

ataxia, at 3 days. He then started 12 cycles of plasma-pheresis, which improved ophthalmoparesis and ataxia. The patient was asymptomatic at 6 months, without recovery of stretch reflexes (with the exception of hypoactive right brachioradialis reflex).

At 2 years, a week after presenting symptoms of cold without fever, he was admitted due to similar symptoms of gait instability and diplopia, generalised tingling sensation, and difficulty speaking. The examination revealed mild dysarthria, complete ophthalmoplegia, universal areflexia, ataxic gait, left-sided dysmetria on the finger-to-nose test, and preserved deep sensitivity, with no dysautonomic signs. Complementary testing yielded normal or negative results, including PCR testing for SARS-CoV-2 in nasopharyngeal aspirate, motor nerve conduction study (performed at 48 hours after symptom onset and repeated after 2 weeks), non-contrast brain MRI scan, and antiganglioside antibody determination, with no changes with respect to previous serology tests. He received treatment with Ig for 5 days, which improved symptoms, and was discharged with mild ophthalmoparesis.

Recurrence of MFS is infrequent.<sup>1,4,5</sup> We present the case of a patient whose symptoms resolved after a first episode, before experiencing a relapse 2 years later, with similar symptoms and an infectious trigger in both episodes. We should highlight the negative results for antiganglioside antibodies during both admissions, as well as the normal findings in the motor nerve conduction study performed during the second admission. This lack of pathological findings has previously been described in other cases of recurrence,<sup>4,7</sup> and may be explained by the early performance of the study.<sup>7,8</sup>

In other reported cases of recurrent GBS spectrum disorders, symptoms are usually more severe in the second episode,<sup>9</sup> which was not the case with our patient. He also presented an excellent response to Ig during the recurrence, unlike in the first episode. We do not know the reason for the lesser severity and better response to Ig during the relapse, although they may be related to immunological factors, as well as aetiological factors of the precipitating agent.

The causes predisposing to recurrent GBS are unclear. Patients younger than 30 years, with moderate impairment and MFS phenotype, are reported to present a higher risk of recurrence.<sup>9</sup> While the reasons for this are not clear, some human leukocyte antigens (HLA-Cw3 and HLA-DR2), as well as some immunological factors, are reported to be involved.<sup>4,6,9,10</sup>

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## COVID-19 related strokes: *Pandora's Box may open as the p(c)lot thickens!*



### Ictus y COVID-19: una nueva caja de Pandora

Dear Editor,

As I read through the interesting literature focusing on COVID-19 related strokes, featured recently in the *Journal*,<sup>1,2</sup> my inquisitiveness regarding the involved mechanisms of neuro-invasion escalates. Moreover, as the COVID-related 'clot' thickens (a result of the pro-inflammatory

hypercoagulable milieu), almost in close conjunction does the 'plot' thicken interrogating whether the direct consequences of disseminated intravascular coagulation can alone explain the intriguing findings of most COVID-associated strokes being ischemic in nature with many researchers also suggesting these cerebrovascular events to be unrelated to age and associated with few vascular risk factors.<sup>1–5</sup>

In this context, while the thrombo-embolic sequel of COVID-19 is being ardently discussed,<sup>1–4</sup> paradoxical embolization into the cerebral circulation through an undetected probe patent foramen ovale (PPFO) (reported to be as common as 20–25% in the general population), can very well be an important contributing factor.<sup>6</sup> The premise for

the same emanates from the comprehension of the fact that an ongoing inflammatory process leads to pulmonary arterial hypertension (aggravated by hypoxia, positive pressure ventilation and stiff-lung syndrome associated with COVID-19) culminating as accentuated right atrium (RA) pressures augmenting paradoxical embolization from the RA to left atrium (LA) through the PPFO (precluded in healthy subjects owing to the positive physiological LA-RA pressure gradient).<sup>7,8</sup>

The aforementioned constitutes a cardiac anaesthesiologists' perspective on opening yet another Pandora's Box (referring to a PPFO in this case) concerning the mechanisms leading to stroke in COVID-19 (which in itself has evolved to be nothing less than a nature's misadventurous stroke) highlighting the significance of a routine echocardiographic surveillance in this predisposed critically ill cohort.

## Authors' contribution

RM conceptualized and wrote the entire manuscript.

## Conflicts of interest

We do not have any conflict of interest, any commercial or financial interest in this material & agree to abide by the rules of your journal regarding publication of this article.

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## Reply<sup>☆</sup>



## Réplica

Dear Editor:

We are grateful to the author of the letter to the editor "COVID-19 related strokes: Pandora's box may open as the p(c)lot thickens!" for his interest in our article.<sup>1</sup> In the early months of the COVID-19 pandemic, it was suggested that the prothrombotic state observed in patients with the disease may be an aetiopathogenic mechanism of ischaemic stroke.<sup>1,2</sup> A year later, this hypothesis seems plausible, given the high frequency of thrombotic events reported in patients with severe COVID-19,<sup>3,4</sup> including ischaemic stroke, with an incidence of 1%-1.7% according to different series.<sup>5,6</sup> The exact mechanism triggering this prothrombotic state is currently unknown, although the process is

probably multifactorial, conditioned by the systemic inflammatory response, increased concentration of angiotensin II in the blood, and direct endothelial invasion by the SARS-CoV-2 virus, as well as other pre-existing prothrombotic risk factors.<sup>7,8</sup>

However, we agree with the author of the letter that the prothrombotic state may not be the only factor involved in stroke in patients with COVID-19, given that "ischaemic stroke may be caused by multiple, complex pathogenic mechanisms, particularly in patients with respiratory involvement."<sup>1</sup> In accordance with the above, the letter to the editor suggests that patent foramen ovale (PFO) may cause ischaemic stroke due to paradoxical embolism, conditioned by a pressure gradient from the right to the left atrium secondary to pulmonary hypertension in patients with COVID-19. This theory seems plausible from a pathophysiological viewpoint, as PFO is present in up to 27% of the general population and more than 40% of patients with embolic stroke of undetermined source.<sup>9</sup> Furthermore, the persistent cough in these patients, a Valsalva manoeuvre, may increase the right atrial pressure gradient caused by pulmonary hypertension, favouring opening of the PFO.<sup>9</sup> A recent meta-analysis estimates the prevalence of stroke in patients with pulmonary hypertension at 8%.<sup>10</sup> Nonetheless,

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