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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Cerebral venous sinus thrombosis associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection

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SUMMARY

Introduction/Objective Coagulopathy induced by severe acute respiratory syndrome coronavirus 2 infection (SARS-CoV-2) can be an underlying cause of cerebral venous sinus thrombosis (CVST), a less common type of stroke with a variable clinical presentation and high mortality rate. The objective of the paper is to present a series of CVST cases associated with SARS-CoV-2 infection.

Methods This retrospective study evaluated clinical, laboratory and radiological presentations, risk factors, barriers to diagnosis, treatment and outcome of patients with SARS-CoV-2 infection-induced CVST.

Results The study comprised six patients diagnosed with COVID-19-induced CVST during an 18-month period. The majority (66.7%) had no significant risk factors for developing CVST. The median time from the initial COVID-19 diagnosis to the onset of neurologic deficit was seven days (interquartile range 0.5–7 days). Clinical presentation comprised non specific neurological symptoms: headache (83.3%) and decreased consciousness (33.3%), together with elevated levels of D-dimer and inflammatory biomarkers. The transverse (n = 4, or 66.7%), superior sagittal sinuses (n = 3, or 50%) and sigmoid sinus (n = 2, or 33.3%) were most commonly affected. Five patients (83.3%) had minimal to no symptoms at discharge (mRS ≤ 2). In-hospital mortality in our current series was relatively high (16.7%).

Conclusion The high mortality rate of SARS-CoV-2-associated CVST urges clinicians to suspect CVST in patients with a history of COVID-19 infection presenting with non-specific neurological symptoms in order to provide proper treatment and prevent complications.

Keywords: COVID-19 coagulopathy; anticoagulation; stroke

INTRODUCTION

Cerebral venous sinus thrombosis (CVST) is a rare form of cerebrovascular incident (< 1%), induced by partial or complete occlusion of the dural venous sinuses and/or cerebral veins. Contrary to arterial stroke, it is more frequent in young adults, mostly affecting women [1]. Predisposing factors for CVST are numerous, but CVST associated with SARS-CoV-2 infection is a less known entity with no identifiable risk factors [2]. SARS-CoV-2 infection induces hypercoagulable state, comprising elevated D-dimer, fibrinogen level, fibrin/fibrinogen degradation product, antiphospholipid antibodies, and thrombocytopenia, which increases the risk of thrombus formation within the dural venous sinuses and/or cerebral veins [3, 4]. Clinical presentation varies, depending on the affected venous sinus and/or cerebral veins, presence of raised intracranial pressure (ICP) or extensive parenchymal damage. Non-specific clinical presentation of CVST urges clinicians to raise clinical suspicion and proceed with neuroradiological assessment. Management of CVST is based on early diagnosis with identification of thrombotic process, together with urgent conservative and endovascular treatment. Up to 80% of patients have a good outcome with a complete recovery. However, the outcome of a small proportion of patients (~13%) is poor (death or severe disability) [2].

The objectives of the present paper were to evaluate a case series of six patients regarding past medical conditions, risk factors, clinical and radiological presentation, barriers to diagnosis, treatment, and outcomes in COVID-19-induced CVST patients.

METHODS

This was a single-center retrospective study at an academic hospital: Emergency Center – Clinical Centre of Vojvodina, Novi Sad, Serbia. We extracted data on six CVST patients with COVID-19 from the hospital information system from March 6, 2020 to September 6, 2021. The individual case data comprised the following: patient demographics, comorbidities, risk

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factors, clinical presentations, National Institutes of Health Stroke Scale (NIHSS), Glasgow Coma Scale (GCS) score on admission and during the clinical course, location of thrombosis and brain lesions (radiological presentation), laboratory results (white cell count, absolute lymphocyte count, platelets, prothrombin time (PT), activated partial thromboplastin time (aPTT), C-reactive protein (CRP), D-dimer, fibrinogen, lactate dehydrogenase (LDH), and ferritin, treatment (anticoagulation, endovascular treatment, or neurosurgery) and inpatient mortality. SARS-CoV-2 infection was confirmed by the real-time reverse transcriptase polymerase chain reaction assay.

The radiologic diagnosis of acute CVST was confirmed by computerized tomography venogram (CTV) or magnetic resonance imaging (MRI) / magnetic resonance venogram (MRV) studies.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written consent to publish all shown material was obtained from the patient.

RESULTS

Patient demographics

Six patients with confirmed SARS-CoV-2 infection developed CVST. Most of the patients were female (n = 5, or 83.3%), with an average age of 44.3 ± 10.5 years old (Table 1).

Table 1. Patient demographics

Variable	Value
Age (years, mean ± SD)	44.3 ± 10.5
Sex – n (%)	
Male	1 (16.7%)
Female	5 (83.3%)

Table 2. Location of cerebral venous sinus thrombosis (computed tomography / magnetic resonance venogram)

Location	n (%)
Superior sagittal sinus	3 (50%)
Transverse sinus	4 (66.7%)
Sigmoid sinus	2 (33.3%)
Deep venous system	1 (16.7%)
Bilateral	2 (33.3%)
Multiple cerebral venous sinuses	3 (50%)

CVST risk factors

Two patients (33.3%) had common risk factors for CVST comprising an underlying pregnancy and malignancy. In most patients (66.7%), no known risk factors for CVST were identified.

Location of CVST

The most common localization of the thrombotic process was in the transverse (n = 4, or 66.7%) and the superior sagittal sinuses (n = 3, or 50%). CVST was also observed in the sigmoid sinuses (n = 2, or 33.3%) and in the deep venous structures (n = 1, or 16.7%). Half of our patients (n = 3, or 50%) developed central venous thrombosis involving multiple cerebral venous sinuses. Bilateral cerebral venous sinus involvement was present in two patients (33.3%), with the transverse sinuses being the most commonly involved (Table 2).

Intracranial hemorrhage was detected in one patient (16.7%) upon repeated CT brain imaging.

Presenting neurological symptoms

The median time to CVST clinical presentation from the initial COVID-19 diagnosis was seven days (interquartile range 0.5–7 days). Symptom occurrence was acute (< 48 hours) in 33.3% of the patients and subacute (> 48 hours to 30 days) in 66.7% of the patients.

Headache of various intensity, as the most common symptom of CVST, was identified in 83.3% of the patients. It was the only early neurologic manifestation in 33.3% of the patients. A CVST-associated headache was generally persistent and had positive correlation to disease severity. Headache occurred in all locations of cerebral venous occlusion, but was more pronounced in the sagittal sinus or straight sinus thrombosis. The headache of CVST was typically described as diffuse, progressive over time. The characteristics of headaches were diverse (Table 3), being unilateral or localized in 50% of the cases.

Focal neurological deficits occurred in three patients (50%). Unlike arterial ischemic stroke or intracranial hemorrhage, focal neurological signs did not occur so suddenly. The most common ones were presented as motor symptoms, followed by visual impairment and aphasia (Table 3).

Focal or generalized seizures occurred in two (33.3%) patients. Generalized seizures occurred in one (16.7%) patient, and focal seizures (simple partial seizures without generalization) in one (16.7%) patient (Table 3).

Altered consciousness, ranging from drowsiness to coma, was observed in two (33.3%) patients with CVST. Among patients with altered consciousness, one patient had moderate (GCS 8–10 points) and one patient had severely altered state of consciousness (GCS 3–7). Altered consciousness in combination with headache, focal neurological deficits and neuropsychiatric manifestations (confusion and amnesia) were most common in patients with deep venous system thrombosis (Table 3).

Neuro-ophthalmological symptoms were papilledema, loss of vision, and constriction of the visual field. Papilledema was identified in 66.7% of the patients with acute and subacute onset of the disease and was most often associated with headache.

Multiple cranial nerve involvement (cranial nerve palsy) occurred in one CVST patient (16.7%).

Psychosis in conjunction with focal neurological signs occurred in one patient (16.7%).

Table 3. Presenting neurological symptoms of cerebral venous sinus thrombosis and location of lesion

Presenting symptoms	Location of lesion	n (%)
Headache		5 (83.3%)
Migraine	Venous occlusion / focal lesion	
Raised ICP	Venous or sinus occlusion / large mass lesion	
Thunderclap	Venous occlusion / subarachnoid hemorrhage	
Focal neurologic deficit		3 (50%)
Hemiparesis	Infarction / hemorrhage / venous oedema	
Aphasia Sensory disturbance Inattention/neglect	Focal infarction / hemorrhage / superficial or deep venous system	
Cranial nerve palsy		
III, IV, V, VI VII, VIII IX, X, XI	Cavernous sinus Transverse/sigmoid sinus Posterior cavernous sinus / internal jugular vein / deep venous system	
Decreased consciousness		2 (33.3%)
Drowsiness, stupor, coma	Deep venous system / straight sinus	
Cognitive impairment		1 (16.7%)
Encephalopathy, disorientation, reduced concentration, amnesia	Deep venous system / temporal-parietal lesion (vein of Labbe) / seizures	
Seizures		2 (33.3%)
Focal	Focal infarction/hemorrhage	
Generalized	Focal infarction/hemorrhage / severely raised intracranial pressure	
Visual disturbance		4 (66.7%)
Reduced/altered visual field diplopia, papilledema	Raised intracranial pressure Posterior infarction/hemorrhage	

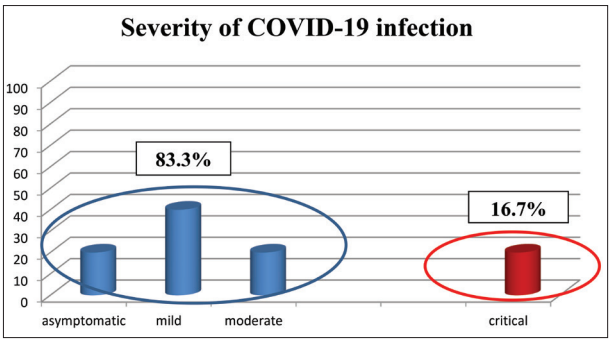

Figure 1. Severity of COVID-19 infection (patients with cerebral venous sinus thrombosis)

Severity of COVID-19 infection

Clinical presentations of the COVID-19 infection at the time of admission to the hospital was classified according to the World Health Organization guidelines into the following five categories: asymptomatic, mild, moderate, severe, and critical [5]. One patient (16.7%) presented with a critical form of the disease. The remaining four patients (83.3%) had asymptomatic to moderate disease (Figure 1).

Inflammatory biomarkers and coagulation studies

Inflammatory biomarkers such as CRP, ESR, ferritin, and LDH were elevated in most patients. Leukocyte count was not significantly elevated above the reference ranges. D-dimer values were significantly elevated. Values of the coagulation studies (aPTT, PT, INR and platelets) were within normal limits (Table 4).

Table 4. Inflammatory biomarkers and coagulation studies

Variable	Values
Inflammatory biomarkers	
CRP	48.2 ± 51.1 mg/L
ESR	51 ± 18.2 mm/hr
Ferritin	560.4 ± 191.3 ng/mL)
LDH	378.1 ± 166.8 units/L
WBC counts	8.8 ± 4.8 (thousand per uL)
Coagulation studies	
D-dimer	4612 ± 1121 ng/mL
aPTT	34.5 ± 14.1 s
PT	12.7 ± 1.1 s
INR	1.03 ± 0.1 s
Platelets	220.6 ± 112.9 × 10^9/L

CRP – C-reactive protein; PT – prothrombin time; aPTT – activated partial thromboplastin time; LDH – lactate dehydrogenase; ESR – erythrocyte sedimentation rate; INR – international normalized ratio

Table 5. Treatment modalities

Treatment modality	n (%)
Pharmacological treatment for COVID-19	6 (100%)
Therapeutic anticoagulation: LMWH and UFH	6 (100%)
Endovascular therapy (aspiration thrombectomy)	1 (16.7%)
Decompressive hemicraniectomy	1 (16.7%)
Anti-epileptic agents	2 (33.3%)
Therapy for elevated intracranial pressure: osmotic therapy, hyperventilation (pCO2 30–35 mmHg)	5 (83.3%)
Steroids (COVID-19 infection indications)	3 (50%)

UFH – unfractionated heparin; LMWH – low-molecular-weight heparin

Treatment modalities

Therapeutic modalities with anticoagulant therapy, treatment of Covid 19 infection, anticonvulsant medication and intracranial hypertension management are shown in Table 5. All patients received pharmacological treatment for SARS-CoV-2 infection recommended by the guidelines (World Health Organization: COVID-19 Clinical Management: Living guidance).

Outcomes

Objective quantification of the impairment caused by CVST (GCS and NIHSS) and mean length of hospital stay are shown in Table 6. Most patients (n = 5, or 83.3%) had good outcome with minimal or no symptoms (mRS ≤ 2) (Table 6). One patient with CVST and the risk factors of older age (> 50 years old), male sex, coma, mental status disorder, hemorrhage on admission CT scan, status epilepticus, deep CVST thrombosis, multiple involved venous sinuses, and severe to critical form of COVID-19 infection, did not respond to treatment and had a poor outcome.

Table 6. Patient outcomes

Outcomes	Value
Death, n (%)	1 (16.7%)
Discharged home (mRS)* ≤ 2, n (%)	4 (83.3%)
Mean length of hospital stay, days	17.2 ± 12.8
GCS (CVST diagnosis), median (IQR)	14 (12–15)
NIHSS (CVST diagnosis), median (IQR)	15 (7–15.5)
Days to clinical presentation of CVST, median (IQR)	1 (0–13)

GCS – Glasgow Coma Scale; CVST – cerebral venous sinus thrombosis; NIHSS – National Institutes of Health Stroke Scale; IQR – interquartile range

DISCUSSION

CVST associated with SARS-CoV-2 infection is a rare event, but it occurs 30–60 times more frequently compared to the non-COVID-19 population [6].

In our study, combination of CSVT and COVID-19 more frequently affected women (83.3%), alike the general population [7]. It occurs predominantly in young population, which was confirmed in our study, where the average age was 44.3 ± 10.5 years old.

Standard risk factors for CVST were not identified in most patients in our study (66.7%), which is in compliance with previous series (74%) [8].

Clinical presentation of CVST is not specific, based on the number and the localization of brain sinuses and veins, time of onset, adaptive mechanisms (collateral venous network), and the severity of brain parenchymal damage. Signs and symptoms comprise headaches (> 80%), seizures (~40%), hemiparesis (~40%), altered consciousness (15–20%), and papilledema (20–30%). The onset of symptoms was acute to subacute in about 80% of patients with CVST. As stated in the references, in our series, median time from clinical presentation to diagnosis of CVST was seven days [9]. Arterial stroke is not strongly associated with headache (25–30%), therefore severe headache in combination with stroke-like symptoms should draw attention to CVST. Seizures also occur more frequently in CVST than in the arterial stroke (40% *vs.* 6%). Focal neurological symptoms and signs are common. Rapid cognitive deterioration leading to drowsiness or coma is a typical clinical presentation of deep venous thrombosis associated with thalamic infarction [10].

Clinical presentation of SARS-CoV-2 infection was mild to moderate in most of our patients (83.3%). Therefore, the gravity of SARS-CoV-2 infection is not closely related to the gravity of CVST , which was also confirmed by other authors [11].

Radiological investigation is important for the diagnosis of CVST. Non-enhanced brain CT scan can confirm CVST in about 1/3 of the patients, based on hyperdensity within the venous sinus or the deep vein (dense triangle sign or the cord sign) [12]. CT can also detect ischemia, parenchymal or subarachnoid hemorrhage, or edema. CT venography has high sensitivity and specificity (95% and 91%). It identifies non-enhancement in thrombosed sinuses and veins and partial circumferential enhancement of thrombosed venous sinuses (empty delta sign) [13].

MRI and magnetic resonance venography (MRV) have higher diagnostic accuracy due to superior resolution and tissue characterization [14]. Additional value of MRV is the capability of confirming sinus thrombosis without administration of a contrast agent [15]. MRI is superior to other techniques in terms of parenchymal assessment involvement (ischemia, hemorrhage, oedema). Indications for digital subtraction angiography are inconclusive CTV or MRV findings, or suspected dural arteriovenous fistula [2].

The transverse sinus and the superior sagittal sinus are most commonly affected by CVST. Another typical finding is multiple vessels' thrombosis involvement, with a transverse sinus predominance [2]. "Deep" venous system affection leads to a poor overall prognosis and high mortality [10]. One of our patients (16.7%) had intracranial hemorrhage, identified by a follow-up CT brain scan. Findings of intracerebral hemorrhage in SARS-CoV-2 patients could indicate potential CVST.

SARS-CoV-2 is an underlying cause of a systemic inflammatory reaction, confirmed by our data on high levels of inflammatory biomarkers (ESR, CRP, ferritin, LDH) [16]. Extreme elevation of D-dimer confirms the assumption that COVID-19 infection may be related to systemic prothrombotic state [17]. In mild cases of CVST, D-dimer level can be normal, but it has a high negative predictive value for excluding CVST in patients with isolated headache. In general, no laboratory analysis can exclude CVST [18].

Treatment of CVST should be aimed at controlling the thrombotic process using anticoagulant therapy/endovascular procedures, treatment of the underlying cause (SARS-CoV-2 infection) and identified risk factors, seizure therapy, and treatment of intracranial hypertension.

Therapeutic doses of anticoagulant therapy should be administered as the basic treatment of CVST, regardless of the presence of intracranial hemorrhage [19]. In systemic VTE, studies suggest that low molecular-weight heparins

(LMWH) have shown better effectiveness compared to unfractionated heparins for the prevention of the thrombotic process progression with a lower risk of bleeding complications [20, 21]. After initial treatment with LMWH, long-term administration of vitamin K antagonists (warfarin) should be used to continue anticoagulant CVST therapy. Recommended durations of the chronic oral anticoagulant treatment are 3–6 months in provoked CVST, 6–12 months in unprovoked CVST, and potentially lifelong in recurrent CVST, CVST associated with venous thromboembolism, or CVST associated with thrombophilia [2].

The most common cause of death in patients with CVST is transtentorial herniation due to raised ICP [9]. Management of elevated ICP comprises osmotic therapy (mannitol), hyperventilation (pCO_2 30–35 mmHg) and head elevation. Carbonic anhydrase inhibitors (acetazolamide) could be useful in patients with severe headaches or visual impairment [2]. Decompressive craniectomy allows the swollen brain to expand and could favor collateral vein drainage in CVST by reducing ICP [22]. Steroid use is not recommended as it is associated with a poorer prognosis in CVST, even if a parenchymal brain lesion is present, unless the presence of the underlying condition, such as COVID-19 infection, require its administration [23].

Indications for endovascular treatment (endovascular thrombolysis or mechanical thrombectomy) are progression of the thrombotic process despite the use of anticoagulant therapy, clinical progression of the disease despite the use of anticoagulant therapy, and in patients with contraindications for the anticoagulant therapy [24].

Antiepileptics are prescribed to control seizures and should not be used routinely for prophylactic purposes [2]. There is no evidence on the optimal duration of the treatment. For seizures associated with oedema, infarction, or hemorrhage, the treatment should be continued for at least one year [25].

In-hospital mortality in our current series was relatively high (16.7%), similar to data from previous studies [26, 27]. Mortality rate is significantly higher compared to non-COVID-19 CVST populations (2–8%), suggesting that COVID-19 CVST patients have a poorer prognosis [28]. Factors predictive of poor prognosis include the following: older age (> 40 years old), male sex, coma, mental status disorder, hemorrhage on admission CT scan, status epilepticus, deep CVST thrombosis, multiple involved venous sinuses, and severe to critical form of the COVID-19 infection. Approximately 80% of the patients have good prognosis (mRS of 0–1), but they usually have consequences in the form of symptoms of depression or anxiety that affect their work ability [11].

Limitations of this study are related to the small statistical sample, which is a reflection of the small number of patients with COVID-19 infection-associated CVST. Given the rapidly growing number of patients with COVID-19 infection worldwide and the severity of CVST as a complication, it is crucial to define their correlation, clinical manifestations, diagnostic-therapeutic protocols, and treatment outcome. Available studies show great diversity in study design, imaging methods, reference standard, patient selection, and sample size, thus they are not feasibly comparable. Larger studies are needed to define more reliable conclusion about this significant health problem.

CONCLUSION

The high mortality rate and significant disability of the most productive population with COVID-19 infection-associated CVST obliges a high index of CVST suspicion in patients with even mild COVID-19 infection with non-specific neurological symptoms, to ensure early diagnosis, application of the most effective individually tailored treatment, and to prevent complications.

Conflicts of interest: None declared.

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Тромбоза церебралних венских синуса повезана са инфекцијом *SARS-CoV-2*

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САЖЕТАК

Увод/Циљ Вирусном инфекцијом САРС корона 2 (*SARS-CoV*-2) индукована коагулопатија може довести до тромботских компликација као што је тромбоза можданих венских синуса (ТМВС), ређи тип можданог удара са различитом клиничком презентацијом и високом стопом смртности. Циљ рада је презентација серије случајева ТМВС повезаних са инфекцијом *SARS-CoV*-2.

Методе Овом ретроспективном студијом евалуирани су клиничка, лабораторијска и радиолошка презентација, фактори ризика, проблеми у дијагностици, третману и исходу оболелих од ТМВС удружених са инфекцијом *SARS-CoV*-2.

Резултати Студија је обухватила шест болесника код којих је током периода од 18 месеци дијагностикована ТМВС удружена са инфекцијом *SARS-CoV*-2. Већина испитаника (66,7%) није имала значајне факторе ризика за развој ТМВС. Просечно време јављања неуролошког дефицита од иницијалне дијагнозе инфекције ковидом 19 било је седам дана (интерквартилни опсег 0,5–7 дана). Болесници су имали неспецифичне неуролошке симптоме као што су главобоља (83,3%) и поремећај свести (33,3%), уз повишен ниво Д-димера и инфламаторних биомаркера. Најчешћа локализација тромбозе била је трансверзални (*n* = 4 или 66,7%), горњи сагитални синус (*n* = 3 или 50%) и сигмоидни синус (*n* = 2 или 33,3%). Пет болесника (83,3%) отпуштено је кући са минималним симптомима или без њих. Морталитет у нашој серији је био релативно висок (16,7%).

Закључак Висок морталитет болесника са ТМВС код инфекције вирусом ковид 19 захтева велики опрез на присуство ТМВС код оболелих са неспецифичним неуролошким симптомима, у циљу адекватног терапијског третмана и превенције компликација.

Кључне речи: ковид 19 коагулопатија; антикоагулантна терапија; мождани удар