

Miller-Fisher syndrome after COVID-19: neurochemical markers as an early sign of nervous system involvement

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Miller-Fisher syndrome (MFS) is classified as a variant of Guillain–Barré syndrome (GBS), accounting for 5%–25% of all GBS cases. Since the coronavirus disease-2019 (COVID-19) outbreak, increasing evidence has been reported of the neurological manifestations of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, affecting both the central and peripheral nervous system. Here we report the clinical course, detailed cerebrospinal fluid (CSF) profile including CSF/blood antibody status, and neurochemical characteristics of a patient with a typical clinical presentation of MFS after a positive SARS-CoV-2 infection test.

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Case presentation

A 61-year-old patient experienced mild breathing difficulties at the end of March 2020. Three days later, he tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA on RT-PCR with a nasopharyngeal swab. Given his mild symptoms, the patient remained in home quarantine. During this period, he developed fever for 4 days with heavy night sweating. Moreover, he reported a weight loss of 12 kg. At the end of quarantine, he experienced a slight unsteadiness during walking, a 'pins and needles' sensation on his fingertips, and slight diplopia. Twenty-seven days after the first symptoms appeared, he found that driving a car was no longer possible. Finally, the patient was admitted to our department presenting with slight sensitive ataxia, ophthalmoplegia, and general areflexia. In the electrophysiological examination, the F-wave was not detectable. Serum

anti-ganglioside antibodies, including anti-GQ1b, were negative.

Cerebrospinal fluid (CSF) analysis revealed a normal cell count (one leukocyte per μl). Cell differentiation showed 90% lymphocytes, 6% monocytes and 4% activated lymphocytes. RT-PCR for SARS-CoV-2 in the CSF and on nasopharyngeal swab was negative. CSF total protein levels and the corresponding albumin quotient were largely increased (1588 mg/l and 24.8, respectively). Intrathecal production of immunoglobulin (Ig)G (either by oligoclonal bands or in the Reiber diagram), IgA or IgM was not detectable [Quotient (Q) IgG: 12.1, QIgA: 7.0, QIgM: 1.1 (Fig. 1)]. Lactate was slightly elevated at 3.4 mmol/l, but the glucose quotient was within the normal range (0.51). CSF total tau and amyloid-beta-42 were normal (265 and 1109 pg/ml, respectively). CXCL13, beta-microglobulin and ferritin levels in the CSF were not affected. CSF-blood antibody indexes for varicella-zoster virus, Epstein–Barr virus and herpes simplex virus were normal. In blood, the antibody reaction against SARS-CoV-2 was positive for IgG and IgA. The response was 8.6 arbitrary units (AU) for IgG (cut-off 1.1 AU, dilution 1:1000) and 2.3 AU

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for IgA (cut-off 1.1, dilution 1:1000, Euroimmun assay). At a CSF dilution of 1:10, a positive signal was observed for IgG (8.6 AU) and IgA (1.3 AU), corresponding to an antibody index below 1, indicating no intrathecal production of SARS-CoV-2 antibodies. Phosphorylated neurofilament heavy chain protein (pNfH) was massively elevated in the CSF, at 2131 pg/ml (normal levels below 560 pg/ml). Neurofilament light chain (NfL) protein in blood measured by Simoa was clearly increased, at 58 pg/ml (normal levels below 30 pg/ml).

After lumbar puncture, the patient was treated for 5 days with intravenous immunoglobulin (30 g/day). Two weeks after the treatment, the patient was free of symptoms. A second and third determination of NfL in blood, 7 and 23 days after the lumbar puncture still showed increased levels (61 and 58 pg/ml, respectively).

Discussion

Miller-Fisher syndrome is classified as a variant of GBS, presenting with ophthalmoplegia, ataxia and areflexia [1]. In summary, we describe a patient with a typical clinical presentation of MFS 20 days after he tested positive for SARS-CoV-2 infection. The latency between coronavirus disease-2019 (COVID-19) manifestations and MFS onset is in accordance with previous single case reports and suggests a typical post-infectious course [2–4]. Moreover, our patient shared the classic MFS clinical features and good response to intravenous immunoglobulins described in other reports [2–4].

Most interestingly, we provide for the first time a detailed and comprehensive overview of the CSF profile in COVID-19-associated MFS. In detail, we found no evidence of intrathecal production of SARS-CoV-2 antibodies as disease-causing antibodies in the CSF. However, we observed a significant rise of CSF pNfH and serum NfL in this patient, reflecting affection of the peripheral nerves. In addition, the absence of serum anti-ganglioside antibodies (including anti-GQ1b) in the present and two other COVID-19-associated MFS cases [2–3], together with positivity for anti-GD1b antibodies in another case [3], might implicate different immune-mediated mechanisms compared to those of non-COVID-19 MFS, although serum anti-GQ1b antibody-negative MFS cases have been described [5].

With the spreading of the SARS-CoV-2 pandemic worldwide, more such cases will probably be described. Measurement of NfL in the blood might be considered an easy tool to detect early affection of the peripheral and central nervous system [6,7].

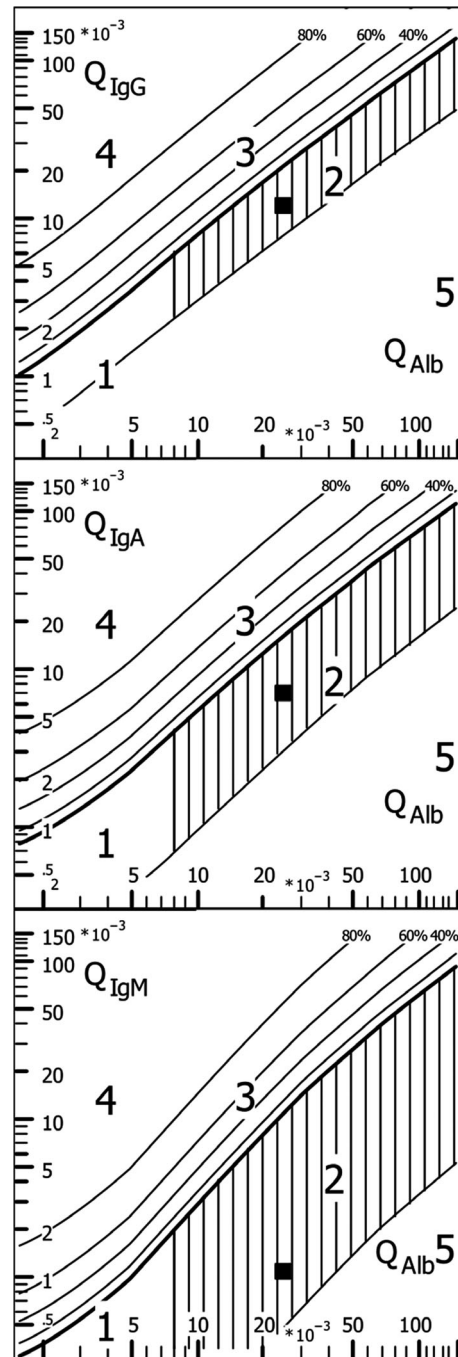


Figure 1 Cerebrospinal fluid (CSF) serum quotient diagram for immunoglobulin (Ig)G, IgA and IgM, with reference range according to Reiber [8]. On the x-axis, the albumin quotient (Q_{alb}) of (1) represents normal blood–CSF barrier function and (2) demonstrates blood–CSF barrier dysfunction. The y-axis shows quotients for IgG, IgA and IgM (Q_{IgG}, Q_{IgA}, Q_{IgM}), whereby values can discriminate the blood-derived IgG/IgA/IgM fraction from intrathecal Ig synthesis either represented by (4) as intrathecally IgG synthesis only, or as (3) demonstrating a combined blood–CSF barrier function together with intrathecal IgG synthesis. (5) analytically not possible and indicates a methodological error in the measurement. The values recorded for our patient (filled squares) demonstrate blood–CSF barrier dysfunction without intrathecal Ig production.

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Disclosure of conflict of interest

The authors declare no financial or other conflicts of interest.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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