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LETTER TO THE EDITOR

Comment on "Neuromuscular complications after COVID-19 vaccination: a series of eight patients" by Leemans et al.

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Leemans et al. [1] published an interesting report of eight patients, who developed a new-onset neuromuscular disorder in the first 6 weeks after receiving a COVID-19 vaccine, either first or second dose. Interestingly, the clinical phenotypes were different, including classical Guillain–Barré syndrome (GBS) in 3, facial diplegia (FD) variant of GBS in 1, acute onset of chronic inflammatory demyelinating polyneuropathy in 2, brachial plexopathy and subacute onset of a sensorimotor axonal polyneuropathy in 1, respectively. In one patient, (case 8), the main clinical differential diagnosis could be a paraneoplastic condition, which the authors [1] correctly considered.

Germano et al. [2] recently described an Italian cohort of patients, admitted from February 1st to October 30th 2021 to six major hospitals of the Liguria Region. Clinical, demographic, and disability score data were retrospectively analyzed and compared with those of 17 incident cases of GBS, unrelated to vaccination, ascertained during the same time frame [2]. Ten out of 13 patients developed GBS after the first dose, 3 after the second dose, showing in 11 features of acute inflammatory demyelinating polyradiculoneuropathy (AIDP); a bilateral seventh cranial nerve involvement followed ChAdOx1 vaccination (AstraZeneca, AZV) in 2 cases [2].

Kaulen et al. [3] among 232,603 estimated vaccinated inhabitants of their University Hospital area, found 21 cases of autoimmune disorders, following vaccinations, either new onset (17) or disease flare (4);among those, 2 had GBS. The results of these papers are impressive and we wish to shortly discuss some of the relevant issues raised by them.

First: as recently stated by Kim et al. [4], it is impossible currently to confirm the causality between COVID-19 vaccine and GBS: indeed, most of the relevant reports are single cases or case series, therefore large scale, systematic, prospective and post-vaccination surveillance studies are warranted. Kim et al. [4] concluded that AZV and mRNA-based COVID-19 vaccines had a "plausible" relationship with GBS, but the risk of developing GBS was found not greater to the risk of GBS associated with other seasonal influenza vaccines [4].

Keh et al. [5] confirmed that in 2021 the first-dose of AZV vaccination was associated with an excess GBS risk, similar to the estimates for the 1976 'swine flu' vaccine, but within the same order of magnitude as the reported excess cases for the influenza, but far below the cases of GBS after *Campylobacter jejuni* gastroenteritis or Zika-virus. A monthly increase in GBS cases in March and April 2021 during the SARS-CoV-2 vaccination campaign was reported in UK, but total numbers fell back into the normal range thereafter, thus such "spike" in GBS cases was considered the only hint to support a causative link with GBS [5]. Indeed, the social distancing and other lockdown measures in all Europe slowly relaxed in the first half of 2021: this could lead to some GBS increase due to circulation of other causative infective pathogens. The numbers of GBS continue to fall to lower than usual numbers of GBS in the second half of 2021, possibly due to also the nationally–mandated socially distancing measures. Finsterer et al. [6] in their narrative review concluded that the prevalence of post-COVID GBS (PCGBS) has decreased, since the introduction of SARS-CoV-2 vaccines, falling down from 192 cases observed in the second half to 2020 to 75 in the first half of 2021. However, the comparison of annualized rates of rare diseases, extrapolated from short periods of time (as some authors previously did) might be susceptible to annual cyclicity [5]. Kaulen et al. [3] pointed out that their study

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was not powered to investigate the incidence of neurological autoimmune disorders, following SARS-CoV-2 vaccination due to single center design and rather small main geographically catchment region. Indeed, any small study might be confounded by a selection bias [7].

Finally, the most relevant issue for clinicians, several authors [8–11] strengthened the occurrence of cases of facial paresis after AZV vaccination. Leemans et al. [1] reported a single patient with FD variant in a context of a subacute demyelinating polyneuropathy with anti-sulfatide IgM antibodies and high protein in spinal fluid. Pegat et al. [8] using data from the French pharmacovigilance database found that among 69 patients with GBS following vaccination, 33.3% experienced facial paresis, including 44.7% who received adenovirus-vectored vaccine, whereas only 9% received an mRNA vaccine, indicating that GBS occurring after administration of adenovirus-vectored vaccines presented with a "specific" phenotype. Other researchers [2] documented the predominance of sensory disturbances, which were overt in 84% of their GBS related to vaccination; Min et al. [12] reviewed the issue of sensory GBS, occurring after ChAdOx1 vaccine. Taken together these results, we have to recall the work of Capasso et al. [13], who demonstrated, with serial recordings, the involvement of sensory fibers in 69% of acute motor axonal neuropathy patients, confirming the presence of sensory involvement in motor subtypes of GBS. By concluding, a sure causal link between COVID-19 vaccination and distinct GBS phenotypes remains plausible, but yet unproven [1].On the contrary, the contribution of antibody-mediated platelet activation has been confirmed in the pathogenesis of vaccine-induce thrombosis and thrombocytopenia (VITT) with distinguishable clinical features and a clear-cut biomarker in the anti-PF4 antibodies following ChAdOx1 vaccination. In respect of possible mechanisms, the vaccines containing SARS-CoV-2 antigens might enhance autoimmunity by several pathways, including polyclonal or bystander activation, epitope spreading or molecular mimicry [14]. Moreover, the inflammatory stimulus, may enhance protective and even hyper-protective autoimmunity in predisposed, previously asymptomatic patients, by driving a pre-existing autoimmune pathways or in patients with new onset autoimmune diseases [14].

Declarations

Conflict of interest The authors do not have conflict to report that are relevant to the content of this article. The authors did not receive support from any organizations for the submitted work.

Consent for publication There are no patient informed consent need.

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