Miller-Fisher syndrome after SARS-CoV-2 infection

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Introduction: On March 11th, 2020, the WHO declared the SARS-Cov-2 pandemic. Syndromes have been detected in relation to COVID-19 such as encephalitis, acute necrotizing hemorrhagic encephalopathy and cerebrovascular complications. There are also cases of peripheral nervous system involvement.

Methods: Our case would be the 3rd patient with MFS associated with COVID-19 as far as we know.

Results: We present a 51 years old female diagnosed with MFS two weeks after COVID-19. RTPCR to SARS-CoV-2 was negative but IgG was positive.

Conclusion: Most of the cases were mild or moderate with typical signs and symptoms. All were treated with IV immunoglobulin with good response in most cases. Despite the short evolution time of the cases surviving the current pandemic, the description of cases of post-infectious neurological syndromes suggests that this is probably not an infrequent complication in the subacute stage of Covid-19 disease.

Introduction

The World Health Organization declared the SARS-CoV-2 pandemic on 11 March 2020. The disease can go unnoticed in asymptomatic infected patients or manifest as a severe acute respiratory syndrome (SARS) with high lethality, especially in older patients with other comorbidities such as cardiovascular risk factors [1]. Since then, we have learned of multiple effects on the nervous system. SARS-CoV-2 has been proposed to have an infective capacity in the nervous system through the angiotensin-converting enzyme 2 receptor and type II transmembrane serine protease, both of which are necessary for the virus to get into the cells [2], which can be identified in neurons, glial cells and respiratory epithelial cells.

Neurological signs have been described in up to 36.4% of a series of 214 hospitalized patients [3].

Most of the neurological symptoms in acute patients are non-specific and probably have a systemic origin (e.g. headaches, myalgia, fatigue, dizziness). However, anosmia and ageusia appear to be very prevalent in the series so far. Other syndromes, such as encephalitis, acute necrotizing hemorrhagic encephalopathy and cerebrovascular complications, have been detected in relation to COVID-19 [4]. There are also cases of peripheral nervous system involvement. According to a Medline search for Miller-Fisher syndrome (MFS) in relation to COVID-19, only two cases have been published as of 30 April 2020 [5]. We present a new case of MFS in a patient following infection with SARS-CoV-2.

Case description

The subject was a 51-year-old female with no personal or family history of interest. She and her husband had contact with a case of COVID-19 on 12 March. On 15 March she developed diarrhea, odinophagia and cough,

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although she did not present thermometered fever. The condition lasted approximately 10 days, after which she continued to feel discomfort in the throat. From 30 March she started having intense root-type pain in all four limbs, especially in the legs, as well as dorsal and lumbar back pain. On 4 April she developed weakness in the lower limbs that progressed, over a few days, to the point of preventing her from walking, associated with double binocular vision. She was admitted to our department on 11 April.

The neurological examination showed paresis of the left external rectus muscle with horizontal diplopia when looking to the left, discrete predominantly inferior bilateral facial paresis, symmetrical paraparesis with 3+/5 weakness in psoas, hamstrings, gluteus and quadriceps, 3/5 in gastrocnemius, 2/5 in posterior tibial and peroneal, and global areflexia. She also presented symptoms of autonomic dysfunction such as dry mouth, diarrhea and unstable blood pressure. She did not report ageusia or anosmia. On admission, Reverse transcription polymerase chain reaction to SARS-CoV-2 was negative but immunoglobulin G was positive using the enzyme-linked immunosorbent assay technique.

The cerebrospinal fluid showed high protein levels with albumin-cytological dissociation (70 mg/dL of proteins and 5 leukocytes/microliter). Anti-ganglioside antibodies were negative. The remaining neuroimaging studies and analysis of infectious and autoimmune pathologies were negative.

The neurophysiological study carried out on 14 April showed F-wave anomalies, such as asymmetric latency for the lower limbs and low A-wave amplitude for the left leg, alteration of bilateral R1 responses in the blink reflex and, in the intermediary standard electromyography, poor activity in right rectus-anterior femoral muscle and little spontaneous denervation activity in left rectus-anterior femoral muscle. All of this was compatible with an acute Guillain-Barré-type demyelinating polyneuropathy at a very early stage. A control neurophysiological study on 30 April showed low F-wave amplitude and disintegrated morphology, similar alteration of blink reflex and spontaneous denervation activity in bilateral rectus-anterior femoral and left anterior tibialis, compatible with polyradiculoneuropathy with proximal and brainstem involvement.

The patient was treated with intravenous immunoglobulin (0.4 mg/kg/24 h) for 5 days (12–16 April) and gabapentin (900 mg/24 h), showing a progressive improvement in facial and limb paresis, diplopia and pain. She is still receiving neurological rehabilitation. She was diagnosed with MFS after SARS-CoV-2 infection.

No ethics committee approval was required as there is no identifiable patient data. The patient gave her express consent for the publication of this article.

Discussion

Guillain-Barré syndrome (GBS) is a group of pathologies that are clinically characterized by flaccid paralysis of the extremities and sensory and autonomic disorders of an autoimmune nature, usually 3–6 days after an infectious process. When ophthalmoparesis is associated with predominantly lower-limb involvement, it is called MFS. The physiopathological mechanism is based on molecular mimicry and anti-ganglioside antibodies (anti-GQ1B in the case of MFS) in people who are genetically predisposed after a bacterial or viral infectious process [6]. We know that human coronaviruses have neuroinvasive capacity, present neurotropism and can induce GBS-type dysimmune phenomena in certain patients [7] as previously seen in the Middle East respiratory syndrome coronavirus epidemic [8]. SARS-CoV-2 also presents this capacity to affect the nervous system, either directly (neuroinvasive capacity) or indirectly by an inflammatory mechanism [4].

The clinical picture of our patient was compatible with MFS, known anti-GQ1b syndrome, although the antibody study was negative. To date, 11 cases of GBS after COVID-19 have been published [9–16]. Most of the cases were mild or moderate with typical signs and symptoms. All were treated with intravenous immunoglobulin with good response in most cases, although some required mechanical ventilation and intensive care unit management. Our case fits most of the cases documented to date. The absence of anti-ganglioside antibodies in all cases determined is remarkable. Although it is still early, this could indicate that the molecular mimicry phenomenon by which SARS-CoV-2 precipitates GBS could be different to that of other bacteria, such as *Campylobacter jejuni*, *Mycoplasma*, etc. Recently, two cases of MFS and cranial polyneuropathy have been described after COVID-19 [16], which presented anti-GD1b-immunoglobulin G antibodies, with good response to treatment with immunoglobulins.

During the evaluation, we conducted an interview where the patient was asked directly about the presence of ageusia or anosmia and she denied the presence of such symptoms. In the articles reviewed, the presence of anosmia and/or ageusia was only present in one case of GBS [11] and in the two patients with MFS [5]. According to the studies, up to 85.6% of patients reported dysosmia or anosmia and up to 88% presented taste alterations [4].

As far as we know, our case would be the third patient with MFS associated with COVID-19. Despite the short evolution time of the cases surviving the current pandemic, the description of cases of post-infectious neurological syndromes suggests that this is probably not an infrequent complication in the subacute stage of COVID-19 disease. It will be necessary to be attentive to their possible appearance after the hospital discharge of the patients.

Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

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