Can other coronavirus infections cause a cryptogenic stroke in a young patient?

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SUMMARY
We present a challenging case of a young patient who presented with focal neurological signs following a course of OC-43 coronavirus-related pneumonia almost 8 months before the COVID-19 outbreak.

BACKGROUND
Parainfectious systemic complications of viral pathogens are well known and described. However, only few cases of neurological complications in upper or lower respiratory viral infections had been reported. These are usually discarded as incidental or unexplained events. In light of the mounting and compelling evidence of the association between COVID-19 and neurological complications,1 we re-evaluated a case of cryptogenic stroke in the beginning of 2019 in a young patient who initially presented with an atypical viral pneumonia.

CASE PRESENTATION
We report a case of a healthy male patient in his early 20s, of Jewish Ashkenazi descent, without any medical and significant family history, and who did not smoke. The patient was admitted to a medical ward in March 2019 presenting with persistent fever over 38°C for almost 1 week, accompanied by severe and excessive cough and mild dyspnea. Chest X-ray exhibited a small opacity in the right lower lobe of the lung (figure 1A). A chest CT was subsequently done which exhibited widespread ground glass-like consolidations (figure 1B). Laboratory and infectious work-up were performed (complete blood count, electrolyte profile and liver function tests, C reactive protein, erythrocyte sedimentation rate, blood and sputum cultures), with only positive findings of elevated C reactive protein level (~100 mg/L) and elevated white cell count (12.11 × 109/L), which subsided later on. Detailed anamnesis revealed a history of rat bite exposure, as a small wound on his arm, and hence the patient received antitetanus passive vaccine and was aspirin once daily based on thrombus resolution on aspirinography within 2 weeks and on subsequent follow-up imaging. CTA findings in the carotid were concluded as a small intraluminal thrombus in the carotid wall.

INVESTIGATIONS
Cerebrospinal fluid analysis did not show any abnormalities (with negative infectious work-up), neither did his first CT scan and awake electroencephalogram. Brain MRI scan had shown a frontal acute infarct on diffusion weighted imaging sequence in the distribution of the left middle cerebral artery, with otherwise normal imaging (figure 1C). Further vascular work-up by CT angiography (CTA) of the neck and head arteries had shown small filling defect in the distal common carotid artery (figure 1D), a finding that was confirmed by a Doppler ultrasound imaging (figure 1E,F). Magnetic resonance angiography of the neck ruled out a possible arterial wall dissection. Extensive stroke work-up was negative. The work-up included complement C3 and C4 levels, antiphospholipid antibody screening, circulating anticoagulant panels, protein C and S levels, activated protein C ratio, factor V Leiden and prothrombin mutation genetic panels, complement levels, anti-RO, anti-LA, anti-Sm (smooth muscle) and antiphospholipidautoantibodies, antineutrophil cytoplasmic and antinuclear antibodies panels, transesophageal echocardiography (TEE), and 24-hour Holter monitoring. Long-term monitoring was suggested but not performed due to limited compliance and absence of atrial or valvular pathologies on TEE; transcranial Doppler bubble test ruled out right to left shunt. The patient’s lipids and haemoglobin A1c levels were within normal limits. Toxicological screening was not performed based on reliable negative history including heteroanamnesis. CTA findings in the carotid were concluded as a small intraluminal thrombus in the carotid wall.

TREATMENT
According to the imaging findings, we considered the case as cryptogenic cerebral thromboembolism, and a full-dose low molecular weight heparin (1 mg/kg body weight two times per day, subcutaneously) was started and later switched to 100 mg aspirin once daily based on thrombus resolution on follow-up imaging.

OUTCOME AND FOLLOW-UP
The patient’s medical course showed gradual clinical improvement and temporal resolution of the suspected thrombus on repeated CTA and Doppler sonography within 2 weeks and on subsequent 1-year follow-up. Currently the patient has residual mild speech fluency and concentration difficulties, but otherwise he had returned to normal functioning. Follow-up chest imaging showed complete resolution of the pulmonary findings. His current
Coronaviruses had been known for many years as common cold pathogens. In the last decade three new strains had emerged with challenging clinical course and parainfectious inflammatory, mainly respiratory, but also neurological complications. In COVID-19, in Middle Eastern respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS), an increased risk of stroke in young patients with COVID-19 was directly involved in the management of the patient.

DISCUSSION
In light of the COVID-19 pandemic and emerging data suggesting increased risk of stroke in young patients with COVID-19, we revised the case and we now postulate that a stroke mechanism in our patient was in fact parainfectious due to coronavirus OC-43 infection.

Coronaviruses had been known for many years as common cold pathogens. In the last decade three new strains had emerged with challenging clinical course and parainfectious inflammatory, mainly respiratory, but also neurological complications. In COVID-19, in Middle Eastern respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS), an increased risk of stroke, encephalitis and peripheral nervous system involvement in young patients had been described. In this report we suggest that neuroinvasion had been existing in infections by other coronaviruses found in our environment even prior to the SARS/MERS era—also in cases of OC-43 strain infection, both on histopathological and clinical levels. However, this is the first report to our knowledge on a possible connection between stroke and OC-43 infection. The connection between coronaviruses infection and systemic or cerebral thromboembolism probably shares similar mechanisms of inflammatory prothrombotic shift found in COVID-19, MERS and SARS that needs further investigation. We hope to get a better understanding of its mechanism in the future.

Figure 1 Cryptogenic stroke in a young patient diagnosed with coronavirus OC-43 infection. (A) Chest radiogram with a small opacity (white circle) on initial presentation. (B) Chest CT later in the disease course with widespread ground glass-like opacities (white circles). (C) Diffusion weighted imaging performed on initial neurological presentation revealed an acute frontal infarction in the distribution of the left main cerebral artery (white circle). (D) Subsequent neck CT angiogram revealed a small filling defect on the medial wall of the left internal carotid artery (white arrow), a finding that was confirmed as a non-mobile thrombus (white arrows) on carotid Doppler ultrasound (E and F for sagittal and coronal left carotid artery images).

In the context of infection and a new-onset encephalopathy, an ischaemic aetiology should always be considered.

Respiratory viral pathogens have a potential for direct neural invasion, as well as a potential for parainfectious neurological complications, including systemic or cerebral thrombosis.

Idiopathic stroke in a young patient should prompt extensive work-up.

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Learning points
- In the context of infection and a new-onset encephalopathy, an ischaemic aetiology should always be considered.
- Respiratory viral pathogens have a potential for direct neural invasion, as well as a potential for parainfectious neurological complications, including systemic or cerebral thrombosis.
- Idiopathic stroke in a young patient should prompt extensive work-up.

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