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Short Communication

Patent Foramen Ovale Related Cryptogenic Stroke during COVID-19 Disease in Three Patients: A Case Series

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Key Words: Cryptogenic stroke—COVID-19—Patent foramen ovale—SARS-CoV-2 disease
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Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), termed COVID-19, first detected in Whuan, was officially declared a pandemic by the World Health Organization on March 11, 2020. The epidemic of COVID-19 has rapidly spread worldwide. Italy was the first European country to be affected and, currently, Italy has reported 4,343,397 COVID-19-positive cases.[1]

Even though the pathogenesis remains not completely understood, it has been proved that SARS-CoV-2 infection causes an unusual pro-coagulant state that significantly increases the risk of arterial and venous thromboembolism and, consequently, increases the risk of stroke.[2–5]

SARS-CoV-2 pulmonary infection could increase pulmonary arterial pressure and eventually right atrial pressure. This scenario, possibly worsened by positive pressure ventilation, pronation and immobilization,[6] could set the stage for paradoxical embolism in patients with a right-to-left shunt.

Therefore, people with Patent Foramen Ovale (PFO) might be at higher risk of paradoxical embolization in the setting of COVID-19. Until now, only anecdotal case reports have been reported on this topic.[7–10]

We present three cases of acute ischemic stroke in patients younger than 55 years-old with PFO and COVID-19, referred on April 2021 to the PFO Clinic of Pediatric Cardiology and Adult Congenital Heart Disease Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Italy.

Case-series presentation

Case 1: A 48-year-old-man was referred to our PFO clinic after a cryptogenic stroke occurred during COVID-19. Prior medical history was negative for deep vein thrombosis (DVT), pulmonary embolism and migraine. He was a former smoker (quit smoking since 6 years). In December 2020, the patient suffered from anosmia and flu-like symptoms. A week after, he presented sudden onset of hypoesthesia and tingling of the right superior limb, lasting 30 seconds, followed by dysarthria. At his arrival in the emergency room, symptoms were nearly completely disappeared. The patient was tested for SARS-CoV2 and resulted negative. D-dimer plasma level was elevated at hospital admission. Head Computer Tomography (CT) scan was performed, revealing a hypodense recent lesion involving the cortical and subcortical white matter in left

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Received August 1, 2021; revision received August 27, 2021; accepted September 7, 2021.

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1052-3057/$ - see front matter
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https://doi.org/10.1016/j.jstrokecerebrovasdis.2021.106115

fronto-opercolar region together with a middle cerebral artery branch (M3) thrombus. Doppler ultrasonography of the supra-aortic trunks resulted free from atheromatous plaques. The patient received thrombolytic therapy, with complete resolution of neurological symptoms.

Subsequently Transcranial Doppler (TCD) ultrasonography showed the presence of a right-to-left shunt: basal 5 microbubbles, > 20 microbubbles after Valsalva manoeuvre. A transoesophageal echocardiography (TOE) was then performed and revealed a PFO with an atrial septal aneurysm, a mild right-to-left shunt was noticed in basal conditions and a severe right-to-left shunt after Valsalva manoeuvre. Lower limb compression ultrasonography was performed after the thrombolytic therapy and excluded DVT of inferior limbs. Thrombophilic abnormalities, and autoimmune diseases were ruled out. Cerebral Magnetic Resonance (MR) confirmed a recent and small ischemic cortical lesion in left temporo-opercolar region. Few days later the SARS-CoV2 probe was repeated and resulted positive.

A 14-days ECG monitoring excluded paroxysmal atrial fibrillation. This patient was referred to our PFO clinic with the diagnosis of embolic stroke of undetermined source (ESUS) as extracranial or intracranial atherosclerosis causing ≥50% luminal stenosis in arteries supplying the area of ischemia, major-risk cardioembolic source and any other specific cause of stroke (eg, arteritis, dissection, migraine/vasospasm, drug misuse) were excluded except the PFO. For this reason PFO closure was advised because the probability of a causal role of the PFO in the clinical event and the risk of recurrence were considered high (ROPE score 8).

Case 2: A 47-year-old-man was referred to our PFO clinic after a cryptogenic stroke occurred during COVID-19. He presented a family history of stroke, and no other cardiovascular risk factors.

Prior medical history included one episode of symptomatic DVT during a long bed rest secondary to bilateral pneumonia (2019) and sporadic migraine episodes without aura. The patient suffered for COVID-19 at the begin of March 2021: the infection course was paucisymptomatic and the patient was treated at home, with negative conversion of the molecular probe 13 days after the first positive result. At the end of March 2021, the patient experienced sudden onset of tinnitus, dizziness, and vomit. In the emergency Room the SARS-CoV2 molecular probe resulted positive. D-dimer plasma level was elevated. During hospitalization, symptoms worsened with onset of horizontal nystagmus and mild dysarthria. Head CT imaging resulted negative for hemorrhagic stroke and the patient received thrombolytic therapy, with complete resolution of neurologic deficits. Cerebral MR revealed multiple subacute left cerebellar hemisphere lesions. In the suspicion of a cryptogenic stroke related to a paradoxical embolism through a PFO, a TCD ultrasonography was performed and demonstrated the presence of a severe right-to-left shunt: basal 30 to 50 microbubbles, curtain of microbubbles after Valsalva manoeuvre. Subsequentely a TOE revealed a PFO with an atrial septal aneurysm, a redundant Eustachian Valve and a severe right-to-left shunt. Thrombophilic abnormalities were ruled out, autoimmune screening resulted low level positive and non-specific. Lower limb compression ultrasonography performed 48 hours after thrombolytic therapy excluded DVT. A 16-days ECG monitoring did not reveal paroxysmal atrial fibrillation. The patient was then evaluated in our PFO clinic and, after exclusion all potential embolic sources (PES) except a PFO with a significant right-to-left shunt, was included in the waiting list for PFO closure because the probability of a causal role of the PFO in the clinical event and the risk of recurrence were considered high (ROPE score 8).

Case 3: A 54-year-old woman was referred to our PFO clinic after a cryptogenic stroke occurred during COVID-19. She presented a history of hypertension and hypercholesterolemia, she was a former smoker and sufferes from migraine with aura. No history of DVT or pulmonary embolism. In February 2021, the patient developed fever and SARS-CoV2 infection was diagnosed. Seventeen days later the patient suffered from aphasia and right hemiparesis, CT angiography (CTA) showed occlusion of the middle cerebral artery and excluded carotid atherosclerotic plaque stenosis. D-dimer plasma level was elevated, but lower limb compression ultrasonography was not performed. The patient underwent thrombolytic therapy and mechanical thrombectomy. After the procedure aphasia and hyposthenia persisted. Cerebral MR revealed a left cortical, subcortical parieto-insular lesion, associated by left temporo-occipital and left frontal dot lesions. A 13-days ECG monitoring excluded paroxysmal atrial fibrillation. Subsubsequently a TCD was performed and demonstrated a basal and significant right-to-left shunt. A TOE revealed a PFO with atrial septal aneurysm, a redundant Eustachian Valve and a severe basal and significant right-to-left shunt (Fig. 1). The patient was then evaluated in our PFO clinic and she was considered eligible for PFO closure because any other specific cause of stroke (intracranial atherosclerosis causing ≥50% luminal stenosis in arteries supplying the area of ischemia, major-risk cardioembolic source and arteritis, dissection, migraine/vasospasm, and drug misuse) were excluded except the PFO and the probability of a causal role of the PFO and the risk of recurrence were considered high (ROPE score was 6).

Discussion

Clinical data has highlighted that COVID-19 is associated with an increased risk of thrombotic complications such as microvascular thrombosis, venous thromboembolic disease and stroke. Endothelial injury and proinfammatory cytokines in the setting of COVID-19 trigger activation of a coagulation cascade, leading to

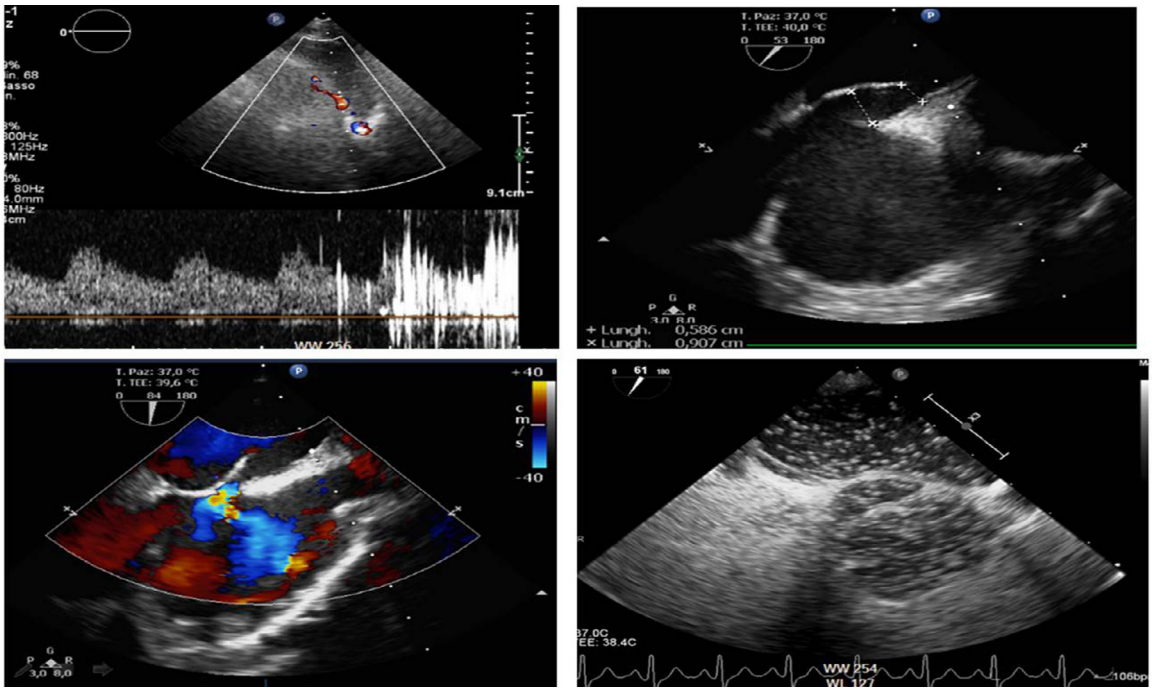

Fig. 1. *TOP LEFT: contrast transcranial Doppler (TCD) for the detection of right−to−left shunt. With patient in a supine position, the contrast agent is prepared using 9 ml of isotonic saline solution, 1 ml of air and 1 ml of patient's blood mixed with a three-way stopcock and injected as a bolus in the antecubital vein through an 18-gauge catheter. High intensity transient signals (HITS), defined as visible and audible short-duration, high-intensity signals within the Doppler flow spectrum, are recorded. The magnitude of right−to−left shunt is determined by counting the number of HITS in the middle cerebral artery in the first 40 s after bolus infusion and by applying the four-level visual categorization of the International Consensus Criteria. In this case grade III: curtain pattern (Adams et al., 1993) or grade ≥ III: >30 signals (Spencer et al., 2004[17]). TOP RIGHT: Transoesophageal echocardiography (TOE) short axis view (53°) showing the right atrium (RA) down, the left atrium (LA) up, and the aorta on the right. The patent foramen ovale (PFO) is a huge tunnel measuring 9 mm in the right side and 5.8 mm in the left side. Bottom Left: TOE long axis view (84°) showing the right atrium (RA) down, the left atrium (LA) up, and the superior caval vein on the right. The color Doppler demonstrates a left-to-right shunt throught the PFO in basal condition. Bottom Right: TOE short axis view (61°) with contrast injection showing the RA on the left, the LA up and right and the aorta down and right. After the RA is completely filled with contrast bubbles there is a severe shunt of contrast into the LA across the PFO.*

thromboembolic events. Stroke was demonstrated to be an infrequent, albeit potentially life- threatening, complication of COVID-19. A systematic review and meta-analysis published in February 2021 found a pooled incidence of 1.4% of acute stroke in COVID-19. The median age of the patients with COVID-19 who experienced concomitant stroke was 65 years and they had more frequently pre-existing cardiovascular comorbidities or severe infections.[11] SARS-CoV-2 increases the odds of cerebrovascular complications by 7.6 folds compared to infection caused by the influenza virus.[12]

For outpatients with mild COVID-19, increased mobility is encouraged, assessment for the risk of venous thromboembolism (VTE) and of bleeding is suggested and pharmacologic prophylaxis could be considered after risk assessment for patients who have elevated risk VTE, without high bleeding risk. For patients with moderate or severe COVID-19 and in disseminated intravascular coagulation (DIC) but without overt bleeding, prophylactic anticoagulation should be administered.[13] The International Society on Thrombosis and Hemostasis has recommended the use of antithrombotic prophylaxis with low-molecular-weight heparin for all admitted patients unless there is a contraindication. In the setting of heparin induced thrombocytopenia, fondaparinux is recommended.[14]

From the beginning of COVID-19 pandemic (March 2020) to March 2021 120 patients with PFO were referred to our PFO clinic: none of them have developed a stroke during or after COVID-19.

In April 2021 we have evaluated 10 patients younger than 55 years old with PFO and cryptogenic stroke, three of them developed symptoms during or after ascertained SARS-CoV-2 infection during the greater diffusion of the "English variant" in our country.[12] The variant VOC 202012/01 (lineage B.1.1.7), named the "English variant", was first detected in the South of the UK in mid-December 2020, began to spread quickly by mid-December in Great Britain and was correlated with a significant increase in SARS-CoV-2 infections in the country. This lineage became the predominant type of SARS-CoV-2 in the UK until reaching a peak in early January 2021. This increase was thought to be related to the presence of multiple mutations in the virus's spike protein and mutations in other regions of the viral genome. From January to April 2021 the prevalence of the "English variant" was quickly increased in Italy from 17.8% to 91.6%.[13,14] In our region,

EmiliaRomagna, the prevalence of the "English variant" was 57.6% in February and 93.2% in April.[15,16]

In our case series neurological signs appeared within a month from the viral infection. Besides the recent SARS-CoV-2 infection characterized by mild symptoms, common features of the three patients were: age < 55 years, low cardiovascular risk profile, high D-Dimer level at first evaluation, ischemic stroke with cardioembolic characteristics confirmed at neurological imaging and no other identifiable aetiology except a significant right-to-left shunt through the PFO with atrial septal aneurysm.

The clinical and instrumental data of the three patients strongly suggest paradoxical embolism as the more likely stroke mechanism and this hypothesis is further reinforced by the recent SARS-COV-2 infection which is now a well-known risk factor for venous thromboembolism, particularly when elevated D-dimer levels are detected. A clear deep vein thrombosis was not diagnosed, but it cannot be certainly ruled out: in one patient lower limb compression ultrasonography was not performed whereas, in the others, it was accomplished only after intravenous thrombolysis, further decreasing the sensitivity of this test. Finally, no virus sequencing was performed in our patients so that we cannot establish which virus variant was actually responsible for the SARS-COV2 infection.

Conclusions

It has been observed that COVID-19 is associated with an increased risk of stroke, mainly in patients over 60 years of age. Throughout the last COVID-19 wave, during the greater diffusion of the "English variant" in our country, we have observed a temporal relationship between stroke and COVID-19 in patients younger than 55 years with atrial septal aneurysm, a PFO with significant right-to-left shunt and no other clear cause of stroke, suggesting paradoxical embolism as a possible mechanism of stroke in young patients with SARS-COV-2 infection.

Further data are needed to confirm this association but the possibility that even young patients with a PFO could be at risk of stroke in case of COVID-19 may be considered. Whether only specific variants are at higher risk of paradoxical embolization remains to be ascertained.

Declaration of Competing Interest

The authors received no funding for this study. The authors have no conflicts of interest to declare.

Acknowledgements: The authors declare that they have no known competing financial interests or personal relations that could have appeared to influence the work reported in this study. This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

References

1. EpiCentro. COVID-19 integrated surveillance data in Italy. Available from: https://www.epicentro.iss.it/en/coronavirus/sars-cov-2-dashboard. Date of update: 31 July 2021
2. Lodigiani C, Iapichino G, Carenzo L, et al. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. Thromb Res 2020;191:9-14.
3. Oxley TJ, Mocco J, Majidi S, et al. Large-vessel stroke as a presenting feature of COVID-19 in the young. N Engl J Med 2020;382(20):e60.
4. Klok FA, Kruip MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res 2020;191:145-147.
5. Nopp S, Moik F, Jilma B, et al. Risk of venous thromboembolism in patients with COVID-19: a systematic review and meta-analysis. Res Pract Thromb Haemost 2020;4(7):1178-1191.
6. Gattinoni L, Coppola S, Cressoni M, et al. COVID-19 does not lead to a "typical" acute respiratory distress syndrome. Am J Respir Crit Care Med 2020;201(10):1299-1300.
7. Rajendram R, Kharal GA, Mahmood N, et al. Systemic thromboemboli in patients with COVID-19 may result from paradoxical embolization. Thromb Res 2020;196:206-208.
8. Rajendram R, Kharal GA, Mahmood N, et al. The importance of detection and percutaneous closure of patent foramen ovale during the coronavirus disease 2019 pandemic. Kardiol Pol 2020;78(6):614-617.
9. Ashraf M, Sajed S. Acute stroke in a young patient with coronavirus disease 2019 in the presence of patent foramen ovale. Cureus 2020;12(9):e10233.
10. Jeyashanmugaraja GP, Shloknik E, Akanya DT, et al. One clot after another in COVID-19 patient: diagnostic utility of handheld echocardiogram. Oxf Med Case Rep 2021;2021(2):omaa141.
11. Nannoni S, de Groot R, Bell S, et al. Stroke in COVID-19: A systematic review and meta-analysis. Int J Stroke Off J Int Stroke Soc 2021;16(2):137-149.
12. Merkler AE, Parikh NS, Mir S, et al. Risk of ischemic stroke in patients with coronavirus disease 2019 (COVID-19) vs patients with Influenza. JAMA Neurol 2020.
13. Bikdeli B, Madhavan MV, Jimenez D, Global COVID-19 Thrombosis Collaborative Group, et al. Endorsed by the ISTH, NATF, ESVM, and the IUA, Supported by the ESC Working Group on pulmonary circulation and right ventricular function. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up: JACC state-of-the-art review. J Am Coll Cardiol 2020;75(23):2950-2973.
14. Thachil J, Tang N, Gando S, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemost 2020 May;18(5):1023-1026.
15. Prevalenza della variante VOC 202012/01 (Regno Unito) in Italia. Studio di prevalenza 4-5 febbraio 2021. Ministero della Salute. Circolare n. 4761 Aggiornamento sulla diffusione a livello globale delle nuove varianti SARSCoV2, valutazione del rischio e misure di controllo. MinSal DGPRE: Roma; -08/02/2021 [citato il 12 febbraio 2021]. Disponibile online: https://www.trovanorme.

salute.gov.it/norme/renderNormsanPdf?anno=2021&codLeg=78758&parte=1%20&serie=null

16. Prevalenza delle VOC (Variant Of Concern) del virus SARS-CoV-2 in Italia: lineage B.1.1.7, P.1 e B.1.351, e altre varianti (Variant Of Interest, VOI) tra cui lineage P.2 e lineage B.1.525. Indagine del 20/4/2021. Ministero della Salute Circolare n.16150 del 16-04-2021 "Indagine rapida per la valutazione della prevalenza delle varianti VOC (Variant Of Concern) in Italia - lineage B.1.1.7, P.1 e lineage B.1.351, e di altre varianti VOI (Variant Of Interest) - lineage P.2 e lineage B.1.525".
17. Spencer MP, Moehring MA, Jesurum J, et al. Power m-mode transcranial Doppler for diagnosis of patent foramen ovale and assessing transcatheter closure. J Neuroimaging 2004;14(4):342-349.