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CORRESPONDENCE

COVID-19, Guillain-Barré syndrome, and the vaccine. A dangerous combination☆

COVID-19, Guillain-Barré y vacuna. Una mezcla peligrosa

Dear Director:

Since the initial outbreak of the novel coronavirus in December 2019 in the city of Wuhan[1], multiple symptoms have been discovered to date, with respiratory symptomatology the most recognisable. In addition, some studies have found cardiology-related, digestive, and renal complications, among others[2].

The most extensive analysis to date regarding nervous system manifestations is that performed by Mao et al.[3], in which 214 hospitalised patients were analysed, of which 36.4% had central nervous system manifestations including anosmia, headache, dizziness, ageusia, or cerebrovascular accidents (ischaemia or haemorrhage), among others. Developing Guillain-Barré syndrome and Miller Fischer syndrome has also been reported within the context of SARS-CoV-2 infection[4,5].

Although the association between Guillain-Barré syndrome and vaccines such as the flu vaccine has been reported[6], only one instance has been described in current medical literature, that of one case following vaccination with an mRNA vaccine[7] and one following adenovirus[8].

We present the first two cases of Guillain-Barré syndrome described in the literature in which this syndrome, vaccination, and infection with SARS-CoV-2 coincide.

Case 1. A 77-year-old male with no history of note. The patient was admitted on 13 March 2021 for COVID-19 pneumonia with mild involvement of the pulmonary parenchyma and evidence of hyperinflammation. He was treated with dexamethasone with subsequent favourable progress and was referred for discharge six days later. Two weeks later he received his first coronavirus vaccine dose (BNT162b2). He received it on 5 April 2021. At 72 h post-vaccination, the patient started to experience symptoms of weakness in the lower limbs and progressive oedema of said limbs. Days later neuropathic pain started in the left lower limb.

The patient went to the Emergency Department on 27 April 2021 due to worsening symptoms and the inability to walk. Neurologically, the patient presented absent bilateral reflexes in the lower limbs, loss of epicritic and protopathic sensation, as well as diminished strength in the flexion-extension of both feet and flexion of the leg (2–3/5). He presented with pitting oedema up to the middle third of both legs. The rest of the physical examination was unremarkable.

In the initial additional tests, elevated acute phase reactants stood out (CRP 233 mg/dL) and D-dimer (8.09 mg/L). A lumbar puncture was performed which showed clear fluid with no increased pressure and lymphocytic pleocytosis (proteins 39 mg/dL and 1 cell). The auto-immune study was negative, including anti-ganglioside antibodies.

A neurophysiology study was performed which confirmed the initial suspicion of Guillain-Barré syndrome, acute motor and sensory axonal neuropathy variant (AMSAN) (Fig. 1). Just hours later, the patient's respiratory situation worsened with desaturation and respiratory effort, so treatment with intravenous immunoglobulins was started (400 mg/kg/day) and, subsequently, plasmapheresis due to refractoriness, with favourable subsequent progress.

Case 2. A 62-year-old patient with no personal history of note and vaccinated with the first dose of the ChAdOx1 vaccine. At 72 h, the patient went to the Emergency Department due to symptoms of progressive fever and respiratory difficulty requiring orotracheal intubation for 8 days due to severe COVID-19 pneumonia confirmed via nasopharyngeal exudate PCR. At 24 h after being moved to the Internal Medicine ward, onset of an acute episode of flaccid, areflexic tetraparesis, hypophonia, and new respiratory failure that required reintubation.

A lumbar puncture was performed with clear CSF, normal pressure with an albuminocytologic dissociation in the cytochemical analysis with proteins 48 mg/dL and 0 cells. Treatment was started with IV immunoglobulins (dose: 400 mg/kg/day for 5 days) with rapid patient progress.

Although many infectious agents have been associated with Guillain-Barré syndrome, the most frequently associated agents are *Campylobacter jejuni*, the Epstein Barr virus, cytomegalovirus, and Zika virus[9]. The mechanism by which SARS-CoV-2 induces Guillain-Barré syndrome could be via viral stimulation of the inflammatory cells, producing a cytokine release syndrome and, subsequently, the creation of immune-mediated processes that can be directed at the myelin or the axon of the peripheral nerve, thus resulting in demyelinating and axonal variants.

Weakness can vary from slight difficulty to walk to almost complete paralysis of the limb, facial, respiratory, and bulbar muscles, as occurred in one of our cases, though this is uncommon since motor muscle weakness that requires ventilatory support occurs in 10%–30% of cases, oropharyngeal weakness in 50%, and oculomotor weakness in 15% of cases[10,11].

There is some controversy surrounding the development of this syndrome and coronavirus vaccination, despite two cases having been previously reported in the literature of individuals developing Guillain-Barré syndrome following coronavirus vaccination with different types of vaccines (ChAdOx1-S and BNT162b2)[7,8]. Nevertheless, some authors believe there is no causal relationship between the two situations[12,13].

There is currently very little information available regarding neurological manifestations following coronavirus vaccination,

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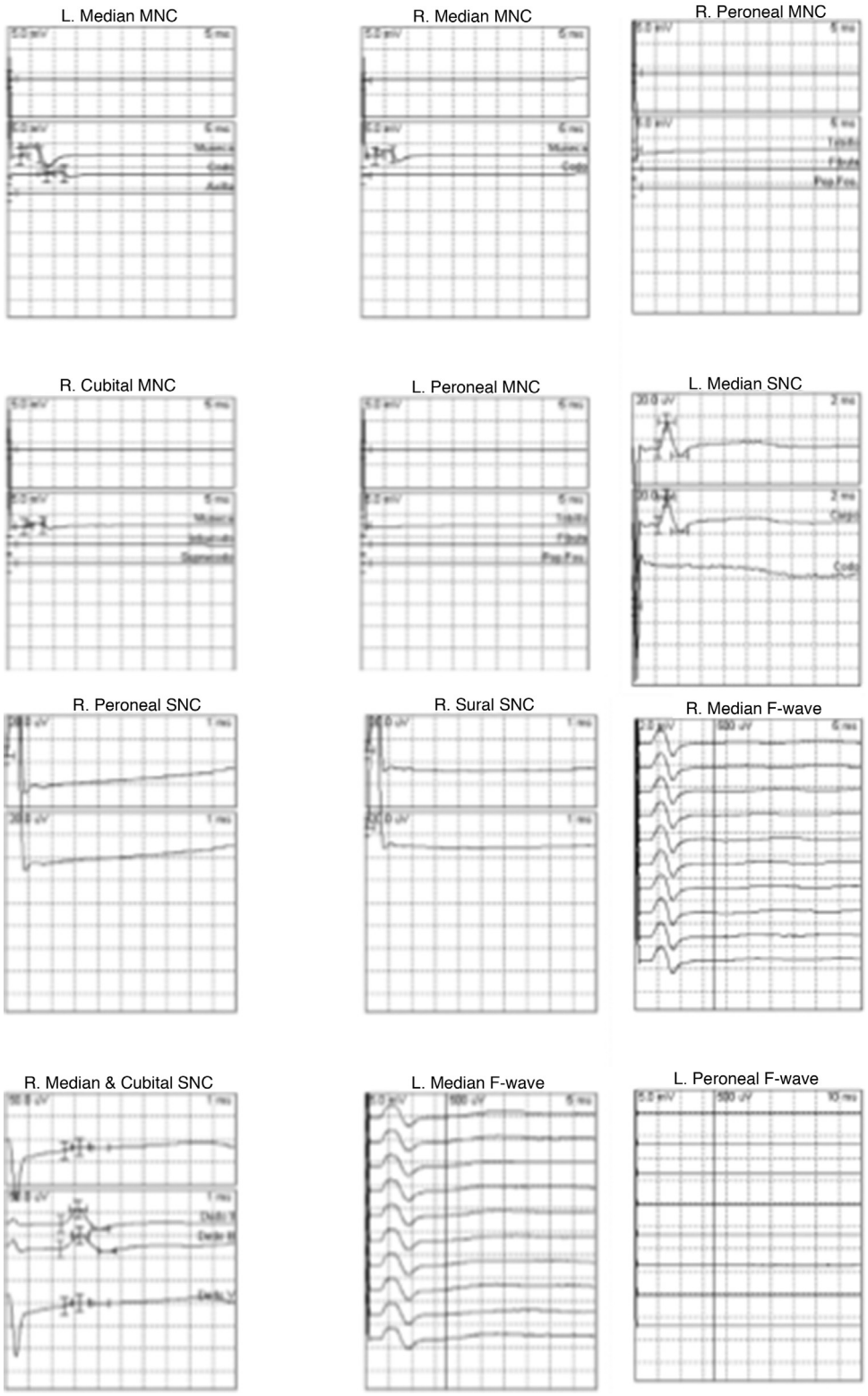

Figure 1 Summary of the neurophysiology testing for patient number 1. No distal motor conductions are obtained corresponding to the main nerves of the upper and lower limbs. No ''F'' responses are obtained in any of the nerves examined. No sensitive responses are obtained in the nerves of the lower limbs.
L: left; MNC: motor nerve conduction; R: right; SNC: sensitive nerve conduction.

or their incidence rates. As such, epidemiological studies and registries of future cases should elucidate the real incidence of neurological complications, their pathogenic mechanisms, and their therapeutic options.

Though a causal relationship between this syndrome and vaccination cannot be demonstrated with the current evidence, we believe that neuromuscular complications could be due to said association, and even more so in the presence of a concomitant, undiagnosed infection of this kind, or recent infection. Both situations could be synergic and could stimulate development of the acute inflammatory demyelinating polyradiculoneuropathy.

Though scarcely reported, it is possible that this complication is under-diagnosed.

Understanding and evaluating neurological manifestations following this vaccine is important as the initial symptoms are rarely assessed in a thorough manner and could interfere with prognosis.

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Immunotherapy for migraine: The use of erenumab in real life☆

Inmunoterapia contra la migraña: uso de erenumab en la vida real

Dear Director,

The use of monoclonal antibodies designed to work against the pathogenic pathway of the calcitonin gene-related peptide (CGRP) and its receptor (CGRP-R) as immunotherapy for the prophylactic treatment of migraines represents a milestone not only for its efficacy, but also for the unprecedented specificity for this pathology.

Erenumab is a 100% human monoclonal antibody that selectively blocks CGRP-R. It is indicated for highly frequent episodic migraines and chronic migraines with eight or more monthly migraine days (MMD) and three or more previous treatment failures during three months, including botulinum toxin in the case of chronic migraine.[1]

After obtaining informed consent, we used erenumab to treat 15 patients with these characteristics within Novartis' compassionate use program, code AMG334A2021 M, which was signed with our center in February 2019 and authorized by the Spanish Agency for Medicines and Medical Devices (AEMPS, for its initials in Spanish) until its marketing in November 2019.

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