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Pharmacotherapy of Gullain Barre Syndrome in Covid-19 A Critical Review

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ABSTRACT:
Coronavirus (CoV) is a large family of positive sense, single stranded RiboNuclicAcid (RNA) viruses that belong to the Nidovirales order. COVID-19 (SARS-CoV-2) is causing a current pandemic. It commonly manifests with fever, dyspnoea, and cough. Few COVID-19 patients with Guillain-Barre Syndrome (GBS) have been reported. The severe inflammatory response and the critically-ill nature of many COVID-19 patients is a challenge to distinguish GBS from critical illness polyneuropathy and myopathy. The respiratory failure is generally related to a worse outcome in GBS. GBS is a disorder in which the immune system attacks gangliosides on the peripheral nervous system. It presents with ascending weakness and can cause total body paralysis and respiratory failure in severe cases. It is associated with a variety of viral and bacterial infections. The clinical characteristics of GBS are the progressive weakness of the limbs and reduction in or loss of tendon reflexes (hypo-reflexia and areflexia, respectivelyIVIg (0.4 g/kg body weight daily for 5 days) and plasma exchange (200–250 ml plasma/kg body weight in five sessions) are equally effective treatments for GBS .IVIg and plasma exchange carry comparable risks of adverse events, although early studies showed that plasma exchange was more likely than IVIg to be discontinued. More cases with epidemiological data should, however, be examined and future studies in this regard should be carried out. Because of the potential link between GBS and COVID19, it is advised that doctors follow up on patients with regard to neurological manifestations. Finally, it is proposed that research on the relationship between COVID-19 and the nervous system should not be restricted to the current time, so that the appropriate steps may be taken in the future if we encounter a new form of this virus.
KEY WORDS: COVID 19, Guillain-Barre Syndrome, Paralysis, Immune system, Nervous system, Respiratory failure and Plasma exchange.

I. INTRODUCTION:

Coronavirus(CoV) is a large family of positive sense, single-stranded RiboNuclicAcid(RNA) viruses that belong to the Nidovirales order. The order includes Roniviridae, Arteriviridae, and Coronaviridae families. The Coronaviridae family is subdivided into Torovirinae and Coronavirinae subfamilies. Coronavirinae is further sub-classified into alpha, beta, gamma and delta Coronavirus [1]. A major difference from common flu virus to Coronavirus disease(COVID-19) is that the latter one originates from including common cold to severe syndrome like middle east respiratory(MERS) and severe acute respiratory(SARS). COVID virus is a new strain that is first discovered in humans. It is a zoonosis type of infectious disease that spreads from nonhumans to humans. Even several known corona viruses are circulating in animals that are not yet infected to humans[2].In the month of December 2019, a novel human coronavirus outbreak started in Wuhan, Hubei Province, China

and then subsequently spread to dozens of other countries becoming a global pandemic[3].On January 22, 2020, novel CoV has been declared to be originated from wild bats and belonged to Group 2 of beta- coronavirus that contains Severe Acute Respiratory Syndrome Associated Coronavirus(SARS-CoV). Although COVID19 and SARS-CoV belong to the same beta coronavirus subgroup, similarity at genome level is only 70% and the novel group has been found to show genetic differences from SARS-CoV [4]. COVID-19 (SARS-CoV-2) is causing a current pandemic. It commonly manifests with fever, dyspnoea, and cough. Few COVID-19 patients with Guillain-Barre Syndrome (GBS) have been reported. With the increasing understanding of the Covid-19 disease, many non-pulmonary symptoms were recognised, including neurological complications such as acute cerebrovascular diseases, seizures, meningitis, encephalitis and skeletal muscle involvement. [5,6,7] Massimiliano Filosto et al, in their study From 1 April to 30 June 2020, 42 patients with SARS-CoV-2 infection and Guillain-Barré syndrome (GBS) have been reported mostly from Europe, and the number of cases is increasing weekly, suggesting a possible association.[8] The severe inflammatory response and the critically-ill nature of many COVID-19 patients is a challenge to distinguish GBS from critical illness polyneuropathy and myopathy [9].The respiratory failure is generally related to a worse outcome in GBS [10][11]

II. LITERATURE SEARCH STRATEGY

In this study, a literature search was done on SCOPUS, PubMed, Cochrane database, Google Scholar, and according to preferred reporting items for GBS related to COVID-19 infection. The used keywords were "SARS-CoV," "MERS-CoV," "COVID-19," "SARS-CoV2," "neurology," nervous system," neurological manifestations," "Guillain-Barre syndrome."

III. GULLAIN-BARRIE SYNDROME

GBS is a disorder in which the immune system attacks gangliosides on the peripheral nervous system. It presents with ascending weakness and can cause total body paralysis and respiratory failure in severe cases. It is associated with a variety of viral and bacterial infections. [9] with an incidence of 1.11/100,000 inhabitants. The etio-pathogenesis of polyneuropathy in GBS is believed to be due to molecular mimicry between epitopes of microorganisms and peripheral nerve glycolipids [12] . In 2/3 of the patients with GBS there is a history of respiratory or gastrointestinal infection in the previous days or weeks. Some viruses have been described as causative agents of GBS (Influenza A, cytomegalovirus, Zika, Chikungunya…) [12] The incidence of GBS can increase during outbreaks of infectious illnesses that trigger the disease [13] Most recently, the Zika virus epidemics in French Polynesia in 2013 and in Latin America and the Caribbean in 2015–2016 were linked to an increase in individuals being diagnosed with GBS[14-16]. a potential causal association with beta-coronaviruses [Middle East Respiratory Syndrome (MERS-CoV)] has already been speculated, the relationship between COVID-19 and GBS deserves undoubtedly further attention [17,18].

i. Gullain – Barrie syndrome COVID -19: There are hardly data in the literature about GBS by coronavirus. 12 cases of GBS have been reported in COVID-19 infection.[9] Guillain-Barré syndrome (GBS) is a serious complication of COVID-19 disease and can occur within days of the first respiratory symptoms.[19] GBS developed within 10 days of COVID diagnosis and presented with ascending progressive, flaccid quadri-paresis.[9] Clinically, mild courses up to severe tetraparesis and cranial nerve involvement are possible. Electro-neuro-graphically, a demyelinating pattern of damage usually dominates, although axonal processes are also reported. CSF diagnosis is necessary to exclude an infectious-aetiology. In most cases a cytoalbuminous dissociation appears. Serological testing of ganglioside antibodies is recommended. On the basis of electrophysiological and pathological characteristics, GBS has been classified into acute inflammatory demyelinating polyradiculoneuropathy (AIDP), acute motor axonal neuropathy (AMAN) and acute motor sensory axonal neuropathy (AMSAN). [20-24] Intravenous immunoglobulins as well as plasma-exchange procedures are to be regarded as equivalent and should be initiated promptly. [19] IVIG was used for all the patients, and one was started on plasmapheresis. The involvement of the PNS supports the coronavirus neurotropic invasion pathway. It is still unclear if SARS-CoV-2 can directly invade neurons and cause neuropathy [9]

ii. Clinical characteristics of GBS: The clinical characteristics of GBS are the progressive weakness of the limbs and reduction in or loss of tendon reflexes (hypo-reflexia and areflexia, respectively). In this disorder, protein concentrations in the cerebrospinal fluid (CSF) increase, while the white cell count is normal [25,26]. Among the fi rst symptoms are pain, numbness, paraesthesia, or weakness in the limbs. GBS is usually caused by a viral or bacterial infection. In response to the antigen, the immune system is activated and the nerve roots and peripheral nerves are injured because of the structural similarity of this antigen to axons and myelin [27]. The symptoms peak within 4 weeks and the patients should be monitored because 20% to 30% of them will need mechanical ventilation [28,29].

IV. DIAGNOSIS

GBS is most commonly a post-infectious disorder that usually occurs in otherwise healthy people, and is not typically associated with an autoimmune or other systemic disorder. In typical cases, among the first symptoms are pain, numbness, paraesthesia, or weakness in the limbs. The main features of GBS are rapidly progressive bilateral and relatively symmetric weakness of the limbs with or without involvement of respiratory muscles or cranial nerve-innervated muscles. [30,31] The diagnosis of GBS can be challenging owing to heterogeneity in clinical presentation, an extensive differential diagnosis, and the lack of highly sensitive and specific diagnostic tools or biomarkers. [32]

Features required for diagnosis: Progressive weakness in both arms and legs (might start with weakness only in the legs), Areflexia (or decreased tendon reflexes).

Features that strongly support diagnosis: Progression of symptoms over days to 4 weeks, Relative symmetry of symptoms, Mild sensory symptoms or signs Cranial nerve involvement, especially bilateral weakness of facial muscles, Autonomic dysfunction, Pain (often present), High concentration of protein in CSF, Typical electro-diagnostic features

Features that should raise doubt about the diagnosis : Severe pulmonary dysfunction with limited limb weakness at onset, Severe sensory signs with limited weakness at onset, Bladder or bowel dysfunction at onset, Fever at onset Sharp sensory level, Slow progression with limited weakness without respiratory involvement (consider subacute inflammatory demyelinating polyneuropathy or CIDP), Marked persistent asymmetry of weakness, Persistent bladder or bowel dysfunction, Increased number of mononuclear cells in CSF (>50×106 Poly-morphonuclear cells in CSF.[33]

V. MANAGEMENT OF GBS DURING THE COURSE OF DISEASE

Diagnosis of GBS is mainly based on clinical features and CSF findings Laboratory investigations include blood studies and electro myography [33] IVIg (0.4 g/kg body weight daily for 5 days) and plasma exchange (200–250 ml plasma/kg body weight in five sessions) are equally effective treatments for GBS [34] [35]. IVIg and plasma exchange carry comparable risks of adverse events, although early studies showed that plasma exchange was more likely than IVIg to be discontinued [34] [36]. As IVIg is also easier to administer and generally, more widely available than plasma exchange, it is usually the treatment of choice. Besides IVIg and plasma exchange, no other procedures or drugs have been proven effective in the treatment of GBS. Although corticosteroids would be expected to be beneficial in reducing inflammation and, therefore, disease progression in GBS, eight randomized controlled trials on the efficacy of corticosteroids for GBS showed no significant benefit, and treatment with oral corticosteroids was even shown to have a negative effect on outcome [37]. Furthermore, plasma exchange followed by IVIg is no more effective than either treatment alone and insufficient evidence is available for the efficacy of add- on treatment with intravenous methylprednisolone in IVIg treated patients [37] [38]. Antimicrobial or antiviral treatment can be considered in patients with GBS who have an ongoing infection. [32]

VI. INDICATION FOR ADMISSION TO AN INTENSIVE CARE UNIT

Rapid progressive severe weakness often with impaired respiration (vital capacity <20 mL/kg) Need for artificial ventilation Insufficient swallowing with high chance of pulmonary infection Severe autonomic dysfunction Fluctuations during the course of disease or continued slow progression? Consider treatment-related fluctuation: repeat treatment Consider acute-onset CIDP (A-CIDP) and treat accordingly Rehabilitation and fatigue Start physiotherapy early during course of disease Start rehabilitation as soon as improvement starts Consider a physical training programme for severe fatigue Consider contacting patients' organisation for additional information and help [33]

VII. TIMING OF TREATMENT

The North American PE trial showed an effect of PE when applied within the fi rst 4 weeks after onset of weakness. [39] The greatest effect was observed when PE was started within the first 2 weeks from onset, in patients who were unable to walk. Patients with the onset of GBS and who are unable to walk without assistance, only in such conditions the patient should be treated with IVIg or PE, within the first 2 weeks. [33]

VIII. TREATMENT OF MILD PATIENTS

"Mildly affected" is arbitrarily defined as being able to walk, with or without assistance. A retrospective study showed that these patients often have residual disabilities. [40] RCTs that have assessed the effect of IVIg have not studied the effect in mildly affected patients. [41] One large French randomized trial studied the effect of PE in patients who could walk with or without aid, but could not run. [42] Onset of motor recovery was faster in patients who received two PE sessions than in those who received no PE. On the basis of this study, there might be an indication to treat mildly affected patients who have GBS with PE, but it should be

kept in mind that no randomized placebo-controlled trials have assessed the effect of PE or IVIg in these mildly affected patients with GBS. [33]

IX. DISCUSSION

GBS is emerging as a relevant disease that may appear in COVID-19 patients. Male predominance of GBS in COVID-19 patients seems to follow reports about more severe presentation versus its female counterparts. GBS in COVID-19 patients shows heterogeneous presentations both clinical (e.g., ascending or cranial nerve paralysis) and electrophysiological (e.g., axonal or demyelinating). Temporal correlation of GBS seems to occur after COVID-19 onset [43] Pieter A van Doorn et al, in their study stated that Guillain-Barre syndrome (GBS) is an important cause of acute neuromuscular paralysis, GBS often remains a severe disease; 3–10% of patients die and 20% are still unable to walk after 6 months, many patients have pain and fatigue that can persist for months or years, effective treatments in GBS are Intravenous immunoglobulin (IVIg) and plasma exchange, mainly for practical reasons, IVIg is the preferred treatment. The timing of treatment for severe GBS illness patients was IVIg or PE treatment within 2 weeks. According to the case study carried out by Gianpaolo Toscano et al, in three hospitals in northern Italy, they examined five patients who had Guillain– Barré syndrome after the onset of coronavirus disease 2019 (Covid-19), the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). During that period, an estimated 1000 to 1200 patients with Covid-19 were admitted to these hospitals. Four of the patients in this series had a positive nasopharyngeal swab for SARS-CoV-2 at the onset of the neurologic syndrome, and one had a negative nasopharyngeal swab and negative broncho-alveolar lavage but subsequently had a positive serologic test for the virus. The interval of 5 to 10 days between the onset of viral illness and the first symptoms of Guillain–Barré syndrome is similar to the interval seen with Guillain–Barré syndrome that occurs during or after other infections. There have been reports of an association between Guillain–Barré syndrome and coronavirus infections. All the patients were treated with intravenous immune globulin (IVIG); two received a second course of IVIG and one started plasma exchange. At 4 weeks after treatment, two patients remained in the intensive care unit and were receiving mechanical ventilation, two were undergoing physical therapy because of flaccid paraplegia and had minimal upper-limb movement, and one had been discharged and was able to walk independently. Recently a new covid strain (B117 CoV- mutated strain) is found in UK which is said to be more virulent than the other strains. without further study we cannot conclude that the latest strain as it is much virulent is directly linked with the increase in incidence of Gillian Barrie syndrome and vice versa. So, we suggest the study should be carried out with respective both the strains of covid which lead to occurrence of Gillian Barrie syndrome. We believe and suggest that an extensive in vivo and in vitro investigational study panels should be set up for IVIg and PE.

X. CONCLUSION

In COVID-19 patients, GBS is emerging as an important neurological condition. Further research remains on its pathophysiology and both clinical and electrophysiological characteristics. The initiation of GBS appears to occur several days after the presentation of COVID-19. As they look after COVID-19 patients, clinicians and investigators should have GBS in mind and perform more research on novel aspects of COVID-19. Although it remains uncertain the mechanism. While GBS is a rare complication due to SARS-CoV-2, we believe it is necessary to recognise this possibility concomitantly or even after weeks following SARS-CoV-2 infection in patients with COVID-19 because it requires a different prognosis and unique care compared with traditional treatment. Our analysis research emphasises that GBS in patients with COVID-19 with ARDS, polyneuropathy, and trouble weaning off the ventilator should be considered as one of the differentials. More cases with epidemiological data should, however, be examined and future studies in this regard should be carried out. Because of the potential link between GBS and COVID19, it is advised that doctors follow up on patients with regard to neurological manifestations. Finally, it is proposed that research on the relationship between COVID-19 and the nervous system should not be restricted to the current time, so that the appropriate steps may be taken in the future if we encounter a new form of this virus.

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