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CASUISTIC PAPER

Cryptogenic stroke in a young patient after COVID-19 infection – a case report

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ABSTRACT

Introduction and aim. Cryptogenic stroke (CS) is a type of cerebral ischemia in which the cause is unknown or unclear. It can be difficult to determine the cause of CS because of various factors, such as incomplete investigations or the transient or reversible nature of the event. Infections can increase the risk of stroke by causing localized inflammation of the meninges and cerebral parenchyma, systemic inflammation, coagulation, and endothelial dysfunction. COVID-19-related cerebrovascular events can happen due to a hypercoagulable state from systemic inflammation and cytokine storm, post-infectious immune-mediated responses, and direct viral-induced endothelitis, which can lead to angiopathic thrombosis.

Description of the case. A 25-year-old male was diagnosed with mild semantic aphasia. The patient had a history of moderate COVID-19 infection. An angiography revealed that the M2 segment of the middle cerebral artery in the left hemisphere was not contrasted, indicating an occlusion. MRI and CT scans showed evidence of ischemic changes in the left hemisphere of the brain. The patient was treated with several drugs, including antiplatelet and neuroprotective drugs.

Conclusion. Our case demonstrates that autoimmune antibody formation, specifically antinuclear antibodies, can cause vasculopathy, leading to thrombus formation and stroke. It suggests a potential link between autoimmune antibody formation and stroke in COVID-19 patients.

Keywords. antinuclear antibody, case report, COVID-19, cryptogenic stroke, etiology

Introduction

Since December 2019, COVID-19, caused by SARS-CoV-2, has spread across the globe and has become a pandemic, infecting over 81 million individuals and resulting in over 1.7 million deaths.[1] While respiratory symptoms are the most commonly reported, there is an increasing understanding of neurological symptoms, with a range of 36% to 56%, based on a comprehensive series of hospitalized patients, with a small yet clinically important risk of acute ischemic stroke.[2-6]

Cryptogenic ischemic strokes are cerebral infarcts that manifest with symptoms, for which no probable cause can be identified after conducting an adequate diagnostic evaluation.[7] The determination of a stroke as cryptogenic is contingent on the extent and quality of the etiological investigation and current knowledge regarding stroke mechanisms. A significant proportion of ischemic strokes are currently classified as cryptogenic or with an undetermined etiology.[8] The incidence of CS varies depending on several factors, including the age of the patients, the definition of CS used, and the range of the etiological investigation. Among young adults, the percentage of strokes caused by undetermined causes decreases from more than 60% in the 15–19 age group to 25% in the 45–49 age interval.[9]

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In populations and hospital records of elderly patients, the prevalence of ischemic stroke ranges from 20% to 40% when using the TOAST criteria (Trial of Org in Acute Stroke Treatment). This percentage has remained consistent over time. The Rochester Epidemiology Project conducted between 1985 and 1989 revealed an incidence rate of 36.1% (164/454). The male sex is associated with an undetermined stroke etiology (odds ratio 1.50; 95% confidence interval 1.08–2.08; p=0.015).[10,11] There are few studies that compare the incidence of cryptogenic stroke between different races. The Greater Cincinnati/Northern Kentucky Stroke Study, which is a biracial population study, found that black patients had a greater prevalence of cryptogenic stroke than white patients (54% to 49%).[12]

In comparison to strokes that have a determined cause, CS usually lead to less severe initial neurological deficits, lower mortality rates, and less final disability.[13] While not all long-term follow-up studies show this, in most cases, patients who have experienced cryptogenic ischemic stroke have a lesser risk of recurrence compared to those who previously had a stroke with an identified cause.[14-16]

The interpretation of CS is conventionally relies on the elimination of other firmly settled causes of stroke.[17] Three classification systems, namely, the Trial of Org 10172 in Acute Stroke treatment system (TOAST), the Atherosclerosis, Small vessel disease, Cardiac causes, other, and Dissection scheme (ASCOD), and the Causative Classification of Stroke System (CCS), have frequently been used to enumerate mechanisms or subtypes of ischemic stroke. However, none of these systems formally details CS.

A comprehensive assessment of CS requires brain imaging, such as magnetic resonance imaging (MRI)/ computed tomography (CT) or, MR angiography (MRA), transcranial Doppler, neurovascular imaging with CT angiography (CTA), and cardiac evaluation using echocardiography, and in some patients hypercoagulable testing, rapid plasmin reagin (RPR), genetic analysis or other tests for atypical causes. Nonetheless, a broader consensus is required to define the features and criteria for diagnosing cryptogenic stroke.[18] In this context, CS are symptomatic cerebral infarcts for which no specific cause is identified after adequate diagnostic evaluation. An accurate and consistent classification of CS is essential for appropriate clinical management and improving patient outcomes.[7]

Managing cryptogenic stroke poses a significant challenge in secondary stroke prevention, particularly in the choosing of suitable antithrombotic therapy. While the administration of oral anticoagulation in the prophylaxis of cardioembolic strokes is a well-established in practice, CS are increasingly being acknowledged as sharing many attributes with cardioembolic strokes. However, there is no well-defined protocol for ideal long-term treatment currently. The American Stroke Association and the American College of Chest Physicians suggest that antiplatelet agents are the preferred option for non-cardioembolic ischemic strokes. According to a recent global survey conducted across 48 countries, it has been observed that the overwhelming majority (94%) of hospitals frequently prescribed antiplatelet therapy for secondary prophylaxis of CS.[19] However, there are mounting evidence that cryptogenic stroke patients may aid from anticoagulation.

Aim

In this article, we present a case of an individual with CS who had a history of COVID-19 infection that was presented to neurology department with several cerebrovascular events. This report is to offer a comprehensive view of the diagnostic process and detailing the advancing from the onset of signs and symptoms to the recognition of the disease. By presenting this case report, we hope it will serve as a valuable resource for medical practitioners.

Description of the case

A 25-year-old East Slavic male, was admitted to the emergency department of the Neurology unit at the Regional Hospital of Grodno, Belarus. The patient presented with speech difficulties, which had developed two weeks after a moderate COVID-19 infection which has been showed positive test result for RT-PCR test.

Clinical findings: At admission, the patient underwent a neurological examination, revealing semantic aphasia. Rest examination was normal, alerted and oriented (Person, place, and time). The Glasgow Coma Scale (GSC) was 15b, while the National Institute of Stroke Scale (NIHSS) was 2b. The pupils were equal, round, and reactive to light, while the visual fields were intact to confrontation. Ocular movements were also intact. The face was symmetric at rest and with activation, with intact sensation throughout. The muscles of the tongue and palate activated symmetrically, while muscle bulk and tone were average. Strength was 5/5 in all extremities (both hands & legs),and both proximally and distally. Fine motor movements were intact bilaterally, and sensation was normal to light touch, vibration, pinprick, and proprioception. The Romberg test was negative, and there was no dysmetria on finger-nose-finger or heel-knee-shin. The patient displayed a narrow-based gait with a good arm swing bilaterally and normal stride length.

Diagnostic assessment: According to the results of angiography, it has been observed that the M2 segment of the middle cerebral artery (MCA) in the left hemisphere is not contrasted, which indicates that there is a blockage or occlusion in that segment.

The results of the MRI and CT scans conducted on the brain indicate evidence of ischemic changes that have occurred within the left hemisphere of the brain, as illustrated in Figures 1 and 2.

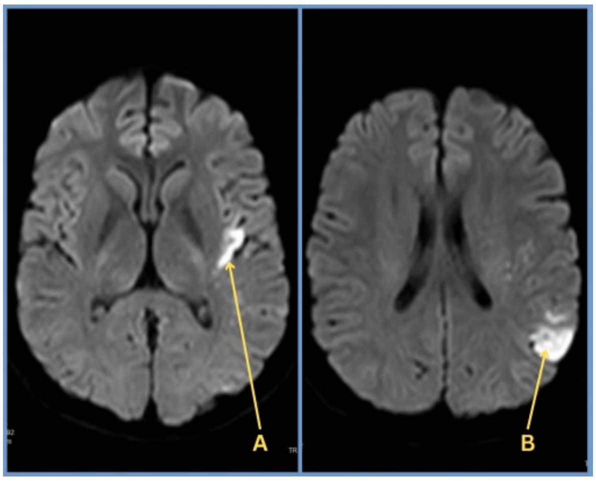

Fig. 1. MRI of the brain showing: A: diffusion-weighted imaging (DWI), a hyperintense area corresponding to acute ischemic changes in insula, B: diffusion-weighted imaging (DWI), a hyperintense area corresponding to acute ischemic changes in parietal lobe, diffusion-weighted MRI (DWI-MRI) showed a hyperintense area in the left parietal lobe (cortical infarction) and insula

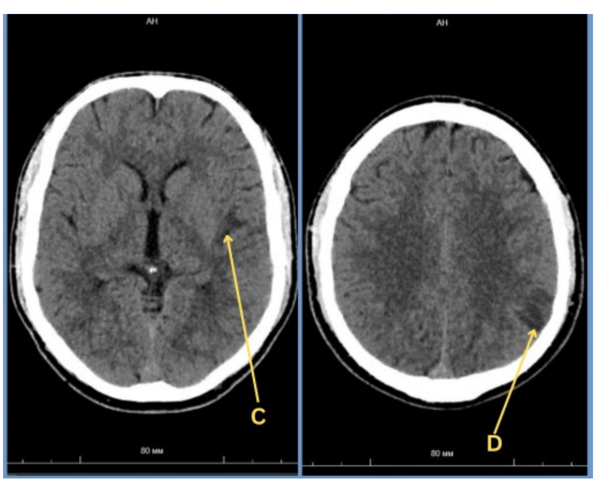

Fig. 2. CT scan of the brain showing: C: lesion in insula, D: lesion in parietal lobe

In the CT scan of the brain on the left in the parietal lobe, subcortically, a hypodense area with unclear contours, a cross-section of about 19×28 mm was identified and a similar area was visualized in the subcortical nuclei about 8×25 mm. CT scan shows a significant signs of ischemic changes in the left hemisphere of the brain.

The electrocardiogram revealed sinus bradycardia, while the complete blood count showed an increase in segmented neutrophils which was 81% (norm 45-70)% (neutrophilia) and a decrease in lymphocytes which was 10% (norm 18-40)% (lymphopenia). Biochemical blood testing results were unremarkable, and the blood lipid profile showed normal glucose and complement levels. Hemostasiogram results indicated elevated levels of D-dimer. ELISA analysis showed normal levels of beta 2 glycoprotein, while the antinuclear antibody (ANA) screen Ig (A, G, M) returned a positive result showing 88.4 U/ml (norm 0-40)U/ml. ANA-2 and ANA-3 tests were not performed. The SS-B (La) (Sjögren syndrome type B antigen) and SS-A (Ro) (Sjögren's-syndrome-related antigen A) were both normal, while the DsDNA (double-stranded DNA) Screen yielded normal results. Immunoglobulin titer showed a result of, IgA 2.2 g/L (norm 0.7-7) g/L; IgG 11 g/L (norm 7-16 g/L), and IgM 0.6 g/L (norm 0.2-5 g/L) which were normal.

Therapeutic intervention: a conservative approach was taken in regards to treatment, with a focus on neuroprotection. A solution of magnesium sulfate (20) and potassium chloride (10) in saline solution (250) was administered through IV drips, along with glycine (0.1) in tablet form three times a day, and alpha choline (1000 mg) with Ringer's solution (500) through IV drops once a day. For antiplatelet purposes, Aspicard (75 mg) was prescribed to be taken daily with lunch. Sol. Emoxypini (0.5%-100 mL) was administered as an antihypoxant, with IV drops once a day. For lipid-lowering purposes, atorvastatin (20 mg) was prescribed. To ensure gastroprotection, omeprazole (20 mg) was prescribed to be taken on an empty stomach in the morning. Additional recommendations were provided to the patient, such as monitoring salt and animal fat intake, avoiding easily digestible carbohydrates, and regularly checking blood pressure and lipid profile. An annual ultrasound of the brachiocephalic artery was also advised.

Discussion

CS are cerebral infarcts that have symptomatic manifestations and lack a discernible cause after thorough diagnostic evaluation.[7] Cryptogenic ischemic strokes are typically associated with less severe neurological deficits, lower mortality, and less severe final disability when compared to strokes with identified origins.[13] Our patient presented mild neurological deficits, including semantic aphasia, and made a complete recovery without any disability at the time of discharge from the hospital. The possible sources of cerebral embolism in patients with CIS include the heart, veins of the lower extremities and pelvis, non-stenotic atherosclerosis of the brachiocephalic arteries (BA), atheromas of the aortic arch, paradoxical embolism, non-atherosclerotic vasculopathy, monogenic diseases, and hypercoagulable conditions, etc.[20] The etiology of the patient's condition may have been autoimmune antibody formation (ANA), which could lead to vasculopathy and the formation of thrombi, ultimately resulting in stroke. ANAs, which can be track down in many autoimmune diseases and viral infections, might be to blame for the vasculopathy. Infections might cause autoimmune reactions through mechanisms such as epitope spreading, molecular mimicry, cryptic antigens, and bystander activation. ANAs, which are typically not associated with autoimmune diseases, have been documented to be caused by transient auto-reactive B and plasma cell reactivation due to infection.[21,22]

Autoantibodies, such as ANAs, lupus anticoagulant, anti-β2 glycoprotein 1, anti-Ro/SSA, and anti-cardiolipin antibodies, have been discovered in individuals infected with SARS-CoV-2.[23,24]

Various studies conducted on patients with SARS-CoV-2 reveal the prevalence of ANAs between 18% and 57.5%.[25] Our patient also tested positive in the ANA screening test.

During the acute stage of the illness, the emergence of autoantibodies is linked to SARS-CoV-2 infections, which supports COVID-19's pathophysiology. Autoantibodies increase in the weeks following recovery but resolve, with a notable reduction in average autoreactivities at 12 months, with some ANAs still detectable.[26-29]

Cryptogenic stroke is a diagnosis that is reached by excluding known causes. The patient's history and physical examination are particularly informative in this regard, and a carefully planned strategy for laboratory and imaging workup is crucial.[7] In our case, the diagnosis was made in accordance with standard guidelines. The physical examination done upon admission revealed only speech impairment. Laboratory diagnostics showed an increase in segmented neutrophils (neutrophilia), a decrease in lymphocytes (lymphopenia), elevated levels of D-dimer, and positive test results for ANA screen Ig (A, G, M).

In modern medical practice, diagnosing and evaluating ischemic stroke patients involves multiple factors. Medical professionals use MRI and CT scans of the brain to determine the location, volume, and number of infarcts. Diffusion sequences in MRI scans are particularly useful for detecting small lesions and those in the brain stem and cerebellum.[7] In our patient's case, the MRI revealed lesions in both the insula and parietal lobe, while the CT scan showed a subcortical hypodense area with unclear brain contours in the left parietal lobe.

Regarding the treatment of stroke, the administration of oral anticoagulant (OAC) is recommended for secondary prophylaxis of stroke. This is indicated in cases of paroxysmal atrial fibrillation, as well as when the morphological pattern of stroke suggests an embolic cause or when there is intracardiac thrombus formation. As per the recent guidelines, OAC is considered reasonable for high-risk patients only if they have other indications for OAC. In most cases, antiplatelet treatment is suggested to prevent a recurrent event.[30] In the case of our patient, antiplatelets have been prescribed for the purpose of treatment, along with neuroprotective drugs.

Conclusion

This report outlines the case of a young male patient who presented with cryptogenic stroke. The report demonstrates a correlation between an increased titer of Ig of ANA test and a history of COVID-19 infection, suggesting evidence of autoimmune antibody production in the patient. Based on this finding, it may be hypothesized that ANAs can cause vasculopathy, leading to thrombus formation and ultimately, stroke. Given the potential link between autoimmune antibody formation and stroke in COVID-19 patients, we recommend that autoimmune antibody tests be conducted in patients with stroke who have a history of COVID-19 infection.

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Declarations

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Author contributions

Conceptualization, L.R.S.D.L. and E.O.A.; Methodology, E.O.A.; Software, L.R.S.D.L. and S.K.P.; Validation, L.R.S.D.L., S.K.P. and E.O.A; Formal Analysis, E.O.A.; Investigation, L.R.S.D.L., S.K.P. and E.O.A.; Resources, E.O.A.; Data Curation, L.R.S.D.L. and S.K.P.; Writing – Original Draft Preparation, L.R.S.D.L. and S.K.P. Writing – Review & Editing, L.R.S.D.L.; Visualization, L.R.S.D.L.; Supervision, E.O.A.; Project Administration, L.R.S.D.L , E.O.A.; Funding Acquisition, E.O.A

Conflicts of interest

None declared.

Data availability

Not applicable.

Ethical approval

Patient signed informed consent was taken regarding publishing their data. And the study was approved by the Institutional Ethics Committee.

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