Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

The Journal of Emergency Medicine, Vol. 61, No. 6, pp. 794–796, 2021

0736-4679/$ - see front matter

Letters to the Editor

□ INVITED COMMENTARY – SARS-COV-2-ASSOCIATED GUILLAIN-BARRÉ SYNDROME REQUIRES APPROPRIATE EXCLUSION OF POSSIBLE DIFFERENTIALS

□ To the Editor:

With interest, I read the letter to the editor by Finsterer et al. regarding the recent report involving Guillain-Barré Syndrome (GBS) after Coronavirus disease 2019 (COVID-19) infection (12). The interest in the report is greatly appreciated. Although the writers do correctly note some limitations, these do not detract from the report's aim of further documenting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as a cause of GBS. Therefore, I would make some further observations of which the authors—and indeed, clinicians the world over—should be reminded regarding the diagnosis of GBS.

It is true that the index patient did not have electromyogram with nerve conduction velocities (EMG/NCS)—which has alternatively been called electromyelogram, to answer one of the authors' questions—as part of the diagnostic workup (1). The patient in the case refused this testing. This is an important part of the workup because GBS is not one homogenous disease process; rather, there are several variant manifestations under the umbrella term GBS, viz., autoimmune inflammatory demyelinating polyneuropathy, acute motor axonal neuropathy, acute motor and sensory axonal neuropathy, Miller Fisher syndrome, pharyngeal-cervical-brachial variant, and even Bickerstaff brainstem encephalitis (2). This limitation does preclude further classification of the patient's symptoms into one of these variants. Finsterer et al. mention the Brighton criteria as being required to diagnose GBS, and that the diagnosis thus remains uncertain.

However, any resulting uncertainty cannot be further from the truth. In fact, this is misleading, as there is no mention that there are various levels of diagnostic certainty according to the Brighton criteria. Level 1 of diagnostic certainty does indeed call for electrophysiologic findings consistent with GBS. However, the patient's lack of NCS findings moves the level of diagnostic certainty to level 2, as all other criteria had otherwise been met (3). Note that level 2 certainty does not debunk the diagnosis. Furthermore, it is imperative to note that EMG/NCS does not necessarily refute the diagnosis of GBS. As pointed out by van den Bergh and Pieret (2004), patients with acute forms of GBS can have normal electrodiagnostic studies early in the course, and clinicians must be mindful, therefore, that a normal study does not, in fact, rule out GBS (4,5).

It is therefore important to consider where the patient may be in the disease course. This is supported by other research, indicating that approximately 10% of patients in the early phase may not have characteristic motor and sensory abnormalities of conduction on electrodiagnostic studies, and that serial examinations are likely of more diagnostic value in such cases to detect these changes with the evolution of the disease process (6,7).

Secondly, although reference limits were not reference for the laboratory parameters, it was communicated whether these were abnormal as per the reference limits of the laboratory. The patient did exhibit mild albuminocytologic dissociation. However, the literature indicates that cerebrospinal fluid analysis may likewise fail to show albuminocytologic dissociation (4,8). Cerebrospinal fluid (CSF) analysis may not be possible in some patients with bleeding diathesis. It is true that the patient's CSF was likewise not tested for inflammatory cytokines nor for SARS-CoV-2. Toscano et al. (2020) found that none of the COVID-19 positive patients with GBS in their study—who tested positive by nasopharyngeal swab—were found to have a positive CSF SARS-CoV-2 (9).

The authors are reminded that CSF inflammatory cytokines are still being investigated, and thus, are not a standard part of the diagnostic criteria for GBS, even in the setting of COVID-19. Although interesting, the

elevation of these levels, or lack thereof, cannot yet be used to confirm or refute the diagnosis. The literature furthermore has shown that COVID-19 patients with peripheral neuropathies often lack any laboratory abnormalities such as lymphopenia, thrombocytopenia, azotemia, or elevated inflammatory markers, compared with those with central nervous system manifestations, adding to the uncertainty of the value or relevance of this testing (11). The role of these investigations needs further analysis, and as of now, may potentially confound the clinical picture if not careful analyzed.

Additionally, testing for the presence of cytokines in the CSF may not be clinically useful for most clinicians faced with this clinical problem. Except for the largest of academic centers, this testing is unlikely to be performed on site, resulting in lengthy delays in receiving test results from the reference laboratory. In the meantime, treatment must be instituted (and indeed, may be well under way or even completed by the time results are received). These reasons informed the decision to forego such testing in the index patient.

The patient's vitamin B12 deficiency is noteworthy. The low serum vitamin B12 was supplemented parenterally, though this is unlikely to explain this patient's symptoms given that serum levels were subsequently low on follow-up, though the patient's symptoms had resolved on neurologic examination. This information was not yet available as of the first follow-up documented in the case. Another interesting aspect of the neurologic examination was the patient's resting tremor of the upper extremities and the left thigh fasciculations. The significance of these findings is unclear and was not explained by any of the investigations undertaken during the hospitalization. However, the remainder of the clinical picture was consistent with GBS, and the patient responded positively to immunoglobulin therapy.

Other anomalies in the diagnostic workup of the index patient include the positive antinuclear antibody (ANA) level 1:320 speckled pattern. However, reflex testing for anti-dsDNA, RF, anti-Sm, anti-SSA/SSB, anti-RNP, and other rheumatologic workup did not reveal any additional abnormality and there was, thus, no clinical concern for systemic lupus erythematosus, Sjögren's syndrome, rheumatoid arthritis, or other rheumatologic conditions. Positive ANA levels have been observed in individuals with hematological malignancy, non-rheumatologic immune disorders, and bacterial and viral infections. A positive ANA alone has no diagnostic utility, and 2.5–5% of the population may have an elevated ANA result (10).

Finally, contrasted spinal magnetic resonance imaging (MRI) to image the caudal nerve roots was not performed on this patient because, although certainly helpful, it is not necessary to confirm the diagnosis of GBS. Indeed, it is not part of the Brighton criteria. It can be considered in cases of clinical uncertainty, while recognizing that several conditions may result in such nerve root enhancement. Interestingly, though, Toscano et al. examined 5 COVID-19 patients in Italy with GBS and found that 2 of the 5 patients did not demonstrate any central nervous system enhancement (9). This did not detract from the diagnosis, as typical clinical signs and EMG findings were present, whereas CSF analysis was *negative* for SARS-CoV-2 even though all patients tested positive for the virus via nasopharyngeal swab. One patient demonstrated only facial nerve enhancement and the other 2 patients demonstrated enhancement in the caudal nerve roots.

GBS is a diagnosis in which the primacy of *clinical* suspicion cannot be underestimated. It can be difficult to diagnose because a small, yet not insignificant number of patients may present with relatively benign CSF, EMG, MRI, and laboratory findings, especially early in the clinical course of the disease process. Clinicians must maintain a high level of alertness to this possibility in patients presenting with neuropathy and acute flaccidity. Despite the limitations of the investigation conducted in the index patient, the above explanations only add to the diagnostic certainty of the patient's diagnosis. Not only are we responsible for providing high-quality patient care, but we must also do so in a cost-effective manner. Tests with unproven value or those that, although potentially valuable and helpful will not change management, can be safely deferred. This additional discussion thus contributes to the clinical thought processes that must occur in deciding which laboratory and diagnostic investigations are essential and should be ordered in the patient with suspected GBS.

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https://doi.org/10.1016/j.jemermed.2021.07.068

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