 1, Table 1).

Concerning the outcome, three patients had died and three were discharged to a rehabilitation center.

Discussion

The mechanisms of ischaemic stroke associated with SARS-CoV-2 infection are poorly understood [6–8].



Figure 1 Ischaemic stroke, 50-year-old patient (case 3). Large intraluminal carotid artery thrombus on the carotid artery angiogram (star, a). Recanalization of the carotid after the endovascular procedure with an underlying mild atherosclerotic lesion (arrow, b).

The prothrombotic state associated with COVID-19 infection has been proposed to be responsible, as for pulmonary embolism [9]. Furthermore, circulating inflammatory factors (e.g. interleukin and C-reactive protein) are responsible for early molecular events triggered by coagulation abnormalities.

Major prognostic factors of the SARS-CoV-2 infection encompass a medical history of vascular disease and risk factors of atherosclerotic disease (obesity, high blood pressure, diabetes). Our observations of acute ischaemic stroke in patients with SARS-CoV-2 infection are in accordance with the reported high-risk profile of patients admitted with the most severe form of SARS-CoV-2 infection [1,10].

Our observations illustrate large vessel occlusion associated with clotting induced by SARS-CoV-2 infection complicating underlying stable atherosclerotic disease. Complications of atherosclerotic disease by viral infection have previously been described [11,12] but the heavy burden of the current COVID

Table 1 Demographic, clinical, paraclinical and outcome findings

Case number	1	2	3	4	5	6
Age (years)	42	60	50	45	60	54
Sex	Male	Female	Male	Female	Male	Male
Medical history	HBP, diabetes	Dyslipidemia	Dyslipidemia	No	None	HBP, diabetes
Symptoms at disease onset	Aphasia and right hemiplegia	Right hemiplegia confusion	Hemiplegia limb ischaemia	Aphasia and right hemiplegia	Fever and mild dyspnea	Right weakness aphasia
Days from disease onset to ischaemic stroke	11	11	13	4	12	13
BMI	33	35	33	26	26	22
NIHSS at stroke onset	20	22	14	26	4	20
Site of occlusion	Common and external and internal carotid artery and MCA	Tandem occlusion with terminus carotid artery and MCA	Tandem occlusion with terminus carotid artery and MCA	Tandem occlusion with terminus carotid artery and MCA	Tandem occlusion with terminus carotid artery and MCA	Tandem occlusion with terminus carotid artery and MCA
Stroke topography	Anterior	Anterior	Anterior	Right	Anterior	Anterior
Side of stroke	Left	Left	Right	Right	Left	Left
Symptoms of COVID-19 severity	Mild (cough)	Severe	Severe (pulmonary embolism)	No	Severe (ARDS)	Cough
COVID diagnosis	Thorax CT scanner	Thorax CT scanner	PCR +	Thorax CT scan + PCR+	PCR+	Thorax CT scan
D-dimers (µg/ml)	19461	5315	13010	11970	>4000	1580
High-sensitivity C-reactive protein (mg/ml)	30	158	32	137.9	288	4
Platelet count	279 000	253 000	211 000	371 000	325 000	424 000
Antiphospholipid antibodies/anti B2-glycoprotein I	Negative/negative	IgM I5/B2GPI = 23	Not done	Negative/negative	Negative/negative	Not done
Lupus anticoagulant	Negative	Negative	Not done	Positive	Positive	Not done
Acute stroke treatment	IVT and EVT	Heparin IV	EVT	EVT	Antiplatelet	Antiplatelet
Etiology work-up	Cryptogenetic	Normal, except a thin atheromatous plaque	Normal, except a thin atheromatous plaque	Normal, except a thin atheromatous plaque	Normal, except a thin atheromatous plaque	Normal, except a thin atheromatous plaque
Etiology classification (TOAST)	Stroke of undetermined etiology	Stroke of undetermined etiology	Stroke of undetermined etiology	Stroke of undetermined etiology	Stroke of undetermined etiology	Stroke of undetermined etiology
Clinical follow-up	Death	Death	Death	Discharge to rehabilitation center	Discharge to rehabilitation center	Discharge to rehabilitation center

ARDS, acute respiratory distress syndrome; B2GPI, beta-2 glycoprotein I; BMI, body mass index; CT, computed tomography; EVT, endovascular treatment; HBP, high blood pressure; IgM, immunoglobulin M; IVT, intravenous thrombolysis; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale; PCR, polymerase chain reaction.

outbreak has permitted an infrequent complication of atheroma associated with viral infection to be described. Direct (invasion by virus) or indirect mechanisms (inflammatory/procoagulant status) have also been debated [7,13]. Our report does not provide definitive evidence whether the clotting in the internal carotid artery is related to the underlying atherosclerosis or whether this is simply an epiphenomenon, given the high prevalence of atherosclerotic disease. However, in the reported cases, clotting was described only at the surface of the atherosclerotic plaque and in the downstream circulation. Multiple clotting in different arteries was not observed in these cases, supporting the potential causal effect of the underlying atherosclerotic lesion.

The observation of these large vessel occlusions amongst COVID patients with mild atherosclerotic disease could represent important clinical findings to warn healthcare providers about the high-risk profile of patients with vascular risk factors. Thus, the community needs to be alerted on the risk of precipitating severe complications due to underlying atheroma.

This study has several limitations. It is a retrospective report. Whilst it may not be generalizable, our study should alert clinicians to scrutinize any new onset of ischaemic stroke during COVID-19 infection, mainly in patients with vascular risk factors or underlying atherosclerotic lesions.

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Disclosure

The authors declare no financial or other conflicts of interest.

Data availability statement

The data will be available to others on reasonable requests to the corresponding author.

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