Letters to the Editor

Cerebral Venous Thrombosis Associated with COVID-19 Infection

Sir,
Coronavirus disease 19 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 is primarily a disease with infectious and respiratory manifestations, as the virus binds to ACE2 receptors in the pneumocytes of the lower respiratory tract. The most common symptoms are dry cough, dyspnea, fever, weakness, and myalgia.[1] However, there is an increasing number of neurological complications of COVID-19, which include nonspecific symptoms (headache, dizziness), anosmia, dysgeusia, acute/subacute consciousness impairment, meningoencephalitis, acute hemorrhagic necrotizing encephalopathy, Guillain-Barré and Miller Fisher syndromes, cranial nerve palsy, and ischemic/hemorrhagic
We contribute to the growing data on the neurological complications of COVID-19 and report a case of cerebral venous thrombosis (CVT) associated with coronavirus infection.

A 47-year-old nonsmoking man without comorbidities had low-grade fever and rare dry cough for 2 days. Chest X-ray imaging revealed no abnormalities. The patient started taking azithromycin, after which the symptoms quickly regressed. After 1 week of hyperthermia, the patient developed a gradually progressing headache. The cephalalgia was bursting, with an intensity reaching 8 points on a visual analogue scale, and worsened in the supine position. Analgesics did not produce any lasting improvement. The patient also reported nausea and episodic diplopia occurring at the time of headache intensification. After 2 weeks of headache, the patient visited a neurologist. Physical examination did not reveal any neurological or somatic abnormalities; the oxygen saturation was 99%. Given the descriptors of secondary headache, a magnetic resonance imaging (MRI) of the brain and MR venography (MRV) were performed, revealing CVT without cerebral infarction. The superior sagittal, transverse, and sigmoid sinuses and the left internal jugular vein were involved in the process of thrombosis. MR signs of intracranial hypertension associated with transient diplopia (compression of the abducent nerves) were also detected [Figure 1]. Blood tests did not reveal serious changes, and a chest computed tomography (CT) showed areas of ground-glass opacity [Figure 2]. A polymerase chain reaction with throat and nasopharyngeal swab material was negative; however, a SARS-CoV-2 immunoglobulin G assay was positive. The patient was administered enoxaparin 80 mg twice a day for 5 days, followed by dabigatran 150 mg twice a day, as well as acetazolamide. During 3 weeks of therapy, the headache gradually resolved, episodes of diplopia did not recur, and there were no focal symptoms indicating a venous stroke.

In December 2019, the world faced a new disease, COVID-19, which over time has become a global pandemic. COVID-19 is a respiratory disease, but there is increasing evidence of its neurological complications. They can be due to the direct neurotoxic effect of the virus, autoimmune reactions, as well as the development of a prothrombotic state.

Abnormal laboratory test results (high C-reactive protein, prolonged prothrombin time, high D-dimers, high fibrinogen levels, etc.) and the observed high frequency of thrombosis support a prothrombotic mechanism. Therefore, expert consensuses propose prophylactic anticoagulation based on risk stratification for patients with COVID-19.

CVT is a rare form of cerebrovascular disease (0.5%–1% of all strokes), which is more common in young patients. There are many causes of CVT, which can be either hereditary (thrombophilia) or acquired (e.g., infection, surgery, trauma, cancer, pregnancy, systemic diseases, hematologic disorders). The first detailed case report of CVT associated with COVID-19 was given by Hughes et al. (April 2020). In our case, we also consider COVID-19 to be the cause of CVT, given the clear causal relationship, the absence of other disorders or a history of thrombotic events, and normal family history.

The range of clinical symptoms of CVT is wide and includes symptoms due to intracranial hypertension [headache, vomiting, visual impairment (papilledema), diplopia (caused by sixth nerve palsy), and depressed level of consciousness] and focal symptoms due to venous ischemia or hemorrhage [paresis, sensory symptoms, hemianopsia, aphasia, neglect and other cortical signs, and seizures]. In 25% of cases, CVT is manifested by an isolated headache without any other symptoms. Our patient had descriptors of secondary cephalalgia [a bursting headache “new” for the patient, progressive course, worsening in the supine position, inefficacy of analgesics, combination with diplopia, a history of systemic symptoms (recent hyperthermia)].

A diagnosis of CVT is confirmed by digital subtraction angiography, CT and CT venography, and MRI and MRV. We
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Correct diagnosis is the key to successful therapy. First-line drugs for the treatment of CVT include unfractionated heparin (UFH) or low-molecular-weight heparins; patients with severe renal impairment or requiring invasive interventions (lumbar puncture or surgery) should be administered UFH. It should be noted that the presence of hemorrhagic venous infarction or intracerebral hemorrhage is not a contraindication for anticoagulant treatment in CVT. For patients with progressive neurological impairment developing despite adequate anticoagulation, treatment options include endovascular thrombolysis or mechanical thrombectomy in dedicated facilities.[6,7] For long-term anticoagulation, the European Academy of Neurology (EAN) recommends using warfarin, but not direct oral anticoagulants.[8] We choose dabigatran for long-term anticoagulation for two reasons. First, regular monitoring of the international normalized ratio (INR) is hard to achieve in a difficult epidemiological situation. Second, at the time the EAN guidelines were released (2017), no results were available of the RE‑SPECT CVT study in which dabigatran 150 mg twice daily showed comparable efficacy with warfarin (INR: 2.0‑3.0) in terms of reducing the risk of recurrence of venous thrombosis, bleeding rate, and success in recanalization of cerebral veins and sinuses.[10] Thus, dabigatran is now considered as an alternative to warfarin in the treatment of CVT. The duration of anticoagulant therapy is 3–12 months or more, which depends on the cause of CVT.[7]

In conclusion, headache is a common symptom of COVID-19. It is important to use clinical alertness (pain descriptors, neurological status) and neuroimaging to be able to detect headache as a symptom of CVT in a timely manner. Timely diagnosis will change (intensify) the anticoagulation regimen, thus allowing prevention of death or permanent neurological deficit due to venous infarction or hemorrhage.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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Figure 2: CT scans show ground glass in lungs (red arrows)