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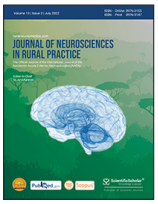

Original Article

Rehabilitation outcomes in patients with post-COVID-19 vaccine-associated Guillain-Barre syndrome

Anupam Gupta[1], Anurag Ranga[1], Naveen B. Prakash[1], Meeka Khanna[1]

[1]Department of Neurological Rehabilitation, National Institute of Mental Health and Neurosciences, Bengaluru, Karnataka, India.

ABSTRACT

Objective: With COVID-19 vaccination campaign worldwide, associated Guillain-Barre syndrome (GBS) is being increasingly reported from different countries. The objectives of the study were to observe the clinical profile and rehabilitation outcomes in patients with post-COVID-19 vaccine-associated GBS.

Material and Method: This prospective study was conducted in neurological rehabilitation unit with in-patients. A detailed customized rehabilitation program was formulated based on the clinical status and associated complications. Outcome measures were documented on the day of admission and at discharge and compared.

Results: The study included 16 patients (eight males) of which 15 (93.75%) received the CoviShield (AstraZeneca) and 1 Covaxin (Bharat Biotech) vaccine. The median (IQR) duration of first symptom was 9 (18.25) days and for motor symptoms 18 (12.75) days. Functional improvement was observed in patients using Barthel index scores and Hughes disability scores and overall neuropathy limitation scale. All rehabilitation outcomes showed a statistically significant improvement ($P < 0.05$) from the time of admission to discharge. At discharge, complete independence in activities of daily living was achieved in 4 (25%) patients and 5 (31.25%) were minimally dependent. Three (18.75%) patients were walking independently, seven (43.75%) with minimal support, and four with walker (25%). Nine (56.25%) patients needed bilateral ankle-foot orthosis and two bilateral knee gaiters for locomotion.

Conclusion: Comprehensive inpatient rehabilitation interventions in patients with post-COVID-19 vaccine-associated GBS result in significant functional recovery.

Keywords: COVID-19 vaccines, Guillain-Barre syndrome, Inpatient rehabilitation

INTRODUCTION

Guillain- Barre syndrome (GBS) is an immune-mediated neurological disease manifesting as acute onset, rapidly developing polyradiculoneuropathy resulting in classically a symmetrical, flaccid, and ascending weakness with hyporeflexia or areflexia. It is typically seen in the post-infectious (viral or bacterial) phase after gastrointestinal or respiratory symptoms. During COVID-19 pandemic, there are reports of GBS occurring both as a neurological manifestation of COVID-19 infection as well as following COVID-19 vaccination.[1-5] The occurrence has been reported to be varying in different countries. A British study found a reduction in GBS during COVID-19 pandemic in comparison to pre-COVID time in the UK residents.[6] Whereas a larger number of GBS cases following COVID-19 infection have been reported from Italy, indicating that environmental and genetic factors might have an important role to play.[7,8]

The underlying pathophysiology of GBS is considered to be molecular mimicry as it occurs following certain infections. The causal link through molecular mimicry or cross-reactive antibodies against ganglioside epitopes has been recognized for limited pathogens such as *Cytomegalovirus* and *Campylobacter jejuni*, predominantly for axonal and Miller Fisher syndrome variants.[9] However, proving the causal relationship between the GBS and vaccine on a molecular level remains a challenge.[1] A probable association of vaccination to GBS, particularly amplified risk of GBS with swine flu (H1N1 influenza) vaccination, has been reported.[2]

Since the first-reported case of severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2) in

***Corresponding author:** Anupam Gupta, Department of Neurological Rehabilitation, National Institute of Mental Health and Neurosciences, Bengaluru, Karnataka, India. drgupta159@yahoo.co.in

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December 2019, COVID-19 has caused a global pandemic associated with significant morbidity and mortality. After more than a year of advances in vaccine research and development, two vaccines against COVID-19: (i) "CoviShield" vaccine manufactured by Serum Institute of India; a version of Oxford-AstraZeneca vaccine and (ii) "Covaxin" developed by Bharat Biotech International Ltd. in association with Indian Council of Medical Research and the National Institute of Virology have been approved for use in India. With progression of COVID-19 vaccination campaign worldwide, the cases of vaccine-associated GBS are increasing.[10-13] Therefore, early recognition and reporting of possible neurological complications post-COVID-19 vaccine is essential.

GBS is usually considered to have favorable prognosis with majority (in percentage) recovering completely but still a large number of patients are left with residual deficits and require long-term rehabilitation.[14] As post-COVID-19-associated GBS is a recent phenomenon, no literature is available about the long-term impairments and disability. There is hardly any study on the rehabilitation outcomes in these patients developing GBS post-vaccine.

The aim of the present study was to observe the clinical profile and rehabilitation outcomes in patients with post-COVID-19 vaccine-associated GBS admitted for inpatient rehabilitation.

MATERIALS AND METHODS

This prospective study was conducted in neurological rehabilitation unit of a tertiary university research hospital, between April 2021 and March 2022. Patients who were diagnosed with GBS based on clinical, electrophysiological, and/or supportive cerebrospinal fluid (CSF) analysis and had a history of being vaccinated with COVID-19 vaccine (Covisheild or Covaxin) in the preceding days/weeks and those admitted for inpatients rehabilitation were included in the study.[15] All patients were initially admitted in the department of neurology, and after confirming diagnosis as GBS, 14 patients were treated with large volume plasmapheresis (LVPP) and two were treated with intravenous immunoglobulins (IvIg).

The study was approved by the Institutional Ethics Committee and the patients willing to give informed consent were enrolled. Men or women above the age of 18 years (vaccination program for <18 years age group was not started in the country then with post-COVID-19 vaccine-associated GBS and was able to participate for at least 2 h/day of inpatient rehabilitation program) were included in the study. Individuals with the previous history of COVID-19 symptomatic/confirmed infection, dyspnea, or other acute medical conditions that prohibit intensive rehabilitation training or patients with post-COVID-19 vaccine-associated long-segment transverse myelitis, leading to tetraplegia/paraplegia, were excluded from the study.

Demographic profile, risk factors, duration of illness, and detailed clinical examination findings were documented. Previously validated assessment tools/outcome measures were used in the present study; severity of muscle weakness was graded using Medical Research Council strength assessment scale,[16] degree of disability was quantified using Hughes GBS disability score (HDS) and overall neuropathy limitation scale (ONLS), independence in performing activities of daily living (ADL) was assessed using Barthel index scale, fatigue level with fatigue severity scale (FSS), sleep quality using Pittsburgh sleep quality index (PSQI), and anxiety and depression were assessed using Hospital Anxiety and Depression Scale (HADS). Outcome measures were recorded at baseline (on day of admission) and at the time of discharge. Analysis was done by comparing outcome measures at admission and at discharge.

Outcome measures

Primary outcome measures

Barthel index

Ten variables are assessed on an ordinal scale (a score of 0–100) to measure independence in ADL, a higher score indicates greater independence.[17]

HDS

This is a 7-point validated tool to assess functional status in individuals with GBS.[18]

ONLS

This is used to measure a person's ability to perform the upper and lower extremity functional activities (arm score 0–5 and leg score 0–7) with score ranging from 0 to 12 (0 – no disability and 12 – maximum disability).[19]

Secondary outcome measures

FSS

It is a 9-item scale measuring the severity of fatigue and its effect on a person's activities and lifestyle, a score ≥4 indicates fatigue.[20]

PSQI

It consists of seven subscores, each of which can range from 0 to 3. These are tallied to calculate a "global" score, ranging from 0 to 21. Poor sleep quality is indicated by a score of ≥5.[21]

HADS

It consists of 14 items with seven each for anxiety and depression, a subscale score >8 indicates anxiety or depression.[22]

A detailed customized program was made for all individual patients based on the clinical status and associated complications, which included managing the medical issues. Dysphagia management and bladder/bowel issues were addressed. A detailed therapy program consisting of physiotherapy, occupational therapy, counseling, and psychosocial rehabilitation (by psychologists and social workers) was made and provided to the patients. Custom-made orthotic devices were provided wherever required. The ultimate goal was to make patients independent in performing ADL and independent community ambulators by the time of discharge from rehabilitation.

Statistical analysis

Descriptive variables are presented as median (IQR) and categorical variables as percentage or proportion. Pre- and post-rehabilitation outcomes were analyzed by Wilcoxon signed-rank test. Statistical analysis was done using RK Ward Ver 0.7.0b. $P < 0.05$ was considered as statistically significant.

RESULTS

The study included 16 patients (eight males) with post-COVID-19 vaccine-associated GBS of which 15 (93.75%) received the CoviShield vaccine. Mean age was 43 years (SD 19.2, range 18–63 years) and 10 patients (62.5%) developed GBS after the first dose of vaccine. In all patients, the real-time polymerase chain reaction test for SARS-CoV-2 was negative.

The median (IQR) duration of onset of first symptom (motor/non-motor) from day of vaccination was 9 (18.25) days and for motor symptoms; 18 (12.75) days. CSF analysis detected albumin-cytological dissociation in all patients. Nerve conduction studies showed 5 (31.25%) patients with typical acute inflammatory demyelinating polyneuropathy (AIDP), 4 (25%) had acute motor axonal neuropathy, and 7 (43.75%) had acute motor-sensory axonal neuropathy variant. Antinuclear antibody profile was positive in 2 (12.5%) and anti-ganglioside antibodies and anti-neutrophil cytoplasmic antibodies were absent in all patients.

Eight patients (50%) required intensive care unit admission, 5 patients (31.25%) required ventilator support secondary to respiratory failure, 3 (18.75%) developed pneumonia, while 4 (25%) required tracheostomy for airway management. Cranial nerve involvement was seen in 8 patients (50%), all had facial diplegia and seven of them had bulbar involvement with dysphagia. One patient had ophthalmoplegia (Miller-Fisher variant). Bladder involvement was observed in 1 individual (8.25%) who underwent filling and voiding cystometrography in the rehabilitation unit. It showed detrusor overactivity and sphincter dyssynergia. By the time of discharge, the patient was continent and self-voiding.

The mainstay of treatment for GBS was LVPP and IvIg, given to 14 and two patients, respectively. Three patients had comorbidities (such as hypertension, chronic obstructive pulmonary disease, Type 2 diabetes mellitus, and seizure disorder). During the course of rehabilitation, no new neurological deficits were observed.

Total median (IQR) duration of inpatient rehabilitation was 20 (21.25) days. Before transfer to rehabilitation, they stayed for about 16 (18.5) days in neurology for diagnosis and medical treatment. Demographic characteristics and clinical features at admission in rehabilitation unit are shown in [Table 1].

Hughes disability scores median score of 4 (3, 4) was observed at the time of admission while at discharge, it was 3 (2.75, 3). Median (IQR) score of Barthel index at admission was 45 (23.75, 56.25) and at discharge was 62.5 (45, 70). Median score of ONLS arm scale at admission was 2 (2, 3) and at discharge 2 (1, 2.25) while median score of ONLS leg scale was 5.5 (3.5, 6) at admission and 4 (2.75, 4) at discharge. Statistically significant recovery ($P < 0.05$) was observed using all these scales when discharge scores were compared with admission scores (HDS, Barthel index, and ONLS). This comparison of outcome measures is shown in [Table 2].

At the end of the rehabilitation program, complete independence in all ADL was achieved in 4 (25%) patients and 5 (31.25%) were minimally dependent. Three (18.75%) patients were walking independently, 7 (43.75%) were able to walk with minimal support (no assistive device), and ambulation with a walker was possible in 4 (25%). Nine (56.25%) patients needed bilateral ankle-foot orthosis and 2 (12.50%) needed bilateral knee gaiters for locomotion.

DISCUSSION

By the end of the March 2022, about 1.82 billion COVID-19 vaccine doses had been given in India and about 0.82 billion people (60% of the population) were fully vaccinated.[23] In this study, GBS was observed following first and second dose of COVID vaccination in 10 (62.5%) and 6 (37.5%) patients, respectively. The time interval from day of vaccination to the onset of first GBS symptom ranged from 1 to 26 days which is in concurrence with earlier case reports and series published (1–39 days).[24-27] The duration between vaccination and the onset of first motor symptom ranged from 3 to 29 days in the study correlating with the probable time needed for immune system to respond to COVID-19 vaccines.

Table 1: Demographic data and medical characteristics of GBS patients post-COVID-19 vaccination (*n*-16).

Age (mean years, range)	43 (18–63)
Sex (males, %)	8 (50)
Vaccine – CoviShield *n*, (%)	15 (93.75)
Symptomatic after vaccination (*n*, %)	First dose – 10 (62.5) Second dose – 6 (37.5)
Number of days to onset of first symptom after vaccination (median, 1st and 3rd quartile)	9 (2.75, 21)
Number of days to onset of motor symptoms after first symptom (median, 1st and 3rd quartile)	3 (1.75, 9.25)
Number of days to onset of motor symptom after vaccination (median, 1st and 3rd quartile)	18 (10.25, 23)
Cranial nerve involvement (*n*, %)	8 (50)
Facial diplegia	8 (50)
Facial diplegia with ophthalmoplegia	1 (6.25)
Bulbar symptoms (*n*, %)	7 (43.75)
Sensory involvement (*n*, %)	8 (50)
Tetraplegia (*n*, %)	15 (93.75)
Paraparesis (*n*, %)	1 (6.25)
Bladder involvement (*n*, %)	1 (6.25)
Patients required ICU (*n*, %)	8 (50)
Tracheostomy support (*n*, %)	4 (25)
Pneumonia (*n*, %)	3 (18.75)
Patients required ventilator support (*n*, %)	5 (31.25)
CSF examination (albuminocytological dissociation) (*n*, %)	16 (100)
Nerve conduction studies (*n*, %)	
Acute inflammatory demyelinating polyneuropathy	5 (31.25)
Acute motor axonal neuropathy	4 (25)
Acute motor sensory axonal neuropathy	7 (43.75)
ANA positive (*n*, %)	2 (12.5)
ANCA positive (*n*, %)	0 (0)
Anti-ganglioside antibody positive (*n*, %)	0 (0)
RTPCR at the time of admission – negative (*n*, %))	16 (100)
Treatment (*n*, %)	
LVPP	14 (87.5)
IVIG	2 (12.5)
Median (1st and 3rd quartile) duration of inpatient rehabilitation (days)	20 (14.25, 35.5)
Median (1st and 3rd quartile) duration of stay in neurology (days)	16 (11.75, 30.25)

LMN: Lower motor neuron, CN: Cranial nerve, ICU: Intensive care unit, CSF: Cerebrospinal fluid, ANA: Antinuclear antibody, ANCA: Antineutrophil cytoplasmic antibodies, RT-PCR: Reverse transcriptase polymerase chain reaction, LVPP: Large volume plasmapheresis, IVIG: Intravenous immunoglobulin

Exact immunopathogenesis of GBS after COVID-19 vaccination is unidentified and numerous mechanisms have been proposed like; (i) resemblance of vaccine epitopes with peripheral nerve's axon or myelin epitopes triggering an immune response, (ii) nerve membrane damage resulting directly from the exposure to vaccine products, and/or (iii) genetic predisposition.[28,29] Greater incidences of GBS have been reported after administration of adenovirus vector-based COVID-19 vaccine (AstraZeneca).[24,26,27] In the present study too, most patients received CoviShield (Serum Institute of India and AstraZeneca), which is a adenovirus vector-based vaccine. These findings suggest that rather than the spike proteins of COVID-19 virus, adenoviral vector may be the causative factor for triggering an immune response following vaccination.[26] Ten out of 16 patients developed paralysis following the first dose of vaccine. Similar observations have been made by the earlier studies reporting occurrence of GBS within 2 weeks after receipt of first dose of CoviShield.[24,26,27,30]

In the present study, 5 (31.25%) patients showed typical AIDP and 11 (68.75%) showed axonal variant on nerve conduction study. A systematic review published recently has shown 3-fold increase in the occurrence of AIDP in COVID-19-infected GBS patients compared to non-COVID-19-infected GBS controls.[31] One of the reasons for this contrasting observation could be that post-vaccine typical AIDP patients developed milder infection, symptoms, and impairments and were not required to undergo inpatient rehabilitation. Hence, they did not report to our department.

In our study, low prevalence of ganglioside antibodies was observed, which is in contrary to an earlier study which showed

Table 2: Analysis of outcome measures.

S. No.	Outcome measures	At admission median (1st and 3rd quartile)	At discharge median (1st and 3rd quartile)	*P*-value
1.	Barthel index score	45 (23.75, 56.25)	62.5 (45, 70)	0.002
2.	HDS	4 (3, 4)	3 (2.75, 3)	0.005
3.	ONLS arm scale	2 (2, 3)	2 (1, 2.25)	0.01
4.	ONLS leg scale	5.5 (3.5, 6)	4 (2.75, 4)	0.003
5.	ONLS scale	6.5 (5.5, 9)	5.5 (3, 6.25)	0.002
6.	FSS	2.85 (1.1, 4)	2.35 (1, 4)	0.02
7.	PSQI	1 (0, 2.25)	0 (0, 1)	0.05
8.	HADS-A	4 (2, 6)	2 (1, 5)	0.01
9.	HADS-D	3 (2, 4.25)	2.5 (1.75, 3.25)	0.02
10.	HADS	6 (4, 11)	5 (3, 7.5)	0.01

HDS: Hughes GBS disability score, ONLS: Overall neuropathy limitation scale, FSS: Fatigue severity scale, PSQI: Pittsburgh sleep quality index, HADS: Hospital anxiety and depression scale

stronger association of ganglioside antibodies with axonal variant of GBS.[32] This difference in observation is difficult to explain. All patients in our study had albumin-cytological dissociation in CSF examination, which suggests prevalence of blood–brain barrier dysfunction in post-vaccine GBS.

Overall, the clinical manifestations were diverse with varying severity; 13 patients presented with the classical GBS phenotype with flaccid tetraplegia, while the other individuals showed distinct clinical features of GBS variants. One patient had paraplegia, one had Miller-Fisher variant (with ophthalmoplegia), and another patient had bladder involvement. Findings in general were comparable and in line with the observations of the previous case studies, which suggest that COVID-19 vaccine-associated GBS has varied clinical presentations such as facial diplegia, complete ophthalmoplegia, bulbar symptoms, severe tetraplegia, paraplegia, and bladder involvement.[24-27,30] Pulmonary dysfunction is common in subacute phase of GBS and may lead to complications.[33] About 50% of patients in the study required intensive care unit and five required ventilator support.

Six (37.5%) patients had fatigue (FSS≥4) at the time of admission, out of which one patient had severe fatigue (FSS≥5). At the time of discharge, five patients still had fatigue but none of them reported severe fatigue. A previous study reported severe fatigue (FSS≥5) in much less proportion of patients who were admitted for inpatient rehabilitation, which improved by the time of discharge.[34] Another study with GBS patients with more than 1 year of disease onset reported 30% prevalence of severe fatigue.[35] Low occurrence of severe fatigue in the present study may have resulted from our assessment during the early recovery phase in these individuals, when their primary concern is significant disability instead of fatigue. Other reasons for improvement in fatigue can be attributed to better motor recovery, response to pharmacotherapy, and optimum rehabilitation strategies.

The previous studies have reported variable occurrence of neuropathic pain (29–89%) in GBS patients.[36-38] In our study, 13 (81.25%) patients had neuropathic pain at admission and 11 (68.75%) patients still had neuropathic pain at discharge. These findings suggest relatively high prevalence of neuropathic pain in GBS patients which correlate with fatigue, physical functioning, and disability.[39]

Khan *et al*. have reported depression along with fear and anxiety to be a significant finding at the onset of symptoms in GBS.[40] In our study, only two patients had HADS-A and HADS-D scores ≥10 at the time of admission while only one had an increased score at the time of discharge. The reason could be good motor and functional recovery by the time of discharge. Anxiety and depression are major finding in acute phase of GBS due to sudden onset and progression of symptoms in relatively healthy patients, whereas in subacute phase, patients showing motor and functional recovery which might allay their anxiety and elevate low mood.[34]

Sleep quality assessment showed that only one patient had sleep disturbance (PSQI ≥5), both at the time of admission and at discharge. This is in contradiction to the greater occurrence (35% and 73%) of sleep disturbance observed in the previous studies.[34,38] Again, this can be attributed to good motor and functional recovery and adequate support and counseling to patients by our rehabilitation team (both the psychologists and the social workers).

Garssen *et al*. noted that a well-customized rehabilitation program and training improves quality of life, fitness, and fatigue in patients with GBS.[41] We observed a significant change in outcome measures in our patients. Barthel score improved and HDS, ONLS, FSS, PSQI, and HADS scores decreased at the time of discharge ($P < 0.05$), suggesting holistic recovery with multidisciplinary rehabilitation.

Limitations of the study

The present study is a hospital-based single-center study with a relatively small sample without follow-up. Affected patients had moderate-to-severe disability; hence, they were

offered inpatient rehabilitation. During the same period, there could have been many more persons who developed COVID-19 vaccine-associated GBS with mild(er) symptoms and recovered with initial treatment in the department of neurology without rehabilitation intervention. We might have missed out on those patients.

CONCLUSION

Post-COVID-19 vaccine-associated GBS has been reported from different parts of the globe. Like the typical GBS cases, these patients need inpatient rehabilitation intervention in case of moderate-to-severe illness. Timely recognition, adequate treatment, and rehabilitation of post-COVID-19 vaccine-associated GBS result in better outcomes and good motor and functional recovery.

Declaration of patient consent

Patients' consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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