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LETTER TO THE EDITOR

Guillain–Barré syndrome following Covid-19 immunization: a report of two cases

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To the Editor,

We hereby report two cases of GBS occurred within a population of 76,640 people who received either the first or second dose of one of the approved Covid-19 vaccines as of April 15th, 2021, in Udine province, Italy (current resident population 516,418 inhabitants). The first patient was a 90-year-old man, previously in good physical and mental conditions, who developed acute progressive gait imbalance three days after receiving the second dose of BNT162b2 vaccine. Electroneuromyography (ENMG) performed at three weeks from the onset of symptoms, showed signs of acute four limbs axonal sensory-motor polyneuropathy, while cerebrospinal fluid (CSF) analysis was normal. Acute motor sensory axonal neuropathy (AMSAN) was diagnosed according to the current electrophysiological criteria [1], the patient was admitted for clinical monitoring and intravenous immunoglobulins (ivIG) were administered. Serum autoimmunity revealed high titer anti-GQ1b and anti-titin antibodies. Considering anti-titin positivity, ENMG was repeated, excluding neuromuscular junction involvement and completion with thoracic computer tomography scan excluded thymoma. During his hospital stay, he remained clinically stable and was discharged home able to stand and walk with minor assistance. The second patient was a 51-year-old woman who developed distal limb paresthesias with new-onset sphincter disturbances and lumbar pain, ten days after receiving the first dose of ChAdOx1 nCoV-19 vaccine. ENMG examination showed F-wave conduction delay while CSF presented marked albumin-cytological dissociation. Acute inflammatory demyelinating polyneuropathy (AIDP) was diagnosed, the patient was admitted for clinical monitoring and ivIG were administered. During her hospital stay she developed facial diplegia, bilateral foot dorsiflexion weakness (MRC 4/5) and lower limbs areflexia. A whole spine magnetic resonance imaging was unremarkable. Serum autoimmunity, including search for anti-ganglioside antibodies, was negative. Distal limb neuropathic pain required introduction of analgesic therapy. The patient was discharged home able to walk unaided. Patients' details are available in Table 1.

GBS is described as a complication following different kinds of vaccinations, and the Brighton Collaboration GBS Working Group has developed guidelines which are intended to help in reporting cases of GBS as adverse events following immunization and to harmonize vaccine safety reporting: in fact, GBS can be temporally associated with, but is not necessarily the result of the vaccine [2]. As regards Covid-19 immunization, a recent report from the Janssen Ad26.COV2.S vaccine trial has highlighted that GBS may occur in the context of the vaccination as well as in the placebo arm with the same incidence, supporting a casual role [3]. Concerning BNT162b2 and ChAdOx1 nCoV-19 vaccines instead, one case of GBS following the administration of each vaccine has been reported so far [4, 5]. Moreover, amid the global vaccination program, it is expected that many GBS cases would be identified by chance in the 10 weeks period following a double dose vaccination and that this association cannot be considered a causal link [6].

GBS has also been extensively reported after Covid-19 infection: AIDP is the most common form, but acute motor

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Table 1 Clinical characteristics of patients with GBS

	Patient #1	Patient #2
Sex	Male	Female
Age	90 years old	51 years old
Medical history	Arterial hypertension, chronic kidney disease, psoriasis, previous gastric resection, and prostatectomy	Unremarkable
Preceding triggering events*	None reported	None reported
Interval of symptoms onset after vaccine first dose (days)	31 days	10 days
Vaccine mechanism	mRNA vaccine	adenoviral vector vaccine
Clinical neurological signs and symptoms	Sensory ataxia	Distal paresthesias; facial diplegia; bilateral foot dorsiflexion weakness; lower limb areflexia; stypsis and difficulty in initiating micturition; neuropathic pain
Serum autoimmunity	Anti-GQ1b Anti-titin	None
Cerebrospinal fluid	Protein: 397 mg/dL Cells: 0.8/µL Glucose: 53 mg/dL Type I Oligoclonal Bands	Protein: 2272 mg/dL Cells: 14.6/µL Glucose: 60 mg/dL Type I Oligoclonal Bands
Nerve conduction studies (NCS)	Motor studies** Right tibialis: *A* = 2.2 mV (n.v. > 4), normal DL and CV = 40 ms (n.v > 44) Left peroneal: *A* = 1.5 mV (n.v > 2); DL = 6.7 ms (n.v. < 6.5), CV = 42.2 ms (n.v. > 44) Sensory antidromic studies Left radialis: *A* = 4.6 mV (n.v. > 15) CV 41 ms (n.v. 50), normal DL Right radialis: *A* = 3.2 mV (n.v. > 15), CV 46.9 (n.v. 50), normal DL Left median (digit 3): *A* = 4.9 mV (n.v. > 20), CV 41 ms (n.v. 50), normal DL Right median (digit 3): *A* = 4.6 mV (n.v. > 20), CV 41.8 ms (n.v. 50), normal DL Left ulnaris (digit 5): *A* = 5.5 mV (n.v. > 17), CV 45.5 ms (n.v. 50), normal DL Right ulnaris (digit 5): *A* = 2.8 mV (n.v. > 17), CV 47.3 ms (n.v. 50), normal DL Left suralis: *A* = 0.78 mV (n.v. > 6), CV 42.3 ms (n.v. 40), normal DL Right suralis: *A* = 0.82. mV (n.v. > 6), CV 41.8 ms (n.v. 40), normal DL	Motor and Sensory studies Upper and lower limbs routine NCS: within normal limits Late responses F-wave left tibialis: 61.2 ms (n.v. < 56) F-wave right tibialis: 59.8 ms (n.v. < 56) H-reflex: bilaterally absent Blink reflex Absent R1 bilaterally, delayed R2 bilaterally***
ENMG classification	AMSAN	AIDP
mEGOS (at admission) range 0–9	2	1
mEGOS (at 1 week) range 0–12	2	1
EGRIS/ICU admission	1/No	1/No
Therapy	ivIG 0.4 g/kg/die for 5 days	ivIG 0.4 g/kg/die for 5 days
Hughes disability score (at 3 months) range 0–6	1	1

A amplitude, *mV* millivolt, *DL* distal latency, *CV* conduction velocity, *msec* milliseconds, *n.v.* normal values, *AMSAN* acute motor sensory axonal neuropathy, *AIDP* acute inflammatory demyelinating polyneuropathy, *mEGOS* modified erasmus GBS outcome scale, *EGRIS* erasmus GBS respiratory insufficiency score, *ICU* intensive care unit, *ivIG* intravenous immunoglobulins

*Excluding Covid-19 vaccination

**motor studies and their normal reference values refer to distal compound muscle action potentials

***The exam was performed on day 15 from symptoms' onset

axonal neuropathy and AMSAN variants have also been described; the suspected pathogenetic mechanism is para-infectious, anti-ganglioside antibodies (including anti-GM1, GM2, GD1a and GQ1b) have been detected and clinical features include a more severe weakness and more frequent need of intensive care unit admission when compared to GBS not related to Covid-19 [7].

Although a causal relationship cannot be ascertained, in the cases here described, the time interval occurring between vaccination and symptoms onset and the absence of other preceding triggering events suggests at least a possible link with the immunization, being the time window in line with the development of an immune-mediated response [8]. We acknowledge that, since serology for common infectious precipitators of GBS was not performed, we cannot exclude a preceding asymptomatic infection. However, a hypothetical infective antecedent does not exclude a concomitant role of vaccination.

There is currently no evidence of an exceeding incidence rate of GBS after Covid-19 vaccine. Nevertheless, while waiting for population studies, any relevant information should be reported to increase the current knowledge regarding this complication, highlighting its diverse clinical and neurophysiological phenotype in the context of Covid immunization programs. In fact, it cannot be excluded that Covid-19 vaccination may represent a trigger for immune-mediated polyradiculoneuropathy, similarly to other vaccines.

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Availability of data and material Anonymized data are available upon reasonable request.

Declarations

Conflict of interest The authors report no disclosure relevant to the manuscript.

Ethical standards All procedures of the study were performed in accordance with the Helsinki Declaration in its most recently amended version.

Informed consent All the patients expressed their informed consent to the anonymous use of their clinical data.

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