Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Toscano G, Palmerini F, Ravaglia S, et al. Guillain–Barré syndrome associated with SARS-CoV-2. N Engl J Med. DOI: 10.1056/NEJMc2009191

Supplementary Appendix

Supplementary Case Histories

Case 1. A 77 year-old woman arrived at the emergency room because of paresthesia in the lower limbs and hands, abruptly started during the night. The neurological examination 36 hours after the clinical onset showed a flaccid areflexic tetraplegia with no bulbar signs; she continued to complain of distal paresthesia. Seven days before the neurological onset, she had a fever (T max 39°C, 102.2°F), responsive to acetaminophen, that lasted for two days, accompanied by cough and decreased sense of taste. At the admission to the hospital, a CT scan of the thorax revealed interstitial bilateral pneumonia. RT-PCR from a nasopharyngeal swab revealed the presence of SARS-Cov-2. An electromyography (EMG) showed an axonal variant of GBS, with sparing of the sural nerve. During IVIg treatment she initially developed bulbar symptoms (dysphagia, tongue weakness), and respiratory failure requiring non-invasive mechanical ventilation, but a few days after the end of the cycle she showed minimal improvement in proximal upper limb weakness and improved respiratory function. Plasmapheresis could not be started for persistent nasopharyngeal swab RT PCR positivity two weeks after the neurological onset, so that she received a second cycle of IVIg, which was ineffective, 7 days after the end of the first cycle.

Case 2. A 23 year-old male arrived at the emergency room complaining of upper and lower facial weakness, which became bilateral and complete within 2 days, accompanied by mastoid pain, loss of taste, and lower limb paresthesia. In the previous 10 days he had a fever and sore throat for three days, treated with amoxicillin for five days. Neurological examination showed complete facial palsy (incomplete eye closure, abolished blinking, inability to whistle, protrude the lips or expose the teeth), generalized areflexia, sensory ataxia. A brain MRI revealed focal contrast enhancement at the internal acoustic meatus. The EMG, on 12^{th} day after admission, showed axonal sensory-motor damage involving the lower limbs, with sural nerve sparing, and decrease in facial nerve cMAP amplitude. The patient received IVIg, with mild improvement of the facial weakness (recovered ability to protrude lips and close eyes) and disappearance of limb paresthesia. Despite normal thorax imaging, his pharyngeal swab was positive for SARS-Cov-2.

Case 3. A 55 year-old male presented fever and cough, treated with azithromycin. Ten days after the fever onset, he complained neck pain, paresthesia in the four limbs and lower limb weakness. He was admitted to the emergency room. A CT scan of the thorax revealed multiple bilateral, ground-glass opacities compatible with interstitial pneumonia; his nasopharyngeal swab was positive for SARS-

Cov-2. On the 12th day after the fever onset he developed flaccid areflexic tetraparesis. EMG revealed severe axonal neuropathy. He was administered IVIg, but during treatment he developed facial diplegia and respiratory failure due to neuromuscular impairment; he was admitted to the Intensive Care Unit and was administered a second IVIg cycle. Now, one month after the neurological onset, his conditions remain critical.

Case 4. A 76 year-old male, complaining of dry cough and loss of smell for five days, was admitted to the neurosurgery ward due to lumbar pain and lower limb weakness which were started the day before. On the 4th day after admission, muscle weakness rapidly evolved to a flaccid areflexic tetraparesis. CSF findings were normal. An IVIg standard protocol was started. He developed fever after the onset of neurological symptoms, and before the infusion cycle; the chest imaging was negative, but his nasopharyngeal swab resulted positive for SARS-Cov-2. IVIg treatment resulted in motor improvement, more evident in upper limbs, but he was still unable to stand and was transferred in the rehabilitation area.

Case 5. A 61 year-old male complained of asthenia, dry cough, loss of taste and smell, for one week, without fever. He worked in a petrol station, and thus he noticed anosmia as a particularly unusual symptom. One week after, he complained difficulties in climbing stairs and lower limb paresthesia; these symptoms rapidly worsened so that on the following day, on awakening, he was unable to stand. At the emergency room, neurological examination showed generalized areflexia and paraparesis. Thorax X-ray and CT showed interstitial pneumonia, without parenchymal opacities nor alveolar damage; a nasopharyngeal swab for Covid-19 was negative. CSF analysis was normal. EMG examination, performed four days after the neurological onset, showed conduction blocks and demyelination. He was started IVIg, but neurological conditions continued to worsen. On the second day of the immunoglobulin cycle he developed flaccid tetraplegia with facial weakness and dysphagia. A second nasopharyngeal swab was still negative. Screening for *Campylobacter jejuni*, EBV, CMV, HSV, VZV, influenza, HIV, was negative. On the third day of the IVIg course he developed respiratory failure with neuromuscular features (hypercapnia, paradox respiration, acidosis) and was referred to the ICU, were he received mechanical ventilation through tracheostomy. RT-PCR search for Covid-19 after bronchoalveolar lavage was still negative. The patient developed *acinetobacter* pneumonia, so that plasmapheresis was delayed and is now in course. He is still tetraplegic and ventilation dependent four weeks after the neurological onset. Once the serological tests became available, we analysed his serum stocked at the onset of the syndrome, and found positive SARS-CoV-2 IgG.

Supplementary Figure S1

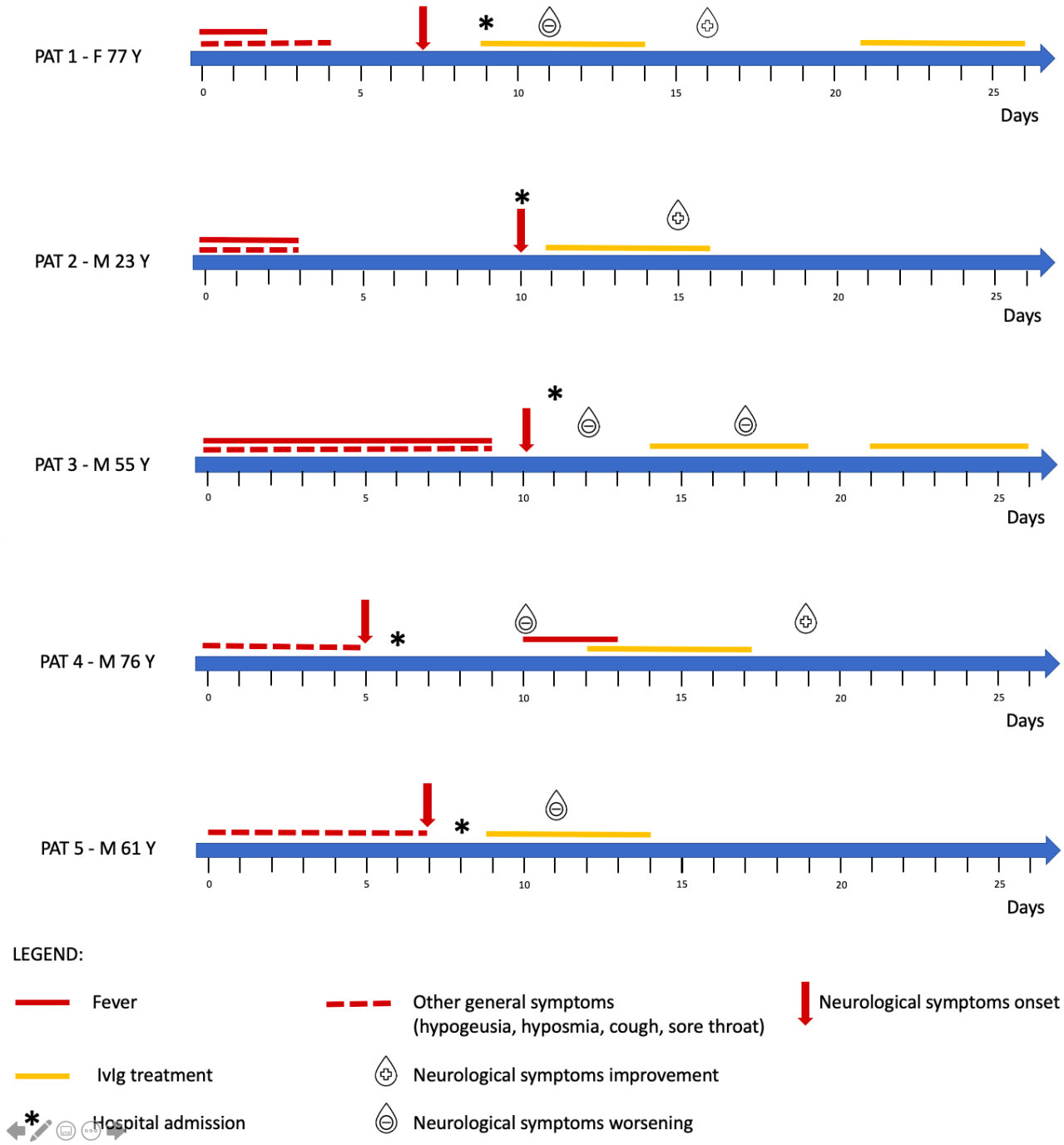

Figure S1. Timelines showing general and neurological symptoms onset, timing of hospital admission, timing of IVIg therapy and of neurological improvement or worsening.

Patient 4 and 5 had complained of dry cough and hyposmia for five and seven days before the neurological onset; patient 4 developed fever shortly after the neurological onset.

PATIENT	GBS subtype *	Timing between neurological onset and EMG examination **	Tibial Motor: Latency (ms) Proximal/Distal CMAP Amplitude (mV) Conduction velocity (m/s)	Ulnar Motor: Latency (ms) Proximal/Distal Amplitude (mV) Conduction velocity (m/s)	Sural sensory amplitude (μV) / ulnar sensory amplitude (μV)	F wave ulnar / tibial	Fibrillation potentials on EMG
1	Sensory-Motor Axonal	3	3,7 ms 2,5/2 mV 43,8 m/s	2,35 ms 4,5/6,6 63 m/s	10,9/0,28	Absent/Absent	+ ***
2	Sensory- Motor Axonal	12	6,4 ms 1,8/2,6 mV 38 m/s	5,2 msec 9,8/12,8 mV 52 m/s	23,6/2,8	32/Absent	+
3	Acute Motor Axonal	11	3,85 msec 2,2/2,3 47,6 m/s	2,4 ms 2,6/2,3 57,9 m/s	7,1/13,8	Absent/Absent	+
4	Demyelinating	2	16,05 msec 0,4/0,4 mV 30,4 m/s	3,2 msec 3,5/6,1 mV 44,4 m/s	4,5/11,3	33,7/68	-
5	Demyelinating	4	15,5 msec 0,7/1,2 mV 25,4 m/s	2,4 msec 3,6/3,6 mV 40,6 m/s	3,1/4,6	31,3/Absent	+

Supplementary Table S1 – Neurophysiological features of the patients - The neurophysiological protocol included: bilateral motor peroneal, tibial, ulnar and median nerves; sensory sural and ulnar nerves; bilateral F wave latency of tibial and ulnar nerves.

The neurophysiological examinations were performed 3 to 12 days from the neurological onset. Three of five patients were classified as axonal variants, while patient 4 and 5 satisfied criteria for demyelination (prolonged motor latencies, severe conduction velocity slowing, and conduction blocks), however with severe, likely secondary, axonal damage. Fibrillation potentials were present in all three patients with axonal variant, and in one of the two patients with a demyelinating process.

* Criteria for defining demyelinating vs axonal GBS were used as described by Hadden et al 1998 [1]

** Days elapsed between neurological onset and EMG examination

*** in this patient fibrillation potentials were absent at onset, and appeared on a follow-up EMG performed 12 days after onset

PATIENT	Sex	Age (y)	Timing between infection and neurological onset (days)	Blood Chemistry on Admission	SARS-CoV-2 IgG *	Thorax CT
1	F	77	7	Lymphocytopenia, Raised CRP, LDH, ketonuria	32,5 AU/ml	Interstitial pneumonia
2	M	23	10	Lymphocytopenia, Raised ferritine, CRP, LDH, AST	Not performed	Normal
3	M	55	10	Lymphocytopenia, Raised CRP, LDH, AST, GGT Ketonuria	Not performed	Interstitial pneumonia
4	M	76	5	Lymphocytopenia Raised CRP, Ketonuria	64,59 AU/ml	Normal
5	M	61	7	Lymphocytopenia Raised CRP, LDH, AST	50,92 AU/ml	Interstitial pneumonia, then *acinetobacter* pneumonia

Supplementary Table S2. Demographic features of the patients and details of non-neurological features

* SARS-CoV-2 IgG (chemiluminescence immunoassay, Maglumi)
The serum samples for SARS-CoV-2 IgG testing were taken on admission, at the onset of GBS syndrome

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