INRODUCTION

The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is a complication of Guillain-Barré syndrome (GBS), associated with a worse prognosis. New-onset euvoletic hyponatremia represents a risk factor for mortality in SARS-CoV-2 disease. GBS complicated by SIADH after recovering from COVID-19 complicated by asymptomatic SIADH was reported.

Guillain-Barré syndrome (GBS) is the most frequent inflammatory polyradiculoneuropathy frequently associated with previous viral infections or vaccines. The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is a well-recognized complication of GBS; it was generally associated with severe GBS and has been considered a negative prognostic factor. The predominant clinical presentation of SARS-CoV-2 disease is the respiratory form, but a multisystemic involvement has been now well described.

COVID-19-induced euvoletic hyponatremia occurs in 20% of hospitalized COVID-19 patients and is associated to higher mortality and higher risk of sepsis. Little is known about long-term complications of COVID-19. We report a case of GBS and symptomatic SIADH after six months from COVID-19 interstitial pneumonia complicated by hyponatremia.

2 | COVID COURSE AND CLINICAL COURSE

In April 2020, a 47-year-old Caucasian man tested positive for nasopharyngeal SARS-CoV-2 swab and was admitted to the Pneumology Unit. Diffuse interstitial-like bilateral pneumonia was found and treatment with azithromycin, hydroxychloroquine sulfate, and enoxaparin were started. Due to worsening of respiratory performance, he required
mechanical artificial ventilation. Considering the high interleukin-6 (IL-6) serum values, tocilizumab 8 mg/kg was administered. As the respiratory function improved, the patient was moved to a step-down unit. His hospitalization was prolonged due to severe euvolemic hyponatremia (115 mg/ml), corrected with hypertonic saline IV over the course of three weeks. In November 2020, the patient complained a ten-day-lasting mild-progressive lower limbs weakness, ataxia, urinary hesitation, and constipation. At the admission, the neurological examination showed sensory ataxia, reduced deep tendon reflexes at lower limbs and only mild strength reduction (MRC 4+ at feet dorsiflexion). Neither history of flu-like episode nor vaccine was reported. Electrophysiological studies revealed acute sensorimotor demyelinating polyneuropathy (Figure 1A) and mild albumin-cytologic dissociation (cerebrospinal-fluid proteins 0.58 g/L) was found at cerebrospinal-fluid examination, confirming the diagnosis of GBS. Cerebrospinal-fluid SARS-CoV-2 polymerase chain reaction and serum anti-ganglioside antibodies were negative. Human immunoglobulins intravenous (0.4 g/kg/day for 5 days) were promptly started, with steady-progressive improvement of gait and lower limbs weakness. Furthermore, at admission a severe hyponatremia (102 mmol/L) with low plasma and high urinary osmolality was detected, prompting a SIADH diagnosis. Free thyroxine, thyroid stimulating hormone measurement and 9 am cortisol test were normal; IL-6 serum levels were slightly elevated (14.5 pg/ml). He was first treated with fluid restriction and hypertonic saline IV, without benefits. Due to the persistent hyponatremia, the patient experienced brief repetitive episodes characterized by impaired awareness with behavioral arrest, followed by oro-facial and sexual automatisms, treated with benzodiazepines. Considering the failure of first-line hyponatremia therapy, tolvaptan 15 mg/daily was started. No further symptomatic seizures were described following hyponatremia correction. After 2 weeks from hospitalization, the neurographic findings improved (Figure 1B), as well as neurological examination. The sodium values remained normal after three months of tolvaptan therapy.

### DISCUSSION

Herein, we report a case of Guillain-Barré syndrome associated with SIADH, after recent recovery from COVID-19 interstitial pneumonia, complicated by hyponatremia. A Guillain-Barré syndrome related to SARS-CoV-2 infection was defined when the onset of neurological symptoms is within 6 weeks of acute infection or SARS-CoV-2 RNA is detected in any sample and there is no evidence of other commonly associated causes of GBS. Accordingly, we excluded an association between COVID-19 and GBS in our patient.

SIADH is best defined by euvolemic hyponatremia, low plasma, and high urinary osmolality and lack of evidence of other hyponatremic diseases. Central nervous system disorders, pneumonia, and drugs may cause

![Electromyographic motor and sensory traces and F-waves recorded before (A) and after (B) human immunoglobulins intravenous therapy](image)
SYNTHESIS. SIADH. New-onset hyponatremia is a reported complication of COVID-19 disease course and recently guidelines for its treatment have been proposed. On the other hand, a strong association between GBS and SIADH has been widely described: older age, need for ventilatory support, a longer duration of hospitalization and high mortality rates were more frequently observed in patients with GBS complicated by SIADH. The median time to onset of hyponatremia is nine days after GBS diagnosis. The patient developed a severe but asymptomatic three-week-lasting hyponatremia during COVID-19 course and, again, experienced severe and symptomatic SIADH from the beginning of GBS course, requiring a 3-month second-line treatment regimen. Nevertheless, the symptomatic SIADH was not associated with a poor outcome of GBS.

The pathogenesis of SIADH in GBS has not been completely understood: abnormalities of peripheral autonomic afferent fibers arising from vascular stretch receptors or the increased renal tubular sensitivity to vasopressin have been proposed as possible mechanisms. On the other hand, the SIADH associated with COVID-19 could be related to cytokine release syndrome (CRS), including IL-6 whose high levels could induce a non-osmotic release of vasopressin. In a retrospective Italian study, 15 patients with new onset of COVID-19 induced hyponatremia and abnormal IL-6 serum levels were treated with tocilizumab (8 mg/kg) with a significant increase of sodium concentrations at 48 h. To our best knowledge, there is still no evidence about the hyponatremia duration or its recurrence after COVID-19 disease. In our case, the patient had developed a relapse of euvolemic hyponatremia 6 months after the onset of pneumonia; during the second hospitalization it was stricter, symptomatic, and resistant to first-line treatment although it did not affect the course of polyneuropathy. In the present case, we could speculate that pathogenesis of SIADH is due to a double mechanism: on one hand an already altered sensitivity of the renal tubule and on the other a rekindling of the cytochemical inflammatory chain. We could hypothesize that in a system already preconditioned by previous damage, as results of the CRS complicating the COVID-19 disease, a small trigger may be sufficient to develop a new autonomic dysfunction (for example SIADH-like) even after a very long time. Longer follow-up time and more cases are needed to fully understand long-term damage due to COVID-19 disease.

4 | ETHICAL STANDARD

Informed consent was obtained from the patient included in the study.

CONFLICT OF INTEREST
Nothing to report.

AUTHOR CONTRIBUTIONS
CS, TG, AI, and MT conceptualized the study, had full access to all data and take responsibility for the integrity of the data. FL interpreted neurophysiological data. AI, TG and CS contributed to the writing of the manuscript. All the authors contributed to the data interpretation and reviewed and approved the final version.

DATA AVAILABILITY STATEMENT
Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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