

Ischaemic strokes associated with COVID-19: is there a specific pattern?

INTRODUCTION

SARS-Cov2 is responsible for COVID-19 that can cause severe respiratory illness, and which can be associated with ischaemic stroke (IS).¹ The objectives of our comparative cross-sectional study were to describe the characteristics of consecutive patients with IS and COVID-19, to compare them to COVID-19-negative IS patients admitted within the same period and to attempt to identify a specific pattern of IS in COVID-19.

METHODS

We conducted a comparative cross-sectional study at two tertiary stroke units, Pitié-Salpêtrière and Saint-Antoine Hospitals, between March 20 and April 20 2020. Cases and controls were all consecutive adult patients hospitalised for recent IS, confirmed on neuroimaging. Cases were diagnosed with COVID-19 if a nasopharyngeal reverse transcription (RT-PCR) test for SARS-CoV-2 (Allplex 2019-nCoV Assay, Seegene) was positive and/or if a chest CT-scan was typical for COVID-19. Exclusion criteria were diagnoses of transient ischaemic attack, haemorrhagic stroke or stroke secondary to cerebral venous thrombosis.

We collected demographic data, cardiovascular risk factors, neurological data, blood test results, in-hospital treatments and discharge outcomes. After reviewing the available workup for each patient (vascular imaging of cerebral and cervical arteries and cardiac evaluation including a 12-lead ECG, 48 hours continuous ECG monitoring and transthoracic echocardiogram), aetiology of IS was classified according to ASCODphenotyping (A: atherosclerosis; S: small-vessel disease; C: cardiac pathology; O: other causes; D: dissection).

Fisher's exact test and Wilcoxon-Mann-Whitney test were used to compare cases and controls for categorical and continuous variables respectively. P values <0.05 defined statistical significance. All data analyses were conducted using Stata V.14.0.

RESULTS

Between March 20 and April 20 2020, 67 patients with IS were hospitalised (41 at Pitié-Salpêtrière and 26 at Saint-Antoine

Hospital). Among them, 12 (17.9%) were infected with SARS Cov-2. Patient characteristics are detailed in [table 1](#).

Stroke revealed COVID-19 in 41.7% of COVID-19 patients. For the other COVID-19 patients with IS, the median delay (P25;P75) between initial COVID-19 symptoms and imaging for stroke was 17 days (7;20). COVID-19 pulmonary severity was mild as only two patients required more than 6L/min of supplemental oxygen, and none of them presented acute respiratory distress syndrome.

The proportion of patients under the age of 60 was higher among COVID-19 patients as well as the proportion of patients of Afro-Caribbean descent (p=0.008). Stroke severity at presentation tended to be higher in the case group which was consistent with a trend towards an increased frequency of proximal arterial occlusion (p=0.053), although none of the COVID-19 patients presented with multiple cerebral large vessel occlusions.

Unusual symptoms at presentation such as delirium or apathy were more frequently found in COVID-19 patients. Among the COVID-19 patients who presented with delirium, two had small infarcts of the corpus callosum (online supplemental figure 1D, F), one of these patients had mild lymphocytic meningitis (with Cerebrospinal fluid [CSF] RT-PCR negative for COVID-19) and sporadic bilateral frontotemporal delta waves at EEG recording.

Arterial causes (atherothrombosis and small cerebral vessel disease) of IS were significantly more frequent in the COVID-19 group (58.3%, n=7/12) than in controls (27.3%, n=15/55) (p=0.049). Potentially causal atherothrombosis was present in 41.7% of cases vs 20.4% of controls. Among the five COVID-19 patients with significant atheroma, four had ipsilateral carotid stenosis superior to 50% according to the North American Symptomatic Carotid Endarterectomy Trial classification. The fifth patient had a floating thrombus in the aortic arch associated with an atherosclerotic plaque <4 mm (online supplemental figure 2).

Inflammatory markers such as C reactive protein, fibrinogen, platelet count and coagulopathy parameters (D-dimer) were found at high levels in cases. Six COVID-19 patients were screened for lupus anticoagulant (LA). Among them, testing was positive in five out of these six patients, whereas it was positive in only one out of nine controls (p=0.011). AntiB2Gp1 antibody was rarely found (one patient in both groups) and none

were positive for anticardiolipin antibody at a significant level.

DISCUSSION

In our study, conducted during the peak of COVID-19 outbreak, IS associated with COVID-19 accounted for nearly one-fifth of hospitalised IS patients. IS was frequently the first manifestation of SARS-CoV-2 infection. Accordingly, stroke neurologists should be aware of this neurological presentation of COVID-19 even in the absence of reported fever or cough. Although the first descriptions of stroke in COVID-19 concerned mostly critically ill patients, our series confirms that IS in COVID-19 occurs even in the absence of severe pneumonia. The mild pulmonary severity may also account for the low mortality observed among COVID-19 IS compared with previous reports,^{2,3} although stroke severity was higher among cases. Individuals of Afro-Caribbean descent represented half of COVID-19 IS in our series. Whether the possible association of COVID-19 IS with Afro-Caribbean origin is due to a biological vulnerability or socioeconomic or environmental factors requires further investigation.

About 40% of COVID-19 patients presented with a pronounced delirium and/or apathy at admission. One of these patients had CSF and electroencephalographic features suggestive of meningoencephalitis. In two of these patients, we found a small infarct of the corpus callosum, a rare ischaemic location, highlighted in another report in COVID-19 patients.⁴ We, therefore, hypothesise that both small deep infarcts and delirium might be at least partially linked to COVID-19-associated acute cerebral endotheliopathy, as described by Hernández-Fernández *et al.*³

We found a marked increase of coagulation activity in the majority of our cases, with the presence of LA. Whether LA is directly involved in the pathogenesis or simply associated with the inflammatory process is uncertain. Moreover, contrary to others series,^{2,3,5} IS aetiological analysis also highlighted a majority of underlying cervico-encephalic arterial injuries among COVID-19 IS, in particular atherothrombotic disease. In these predisposed patients, COVID-19-associated hypercoagulable state may have precipitated atherosclerotic plaque disruption, lowering the threshold for cervico-encephalic arterial disease to become clinically manifest.

In conclusion, our study highlights the characteristics of IS in COVID-19

Table 1 Characteristics of patients hospitalised for ischaemic stroke with COVID-19 versus ischaemic stroke without COVID-19

Characteristics of included patients	COVID-19 patients (12)	Non-COVID-19 patients (55)	P value
Demographic, N (%) if not stated			
Female gender	3 (25.0)	23 (41.8)	0.343
Age, years, median (P25;P75)	66 (53;73.5)	75 (63;84)	0.072
Age <60 years	5 (41.7)	8 (14.6)	0.046
Origin, N (%) if not stated			
Caucasian	4 (33.4)	41 (74.6)	
Afro-Caribbean	6 (50.0)	7 (12.7)	
Asian	1 (8.3)	1 (1.8)	
Other	1 (8.3)	6 (10.9)	
Baseline cardiovascular risk factors, N (%) if not stated			
Hypertension	10 (83.3)	30 (54.6)	0.104
Diabetes mellitus	5 (41.7)	12 (21.8)	0.164
Dyslipidaemia	6 (50.0)	22 (40.0)	0.538
Tobacco intoxication, N (%) (data not available)	3 (30.0) (2)	17 (33.3) (4)	1
Obesity, N (%) (data not available)	3 (25.0)	11 (21.2) (3)	1
History of ischaemic stroke or coronary disease or lower limb arteriopathy	4 (33.3)	20 (36.4)	1
History of atrial fibrillation	1 (8.3)	5 (9.1)	1
Chronic kidney disease	3 (25.0)	6 (10.9)	0.345
Clinical and radiological characteristics, N (%) if not stated			
NIHSS, median (P25;P75)	9 (4;20.5)	3 (2;10)	0.053
Delirium at admission	5 (41.7)	7 (12.7)	0.032
Delay symptom onset—brain imaging <6 hours	5 (41.7)	25 (45.5)	1
Proximal arterial occlusion	6 (50.0)	11 (20.0)	0.061
Involvement of anterior circulation	12 (100)	39 (70.9)	0.056
Blood biological data at admission, median (P25;P75) (data not available) if not stated			
Lymphocytes/ μ L	1130 (880;1330)	1525 (1100;2060) (1)	0.065
Neutrophils/ μ L	6200 (2970;7890)	5800 (4640;6930) (1)	0.406
Eosinophils/ μ L	30 (0;90)	120 (40;200) (1)	0.008
Platelets $\times 10^9$ /L	337 (254;423)	238 (199;302)	0.025
Fibrinogen, mg/dL	560 (480;724) (1)	361 (319;400) (2)	<0.001
D-dimers, μ g/mL	1.79 (1.37;13.60) (4)	0.64 (0.37;2.17) (31)	0.030
C reactive protein, mg/dL	3.115 (1.520;5.000)	0.400 (0.179;0.606) (1)	<0.001
Alanine aminotransferase, U/L	31 (25;40)	21 (17;25) (1)	0.018
Potential causes for IS, N (%) if not stated			
Arterial disease	7 (58.3)	15 (27.3)	0.049
Atherothrombosis†	5 (41.7)	11 (20.0)	0.140
Small vessel disease†	2 (16.7)	4 (7.3)	0.291
Cardiac pathology (atrial fibrillation or significant PFO)‡	1 (8.3)	14 (25.5)	0.273
Floating thrombus	1 (8.3)	0 (0)	
Lupus circulating anticoagulant, N/N screened	5/6 (83.3)	1/9 (11.1)	0.011
Associated meningitis	1 (8.3)	0 (0.0)	
Treatment and outcomes, N (%) if not stated			
Reperfusion therapy	3 (25.0)	15 (27.3)	1
Death	2 (16.7)	3 (5.5)	0.216
mRS ≤ 2 at discharge	6 (50.0)	33 (60.0)	0.538

*SI conversion factors: To convert lymphocytes, neutrophils and eosinophils to $U/10^9$, multiply values by 0.001. To convert fibrinogen in g/L, multiply values by 0.01. To convert D-dimer in nmol/L, multiply values by 1000. To convert C reactive protein in mg/L, multiply values by 10. To convert alanine aminotransferase in μ kat/L, multiply values by 0.0167.

†Potentially causal atherothrombosis and cerebral small vessel disease are defined following ASCOD phenotype.

‡Potentially causal cardiac pathology is defined following ASCOD phenotype updated to include patent foramen ovale-associated stroke.

ASCOD phenotyping, A: atherosclerosis; S: small-vessel disease; C: cardiac pathology; O: other causes; D: dissection; mRS, Modified Rankin Scale; NIHSS, National Institute of Health Stroke Score; PFO, Patent Foramen Ovale.

patients admitted to stroke units during the outbreak. Several non-exclusive and synergistic mechanisms seem at work in this novel infectious disease, including atherosclerotic plaque vulnerability, coagulopathy and microvasculature impairment. Because of the small sample size

of our study, further larger confirmatory studies are warranted to corroborate our findings.

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