eNeurologicalSci 20 (2020) 100256

Contents lists available at ScienceDirect

eNeurologicalSci

journal homepage: www.elsevier.com/locate/ensci

Letter to the Editor

Cerebral venous sinus thrombosis might be under-diagnosed in the COVID-19 era

ARTICLE INFO

Keywords:
COVID-19
Coronavirus
Stroke
Cerebral venous thrombosis
Cerebral venous sinus thrombosis
Thrombosis

Dear Editor,

The new Coronavirus (SARS-CoV2) causing Coronavirus disease 2019 (COVID-19), is widely spread throughout the world and has become a major global health threat. Although the primary manifestation of the disease is respiratory tract infection and pneumonia, multiple organs can be affected.

Coagulopathy and hypercoagulable state is a new feature of COVID-19 and is associated with poor outcome [1]. Elevated D-dimer, fibrinogen level, fibrin/fibrinogen degradation product (FDP), and thrombocytopenia are commonly reported laboratory abnormalities in COVID-19 patients with higher rates in severe disease [1]. Several studies have shown the evidence of increased risk of both venous and arterial thrombotic complications in patients with COVID-19, especially in severe cases. Llitjos, et al. systematically assessed the presence of venous thromboembolism (VTE) among all ICU patients who received either prophylactic or therapeutic doses of anticoagulants in a three-week period. They reported an overall VTE rate of 69%. Interestingly, the rates of VTE and PE were high even among patients who received therapeutic doses of anticoagulant (56% and 33%, respectively). [2]

The higher frequency of VTE among COVID-19 ICU patients compared to the ICU patients with other conditions (12.7%) [3] shows that the novel Coronavirus might increase the risk of thrombosis through additional pathophysiological mechanisms. Endothelial cell injury, cytokine release, immune-mediated vascular inflammation, down-regulation of ACE2 and unopposed pro-inflammatory and pro-thrombotic effects of angiotensin II may contribute to the elevated risk of thrombosis formation in COVID-19. [4]

The emergence of ischemic stroke have been reported in patients with COVID-19. [5,6] Most of these cases presented with arterial stroke. However, to date, there have been a few reported cases of cerebral venous sinus thrombosis (CVST), a venous type of stroke, associated with severe COVID-19 throughout the world. [6–10]

CVST is associated with any prothrombotic conditions, including pregnancy, puerperium, oral contraceptive pills (OCP), fasting/ dehydration, malignancy, infection, trauma, and inherited or acquired thrombophilia. [11] Thus, considering the high frequency of venous thromboembolic events such as PE and DVT in COVID-19 patients, we assume that there might be an increased risk of CVST among these patients. In addition, the presence of antiphospholipid antibodies has been reported in the COVID-19 cases of arterial ischemic stroke. [12] Although the mechanism is still unclear, we postulate that this may play a role in COVID-19 associated venous infarcts as well. Both prothrombotic state and direct CNS invasion can contribute to the pathogenesis of CVST in the context of COVID-19.

The main presenting manifestations of CVST are symptoms and signs of increased intracranial pressure (ICP) such as headache, blurred vision and papilledema, decreased consciousness, focal neurologic deficits, and seizures. [11] Coronavirus infection can also present with neurologic manifestations. Table 1 shows the reported neurological manifestations of COVID-19 which could also be observed in CVST. As CVST shares common neurological symptoms with coronavirus infection, the diagnosis of CVST might be challenging among these patients. For example, a study in China shows that 13% of COVID-19 patients can present with headache [13], whereas headache is the most common symptom of CVST and can occur in up to 95% of all CVST patients. Also, up to 25% of CVST patients can present only with headache, without any other neurological symptoms and signs [11,14,15]. On the other hand, headache usually occurs early in the course of COVID-19 and subsides spontaneously [13], but is usually progressive in CVST. [15] Therefore, the whole picture of clinical course and neurological deterioration should be considered if there is any suspicion of CVST in order to avoid unnecessary work-ups. Table 2 summarizes the presentation and characteristics of current reported cases of CVST and COVID-19. In most cases, neurological manifestations occurred 1–2 weeks after the onset of COVID-19-attributed symptoms.

It is also *worth emphasizing* that patients with CVST and COVID-19

Table 1
Neurological manifestations common between COVID-19 and CVST.

Neurological manifestations	COVID-19 [13]	CVST [11]
Headache	13%	95%
Impaired Consciousness	7.5%	30%
Dizziness	17%	Rare
Seizure	0.5%	17%
Ataxia	0.5%	Rare
Focal neurological deficit	Reported in cases of ischemic stroke [5]	37%

https://doi.org/10.1016/j.ensci.2020.100256
Received 14 May 2020; Received in revised form 26 June 2020; Accepted 10 July 2020
Available online 15 July 2020

Table 2
Summary of clinical presentations and imaging findings of reported cases of CVST and COVID-19.

Case Number	Age	Gender	Presentation	Imaging findings	COVID-19 onset/diagnosis
1 [16]	29	Female	New onset generalized tonic-clonic seizures.	Thrombosis in transverse and sigmoid sinus + temporoparietal hemorrhagic infarct	One week prior to CVST presentation
2 [8]	59	Male	Initial headache, later presented with reduced power and numbness in the right side, slurred speech and expressive dysphasia.	Thrombosis in sigmoid and transverse sinus involving the torcula	Accidentally found in chest radiograph at the time of CVST diagnosis and then confirmed by PCR
3 [10]	38	Male	Headache and altered mental status	Thrombosis in straight sinus, distal superior sagittal sinus, torcular, and transverse sinus, cortical veins, and internal cerebral vein	10 days prior to CVST presentation
4 [10]	41	Female	Confusion and aphasia	occlusion of the internal cerebral veins with reduced enhancement of the vein of Galen and distal straight sinus + venous infarction in the left basal ganglia, thalamus, and mesial temporal lobe with hemorrhagic transformation, intraventricular hemorrhage, and obstructive hydrocephalus	Prior to CVST presentation
5 [17]	72	Male	Hemiparesis, altered mental status, and refractory status epilepticus.	Deep hemispheric hypodensity with hyperdense areas, involving the thalamus, basal ganglia, internal capsule and splenium of the corpus callosum, and the deep white matter + Thrombosis of internal cerebral veins and the vein of Galen	Few days prior to CVST presentation
6 [18]	44	Female	Headache, altered mental status, aphasia and hemiparesis	Filling defect in the vein of Galen, straight sinus and in the torcular herophili with poor rappresentation of left internal cerebral vein.	Two weeks prior to CVST presentation
7 [9]	65	Male	Loss of consciousness, upward gaze and tongue biting	Sigmoid and transverse sinus thrombosis + hemorrhagic infarct in temporal lobe	At the time of admission for CVST
8 [19]	62	Female	Hemiparesis and altered consciousness	Thrombosis of the transverse sinus, straight vein, vein of Galen and internal cerebral veins + intraparenchymal hemorrhage in the fronto-temporal lobes.	2 weeks prior to CVST presentation
9 [19]	54	Female	Severe headache	Thrombosis of transverse sinus + hemorrhagic infarction in temporal lobe	2 weeks prior to CVST presentation

might present with hemorrhagic infarction as the first imaging manifestation of CVST. [9,16,19] Given the high rate of early hemorrhagic infarction in CVST patients (up to 35%) [20], the presence of any unexplained and atypical hemorrhagic lesion in the initial brain CT of these patients should raise the suspicion to CVST.

We hypothesize that up to date, CVST may have not been adequately diagnosed in COVID-19 patients. CVST may progress to major complications such as intracranial hemorrhage and subsequent sequelae such as poor outcome and even death if its diagnosis and the initiation of treatment are delayed. [11] Therefore, timely diagnosis and treatment of CVST should be a priority in all suspected patients.

For this reason, we recommend appropriate imaging to exclude CVST in the COVID-19 patients who present with focal neurological deficits, progressive headache and signs of increased ICP, decreased consciousness, and seizures, and also hemorrhagic infarct on the initial brain CT. Specifically, COVID-19 patients with a preexisting hypercoagulable state, such as pregnant/ postpartum women, women using OCPs, those in a fasting state, and those with history of thrombophilia, malignancy, and chronic inflammatory diseases are high-risk groups. Close clinical monitoring for neurological deterioration and laboratory monitoring with coagulation markers such as D-dimer in high-risk groups are suggested. As a normal D-dimer is associated with a low probability of CVST. [15]

CVST is diagnosed based on the clinical and radiological criteria. Magnetic resonance imaging and venography (MRI /MRV) and computed tomographic venography (CTV) are the two most frequently used non-invasive imaging modalities in diagnosis of CVST. American Heart Association/American Stroke Association recommends the use of MRI /MRV over CTV due to higher sensitivity and lower risk of contrast-induced nephropathy. [15] A higher risk of acute kidney injury in severe cases of COVID-19 further limits the application of contrast in these patients. However, CTV should be considered while MRI/MRV is not available or in unstable patients who cannot undergo MRI/MRV.

Initial management of CVST includes anticoagulation with therapeutic doses of low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH). [15] Current statement on anticoagulation in COVID-19 patients recommends LMWH as the first-line therapy and UFH in case of severe renal impairment (creatinine clearance rate: < 30 mL/min) if there is no contraindication for anticoagulant treatment. [21]

Conclusion

Considering the high risk of thrombotic events in novel Coronavirus infection, CVST could be a possible complication. Therefore, we recommend close monitoring of neurological manifestations and deterioration in COVID-19 patients, especially in high-risk groups with underlying predisposing prothrombotic conditions. Physicians must consider CVST as a probable differential diagnosis in COVID-19 patients with progressive headache, signs of elevated ICP such as diplopia and papilledema, decreased consciousness, seizure, focal neurological deficit and also hemorrhagic infarct on the initial brain CT. Prompt diagnosis and initiation of treatment are essential to prevent poor outcomes.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declarations of interest

None.

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