Guillain-Barré Syndrome Related and Unrelated to COVID-19: Clinical Follow-up in the

COVID-19 Era

Guillain-Barré Syndrome: Follow-up in COVID Era

COVID-19

Original Research

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[H1]Abstract

Objective. COVID-19 has been associated with neurological complications such as Guillain-Barre syndrome (GBS). Several cases have been reported, but without functional outcome data after intensive rehabilitation and medium-term follow-up. **Methods.** In this observational study, patients were admitted in 2019 and 2020 to inpatient rehabilitation for GBS and were examined using the Barthel index, GBS-Disability Scale, and Medical Research Scale-sum score at admission, discharge, and at least 6 months after onset of symptoms. All the participants received personalized, goal-oriented inpatient rehabilitative treatment for the recovery of self-sufficiency in everyday life.

Results. Eleven people with GBS—3 cases related to COVID-19—were admitted in 2019 and 2020 to inpatient rehabilitation. Eight patients with GBS not related to COVID-19 experienced a high complication rate during inpatient rehabilitation, with 2 deaths due to sepsis. In this cohort, a higher prevalence than expected of acute motor axonal neuropathy was also detected. The COVID-19–related GBS (C-GBS) group did not have any complications. After a mean of 10.11 months (SD = 4.46 mo), 55.55% of patients regained autonomous walking.

Conclusion. COVID-19–related GBS appeared to have a better clinical outcome than GBS that was not COVID-19 related (NC-GBS). A higher than usual prevalence of acute motor axonal neuropathy form was encountered. More follow-up studies are needed to understand whether the recovery of GBS related to COVID-19 might be different from that of GBS unrelated to COVID-19.

Impact. No data are currently available on the follow-up of Guillain-Barré syndrome in the COVID-19 era and on the functional outcome of those patients. This study provides important information indicating that GBS related to COVID-19 might have a better clinical outcome than GBS unrelated to COVID-19.

KEYWORDS: COVID-19; Guillain-Barré; Inpatient Rehabilitation; SARS-CoV-2.

Continnation

[H1]Introduction

The pandemic spreading of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) overwhelmed health care systems worldwide. Considered a respiratory disease, coronavirus disease (COVID-19) has also provoked neurological manifestations,¹ such as Guillain-Barrè syndrome (GBS).^{2–4}

GBS is an acute autoimmune neurological disease involving the peripheral nervous system, (global yearly prevalence = 0.8–1.9 cases per 100,000 people).⁵ The principal clinical feature is an acute or subacute onset of progressive weakness in the 4 limbs, potentially involving the respiratory muscles and needing mechanical ventilation. GBS is often preceded by a respiratory or gastrointestinal infection, usually 2 or 3 weeks before symptom onset.⁵ The electrophysiological pattern formerly defines a demyelinating and an axonal variant, that is, an acute inflammatory demyelinating polyradiculopathy (AIDP) and an acute motor axonal neuropathy (AMAN), although mixed forms can be detected.⁵

Some authors theorized that SARS-CoV-2 might cause GBS with both a para-infectious and a postinfectious mechanism of action,^{6,7} but this has not been confirmed yet. Although several COVID-19–associated GBS (C-GBS) cases have been reported,^{2,3,6,8,9} data are lacking on the follow-up of C-GBS and non-COVID-19–associated GBS (NC-GBS) after neurology department discharge.

In this article, we present the functional outcomes of the patients admitted to an inpatient rehabilitation unit for GBS in 2019 and 2020, and the follow-up performed at least 6 months from symptom onset.

[H1]Methods

All patients admitted for inpatient intensive rehabilitation after GBS in 2019 and 2020 in the Mons. L. Novarese Inpatient Rehabilitation Center (Italy) were retrospectively selected and prospectively recalled at follow-up (T2). After 1 month (T0 - admission to rehabilitation), 3 months (T1 - discharge from rehabilitation) and at least 6 months (follow-up - T2) from symptom onset, they were evaluated by the same clinician (F.G.M.) at T0 and T1, according to the internal protocol, and at T2 by a blinded evaluator (T.V.) using the following tests: (1) the Barthel Index (BI),¹⁰ a 10-item scale that assesses: feeding, bathing, personal grooming, dressing, toilet use, bladder and bowel continence, mobility, and climbing stairs (autonomously, with partial or complete dependence) (score ranges from 0 =complete dependence to 100 = complete autonomy); (2) the GBS-Disability scale (GBS-DS),¹¹ a 7point scale (0-6) describing the disability deriving from GBS, (0 = no disability; 1 = minor)symptoms and capable of running; 2 = able to walk 10 meters or more without assistance but unable to run; 3 = able to walk 10 meters across an open space with help; 4 = bedridden or chairbound; 5 = requiring assisted ventilation for at least part of the day; 6 = dead); and (3) the Medical Research Council sum score (MRC-ss),12 which measures the sum strength of 6 key muscles (ie, deltoid, brachial biceps, wrist extensor, iliopsoas, quadriceps femoris and anterior tibial) per side (score = 0-60).

Age, sex, cranial nerve involvement, sensory deficits, previous infections, electrophysiological and cerebrospinal-fluid characteristics, anti–ganglioside antibodies positivity, acute GBS medical treatment, and complications were registered in an ad-hoc electronic chart at admission.

All patients gave written informed consent for the inclusion of anonymized clinical data in a scientific publication, in agreement with the Declaration of Helsinki.

During inpatient rehabilitation, all patients received a personalized, goal-oriented rehabilitative intensive program for self-sufficiency recovery, based on a multidimensional approach. Rehabilitation started the day after admission (6 days out of 7), lasting 3 hours per day (3 sessions of 1 hour each), with personnel trained in neurorehabilitation (physical therapists, occupational therapists, and speech therapists). Rehabilitation times were reduced if medical complications occurred.

Trunk control recovery was practiced with a core strengthening program, and upper and lower limb function was addressed through passive (to avoid deformities and also using nocturnal position devices) and active limb mobilization. To ameliorate strength, low-resistance and low-repetition exercises were applied, gradually progressing in resistance (without eccentric load). Change of position training was actuated through supine and side-lying exercises for abdominal strength. Standing position training was initially performed with an electric sit-tostand standing frame, the use of which was progressively dismissed. Occupational therapists intervened in activities-of-daily-living training, in particular to help the functional recovery of the upper limb with functional tasks and to provide training in the use of assistive devices. The intensity of the exercise was gradually increased according to tolerance. Gait and cardiovascular resistance training were begun as soon as possible, also utilizing exercise bicycle and treadmill training. Periodic resting was used to avoid fatigue.

[H1]Results

Eleven cases (all, mean age = 71.89 years [SD = 9.13 y]); 3 with C-GBS, mean age = 71.67 years [SD = 11.43 y]; 8 with NC-GBS, (mean age = 72.33 years [SD = 2.52 y]) were included (see Tab. 1 and Tab. 2). The last follow-up was performed after a mean of 10.11 months (SD = 4.46 mo) from symptom onset (NC-GBS = 11.67 months [SD = 4.23 mo]; C-GBS = 7 months [SD = 3.60 mo]). The Figure shows the recovery trajectories of all cases. The most common clinical presentation was tetraparesis, and all patients were acutely treated with intravenous immunoglobin therapy (IVIG), only 2 patients after plasma exchange.

The 3 patients with C-GBS had experienced SARS-CoV-2 infection approximately 3 weeks before symptom onset. In 1 case, serum SARS-CoV-2 IgG were detectable, with negative reverse transcription-polymerase chain reaction (RT-PCR) nasopharyngeal swabs,¹³ whereas 2 patients had a positive RT-PCR swab at emergency department admission, 1 needing mechanical ventilation due to GBS. Patients with C-GBS did not experience complications during the post acute inpatient rehabilitative phase (mean length-of-stay = 55.3 days [SD = 14.47 d]).

At discharge from the neurorehabilitation unit (T1), after undergoing rehabilitation, a BI and MRC-ss increase and a GBS-DS decrease occurred in 2 patients, who regained a satisfying autonomy at home (walking autonomously at home and on uneven surfaces and climbing stairs). In one C-GBS case, only a light BI increase was noticeable, without GBS-DS lowering. At the follow-up (T2), this was the only patient who received outpatient rehabilitation (3 days/week), reacquiring the ability to ambulate with help and not being able to walk on uneven surfaces or stairs. This patient had a concomitant myelitis, possibly negatively affecting the recovery.¹³

All patients with C-GBS regained satisfactory upper limb utilization, feeding themselves independently since rehabilitation discharge.

In the NC-GBS group, 1 patient had a recognizable source of infection (herpes zoster virus). One patient was treated with plasma exchange, and the other with IVIG. Two patients had AIDP, 5 had AMAN, and 1 had an AMAN/AIDP mixed form.

In the NC-GBS group, a high rate of complications occurred during inpatient rehabilitation. Two patients had a chronic obstructive pulmonary disease (COPD) exacerbation, and 1 had lobar pneumonia. Urinary tract infections (UTIs) were detected in 2 patients, and the younger patient had a myocardial infarction with nonobstructive coronary artery disease. In 1 case, readmission to hospital and IVIG treatment was needed due to GBS recurrence, with subsequent readmission to rehabilitation. Unfortunately, 2 of the patients with AMAN died due to sepsis.

At discharge (mean length-of-stay = 61.37 days [SD = 13.391 d), BI scores improved in the 6 survivors. A concomitant decrease of GBS-DS scores was detectable in 4 patients. Three patients regained autonomous walking, including on uneven surfaces and stair climbing. One patient walked with help on uneven surfaces but was not able to climb stairs, and 2 patients did not walk and used a wheelchair.

Six patients were followed-up at T2, with further increase of BI and MRC-ss scores and a concomitant decrease in GBS-DS scores. Walking abilities were preserved in 2 patients, whereas 1 patient lost autonomy and could ambulate only with help because of worsening of COPD symptoms. Patient 4, who could walk with help, continued outpatient rehabilitation at

T1 (3 times weekly), regained autonomous walking, and acquired the ability to climb stairs with 2 crutches. Patients 3 and 8 did not reach walking ability.

All patients with NC-GBS recovered both proximal and distal upper limbs function and could feed themselves independently at T1.

When considering all cases, at T1, 6 out of 11 patients (55.5%) recovered autonomous walking, including on irregular surfaces. Of these 6 patients, 4 (66.7%) ambulated with an assistive device. Climbing the stairs was achieved by 4 out of 9 patients (44.4%). At T2, the percentage of patients ambulating with autonomy did not change, as 1 patient lost this ability, whereas another patient recovered it. Stair climbing was possible in 5 out of 9 patients (55.5%).

[H1]Discussion

GBS can be associated with long-term disability, potentially limited through inpatient intensive and outpatient rehabilitation.¹¹ Due to the necessity to reallocate resources in the acute care setting, 2020 was characterized by several difficulties in delivering rehabilitation services. In Piedmont, several inpatient rehabilitative centers had been converted into COVID-19-units to handle the pandemic. In this context, rehabilitation represented a crucial player in fighting disability.⁴⁴

Two systematic reviews on C-GBS have been published,^{2,4} but no data on medium-term functional outcome during the COVID-19-era are available. This study reports on the followup of patients with C-GBS after inpatient rehabilitation and at least 6 months after symptom onset. The evaluation involved the use of 3 well-validated scales for the examination of patients affected with GBS. In particular, the GBS-DS is accepted at an international level, being included in the Erasmus GBS outcome score.¹⁵ Functional recovery appeared more successful in C-GBS patients. Patients with AIDP showed a benign course at T1 and T2 with an excellent recovery in terms of MRC-ss, BI, and GBS-DS scores, whereas the patient with AMAN had a partial recovery, possibly negatively influenced by a concomitant myelitis.¹³

In C-GBS, we expected negative effects on rehabilitation because of the possible delay in admission to neurorehabilitation,¹⁶ with the necessity of a negative RT-PCR nasopharyngeal swab and a fully stable clinical condition. In fact, in Piedmont, very few rehabilitation departments have been dedicated to patients with positive swab results, and it must be considered that the risk of respiratory complications might be higher in patients with COVID-19. However, we found that these factors did not influence recovery. Conversely, patients with NC-GBS experienced an unexpected high rate of complications and an AMAN prevalence higher than usual (6 patients with axonal damage, 1 with mixed AMAN/AIDP form). These factors might feasibly explain the poorer functional outcome in this cohort.⁵ In fact, it is well recognized not only that AMAN forms are associated with a worse recovery, ⁵ but also that medical complications during neurorehabilitation are linked to worse rehabilitative and quoad-vitam prognoses.

All patients received personalized physical therapist and occupational therapist treatment during the length of stay. In this regard, it could be argued that the number of rehabilitation hours might have affected the recovery. In particular, Barthel Index scores might have been influenced by occupational therapy. Due to the nature of this report, however, we are unable to give further consideration to these possible relationships. The most important factors

influencing a worse recovery might have been represented by the complications encountered and the GBS subtype; however, this is a single-center experience and not a population-based study, and epidemiological deduction is not appropriate.

The capacity to walk autonomously, a key feature in these individuals' independence, was reached in 55.5% of the cases. In 1 case, walking was possible with help (11.1%). This proportion remained the same at T2, as the worsening of COPD compromised 1 patient's ability to march autonomously, whereas another patient regained this ability after outpatient rehabilitation.

The observation is in line with a recent study,¹¹ in which the 58.5% of the patients reacquired autonomous walking ability after 3 months since discharge from an intensive rehabilitation facility and subsequent outpatient rehabilitation. In our report, only 3 of 9 patients continued rehabilitation in an outpatient setting. In this respect, the forced closure of some of the local rehabilitative services in the COVID-19 lockdown period might have contributed to the rise of the GBS disability burden.

In summary, the medium-term follow-up revealed a better functional outcome of the C-GBS group, compared with a NC-GBS group that had a higher-than-expected rate of AMAN and complications, which might have easily caused an inferior recovery. The small sample represents a limitation—specifically, excluding further speculation on the functional outcome of these patients and allowing only a descriptive analysis of the medium-term follow-up. Longitudinal studies are needed to identify whether C-GBS or NC-GBS might have substantial differences in terms of onset and recovery.

Commented [FGM1]: (I corrected the sentence FGM)

Analyzing the follow-up of neurological complications is mandatory to refine the methods of treatment and understand the prognosis of these patients more accurately. Furthermore, addressing the pitfalls in the management of the neurological pathologies is also necessary in the COVID-19 era, as rehabilitation is an essential step toward disability reduction.

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Author Contributions

Concept/idea/research design: F.G. Masuccio, V. Tipa, C. Solaro

Writing: F.G. Masuccio, V. Tipa

Data collection: F.G. Masuccio, V. Tipa

Data analysis: V. Tipa

Providing participants: C. Solaro

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Consultation (including review of manuscript before submitting): F.G. Masuccio, M.

Invernizzi

Ethics Approval

The Ethics Committee considered this manuscript as an observational case series that did not require approval. All the patients gave written informed consent for the inclusion of anonymized clinical data in a scientific publication, in agreement with the Declaration of Helsinki. The authors received Ethical Committee approval for the study of COVID-19 and related consequences.

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Disclosures

The authors completed the ICMJE Form for Disclosure of Potential Conflicts of Interest and reported no conflicts of interest.

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Clinical Presentation	Case 1 (F)	Case 2 (F)	Case 3 (F)		
Clinical Presentation	Tetraparesis	Tetraparesis	Paraparesis		
Albumin-cytological	Yes	Yes	No		
dissociation			NO		
Electrophysiology	AIDP	AMAN	AIDP		
Anti-ganglioside antibodies	Yes Yes		No		
Treatment	IVIG PLEX, IVIG		IVIG		
Comorbidities	Hypertension T2DM				
Complications	None None		None		
BI TO	30	5	25		
BI T1	85	15	95		
BI T2	95	40	95		
GBS-DS T0	3	4	3		
GBS-DS T1	2	4	2		
GBS-DS T2	2	3	1		
MRC-ss T0	36	36	48		
MRC-ss T1	59	40	60		
MRC-ss T2	60	52	60		
Walking/US/St T0	Yes/No/No	No/No/No	Yes/No/No		
Walking/US/St T1	Yes/Yes/Yes	No/No/No	Yes/Yes/Yes		
Walking/US/St T2	Yes/Yes/Yes	Yes/No/No	Yes/Yes/Yes		
Outpatient rehabilitation	Yes	Yes	No		
AD T0	Walker and aid	Wheelchair	Walker (aided)		
AD T1	Crutches (alone)	Wheelchair	One cane (alone)		
AD T2	One cane (alone)	Walker (aided)	None		
Physical therapy hours	100	150	103		
Occupational therapy hours $^{a}AD = assistive device: AIDP =$	23	59	26		

Table 1. Clinical Characteristics of the Cases of Guillain-Barre Syndrome Related to COVID-19 (C-GBS)^a

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^{*a*} AD = assistive device; AIDP = acute inflammatory demyelinating polyradiculopathy; AMAN = acute motor axonal neuropathy; BI = Barthel Index; COPD = chronic obstructive pulmonary disease; GBS-DS = Guillain-Barre Syndrome Disability Scale; IVIG = intravenous immunoglobulins; MRC-ss = Medical Research Council sum score; MINOCA = myocardial infarction with nonobstructive coronary artery disease; PLEX = plasma exchange; St = stair climbing; T2DM = type II diabetes mellitus; T0 = after 1 month from symptom onset; T1 = after 3 months [SD = 3.60 mo] from symptom onset; US = uneven surfaces walking; UTI = urinary tract infection.

Clinical Presentation	Case 1 (Male)	Case 2 (Male)	Case 3 (Female)	Case 4 (Female)	Case 5 (Female)	Case 6 (Female)	Case 7 (Male)	Case 8 (Male)
	Tetraparesis	Tetraparesis	Tetraparesis	Tetraparesis	Tetraparesis	Paraparesis	Paraparesis	Tetraparesis
Albumin-cytological dissociation	No	Yes	Yes	No	No	Yes	Yes	Yes
Electrophysiology	AIDP	AIDP	AMAN	AIDP/AMAN	AMAN	AMAN	AMAN	AMAN
Anti-ganglioside antibodies	No	No	No	No	No	No	No	No
Treatment	IVIG	PLEX-IVIG	IVIG	IVIG	IVIG	IVIG	IVIG	IVIG
Comorbidities	Hypertension Hypercholeste rolaemia	Hypertension	Hypertension Type II DM Lower limb amputation	Hypothyroidism	Hypertension Hypothyroidism T2DM	COPD	COPD Hypertension T2DM Hypercholestero laemia	Hypertension T2DM Hypercholestero laemia
Complications	GBS recurrence	-	-	MINOCA UTI	Lobar Pneumonia Death due to sepsis	Atrial Fibrillation COPD exacerbation	COPD exacerbation Death due to sepsis	UTI
BI TO	45	40	10	0	15	35	5	5
BI T1	80	85	30	65		70	-	20
BI T2	85	100	30	75	~ 7	45	-	10
GBS-DS T0	4	3	4	4	4	4	4	4
GBS-DS T1	2	1	4	2	6	2	6	4
GBS-DS T2	1	0	4	2	6	3	6	4
MRC-ss T0	25	32	30	15	42	43	30	33
MRC-ss T1	58	56	40	38	-	52	-	48
MRC-ss T2	60	60	40	45	-	51	-	42
Walking/US/St T0	No/No/No	Yes/No/No	No/No/No	No/No/No	No/No/No	No/No/No	No/No/No	No/No/No
Walking/US/St T1	Yes/Yes/Yes	Yes/Yes/Yes	No/No/No	Yes/No/No	-	Yes/Yes/No	-	No/No/No
Walking/US/St T2	Yes/Yes/Yes	Yes/Yes/Yes	No/No/No	Yes/Yes/Yes	-	Yes/Yes/No	-	No/No/No
AD T0	Wheelchair	Walker (aided)	Wheelchair	Wheelchair	Wheelchair	Wheelchair	Wheelchair	Wheelchair
AD T1	Cane (alone)	None	Wheelchair	Walker (aided)	-	Walker (alone)	-	Wheelchair
AD T2	None	None	Wheelchair	Crutches(alone)	-	Walker (aided)	-	Wheelchair
Physical therapy hours	98	112	100	163	92	101	80	135
Occupational therapy hours	30	25	56	62	22	32	19	36
Outpatient rehabilitation $^{4}AD = assistive device: A$	Yes	No	No	Yes	-	No	-	No

Table 2. Clinical Characteristics of the Cases of Non-COVID-19 Related Guillain Barre Syndrome (NC-GBS)^a

 ${}^{a}AD$ = assistive device; AIDP = acute inflammatory demyelinating polyradiculopathy; AMAN = acute motor axonal neuropathy; BI = Barthel Index; COPD = chronic obstructive pulmonary disease; GBS-DS = Guillain-Barre Syndrome Disability Scale; IVIG = intravenous immunoglobulins; MRC-ss=Medical Research Council sum score; MINOCA = myocardial infarction with nonobstructive coronary artery disease; PLEX = plasma exchange; St = stair climbing; T2DM = type II diabetes mellitus; T0 = after 1 month from symptom onset; T1 = after 3 months from symptom onset; T2 = last follow-up (after 11.67 months [SD = 4.23 mo] from symptom onset); US = uneven surfaces walking; UTI = urinary tract infection.



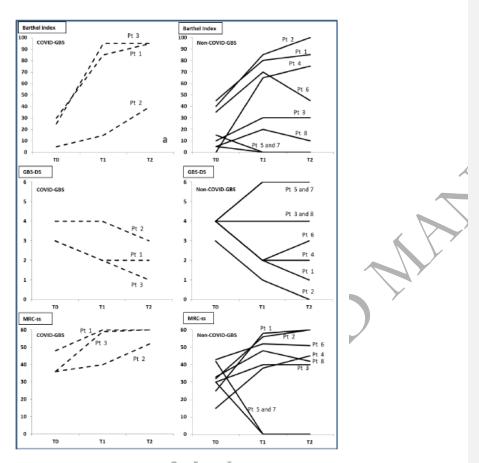


Figure. Recovery trajectories of patients with C-GBS and patients with NC-GBS. C-BGS =

COVID-19 associated GBS; NC-GBS = non-COVID-19 associated GBS.

