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GUILLAIN-BARR É SYNDROME IN COVID-19: A LITERATURE REVIEW

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ABSTRACT:

The novel coronavirus (COVID-19) can result in several neurological complications including Guillain-Barré Syndrome (GBS). It is an acute parainfectious paralytic neuropathy. This review summarizes the demographic features, clinical presentation, diagnostics workup, and management strategies of COVID-19 associated GBS reported in the literature. We searched Medline, PubMed Central, SCOPUS, and Google Scholar using pre-defined keywords. We included all kinds of manuscripts in the English language only. Demographics, clinical features, diagnostic workup, management, and outcomes were documented in the datasheet. We identified 24 cases of COVID-19 associated GBS. Most were reported from Italy, followed by the USA. The majority were males (18/24) and the age ranged from 23 -84 years. Clinical presentation was typical sensory-motor GBS in most. Nine patients had facial palsy of which five had bilateral involvement. Two patients had bilateral abducent nerve palsy while two presented as paraparetic GBS variant with autonomic dysfunction. Electrodiagnostics studies were conducted in 17 patients only and 12 had typical features of acute inflammatory demyelinating polyradiculoneuropathy. Intravenous immunoglobulin was the preferred mode of treatment in most of the patient. There was one death, and most were discharged to rehabilitation or home. GBS is an important neurological complication associated with COVID-19. More data are needed to establish a casualty. However, most cases have a post-infectious onset with male preponderance. Most of the cases have a typical presentation but some may present atypically. The prognosis is generally good.

Keywords: Neurology, Clinical features, Coronavirus, GBS, Polyneuropathy, Rehabilitation

INTRODUCTION:

The novel coronavirus (COVID-19) infection originated from Huanan seafood market in Wuhan city China in December 2019. It rapidly spread to more than 200 countries of the world. The World Health Organization (WHO) has reported more than 166 million cases all around the globe with a death toll more than 34 million.[1] COVID-19 primarily affects the respiratory tract and the lungs. However, other organs including cardiovascular, renal, and neurological system have also been reported. The reported neurological manifestations and complications of COVID-19 include anosmia, headaches, dizziness, delirium, stroke, epilepsy, encephalitis, encephalopathy, myalgia and Guillain-Barr é syndrome (GBS),[2,3,4] This review summarizes the important demographic features, clinical presentation, diagnostics, and management strategies of COVID-19 associated GBS reported in literature so far. We inform the readers about this important neurological manifestation of COVID-19 in order to formulate better diagnostic and management strategies.

Pathophysiology and Clinical Features of Guillain-Barr é syndrome

GBS is acute onset immune mediated disorder characterized by rapidly progressive limbs and bulbar weakness which can lead to respiratory failure.[5] Many triggers for GBS have been identified including bacterial and viral infections, surgery, and pregnancy. The link of GBS with vaccination is controversial. Respiratory and Gastrointestinal infections constitute two third of cases. The molecular mimicry between the cell membrane antigen of microbe and ganglioside component of nerve antigen misdirects the immune response. This immune

response is humoral mediated and not T cell mediated. The prototype example is of Campylobacter Jejuni infection. The carbohydrate moiety of liopooligosaccahrides of Campylobacter Jejuni is capable of inducing antibodies that cross react with glycans present on nerve gangliosides.[6] The exact trigger to mount this misdirected immune response is still not known. There is no specific genetic predisposition as only 1% of all campylobacter infections will result in GBS. GBS has also been reported after viral infections for example Cytomegalovirus, Ebstein-Barr virus, Influenza, Zika, and Chikungunya virus.[9,13] The clinical hallmark is hyporeflexia or areflexia. The course of the disease is monophasic. Recommended treatment for GBS includes plasmapheresis (PLEX) and immunoglobulins (IVIG) infusion.[7] GBS was initially described only as a demyelinating polyneuropathy. Typical features of demyelination on electrodiagnostic studies (EDX) include prolong distal latencies, reduction of conduction velocity, prolong F-waves, temporal dispersion, and conduction block. Clinically many different variants with distinct clinical and electrophysiological features have been reported in literature.[8] These include cranial, autonomic, ataxic, paraparetic and mixed variety. The GBS reported from North America and Europe is predominantly demyelinating type while in Asian countries the axonal type of GBS constitutes 30-50 % of the reported cases.[9,10,11,12] The mortality of GBS reported from European and North American studies ranges from 3-7%, and is mainly due to respiratory failure, deep vein thrombosis and autonomic dysfunction. The axonal variants of GBS mostly reported in the Chinese and Asians populations have a poor prognosis i.e. slower recovery and prolonged disability.[13] In case of axonal variant of GBS, once the axonal integrity is damaged, it does not be regenerate actively and completely. [1]

Neurological injury due to Coronavirus

Coronaviruses are not primarily neurotropic viruses, and their primary target is respiratory and cardiovascular systems. However other organs including gastrointestinal tract, renal, eyes and nervous system can also be involved. It is through the Angiotensin-converting enzyme 2 (ACE-2) receptors the virus is attached to host cells leading to internalization and subsequent viral replication. This receptor is also found in glial cells in the Central Nervous System (CNS) and spinal neurons. Very rarely the virus can invade peripheral nerves and lead to retrograde transfer via synapse mediated route to CNS. Another proposed route of entry is through the olfactory nerves.[14,15] Past experience with Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory syndrome (MERS) related cases has also provided insights into the neuro invasive potential of Coronaviruses.[16,17] As the number of COVID-19 cases with neurological manifestations and complications are being reported more frequently, there is growing evidence for neurotoxic potential of COVID-19. This neurotoxicity can occur because of direct or indirect insult by virus and may manifest in form of post-infectious complications like GBS. In this review we will focus only on the post infectious complications.

Mechanism of GBS in COVID-19

COVID-19 does not directly invade peripheral nerves, nerve roots, or anterior horn cells leading to inflammation and death of motor neurons as seen in polio virus or West Nile virus. The Cerebrospinal fluid (CSF) Polymerase chain reaction (PCR) for coronavirus in multiple reported cases of COVID-19 related GBS has been negative.[19] It is likely a post infectious or may be a para-infectious complication resulting from an aberrant immune response. During the inflammatory phase numerous mediators of inflammation are released from activated leukocytes including Interleukin-6 (IL-6), named as Cytokine storm. This can result in major organ damage, rapid deterioration of the patient and ultimately death.[20] However, due to lack of experimental data it is difficult to deduct if IL-6 is also responsible for the neurological damage.[36] However, after the acute phase of the infection, an immune response is generated by the host and may lead to a misdirected reaction against host epitopes. It can result in an autoimmune, response directed against peripheral nerves and nerve roots in susceptible individuals. This may be either demyelinating or axonal degeneration type. This results in a typical GBS like presentation in the peripheral nerves and spinal roots. However, due to lack of clear data, there is still not enough evidence available to conclude if antibodies to any specific ganglioside antigen are present in these cases or not. There is also speculation that the neuropathy in viral infections related GBS could be due to other autoantibodies that are not detected as yet, or the viruses produced nerve damage due to other neurotoxic effects.

Literature Search strategy

We searched Medline, PubMed Central and Google Scholar using keywords “COVID-19”, “Coronavirus”, “Coronavirus Infections”, “Coronaviridae”, “2019 nCoV “.“pandemic”, “SARS-COV-2”, “neurology”, “neurological”, “complications”, “manifestations”,

"Guillain-Barr é syndrome" , "GBS", "acute inflammatory demyelinating polyneuropathy"," Demyelinating Polyradiculoneuropathy", "polyneuropathy", and "Miller Fisher syndrome". Different combinations of Boolean logic (AND, OR and NOT) were used to identify relevant articles. Search was limited only to English language manuscripts with no time limit. It is important to note that new data is being shared regularly and at the time of the literature search it consisted mostly of pre-prints, letters to editor, single case reports, small case series, and part of an article describing clinical features of COVID-19. Most of the data on COVID-19 is published from countries most severely affected, including China, Italy, Spain, and USA. The last literature search was done on 18th May 2020. At that time there was no specific research article, systematic or narrative review describing COVID-19 associated GBS. However, we identified two systematic reviews protocols on this topic registered in the International prospective register of systematic reviews.[21,22] Both authors independently performed the literature search and compared the results for any major discrepancies. The information was extracted on a pre-designed data sheet. The items of interest were the demographic data, presenting features, clinical examination, laboratory and radiological investigations, treatment protocol and outcomes. Due to the limited number of cases and nature of the review, a quantitative analysis was not done, and we have only provided a qualitative review of the retrieved information. This was a scoping literature review of the published data and did not involve interaction with humans or primary data collection. Therefore, a formal ethics review committee approval was not obtained.

Results

Characteristics of included studies

After removing duplicates, non-English manuscripts, and unrelated articles, we identified 24 cases of GBS in COVID-19, published in English biomedical literature till 18th May 2020. These were published as letter to editor, case reports or case series. The results are summarized in the Tables 1 and 2.

Demographics

Most of the cases (8) were reported from Italy[23,24,25,26] followed by USA (4 cases)[27,28,29] Iran (3 cases)[30,31] Spain (3 cases),[32,33] Germany (2 cases)[34,35] and one case each from China[36], France[37], Switzerland[38] and Morocco.[39] Majority of the patients were males 18(/75%). The age ranged from 23-84 years and mean age was 60 years.

Clinical Features

Most of the patients (17/24) had typical presenting features of GBS with sensory paresthesia followed by ascending paralysis. Three patients had Miller Fisher variant presenting as ataxia, ophthalmoplegia and areflexia. One case had only bilateral facial palsy without any peripheral manifestations and was labeled as facial diplegic variant of GBS. One case each from the US[30] and Switzerland [40] initially presented with paraparesis and bladder and bowel dysfunction. Spinal cord imaging was normal in both these cases and these were labeled as paraparetic variant with autonomic dysfunction Total of nine patient developed facial palsy out of which six had bilateral facial palsy. Two patients developed bilateral six nerve palsy. One patient among above who initially presented with bilateral facial and hypoglossal palsy and progressed to a locked in syndrome like condition. An important peripheral nervous manifestation i.e., hyposmia and hypogeusia was reported in Five patients. One of them had complete reversal of hyposmia at the time of discharge. The predominant clinical presentation in majority of the cases was post-infectious. However, in three cases the onset of symptoms suggested a para-infectious course of disease.

Laboratory and Radiological Investigations

Nasopharyngeal swab samples of all cases were PCR positive for COVID-19, except one case. That patient repeatedly tested negative but, later his serology tested positive for COVID-19. CSF PCR for COVID-19 was tested in twelve patients and it was negative in all. Ganglioside antibody was tested in twelve cases. Ganglioside Ab GM2 IgG/IgM and GD 1b were positive in one case each only. One of them was the Miller Fisher Variant. CSF analysis was performed in 20 cases. Four patients had a normal CSF analysis while in 16 cases it showed albuminocytological dissociation of GBS. COVID-19 associated lung changes were detected on High-Resolution Chest Tomography (HRCT) chest in fourteen cases. X-ray chest was normal in six cases and revealed pneumonia in one case. Chest imaging was not reported in two cases. This can potentially guide the clinicians. During this pandemic, in a patient with GBS, HRCT chest should be ordered in case of any doubt to detect possible COVID-19 associated pneumonia as both can be contribute towards respiratory failure.

Electrodiagnostic Findings (EDX)

Nerve conduction studies/ Electromyography (NCS/EMG) were performed in 17 cases. Out of these twelve cases had prolongation of distal latencies (DML) and absent F waves suggestive of a typical demyelinating polyneuropathy. Four cases had Acute Motor and

Sensory Axonal Neuropathy (AMSAN) variant and one had Acute Motor Axonal Neuropathy (AMAN) variant of GBS. However, in the Italian case series, the author reported their NCS/EMG as a mixed picture whereas in our opinion, a prolong DML and absent F waves favors a demyelinating variant. [26]

Treatment

Three cases were ambulatory with minimum motor deficit and were not offered any treatment for GBS. One of them was a Miller Fisher variant. Nineteen patients were given IVIG. Among these two cases had repeat sessions of IVIG and two cases had PLEX after IVIG due to initial inadequate response. Two case had PLEX sessions as primary treatment one among them had IVIG after PLEX also.

Outcomes and discharge status

One case expired due to complications. Nine patients were either discharged to nursing homes or shifted to rehabilitation for exercise. Complete recovery was reported in eight patients. At the time of publication of cases, three patients were on mechanical ventilation, one was critically ill, and no improvement was reported in one case. Outcome and discharge status were not mentioned for three cases.

Discussion

This review suggests that COVID-19 associated GBS has emerged as an important neurological manifestation and complication of this global pandemic. Experts have suggested that in this pandemic any patient presenting with an acute paralytic disease-like GBS, may represent the first manifestation of COVID-19.[40] It is therefore important to know the clinical features and associated manifestations in a case of GBS due to COVID-19. Although, a clear association of COVID-19 leading to triggering of GBS is lacking at present, experience with Zika Virus associated GBS suggests a possibility of causality between GBS and COVID-19 infection. The onset of GBS was post infectious in all the cases in this review, except three in which it was para infectious. A similar pattern has also been seen in Zika Virus infections. Therefore, the treating physician should have a high index of suspicion in managing such cases. The patient might be in the infective stage of COVID-19 and personal protective equipment will be necessary for the safety of hospital staff. Lung changes due to COVID-19 infection were seen in many patients in this review (15/24). Fourteen had a positive HRCT and one had pneumonia on X ray chest. All these cases had a positive Nasopharyngeal PCR. Therefore, it is important to consider that during the current pandemic respiratory compromise in GBS may not be entirely due to neuromuscular failure but may also be due to COVID-19 pneumonia. At the same time if the patient with COVID-19 is having deterioration of respiratory function or is difficult to wean from ventilator GBS should also be considered as one of the possible reasons. This review suggests that in COVID-19 associated GBS, AIDP variant is more common followed by AMAN and AMSAN variants. However, Umapathi has recently suggested that there is a possibility that there may be an underlying paranodal axonal pathology in these cases and serial EDX follow up studies might help in reaching a firm conclusion about the actual nature of the problem.[41] Three patients presented as Miller Fisher syndrome variants of GBS. Similarly, craniobulbar involvement was seen in four cases beside three quoted above. This is a large number considering the very low incidence of Miller Fisher syndrome variant of GBS in general population.
The experience with Zika virus related GBS suggests that the patient present with typical symptoms including facial palsy on presentation, male predominance, and AIDP on EDX. A similar pattern was documented in this review. In a review from Puerto Rico facial weakness was seen in 62% cases of Zika Virus associated GBS as compared with 10% in non- Zika related GBS.[42] In this review 37.5 % of the cases had facial weakness with 5 having bilateral facial paralysis. The incidence of dysphagia in Zika Virus associated GBS has been reported to be 53.5% while it is low in COVID-19 associated GBS 5/24 (20%). Two patients had paraparesis at presentation followed by urinary retention and were later diagnosed as GBS. [29,39] This paraparetic pattern is seen more commonly in Zika Virus associated GBS cases. We do not know the exact mechanism of this phenomenon. In 5 cases hyposmia and hypogeusia were either the presenting or co-existing features. [28,34] These were likely due to the COVID-19 infection and not because of GBS. This is an important finding and can be used as a clinical indicator of COVID-19 infections in suspected GBS cases. Especially if this is combined with the presence of lymphopenia on blood counts and the presence of other cranial neuropathies on examination. Seropositivity of GBS for ganglioside antibody is reported to be around 30% with the cases of MFS having 95% GQ1b positivity. In this review only one case was positive GD 1b ganglioside antibody. However, this data is too small to make a conclusion. Most of the cases in this review were treated with 5 sessions of IVIG. In two cases, IVIG was repeated while in two cases PLEX was also done after giving IVIG. PLEX has been used in two cases as initially and in one it was

followed by IVIG due to inadequate response. One of the possible reasons for use of frequent use of IVIG in all these cases is that all of them were in high income countries with adequate resources and easy access to IVIG. We would like to suggest that in resource constrained areas and the developing world PLEX might prove to be equally beneficial as this is the preferred mode of treatment in cytokine storm syndrome due to COVID-19.[43] Most of the patients had a good outcome and were either discharged to home with complete recovery or were referred to rehabilitation for management of residual weakness and motor deficits. There was one death, and four patients were reported to be on mechanical ventilation at the time of publication of the case reports. However, due to the limited data, it is difficult to comment if COVID-19 associated GBS increases severity of illness, length of Intensive care Unit (ICU) admission and prolongs ventilatory support along with residual disability at six months post treatment.

Comparison of MERS associated GBS Vs. COVID-19 associated GBS

The published data regarding neurological complication and manifestations associated with MERS is limited.[44,27,28] In addition, MERS was an epidemic limited to one geographic area and GBS associated with MERS was rarely reported so it is not possible to make a detailed comparison between this and COVID-19 associated GBS due to paucity of data. There is one case report of a critical illness neuropathy due to prolong intensive care unit stay reported from Saudi Arabia.[45] Kim et.al identified only four cases from Korea during the 2015 our break of MERS, which presented with neurological features. [26] One was diagnosed as GBS Bickerstaff variant, second one as Intensive care unit associated neuropathy overlapping with GBS and last 2 were labeled as toxic neuropathy. All four had sensory features on presentation and one of them developed motor weakness and ophthalmoplegia. However, EDX evaluation and CSF examination was normal in all patients. Ganglioside antibody was also negative. Only one patient required mechanical ventilation and was given IVIG. The other three did not have motor weakness and were only kept under medical observation, provided supplemental oxygen and no specific treatment was offered. These epidemics limited to a specific geographic zone affecting only 2494 people (WHO estimates), unlike COVID-19 which is a global health care crisis affecting millions. However, the common feature among both is the craniobulbar involvement in both.[46]

Comparison of Zika Virus associated GBS Vs. COVID-19 associated GBS

The comparison of GBS due to COVID-19 with Zika Virus associated is presented in Table 3. In Zika Virus-GBS the median time from symptoms to disease onset was seven days consistent with para infectious GBS whereas in this review the median time was 11 days (3-28) days. In Zika Virus GBS the disease was more aggressive with frequent ICU admission and need for ventilatory support. Our data reports a similar pattern with a total of nine patients needing respiratory support. Seven were placed on mechanical ventilation and two were on noninvasive ventilation. On EDX evaluation demyelinating type is the most finding both with Zika Virus and COVID-19 associated GBS. Cranial involvement is another feature common to both types of GBS.

Limitations

Despite a rigorous search methodology used for this scoping review, we were not able to perform literature search across every major English bio-medical literature search database due to lack of resources and access. There is a possibility that we might have missed some cases which hopefully will be identified in the systematic reviews registered in the International prospective register of systematic reviews. The total number of confirmed cases of COVID-19 globally as of May 2020 were more than 7 million but we were able to document only 24 cases of GBS reported in the English biomedical literature. This is a small number of cases to make a causal relationship or a definitive conclusion regarding COVID-19 associated GBS. Due to the wide spread of the disease and wide variations in the documentation and reporting of data from different parts of the world, there are chances that mild cases of GBS or cases with limited involvement might be missed or do not report to hospitals. Moreover, neurological services are not widely available in many developing countries and there is a possibility that some COVID-19 associated GBS cases remain undiagnosed due to lack of expertise in neurology. In addition, mortality in COVID-19 cases due to rapidly progressive respiratory failure is usually attributed to the COVID-19 itself. There is a possibility of co-existing GBS which may contribute to the worsening of the condition. We hope that as more data from different parts of the world is shared, things will become clearer in future and provide further insights into the COVID-19 associated GBS.

Conclusion

The primary presentation of COVID-19 is respiratory but neurological manifestations and complications are

increasingly being reported in the literature. GBS is one of the frequent neurological complication associated with COVID-19. There is no clear causative relationship between GBS, and COVID-19 at present and more data are needed to establish the casualty. However, from the available data we conclude that most of the cases present as a post-infectious disease with male preponderance. The EDX reveal a demyelinating type of polyneuropathy in most of the cases with few being AMAN and AMSAN variants. IVIG is the preferred mode of treatment and prognosis is generally good with most of the patients responding to treatment and rehabilitation plan. There is a need for large scale data collection on GBS and other related neurological manifestations and complications of COVID-19 to formulate better care plans in future.

Table 1: Details of the Demographics and clinical features of COVID-19 related GBS

	Country	Author	Age (Years)	Gender	Presenting symptoms	Clinical Examination	H/o Respiratory or GIT infection	Travel history
1.	China	Zhao	61	Female	Acute weakness both legs, Severe fatigue	Symmetrical weakness grade 4/5 on MRC Scale Areflexia After three days power 3/5 legs Sensations decreased to light touch in feet	Develop fever and cough on eight day of illness.	Travel to Wuhan City, Ch
2.	Iran	Sedaghat	65	Male	Started from lower limbs. Five days upper limbs involved.Symmetrical ascending quadriparesis, Bilateral facial palsy	UL Muscle Power 2/5 proximal and 3/5 distal LL Muscle Power 1/5 proximal and 2/5 distal Areflexia Impaired vibration and proprioception distally (DM)	Cough, Fever, and dyspnea 02 weeks prior to admission	Not Reported
3.	France	Camdessanche	65	Male	paresthesia hands and feet progressed to Quadriplegia in 3 days	2/5 in legs and arms proximally, 3/5 forearm and 4/5 hand Areflexia Absent vibrations Dysphagia present	Cough and fever 11 days before admission	No
4.	USA	Virani	54	Male	Numbness and weakness.	Power 4/5 LL initially	Fever at presentation.	No
					followed by Urinary retention and ascending paralysis	Progressed to 2/5 Areflexia	Cough for 10 days	
5.	Spain - case 1	Gutiérrez-Ortiz	50	Male	Vertical diplopia, Gait instability, perioral paresthesia Headache	Ataxia and Areflexia Right INO, Right 3rd nerve palsy No facial weakness Anosmia and ageusia	Five days back Fever, cough Malaise and backache	No
6.	Spain - Case 2	Gutiérrez-Ortiz	39	Male	Diplopia and ageusia	Bilateral abducent palsy Areflexia No ataxia and Gait instability	Fever and diarrhea 3 days before admission. No respiratory symptoms No respiratory symptoms	No
7.	Italy- Case 1	Toscano	77	Female	Paresthesia in lower limbs and hands, Acroparesthesia and hypogeusia	Flaccid quadriplegia Areflexia Later on dysphagia and respiratory difficulty	Fever and cough 7 days before admission	No
8.	Italy- Case 2	Toscano	23	Male	Facial weakness, mastoid pain and lower limb paresthesia	Hypogeusia Areflexia Bilateral facial palsy Sensory ataxia	Fever and sore throat for 10 days before admission	No
9.	Italy- Case 3	Toscano	55	Male	lower limb weakness, Paresthesia, and neck pain	Areflexia Quadriplegia bilateral facial palsy	Fever and cough for 10 days before admission.	No
10.	Italy- Case 4	Toscano	76	Male	Back pain, lower limb weakness and anosmia	Areflexic Quadriparesis	Dry cough for five days before admission and	No
							weakness on ninth day	
11.	Italy- Case 5	Toscano	64	Male	Cough, asthenia, hyposmia and hypogeusia followed by proximal weakness and paresthesia	Areflexic paraparesis later on Quadriplegia, facial palsy, bulbar weakness and dysphagia	Cough seven days before onset of neurological symptoms	No
12.	Italy	Alberti	71	Male	Paresthesia, Distal weakness progressing to quadriparesis in 3 days	Symmetric limb weakness 2/5 LL and 3/5 UL. Glove and stocking paresthesia and Areflexia	Fever for few days in the previous week	Not Reported
13.	Italy	Padroni	70	Female	Paresthesia Asthenia and gait difficulty	4/5 power Areflexia Sensations intact	24 days back fever and cough	No

14.	USA	Dinkin	36	Male	Bilateral distal Leg Paresthesia and diplopia	Left eye ptosis Mydriasis and partial 3rd nerve. Bilateral abducent palsy Gait ataxia, hypoesthesia and Areflexia	Fever, cough and myalgias four days before admission.	Not Reported
15.	Switzerland	Coen	70	Male	Paraparesis, allodynia, Myalgia, Difficulty in voiding and constipation	Bilateral lower limb Flaccid paraparesis Areflexia in all limbs Planters down going	Myalgia, fatigue, dry cough 10 days before admission	No
16.	Morocco	Otmani	70	Female	Tingling and rapidly progressive weakness	Areflexia and quadriplegia	Dry cough and fever three days before admission total 10 days before first	Not Reported
							symptom	
17.	Italy	Ottaviani	66	Female	Difficulty walking and fatigue. Rash on hands	Initially symmetric paraplegia UL power 4/5 Unilateral facial palsy Areflexia	Mild fever and cough 10 days before presentation	Yes
18.	Germany	Pfefferkorn	51	Male	Progressive upper and lower limb weakness Acroparesthesia	2/5 Muscle power with Quadriplegia Areflexia Later, locked in syndrome Bilateral facial Palsy, Bilateral hypoglossal paresis Complete sensory loss	Fever and flu, 02 weeks ago.	Not Reported
19.	Germany	Scheidl	54	Female	Paraparesis, Distal numbness and tingling Later on, developed Dysphagia	Proximal 3/5 Distal 4/5 Areflexia	PCR positive after positive contact 3 weeks before. No symptoms of cough and fever However, had anosmia and ageusia	Not Reported
20.	Iran	Ebrahimzadeh-Case 1	46	Male	Pain, and numbness in distal lower and upper extremities for a Week followed by ascending paralysis.	Mild facial nerve palsy on the right side. Muscle Power 4/5 LL progressed to 3/5 UL power 5/5 progressed to 4/5 Areflexia	Sore throat, dry cough, and mild dyspnea 18 days prior to developing neurological symptoms.	Not Reported
21. Iran	Iran	Ebrahimzadeh-	65	Male	Ascending upper and lower	Muscle Weakness 2/5 proximal	Fever and cough ten days	Not Reported
		Case 2			extremity weakness and paresthesia.	and 3/5 distal UL UL power 4/5 Areflexia in lower limbs UL reflexes +1	before PCR	
22. USA	USA	Chan-Case 1	68	Male	Gait disturbance Paresthesia hands and feet	4/5 power hip flexors Absent vibratory and proprioceptive sense at the toes and areflexia in LL and present in UL Later, bilateral fascial palsy, dysphagia, dysarthria and neck flexion weakness Dysarthria and Gait problem	Fever and Cough 18 days back	Not Reported
23. usa	USA	Chan –Case 2	84	Male	Paresthesia of hand and feet 07 days back 03 days gait disturbance	Power 3/5 proximally, unable to walk independently Gradually progressed bilateral facial palsy Autonomic dysfunction, areflexia in LL and present in UL	23 days before fever and cough	Not Reported
24.	Spain	Caamaño	61	Male	Facial Muscles weakness	Bilateral facial nerve palsy with absent blink reflex Rest of the neurological examination including reflexes were normal.	Fever and cough without dyspnea 10 days prior to admission	Not reported

ADIP: Acute Inflammatory Demyelinating Polyneuropathy; AMSAN: Acute Motor Sensory Axonal Neuropathy; AMAN: Acute Motor Axonal Polyneuropathy; CSF: Cerebrospinal fluid; GIT: Gastrointestinal tract; IVIG: Intravenous Immunoglobulins; HRCT; High Resolution Computed Tomography scan; LL: lower limbs; ;MRC: Medical Research Council; MRI: Magnetic Resonance Imaging; PCR: Polymerase Chain Reaction; PLEX: Plasma Exchange; UL; upper Limb

Table 2: Details of the diagnostics, management, and outcomes of COVID-19 related GBS

S/No	Country	Associated features and Co-morbidities	CSF / Ganglioside antibody /MRI/ CT scan findings	CT chest findings	EMG/NCS Findings	PCR for COVID-19	Respiratory failure	Mechanical Ventilation	Management	Outcomes
1.	China	Nil	CSF Analysis: Proteins 124 mg/dl, 4 cells	Ground glass opacity both lungs	AIDP	PCR Positive on Day 8 of admission	No	No	IVIG	Discharged on day 30 with normal strength and reflexes
2.	Iran	Diabetes Mellitus	Not done	Diffuse consolidation, Ground glass opacity and bilateral pleural effusions	AMSAN Day nine	PCR Positive before admission	No	No	IVIG	Not Reported
3.	France	Nil	CSF Analysis: 1.66 g/dl proteins and normal cell count Ganglioside antibodies negative	Ground glass opacity both lungs	AIDP Day five	PCR Positive before admission	Yes	Yes	IVIG	Not Reported
4.	USA	Antibiotic induced colitis	Not done	Bilateral basal opacity in lungs Whole spine imaging normal	Not done	Initially PCR was positive for Rhinovirus. On Repeat test COVID-19 PCR was positive	Yes	Yes	IVIG	Weaned off from Ventilator on day 4. Discharged to rehabilitation
5.	Spain case 1	Asthma	GD1b-IgG positive in serum	Chest X ray normal	Not done	PCR positive	No	No	IVIG	Complete recovery at discharge. Anosmia and
			CSF analysis: proteins 80mg/dl and 0 cells							agnosia persisted
6.	Spain case 2	Nil	CSF Analysis: 2 cells and 62 mg/dl proteins CSF PCR negative for Covid-19	Chest x ray normal	Not done	PCR positive	No		No	Complete recovery with no residual deficit at discharge Ageusia also resolved
7.	Italy	Nil	CSF Analysis: Protein level, 101 mg/dl; Cells 4 per mm3; Negative CSF PCR Ganglioside Ab: negative	Bilateral interstitial pneumonia	AMSAN	PCR positive	Yes	Non-Invasive Ventilation	IVIG (two sessions)	Minimal improvement
8.	Italy	Nil	CSF Analysis: : Proteins 123mg/dl, No cells, Negative CSF PCR MRI: focal contrast	CT chest was normal	AMSAN	PCR positive	No	No	IVIG	Discharged
			enhancement in internal acoustic meatus							
9.	Italy	Nil	Proteins 193 mg/dl No cells Negative CSF PCR Ganglioside AB negative	Bilateral ground glass opacity	AMAN Variant	PCR positive	Yes	Yes	IVIG two sessions	Still critical at the time of publication Poor outcome

10.	Italy	Nil	Normal proteins and no cells Negative CSF PCR	Normal	AIDP Variant	PCR positive	No	No	IVIG	Undergoing Rehab at the time of publication
11.	Italy	Nil	proteins 40mg/dl Cell count 3 Negative CSF PCR Ganglioside Ab negative	Interstitial pneumonia	AIDP Variant	PCR Negative. Serology was Positive for COVID-19	Yes	Yes	IVIG followed by PLEX	Patient was on ventilatory support at the time of publication
12.	Italy	HTN, Aortic aneurysm repair and lung cancer treated by surgery alone	CSF Analysis: 9 cells and proteins 54 mg/dl CSF PCR negative	Multiple bilateral ground glass opacity and consolidation	AIDP Variant	PCR positive	Yes	CPAP with Prone Positioning	IVIG	Expired
13.	Italy		CSF Analysis: proteins 48 mg/dl and 1 cell	Some ground glass areas in both lungs	AIDP	PCR positive	Yes	Yes	IVIG	Not Reported
14.	USA		CSF Analysis: Not done MRI showed enhancement of 3rd nerve Ganglioside antibody negative	X ray chest Normal	Not done	PCR Positive	No	No	IVIG	Partial recovery at the time of discharge
15.	Switzerland		CSF Analysis: Proteins was raised no values provided CSF PCR negative	Chest x ray normal	AIDP	PCR Positive	No	No	IVIG	Day 11 patient Discharged to Rehab facility
			Ganglioside Ab negative MRI no evidence of myelopathy							
16.	Morocco	rheumatoid arthritis	CSF Analysis: Proteins 1gm/l , normal cells. CSF PCR negative	Ground glass opacity left lung	AMSAN	PCR positive	No	No	IVIG	No improvement
17.	Italy	Mild Hypertension	CSF Analysis: Proteins 108mg/dl, No cells CSF PCR negative	Bilateral ground glass opacity	Demyelination with axonal damage likely mixed picture	CSF PCR negative Antiglycolipid e Ab negative	Yes	Yes	IVIG	critical
18.	Germany		CSF Analysis: Normal proteins,9 cells. CSF PCR negative Ganglioside AB negative MRI spine: enhancement of	Bilateral interstitial infiltrates	AIDP	Nasal swab PCR +	Yes	Yes	IVIG followed by PLEX	Still on mechanical ventilation but showing signs of motor improvement and Undergoing Rehabilitation
			spinal nerve roots							
19.	Germany		CSF Analysis: Increase proteins 140g/l, and normal cells MRI cervical spine: normal	Chest X ray normal	AIDP	PCR positive	No	No	IVIG	Complete Recovery Discharged

20.	Iran	Nil	CSF Analysis: 78mg/dl Proteins 4 cells Gq1b antibody negative Brain and spine MRI: Normal	Multiple ground glass opacity in both the lungs	AIDP	PCR Positive	No	No	No active treatment	Muscle Power improved to near normal and discharged.
21.	Iran	Hypertension	CSF Analysis: Not done Gq1b antibody negative	HRCT positive Details not provided	AIDP	PCR Positive	No	No	IVIG	Muscle power improved to 4+/5. Discharged
22.	USA		CSF Analysis: 226mg/dl proteins 3 cells, CSF PCR negative Ganglioside Ab negative		Not done	PCR Positive	No	No	PLEX	Discharged to Rehabilitation. Can ambulate with minimal assistance. Dysphagia resolved
23.	USA	Nil	CSF Analysis: 67mg/dl l protein,1 cell. CSF PCR negative Ganglioside Ab GM2 IgG/IgM +	Not done	Not done	PCR Positive	Yes	Yes	PLEX followed by IVIG	Quadriplegic with intermittent autonomic dysfunction. Being weaned from the ventilator
24.	Spain		CSF Analysis: Mildly elevated levels of proteins (44 mg/dL), absent leukocytes CSF PCR negative. CT scan and brain MRI normal	X ray chest pneumonia	Not done	PCR Positive	No	No	Low dose oral Prednisolone	No significant improvement in facial muscle weakness after 2 weeks

ADIP: Acute Inflammatory Demyelinating Polyneuropathy; AMSAN: Acute Motor Sensory Axonal Neuropathy; AMAN: Acute Motor Axonal Polyneuropathy; CSF: Cerebrospinal fluid; GIT: Gastrointestinal tract; IVIG: Intravenous Immunoglobulins; HRCT; High Resolution Computed Tomography scan; LL: lower limbs; ;MRC: Medical Research Council; MRI: Magnetic Resonance Imaging; PCR: Polymerase Chain Reaction; PLEX: Plasma Exchange; UL; upper Limb

Table 3: comparison of COVID-19 associated GBS with Zika associated GBS

S No	Parameters	Zika Associated GBS – Puerto Rico [46]	Zika Associated GBS	COVID-19 associated GBS
1.	Number of reported cases	71	23	24
2.	Mean Age	54 Years	61 Years	60 Years
3.	Gender Distribution females	3752.1)	8(34)	6(25%)
4.	Facial weakness	44(62%)	9(39%)	9(37%)
5.	Dysphagia	38(53%)	16(70%)	2(8%)
6.	Cough	3(4.2%)		21(87%)
7.	Shortness of breath	33(46.5%)	Not mentioned	
8.	Hyporeflexia/areflexia	71(100)	23(100%)	23(99%)
9.	Antecedent illness to neurological signs	7 (0-21)	5.9 (1.5–6.5)	11(3-28)
10.	Antecedent illness fever	28(39.4)	5(22%)	18(72%)
11.	Elevated proteins in CSF	49/52(94.2%)	Not reported	16(80%) Not done in 4 Normal in 4
12.	ICU admission	47(66.2%)	14(61%)	9(36%)
13.	Mechanical ventilation	22(31%)	10(43%)	9(36%)
14.	Outcomes and discharge to rehab/nursing home	35 (49.3)	Not mentioned	3 still critical 2 no improvement 3 not reported
15.	Discharge home	32 (45.1)	Not mentioned	16
16.	Death	2 (2.8%)	2	1

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