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.

Journal of Neuroimmunology 369 (2022) 577901

Contents lists available at ScienceDirect

Journal of Neuroimmunology

journal homepage: www.elsevier.com/locate/jneuroim

Letter to the Editor

Comment on "SARS-CoV-2 vaccinations may not only be complicated by GBS but also by distal small fiber neuropathy by J. Finsterer

ARTICLE INFO

Keywords
Sensory Guillain Barre' syndrome
COVID-19
Small fiber neuropathy
Demyelination
Vector-based SARS-CoV-2 vaccine

Min et al. (2021) described two patients, who developed sensory Guillain-Barre syndrome (SGBS) shortly after receiving the first dose of the vector-based SARS-CoV-2 vaccine (ChAdOx1) and provided an elegant summary of published post-ChAdOx1 vaccine-GBS cases, highlighting their features. Other authors (Finsterer, 2021) rised concerns and themes of discussion, which might address the following key questions.

First: how should we define clinically and electrophysiologically a SGBS? As pointed out by Oh et al. (2001) and by Uncini and Yuki (2012), it is clear that SGS covers a clinical spectrum of overlapping phenotypes, that include acute sensory demyelinating neuropathy, involving mainly nerves and dorsal root ganglion, acute sensory large-fiber axonopathy -ganglionopathy, presenting clinically with ataxia and "insignificant" weakness, acute sensory small-fiber neuropathy-ganglionopathy and acute autonomic and sensory ganglionopathy, the latest condition exhibiting profound autonomic failure and various degrees of sensory impairment,without motor dysfunction. The main clinical differential diagnosis of SGBS is a paraneoplastic condition and it should help clinicians in planing therapies and immunotherapies (Oh et al., 2001; Uncini and Yuki, 2012). Indeed, diagnosis might be challenging.

Min et al. (2021) confirmed that SGBS can be categorized into the above mentioned subtypes, according to the involved fiber types and locations: patient 1 would represent an acute sensory demyelinating polyneuropathy and patient 2 an acute small fiber neuropathy-ganglionopathy. In our view, it is clinically ininfluent in respect of diagnosis to discuss about the site of skin biopsy in the cases of Min et al. (2021), who showed decreased intraepidermal nerve fiber density. Indeed,whereas a small fiber neuropathy (SFN) is considered a structural abnormality of fibers with degeneration of the distal terminals of nerve endings, a multifocal and non length-dependent pattern of abnormalities can be observed (Raasing et al., 2021).

As a second point, Oh et al. (2001) over 20 years ago pointed out that nerve conduction studies performed in their cases of SGBS within 4 weeks from symptom onset showed abnormalities in motor nerves. Indeed, there were electrophysiologic signs of demyelination in at least two nerves in all cases and evidence of demyelination was observed in motor nerve conduction in seven and in the sensory nerve conduction in two patients (Oh et al., 2001). Given that, there is general agreement that weakness in classic GBS results from conduction block or axonal degeneration of motor axons and not from conduction slowing or increased temporal dispersion (Uncini and Yuki, 2012). The latter feature might explain the absence of weakness in the patients,who had only increased distal motor latency or slowed conduction.

Third: whether the diagnosis of SGBS depends on the finding of altered cerebro spinal fluid (CSF) content. Indeed, CSF protein level is helful in deciding diagnosis and treatment in cases of clinical uncertainty, especially to exclude other causes associated with CSF pleocytosis, such as infectious polyradiculitis. Given that, in all 455 patients reported by Fokke et al. (2014). the cyto-albuminologic dissociation' in CSF, commonly regarded as one of the hallmarks of GBS,was found in less than half of the patients when tested within the first days after onset of weakness. Therefore, normal CSF protein levels do not rule out a diagnosis of GBS.

As a fourth consideration, in our view, the most intriguing issue in Min et al. (2021) was the short time-linked to the vaccination, ranging from 3 to 4 days. A previously proposed pathophysiologic mechanism in Waheed et al. (2021) patient was an immune-mediated hypersensitivity to the solvent/adjuvant (polyethylene glycol) . Indeed, the relationship between three major links of pathogenesis of SGBS, i.e. autoimmunity trigger, neuroinflammation and acute sensory fiber neuropathies, opens an interesting scenario closely linked with the signaling pathways of neuropathic pain. Generally, major evidences of causality for neuromuscular events following immunization against SARSCoV-2 has been the time-linked to the vaccination, the absence of other possible causes, the fact that vaccination stimulates the production of T-cells and antibodies, which could cross-react with the structures of the nerve. Indeed, for DNA vaccines, adenovirus vectors or aberrant splice variants may be really considered sources of autoimmunity possibly triggering an excessive inflammatory response.

As last comment, SGBS might bear subtypes of acute neuropathy with profound autonomic failure with various degrees of sensory impairment (Oh et al., 2001; Uncini and Yuki, 2012) and SFN frequently

Abbreviations: SGBS, Sensory Guillain Barre'; SFN, Small fiber neuropathy.

https://doi.org/10.1016/j.jneuroim.2022.577901
Received 25 May 2022; Accepted 29 May 2022
Available online 1 June 2022

involves autonomic fibers. Given that, in the case of biopsy–proven post-COVID 19 SFN described by Waheed et al. (2021), the involvement of autonomic functions was not mentioned.

By concluding, after reading the recent reports of Min et al. (2021), Maramattom et al. (2021), Waheed et al. (2021), in our view the possible causal relationship between COVID-19 vaccination and GBS remains under discussion. We think that clinicians should be aware of such rarely occurring neurological conditions, while we fully support the safety of SARS-CoV-2 vaccination in the general population, because the induced immune response represents a potent, unique protection against the infection (Forni and Mantovani, 2021).

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contribution

Giuliana Galassi was responsible for design, literature search, draft, writing, discussion and conclusions.

Acknowledgements

The author has no aknowledgements.

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