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LETTER TO THE EDITOR

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Guillain-Barré syndrome is immunogenic in SARS-CoV-2 infected

To the Editor,

With interest, we read the article by Khan et al. about five adult patients with SARS-CoV-2 associated Guillain-Barré syndrome (SACAG) of whom one tested positive for virus RNA in the cerebrospinal fluid (CSF).[1] Three patients were classified as acute, inflammatory, demyelinating polyneuropathy (AIDP) and one each as acute, motor, axonal neuropathy (AMAN) respectively acute, motor, and sensory, axonal neuropathy (AMSAN).[1] It was concluded that "in a few cases where the symptoms of COVID-19 and GBS occur concurrently (corresponding to the viremic phase), a separate, para-infectious pathogenesis needs to be thought of".[1] The study is appealing but prompts comments and concerns.

There is currently no evidence that SACAG is infectious. In a recent review of 300 patients with SACAG, of whom 68 underwent investigations for virus-RNA in the CSF, virus-RNA was detected only in a single patient.[1] A second SACAG patient has been recently reported in whom CSF tested positive for the virus.[2] Whether the presence of virus-RNA in these two cases represents false-positive results is unknown as no results of test-/retest-reliability were provided in either case.[1,2] Though it is conceivable that the low number of patients positive for virus-RNA in the CSF is due to the low number of SACAG patients undergoing investigative workup for virus-RNA in the CSF, there are several arguments that favor the immunogenic etiology of the condition.

The first argument for immunogenic pathophysiology is that most SACAG cases respond favorably to immuno-suppressive or immune-modulating treatment. In the review elucidating 300 SACAG cases, 241 patients received intravenous immunoglobulins, 28 plasma exchange, and eight patients glucocorticoids [submitted]. Complete recovery from SACAG was achieved under these treatments in 42 patients, and incomplete recovery from SACAG in 163 patients at last follow-up respectively at discharge [submitted]. Merely 17 of the 300 patients died but it was not specified whether these patients deceased from COVID-19 or from SACAG. The second argument for an immunogenic pathophysiology is that virus-RNA has been detected in the CSF in only two patients so far reported.[1,2] Even if virus-RNA is present in the CSF of a SACAG patient, this does not exclude an immunogenic mechanism. The virus may be present transiently in all tissues, including the CSF, but perhaps does not attach to ACE-2 receptors if these are not expressed on specific surfaces. A third argument is that SARS-CoV-2 vaccinations markedly reduced the prevalence of SACAG. In a recent review of 300 SACAG patients, it has been shown the number of SACAG patients reported in the second half of 2020 (n = 192) declined by 61% in the first half of 2021 [submitted]. As SARS-CoV-2 vaccination had been introduced by December 2020, this finding suggests that vaccinations reduce the prevalence of SACAG patients. Vaccinations not only reduce the virus load but also evoke an immune reaction against the virus, which vehemently supports an immune mechanism. A fourth argument in favor of the immune hypothesis is that SACAG develops with a latency of up to 90 days after onset of clinical COVID-19 manifestations.[3] As the virus can be found by nasopharyngeal swab tests only transiently, the long latency favors the immunogenic hypothesis. A fifth argument in favor of the immunogenic origin of SACAG is that cytokines are elevated in the CSF of SACAG patients.[4] In particular, interleukin-8 has been found to be elevated in the CSF of SACAG patients.[4] In addition to interleukin-8, interleukin-6 was elevated in the serum and CSF in the acute phase of SACAG patients.[5] At the 4 months follow-up, only interleukin-8 had remained elevated in the serum.[6] A further argument is that certain HLA alleles known to be associated with GBS, such as class-I (HLA-A33) and class-II alleles (DRB1*03:01 and DQB1*05:01), have also been detected in SACAG patients, further invoking an underlying immunogenic etiology.[4] Another indication for an immune reaction is that CSF protein is usually elevated in the absence of pleocytosis.[6]

Overall, there are more arguments in favor of the immunogenic pathophysiology of SACAG than in favor of the infectious pathophysiology. The presence of virus-RNA in the CSF does not necessarily imply an infectious cause of SACAG. In light of the aforementioned points, this notion should be construed with due caution.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

ETHICS STATEMENT

Was in accordance if ethical guidelines. The study was approved by the institutional review board.

AUTHOR CONTRIBUTIONS

Josef Finsterer: design, literature search, discussion, first draft, critical comments, final approval. Talal Almas: literature search, discussion, critical comments, final approval.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Josef Finsterer[1]
Talal Almas[2]

[1]*Klinik Landstrasse, Messerli Institute, Vienna, Austria*
[2]*RCSI University of Medicine and Health Sciences, Dublin, Ireland*

Correspondence
Josef Finsterer, Klinik Landstrasse, Messerli Institute, Postfach 20, 1180 Vienna, Austria, Postfach 20, 1180 Vienna, Austria.
Email: fifigs1@yahoo.de

ORCID

Josef Finsterer https://orcid.org/0000-0003-2839-7305
Talal Almas https://orcid.org/0000-0002-8867-600X

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