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Ischemic cerebrovascular diseases in patients with COVID-19

The severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) had newly emerged and became an evolving pandemic of international concern. Its major clinical features are due to respiratory complications. Recently, some publications illustrate the neuroinvasive potential of COVID-19 [1–3].

A total of 359 patients were diagnosed with confirmed SARS CoV-2 infection in Saint-Camille Hospital in France between 8 March and 1 May 2020. Only four patients presented acute ischemic cerebrovascular diseases (ICVD). The first patient was a 93-year old female presenting with a cardioembolic stroke. His blood cultures were negative after taking antibiotics for 48 hours. She had positive lupus anticoagulants (LA) Transthoracic echocardiography (TTE) revealed mitral endocarditis. Therefore, she was excluded from this study. Here, we describe the other three cases in whom oropharyngeal swabs were positive for SARS-CoV-2 on reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay on admission. Their lung computed tomographic (CT) imaging showed typical features of COVID-19 with different degrees of lesion extent. Their laboratory results showed increasing inflammatory parameters in the acute phase of stroke setting.

Further details are summarised in Table 1.

1. Case patient 1

A 65-year old man, with no medical history, was referred to our department for major psychomotor slowing progressing within 9 days. His body temperature was 38 °C and his oxygen saturation was 92% on room air. His blood pressure was 120/85 mmHg; it was stable during hospitalisation. He was well oriented in time and space. He had bradyphrenia but his verbal responses were appropriate. His spontaneous and organised movements in response to command were clearly executed weakly and slowly highlighting cognitive and motor components impairment. Cerebrospinal fluid (CSF) examination was normal. Electroencephalogram showed slow oscillations without epileptiform features. CT imaging of the brain was normal. Brain magnetic resonance imaging (MRI) disclosed multiple subcortical periventricular stroke with corona radiata damages (Fig. 1 A1-2, B1-2). CT imaging of the supra-aortic vessels, TTE and holter electrocardiogram (HE) were normal. He was treated with antiplatelet agents and prophylactic anticoagulation. After one month of follow-up, psychomotor impairment had gradually improved.

2. Case patient 2

A 75-year old man, with previously smoking and alcohol consumption history, presented with fever and cough. His respiratory function was gradually worsening leading to start oxygen therapy, antibiotics. He was given anticoagulation with enoxaparine at the dose of 4000 UI every 12 hours due to his disease severity. Ten days later, he presented bilateral visual loss with majoration of his biological inflammatory syndrome. Brain MRI demonstrated vertebrobasilar ischemic stroke with infarctions in the right cerebellar hemisphere and bilateral occipital lobe (Fig. 1 C1-2, D1-2). Vertebrobasilar artery was permeable. LA were positive. CT imaging of the supra-aortic vessels revealed atherosclerosis in the carotid artery bulb without significant stenosis. TTE showed left ventricular hypertrophy and HE was normal. He was treated with aspirin. His visual function had slightly recovered within three weeks.

3. Case -patient 3

An 81-year-old man, with history of hypertension, was admitted to our department for confusion. He was afebrile and had an oxygen saturation of 89% on ambient air. He had polypnea with a rate at 24 breaths per min. Neurological examination showed aphasia and apraxia. CT imaging of the brain disclosed left superficial sylvian ischemic stroke (Fig. 1E). IgG anticardiolipin antibodies (ACL) were positive at 63 GPL (N < 20 GPL). CT imaging of the supra-aortic vessels revealed atherosclerosis in the cervical carotid artery bifurcation without significant stenosis. TTE showed mitral and aortic valve calcification. HE was normal. He was treated with aspirin. Two weeks later, his mental status had gradually improved with complete recovery of his language disorders.

Ischemic stroke is considered as a rare complication of SARS CoV-2 infection. It is noted in 0.83% in our cohort.

Table 1 – Baseline characteristics of COVID-19 patients with new onset of ICVD.

	Case patient 1	Case patient 2	Case patient 3
Age (years)	65	75	81
Sex	Male	Male	Male
Medical history	None	Smoking and alcohol consumption history	Hypertension
Onset time of SARS-CoV-2 infection	11/03/2020	29/03/2020	24/03/2020
Extra neurological symptoms	Fever	Fever, cough	Polypnea
Oxygen therapy (l/min)	2	5	5
Onset time of ICVD	11/03/2020	09/04/2020	24/03/2020
Neurological symptoms	Psychomotor slowing	bilateral visual loss	Confusion, apraxia/aphasia
Pulmonary imaging features (lesions extension)	Ground-glass opacities Nodular consolidations Crazy paving pattern (26%)	Ground-glass opacities (10%)	Ground-glass opacities Consolidations (15%)
Stroke vascular territory	Bilateral junction between the anterior and middle cerebral arteries	Basilar artery	Middle cerebral artery
White-cell count (per mm^3)	5300	11,400	10,000
Total neutrophils	4000	8200	8000
Total lymphocytes	900	1300	1200
Platelet count (per mm^3)	250,000	325,000	225,000
Hemoglobin (g/dL)	14.2	11	13.4
Procalcitonin (ng/mL)	0.13	0.12	0.2
C-reactive protein (mg/L)	98	254	98
Serum ferritin (μg/L)	200	1273	279
Fibrinogen (g/L)	4.5	4.47	5.76
Prothrombin time (sec)	13.8	14.6	17.3
Activated partial-thromboplastin time (sec)	32	44	43
D-dimer (ng/mL)	15,000	19,350	20,000
Antiphospholipid antibodies	Not done	Positive LA Negative ACL	Positive ACL = 63 GPL Negative LA
Treatment	Antibiotics Antiplatelet agent	Antibiotics Antiplatelet agent	Antibiotics Antiplatelet agent
Outcome	Survival	Survival	Survival

SARS-CoV-2: severe acute respiratory syndrome Coronavirus 2; ICVD: ischemic cerebrovascular diseases; LA: lupus anticoagulants; ACL: anti-cardiolipin antibodies.

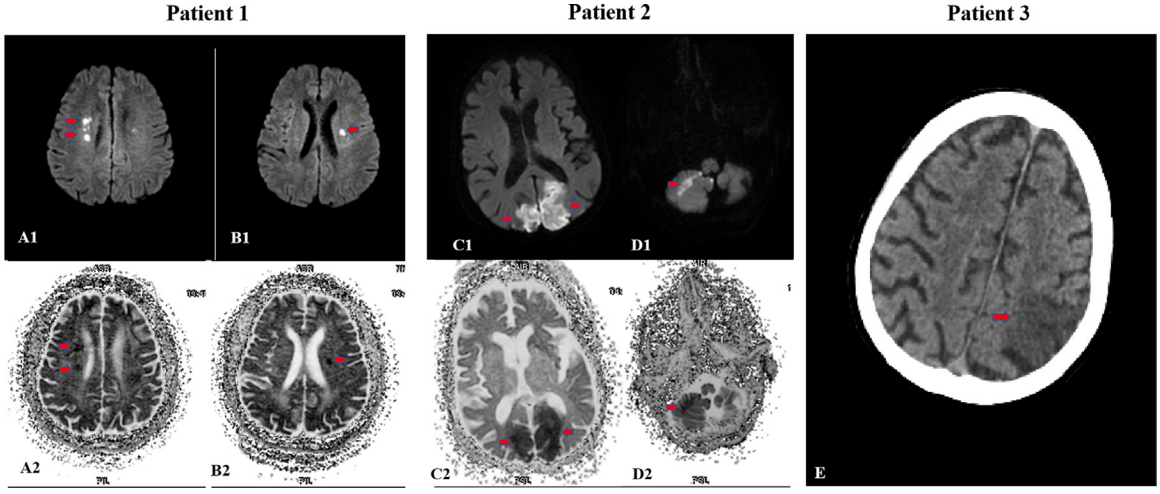

Fig. 1 – A. Representative lung and B. brain imaging in COVID-19 patients with ICVD. Case patient 1: Diffusion weighted images (DWI) showed multiple subcortical periventricular hyperintensities (A1-B1) with decreased ADC values (A2, B2). Case patient 2: DWI revealed hyperintensities in bilateral occipital lobe (C1) and right cerebellar hemisphere (D1) with reduced apparent diffusion coefficient (C2, D2). Case patient 3: CT imaging showed hypodensity in the left parietal lobe (E).

Nevertheless, more significant results were found in Italy [4] and China [1,2] with a frequency of ischemic stroke assessed between 2.33 and 5%.

Oxley TJ et al. [5] reported five cases of large-vessel stroke in COVID-19 patients younger than 50 years of age with cardiovascular risk factors in three cases. Nevertheless, in a recent Chinese study, eleven COVID-19 patients with new onset of ischemic stroke were significantly older [2]; the youngest patient was 57 years of age. They were more likely to have cardiovascular risk factors, including hypertension and diabetes [2]. Ischemic stroke was more common in severely infected patients [1,2]. Our three patients had a mean age of 73.66 years with cardiovascular risk factors in two cases. All patients required oxygen therapy.

In Helms et al.'s report [3], MRI brain was performed in 13 of 58 cases with COVID-19 revealing ischemic stroke in 3 asymptomatic patients. These findings suggest the possibility of underdiagnosed ICVD in affected patients due to subclinical presentation. In our report, patients with ischemic stroke had psychiatric, cognitive and/or focal signs as presenting features leading to MRI practice. Ischemic stroke was revealing SARS-COV-2 in our case patients 1 and 3.

There is increasing evidence that COVID-19 may predispose to brain thromboembolic events [4]. During the acute stage of the infection, rising D-dimer levels reflect hypercoagulable state due to severe inflammatory response, platelet activation and vascular endothelial injury with consequent prothrombotic properties [4,6]. Our three patients had high serum levels of D-dimer, which is consistent with other reports findings. Interestingly, two of them had increased antiphospholipid antibodies (APLA). They didn't receive any drugs that could potentially induce antiphospholipid syndrome (APS). A similar finding was reported in a recent Chinese study [7]. These antibodies confer a higher risk of thrombosis in several situations especially positive LA or triple positive APLA specificities (LA, ACL, and anti-beta2 glycoprotein), high levels of Ig G antibodies and persistent APLA during weeks or months such in the case of APS. Nevertheless, APLA can be transiently positive in infectious, iatrogenic and autoimmune conditions. Their eventual role in stroke setting in patients with COVID-19 is not yet evident and requires further monitoring of these antibodies during disease follow-up.

Other pathophysiological hypotheses explaining stroke onset during acute phase of COVID-19 could be discussed. Our patient 1 had multiple subcortical periventricular strokes without evident cause of cerebral hypoperfusion. Interestingly, small-vessel vasculitis complicating COVID-19 infection were recently reported [8], which suggests that cerebral vasculitis associated endotheliopathy of perforating arteries might be a possible mechanism of this stroke. Additionally, a recent study [9] demonstrated linear association between elevated plasma angiotensin II levels and COVID-19 disease severity. The vasoconstrictive action of angiotensin II might possibly induce transient arterial stenosis resulting in stroke onset. On the other hand, our patients 2 and 3 had cardiovascular risk factors with carotid atherscerosis. The decompensation of their atherosclerotic disorders is probable since the inflammatory response and cytokine storm during infection could trigger and destabilise thrombotic plaque leading to stroke onset [10]. Finally, ischemic stroke could be due to cardio embolism from virus-related cardiac injury. In our report, TTE and HE findings of all patients ruled out atrial fibrillation and morphological heart disease.

During COVID-19 infection, regular laboratory monitoring of inflammatory and hemostasis parameters, including C-reactive protein, ferritin, platelet count, prothrombin time, and fibrinogen, is crucial to detect early coagulation changes progression. Interestingly, high serum ferritin level was significantly correlated with COVID-19 infection severity in recent reports [11]. It may not only reflect acute symptomatic phase but also has a pro-inflammatory activity. Colafrancesco et al. [11] suggested that COVID-19 systemic inflammation could be a part of the spectrum of hyerferritinemic syndromes due to several clinical, laboratory and autoptic similarities including hyperferritinemia, lymphopenia, reduced natural killers number and activity, abnormal liver function tests and coagulopathy. This finding supported the hypothesis of probable common pathogenic background. Thus, serum ferritin level might be considered as an important marker to predict coagulopathy disorders and stroke risk in COVID-19 critically ill patients. Prophylactic anticoagulation should be strictly applied to prevent thrombosis and improve patients' outcome [6].

In conclusion, the incidence of acute ICVD in patients with COVID-19 is probably underestimated due to the atypical clinical symptoms. Our report illustrates the heterogeneity of the clinical and radiological presentation of ischemic stroke in COVID-19 patients. During this pandemic, a better comprehension of the different probable mechanisms of stroke onset, clinicians' vigilance, thromboembolic risk stratification and careful evaluation of laboratory parameters can lead to an optimised therapeutic management and reduced ICVD-related mortality.

Consent

Written informed consent was obtained from the patients for the publication of this article.

Authors' contribution

SE and PR did the literature search. Data were collected by SE, BB, HC and DS; and analysed and interpreted by SE, who also made the figure and analysed the literature search, as well as the writing and review of the manuscript. Furthermore, SE, CM and LT were responsible for the concept of the study. All authors participated in the therapeutic management of the patients and approved the final version of the manuscript.

Disclosure of interest

The authors declare that they have no competing interest.

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A first case of Mild Encephalitis with Reversible Splenial Lesion(MERS) as a presenting feature of SARS-CoV-2

The entire clinical spectrum of COVID-19 is not limited to pulmonary manifestations. Recently, neurological complications associated with COVID-19 were increasingly reported giving evidence that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has a potential for central nervous system (CNS) invasion. Manifestations have included ischemic stroke, Guillain-Barré syndrome, meningitis and encephalitis [1–3]. To the best of our knowledge, COVID-19 presenting with mild encephalitis with reversible splenial corpus callosum lesion (MERS) has not been previously reported.

A 60-year-old man, with a medical history of dyslipidemia, presented to the Emergency Department with cough, headaches and short loss of consciousness lasting 4 minutes. He was afebrile and had bibasilar rales. His oxygen saturation was 99% on room air. Neurological examination was normal. Laboratory tests showed normal white blood cell (WBC) count, lymphopenia at 700 per mm^3, 0 eosinophils per mm^3, normal hemoglobin (Hb) and platelet count. C-reactive protein (CRP) concentration was at 4 mg/l. Procalcitonin value was 0.02 ng/ml. Cerebrospinal fluid (CSF) examination showed normal protein level 0.49 g/L (N:0.2–0.55), glucose 0.55 g/L (N: 0.45–0.75) and 1 white cell per mm^3. CSF culture was sterile. Computed tomographic (CT) imaging of the brain was normal. Neither nasal swab nor chest CT imaging were performed. The patient was discharged with symptomatic treatment. Nine days later, he was referred to our Department of Internal Medicine for vertigo, persistence of headaches and intermittent disturbance of consciousness. He suffered from myalgia, loss of appetite and tiredness. He remained afebrile with bibasilar rales, normal oxygen saturation on ambient air and stable hemodynamic parameters. His Glasgow coma scale (GCS) was 15. Neuropsychiatric examination showed psychomotor slowing, good orientation in time and space with appropriate verbal responses and a vestibular syndrome. He had no neck stiffness. On day 1, he had a brief episode of consciousness loss. Electroencephalogram revealed slow oscillations without epileptiform features. Laboratory examination showed lymphopenia at 900 per mm^3, 0 eosinophils per mm^3, elevated CRP and serum ferritin levels at 50 mg/L and 703 ng/ml respectively. Protein electrophoresis showed hypoalbuminemia at 26.9 g/L, and elevated $\alpha 2$ globulin at 15.5 g/L. Investigations for *Mycoplasma pneumoniae*, syphilis, human immunodeficiency virus, influenza A and B, antinuclear and antineutrophil cytoplasmic antibodies were negative. Oropharyngeal swab was negative for SARS-CoV-2 on reverse-transcriptase– polymerase-chain-reaction (RT-PCR) assay but serologic analysis for COVID-19 was subsequently positive. The test used was ELISA SARS-CoV-2 (EUROIMMUN 2606-9601 G) revealing high serum level of IgG antibodies at 18.9 U (the test is considered as positive if IgG levels $>$ 1.1 U).

Brain magnetic resonance imaging (MRI) demonstrated a focal hyperintense signal in the splenium of the corpus callosum (SCC) on T2-fluid-attenuated inversion recovery (FLAIR) and