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Neuromuscular disorders relationship with COVID-19 infection

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Abstract
Background: Coronavirus (COVID-19) appeared in China in December 2019, with neuromuscular complications including: acute inflammatory demyelinating polyneuropathy (AIDP), acute motor axonal neuropathy (AMAN), Miller Fisher syndrome and polyneuritis cranialis, pharyngeal-cervical-brachial variant of GBS, facial diplegia and myositis.
Methods: The study included 71 GBS cases which were divided into three groups: GBS following COVID-19 infection, GBS following COVID-19 vaccine and GBS without COVID vaccine or infection and also included a few number of other neuromuscular disorders as myathenis gravis and inflammatory myositis.
Results: Preceding diarrhea was significantly higher in infection group and control group than vaccine group. EGOS1, EGOS2, EGRIS, NEDS mean values were significantly lower in vaccine group. Total MRC was of significantly higher value in vaccine group. Olfactory nerve and bulbar affection were significantly higher in infection group. Pattern of neuropathy was predominantly sensorimotor axonal in the 3 groups. CSF proteins showed higher level in infection and control groups. There was no significant difference in response to plasma exchange or IVIG in 3 groups. Other COVID positive cases were de novo diagnosed as MG and myositis.
Conclusion: There were milder symptoms with better outcome in vaccine group with no specific pattern of clinical presentation in each group or superiority of one modality of treatment over the other. Also, our study included few other cases of de novo neuromuscular disorders. It is not clear if there is casual relationship between COVID and these disorders or just unmasked by the infection or subsequent immune process.

Keywords: Coronavirus disease 2019 (COVID-19), neuromuscular, COVID vaccine, guillain barré syndrome, myositis, myathenia gravis

1. Introduction
December 2019 saw the arrival of the coronavirus (COVID-19) in China, which has a significant potential for mortality and spread, particularly in older people with multiple medical conditions [1].
Neuromuscular complications such Guillain-Barré syndrome (GBS) and critical illness myopathy/polyneuropathy (including its variant Bickerstaff brainstem encephalitis) and toxins- or virus-related sensory neuropathy have been reported with prior severe acute respiratory syndrome (SARS) outbreaks of 2003 and Middle East respiratory syndrome (MERS) of 2012 [2].
About 36.4% of hospitalized Covid-19 patients in Wuhan had neurologic signs, including 24.8% with symptoms related to the central nervous system (CNS), 8.9% with symptoms related to the peripheral nervous system (PNS), and 10.7% with skeletal muscle damage [3].
Numerous papers over the past few months have detailed various neuromuscular complications in SARS-COV2 infected individuals. Acute inflammatory demyelinating polyneuropathy (AIDP) [4], acute motor axonal neuropathy (AMAN) [5], polyneuritis cranialis and Miller Fisher syndrome [6], pharyngeal-cervical-brachial form of GBS [7], facial diplegia [8], and myositis [9] are some of these complications.
For individuals suffering from severe symptoms of neurologic diseases, particularly those who are old or immunocompromised, the COVID-19 pandemic has left many unsolved issues.

Although there are worries about the theoretical dangers of vaccination, such as vaccine safety and efficacy in the context of immunotherapy and the potential to cause or worsen neurologic symptoms, emerging SARS-CoV-2 vaccines provide significant protection against symptomatic infection [10].

Vaccination against COVID-19 involves risks, as is common with most therapeutic methods for the treatment and prevention of any illness. These might be as little as fever, local pain, or myalgias, or as serious as many potentially fatal cardiac and neurological complications. The latter group involve, among other things, acute inflammatory demyelinating polyneuropathy, transverse myelitis, and cerebral venous thrombosis-which is oddly frequently associated with thrombocytopenia [11].

2. Subjects and Methods

This cross-sectional study was carried out in the Neuropsychiatry and Radiology departments in Tanta University Hospitals in the period from 1st of December 2019 till the end of April 2022.

2.1 Participants

This study involved 74 cases of de novo neuromuscular disorders post COVID-19 infection and vaccination including 71 cases of GBS, one case of MG and 2 cases of myositis. GBS cases were devided into three groups:

- **Group A):** 27 patients presented with GBS following COVID19 infection
- **Group B):** 24 patients presented with GBS following COVID vaccine.
- **Group C):** 20 patients presented with GBS not preceded by COVID vaccine or infection (control patients).

2.2 Methods

After taking the needed permissions from the research ethics committee and obtaining a written consent from participants, each participant was subjected to the following:

2.2.1 Clinical assessment which included the following items

History taking: including personal history, complaint, past medical history, social history and habits.

- Neurological examination: including cranial nerve examination, motor system examination using MRC scale, superficial and deep sensory examination.
- Clinical assessment of neurological and muscular symptoms using the following scales:
- The medical research council (MRC) scale for motor power examinaton [12]
- Utah early neuropathy scale (UENS) [13].
- modified Erasmus GBS outcome score (mEGOS). [14, 15].
- Erasmus GBS Respiratory Insufficiency Score (EGRIS) [15].
- Myasthenia Gravis Composite scale (MGC) [16]
- MG Foundation of American [17]

Radiological investigations

a) Computarized tomography (CT) or magnetic resonant imaging (MRI) brain (if needed).
b) Magnetic resonant imaging (MRI) of spinal cord (if needed).
c) Computerized tomography (CT) chest with Coronavirus disease Reporting And Data System (CORADS) (18)

Neurophysiologic investigations

The studies were performed by an EMG device called the Viking Quest NicoletOne EMG, the manufacturer is the Viasys. Healthcare company in USA, the system serial number is OP060166.

a) Nerve conduction study (NCS)
b) Routine nerve conduction studies were done by conventional methods, using Viking Quest EMG machine.
c) Electromyogram (EMG).
d) Repetitve nerve stimulation test.(If needed).

Was done for assessment of the neuromuscular junction disorder

3. Results

Table 1: Demographic data of GBS patients

	Infection Group (n=27)	Vaccine group (n=24)	Control group (n=20)	P
Age				
Mean ± SD	51.5 ± 15.75	45.8 ± 10.26	51.2 ± 20.73	
Min.-Max.	17.0 – 67.0	22.0 – 60.0	24.0 – 91.0	0.270
Median (IQR)	58.0 (39.0-65.0)	46.5 (36.25-55.0)	51.0 (32.0-64.5)	
Sex				
Male	12	17	15	
	44.4%	70.8%	75.0%	0.060
Female	15	7	5	
	55.6%	29.2%	25.0%	

Table 2: Preceding diarrhea in GBS patients

	Infection Group (n=27)	Vaccine group (n=24)	Control group (n=20)	P
Preceding diarrhea				
Yes	8	0	5	
	29.6%	0.0%	25.0%	**0.017***
No	19	24	15	
	70.4%	100.0%	75.0%	
P1= 0.005* p2= 0.726 p3= 0.014*				

*p≤ 0.05 (Statistically significant)
(p1: Infection & Vaccine) (p2: Infection & Control) (p3: Vaccine & Control) in infection

Table 3: Severity of infection and hospitalization group,

		No.	%
Infection Severity	Mild	10	37.0
	Moderate	6	22.2
	Severe	11	40.8
Hospitalization	Yes	12	44.4
	No	15	55.6

Table 4: Vaccine type in vaccine group

	Vaccine type	No	%
Vaccine Type	AstraZeneca	12	50.0
	Sinopharm	7	29.2
	Sinovac	5	20.8

Table 5: Scales of GBS patients (EGOS1 and EGOS2)

	Infection Group (n=27)	Vaccine group (n=24)	Control group (n=20)	P
EGOS1				
Mean ± SD	3.4 ± 2.86	1.5 ± 1.10	4.9 ± 2.25	<0.001*
Min. – Max.	0.0 – 8.0	0.0 – 3.0	0.0 – 8.0	
Median (IQR)	4.0 (1.0 – 6.0)	1.0 (1.0 – 2.75)	5.0 (3.25 – 6.75)	
P1= 0.035* p2= 0.159 p3= <0.001*				
EGOS2				
Mean ± SD	4.5 ± 3.85	1.6 ± 1.38	5.4 ± 3.88	0.005*
Min. – Max.	0.0 – 11.0	0.0 – 4.0	0.0 – 11.0	
Median (IQR)	5.0 (1.0 – 8.0)	1.0 (1.0 – 3.0)	5.5 (1.0 – 9.25)	
P1= 0.032* p2= 1.000 p3= 0.007*				

Table 6: Scales of GBS patients (EGRIS)

	Infection Group (n=27)	Vaccine group (n=24)	Control group (n=20)	P
EGRIS				
Mean ± SD	2.0 ± 2.05	1.1 ± 1.21	2.0 ± 1.26	0.038*
Min. – Max.	0.0 – 7.0	0.0 – 3.0	1.0 – 4.0	
Median (IQR)	2.0 (0.0 – 3.0)	1.0 (0.0 – 2.5)	1.5 (1.0 – 3.5)	
P1= 0.172 p2= 1.000 p3= 0.046*				

Table 7: Scales of GBS patients (NEDS)

	Infection Group (n=27)	Vaccine group (n=24)	Control group (n=20)	P
NEDS				
Mean ± SD	3.1 ± 1.68	2.7 ± 1.05	3.7 ± 1.08	0.037*
Min. – Max.	1.0 – 6.0	1.0 – 4.0	2.0 – 6.0	
Median (IQR)	3.0 (1.0 – 4.0)	3.0 (2.0 – 3.75)	4.0 (3.0 – 4.0)	
P1= 0.593 p2= 0.472 p3= 0.030*				

Table 8: Scales of GBS patients (UENS)

	Infection Group (n=27)	Vaccine group (n=24)	Control group (n=20)	P
UENS				
Mean ± SD	12.3 ± 5.17	11.8 ± 3.19	9.4 ± 7.23	0.388
Min. – Max.	4.0 – 22.0	6.0 – 18.0	0.0 – 22.0	
Median (IQR)	12.0 (8.0-16.0)	11.0 (10.0-12.0)	11.0 (1.0-14.0)	

UENS mean value was significantly lower in vaccine group than the other 2 groups

Table 9: Scales of GBS patients (MRC)

	Infection Group (n=27)	Vaccine group (n=24)	Control group (n=20)	P
Total MRC				
Mean ± SD	45.1 ± 15.34	52.2 ± 4.49	35.7 ± 11.97	<0.001*
Min. – Max.	8.0 – 60.0	48.0 – 60.0	18.0 – 54.0	
Median (IQR)	48.0 (36.0 – 60.0)	52.0 (48.0 – 56.0)	38.0 (24.0 – 44.0)	
P1= 0.224 p2= 0.013* p3= <0.001*				

Table 10: Treatment received and treatment response in GBS patients

	Infection Group (n=27)	Vaccine group (n=24)	Control group (n=20)	P
Treatment received				
Plasma exchange	14	19	14	0.110
	51.9%	79.2%	70.0%	
IVIG	13	5	6	
	48.1%	20.8%	30.0%	
Treatment response to Plasma exchange				
Favorable	9	18	11	0.092
	64.3%	94.7%	78.6%	
Unfavorable	5	1	3	
	35.7%	5.3%	21.4%	
Treatment response to IVIG				
Favorable	9	4	5	0.839
	69.2%	80.0%	83.3%	
Unfavorable	4	1	1	

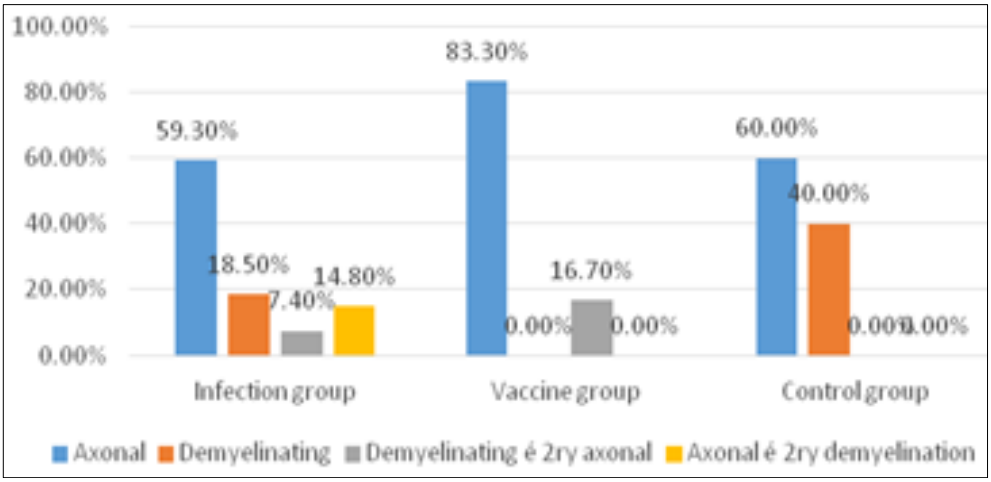

Fig 1: Neuropathy axonal demyelinating in the 3 groups

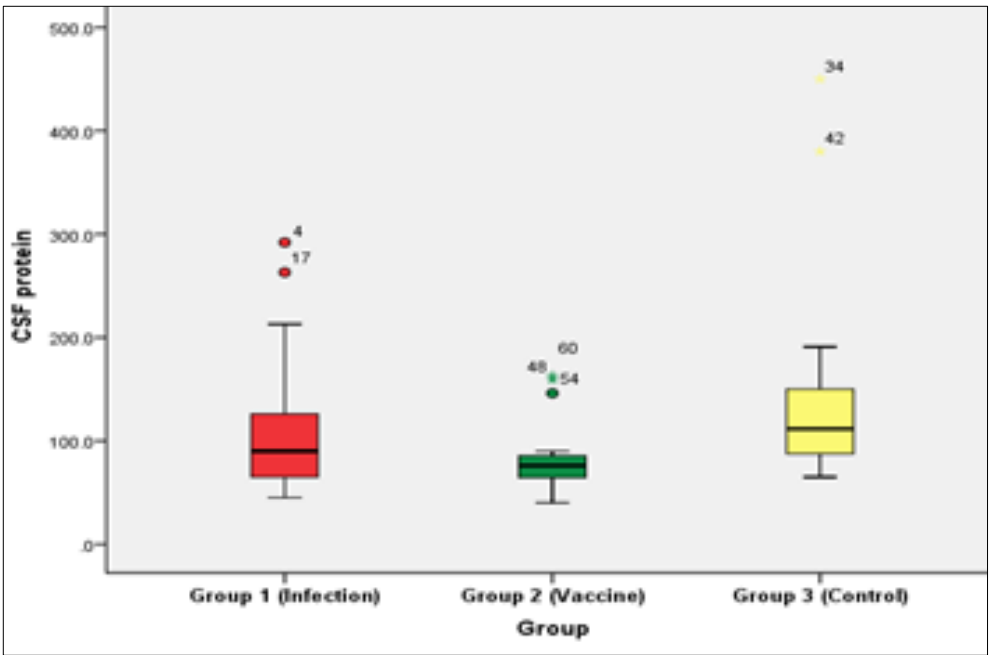

Fig 2: Box and Whisker plot for CSF protein in the 3 groups

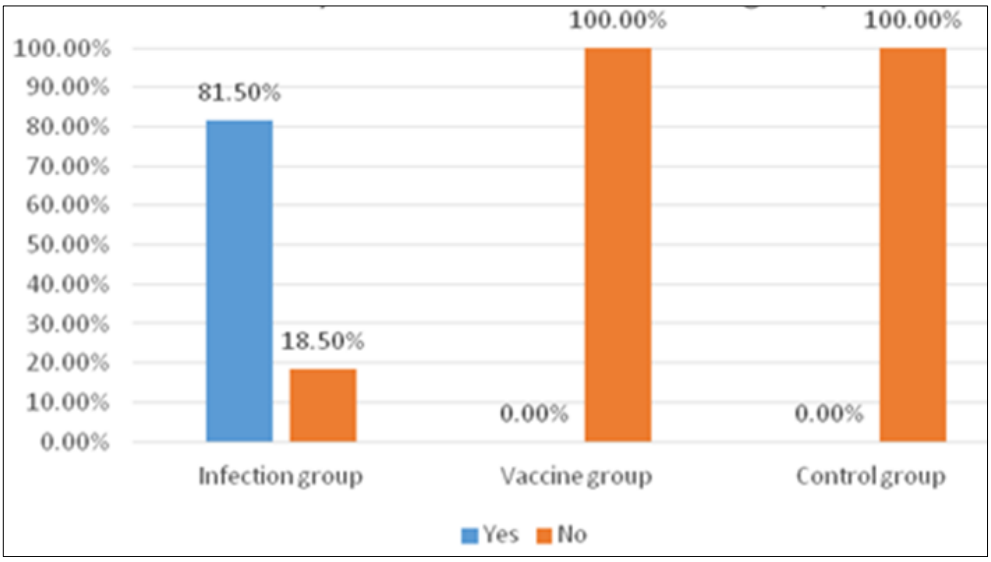

Fig 3: Olfactory nerve affection in the 3 groups

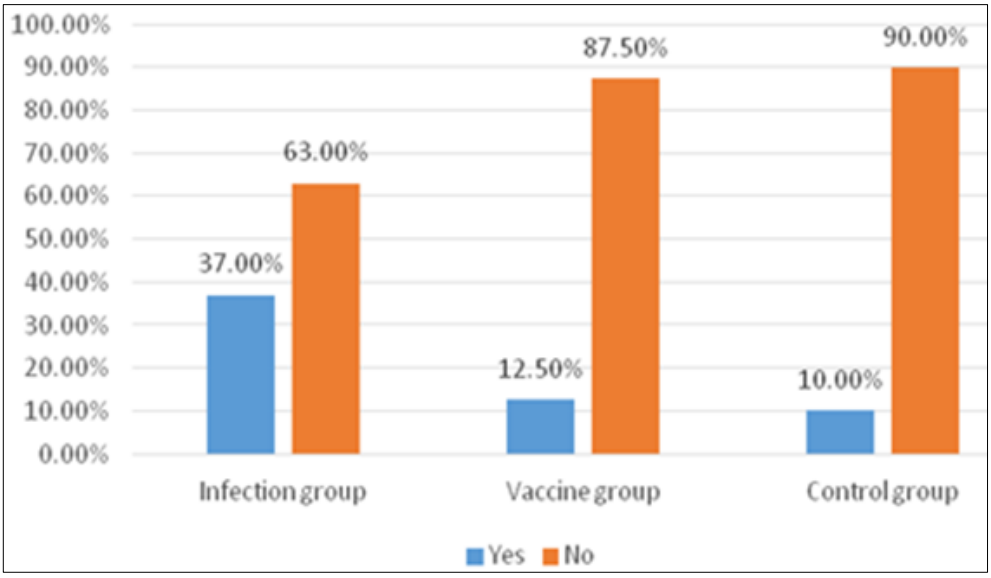

Fig 4: Bulbar nerve affection in the 3 groups

4. Discussion

This study assessed the association between COVID-19 infection or vaccination and neuromuscular diseases.

Regarding GBS, case-controlled study was done comparing between 3 groups: Infection group, vaccine group and control group.

As regards age: Mean values of age were (51.5 ±15.75), (45.8 ± 10.26), (51.2 ± 20.73) in COVID-19 infection, vaccine and control groups respectively with no significant difference between 3 groups. Many studies showed that the age is the most important predictor for outcome and susceptibility to infection. Susceptibility to infection generally increases with age [19].

As regards gender: Our study showed that male: female ratio was 0.7, 2.4, 3 in infection, vaccine and control groups respectively.

Female predominance in infection group may be due to increased infection severity and mortality in males. Increased COVID-19 infection severity and mortality in males was reported by Mukherjee and Pahan in 2021 and also by Peckham *et al*. in 2020 [20, 21] and According to a study of 54 COVID-19 died cases in South Korea, 61% of the patients were men [22], suggesting that although women have higher survival rates than men, long-term complications may mostly affect them. Furthermore, research investigating 799 patients at Wuhan, China's Tongji Hospital discovered that out of 113 COVID-19 deaths, 27% were female and 73% were male [23].

Also, more female affection in our study may be related to more prevalence of vitamen D deficiency in females which may increase risk of infection in females than males. There may be a connection between COVID-19 cases and mortality and the average vitamin D levels in different nations. There were found to be adverse relationships between the average vitamin D levels in each nations and the number of COVID-19 cases [24].

Even though Egypt has a high level of year-round UV exposure and sunshine, a significant prevalence of vitamin D insufficiency exists there, particularly in females [25].

Some studies showed male predominance while others showed female predominance. A research conducted at Wuhan University's Zhongnan Hospital on 155 individuals who confirmed COVID-19 revealed that 56% of the patients were male [26]. Newer studies suggest that females could be more vulnerable to COVID-19, even though men made up the bulk of COVID-19 patients in the first Chinese reports. From a total of 4,212 COVID-19 cases, the Korean Society of Infectious Diseases reported that 37.7% were male and 62.3% were female [27].

The authors speculate that this difference could be due to variations in social activities between different countries. In addition, the COVID-19 epidemic in South Korea's contact tracing revealed that female members of the Daegu religious sect could have had a role in the outbreak. Consequently, gender variation in COVID-19 may be a reflection of social and cultural variations in different countries [27]. The male majority in the vaccination group might be the result of females' greater worry and fear of vaccine side effects. It was discovered that those in younger age groups, those who were married, and women showed greater concerns about vaccine-related problems. Additionally, women showed more reluctance [28].

Regarding comorbedities including HTN, DM, liver, renal and cardiac diseases there was no significant difference between 3 groups.

A patient's risk of mortality is increased if they have autoimmune illnesses, cardiopulmonary or metabolic comorbidities (Such as diabetes mellitus), or are receiving any treatment that may lower their immunity (Such as corticotherapy, radiation, or chemotherapy) [29].

Our study showed that 29.6% of infection group patients reported presence of Preceding diarrhea VS 25% in control group while there is no diarrhea reported in vaccine group which may be related to poorer outcome in these 2 groups in comparison to vaccine group.

Typically, the pathogenesis of diarrhea in SARS-CoV-2 infection encompasses the involvement of two distinct mechanisms. Initially, there is a reduction in the surface area available for digestion and absorption, along with cytopathic damage that often leads to cellular demise. Additionally, the presence of unabsorbed nutrients triggers passive water influx into the intestinal lumen, resulting in osmotic diarrhea. The second method entails the active secretion of ions induced by enterotoxins, resulting in the alteration of

ion transport. This process is characterized by a functional pathogenic mechanism rather than a structural one [30].

According to current analyses, the spike protein, which is necessary for SARS-CoV-2 binding and internalization, resembles nonstructural protein 4 (NSP4) in models of rotavirus-induced diarrhoea in terms of typical enterotoxin features. However, we cannot be certain of this relationship because genomic subtyping was not available in Egypt due to economic reasons [31].

In 1982, a 45-year-old man who suffered from severe GBS with irreparable neurological damage 2 weeks following a gastrointestinal disease brought on by a Campylobacter infection was the first person to be linked to the infection as a possible cause of GBS. It was obvious from the beginning that GBS cases linked to C. jejuni were more severe and more likely to include axonal damage [32].

As regards infection severity, in our study we found that 11 out of 27 cases (40.8%) had severe infection, 6 cases (22%) were moderate and 10 cases (37%) were mild from which 12 cases required hospitalization. About 66% of cases had moderate to severe infection which may be implicated with poor outcome in infection group.

A COVID-19 infection is linked to short-term morbidity and, in extreme circumstances, mortality. Complications from COVID-19 may have a significant long-term influence on communities and healthcare systems. This is because a major increase in pulmonary sequelae cases is anticipated as a result of the high number of former COVID-19 patients [33].

As regards vaccine type used, in our study we noticed that 50% of vaccine group cases developed GBS followed AstraZeneca type while 29.2% and 20.8% followed Sinopharm and Sinovac respectively. This means that AstraZeneca is more risky in developing GBS than Sinopharm and Sinovac and this may be due to different preparation methods and different mechanisms of action.

The AstraZeneca vaccine is a viral vector vaccine that utilizes a replication-deficient chimpanzee adenovirus vector to encode the Spike glycoprotein of the SARS-CoV-2 virus. The vaccines developed by Sinopharm and Sinovac are manufactured using genetically engineered human embryonic kidney (HEK) 293 cells. The COVID-19 vaccines are classified as inactivated vaccines, which include the introduction of an inactivated form of the SARS-CoV-2 virus into the human body**.**

The findings of a retrospective cohort study indicate that the incidence of Guillain-Barré Syndrome (GBS) following vaccination with non-replicating adenovirus vector vaccines (such as AstraZeneca and Johnson & Johnson) is higher compared to mRNA COVID-19 vaccines. This suggests that the cases of GBS observed after mRNA COVID-19 vaccination may be reflective of the underlying background incidence of GBS [34].

Theoretically, GBS might arise from antibodies produced by adenovirus vector-mediated vaccines (Johonson & Johonson and AstraZeneca) cross-reacting with glycoproteins on the myelin sheath of peripheral nerve axons.

An increased risk of GBS after ChAdOx1 nCov-19 (ChAdOx1 nCoV-19 is a chimpanzee (Ch) adenovirus-vectored vaccine (Ad), whose development was led by the University of Oxford (Ox). It has been shown to stimulate an immune response to nCoV-19, the novel coronavirus first identified in 2019) AstraZeneca's COVID-19 vaccine has also been reported. This vaccine has been frequently used in Europe and employs a chimpanzee adenovirus vector that is replication-incompetent (35, 36).

In one study, there were 1.4–10 times as many GBS infections after 14 days following ChAdOx1 nCov-19 immunization than anticipated [36]. Additionally, in 2021, population-based research using data from the National Health Service in England found a link between a higher risk of GBS and the delivery of the first dose of the AstraZeneca vaccine, which is based on a modified chimpanzee adenovirus (ChAdOx1) [37].

Regarding EGOS1 (modified Erasmus GBS outcome scale 1): our study showed that mean values are (3.4 ± 2.86), (1.5 ± 1.10), (4.9 ± 2.25) in infection, vaccine and control groups respectively. EGOS 2 mean values were (4.5 ± 3.85), (1.6 ± 1.38), (5.4 ± 3.88) in infection, vaccine and control groups respectively. NEDS mean values were (3.1 ± 1.68) (2.7 ± 1.05) (3.7 ± 1.08) in infection, vaccine and control groups respectively. MRC scale mean values were (45.1 ± 15.34) (52.2 ± 4.49) (35.7 ± 11.97) in infection, vaccine and control groups respectively.

So, EGOS1, EGOS2, NEDS, MRC scale values in our study indicate that control group and infection group had more severe manifestations with milder symptoms and better outcome in vaccine group.

Disease severity and outcome did not differ between GBS post COVID infection and non COVID GBS in a study comparing two groups which is in contrast to the results of recent studies that showed that patients with GBS associated with COVID-19 are more likely to require MV [38].

A study showed Long-term features of neurological autoimmunity, including GBS, that develop following SARS-CoV-2 immunizations are defined. In most cases, the outcome was positive. Patients with inflammatory neuropathies exhibited no symptoms, little residual sensory impairments in the lower limbs, and improved sensorimotor weakness in the lower extremities, but they occasionally needed walking assistance to go around [39].

Regarding cranial nerves affection, our study showed significantly involved olfactory cranial nerve in infection group in 22 cases out of 27 cases while there is no affection in other 2 groups. Facial nerve was involved in 40.7%, 25% and 20% of infection, vaccine and control groups respectively. Occulomotor nerve was involved in 2 cases and abducent was involved in 1 case of infection group. Also bulbar affection showed significant difference between infection group and the 2 other groups with 37%, 12.5%, and 10% affection in infection, vaccine and control groups respectively.

In a systematic review, cranial nerve involvement was reported in 24 out of 56 individuals with GBS; the most involved cranial nerves are cranial nerves VII, VI, and III, which can present as ophthalmoparesis, facial palsy, or hypogeusia / ageusia [40].

The causal relationship between anosmia/hyposmia and ageusia/hypogeusia with the involvement of cranial nerves I, VII, IX, and X remains uncertain. This uncertainty arises due to limited investigations conducted on cranial nerve involvement in these patients, as well as the possibility that ageusia or anosmia may be a consequence of receptor impairment in mucous membranes rather than nerve dysfunction. Nevertheless, in the event that the virus spreads intracellularly, there is a considerable probability that cranial nerves I, VII, IX, and X are the most often affected in cases of COVID-19. The claim is supported by several

studies that have shown a high incidence of hyposmia/anosmia and hypogeusia/ageusia [40].

Using a standardized questionnaire, a multicenter case series with 1420 European COVID-19 cases (diagnosed laboratory-using RT-PCR) revealed that 997 cases (70.2%) reported having lost their sense of smell (41), indicating a significant incidence of anosmia in COVID-19 patients.

A multicenter European study was conducted, utilizing specific questionnaires derived from the National Health and Nutrition Examination Survey, focusing on the olfactory and gustatory aspects. Additionally, the short version of the Questionnaire of Olfactory Disorders-Negative Statements (sQOD-NS) was employed. The findings of this study revealed that out of the 417 laboratory-confirmed COVID-19 patients with RT-PCR, a total of 357 cases (85.6%) exhibited olfactory impairment. Among these cases, 284 (79.6%) were diagnosed with anosmia [41].

As regards CSF analysis, we noticed presence of cytoalbumin dissociation in all three groups. Protien mean values are (109.2 ± 63.09) (81.6 ± 31.78), (143.9 ± 99.94) in infection, vaccine and control groups respectively and cells mean values are (4.8 ± 4.04), (4.6 ± 2.52), (5.0 ± 2.29) in infection, vaccine and control groups respectively.

Finsterer *et al*. reported in 2022 that Most of the cases reported in a systematic review of post covid GBS had cytoalbumin dissociation. Vidrio-Becerra and colleagues in 2018 reported that A protein level higher than 100 indicates a greater possibility of more complications, and CSF can be employed as a predictive indication of severity [40, 41].

Regarding pattern of polyneuropathy in our study, there was sensorimotor affection in 55.6%, 70% and 50% in infection, vaccine and control groups respectively. Pure motor affection was in 18.5%, 12.5% and 50% in infection, vaccine and control groups respectively. While pure sensory appeared in 25.9%, 16.7% in infection and vaccine groups respectively while no pure sensory cases were reported in control group in our study.

According to neurophysiology, we noticed that in infection group axonal pattern represented 59.3%, demyelination pattern represented 18.5%, demyelinatig with 2ry axonal was in 7.4% and axonal with 2ry demyelination 14.8%. This indicates that different forms of polyneuropathy can be associated with or occur as a complication of COVID-19 infection. In vaccine group, 83.3% of case were axonal while 16.7% of cases were demyelinating with 2ry axonal.

A study performed in on 42 patients revealed that eight patients presented by acute flaccid quadriparesis, more severe in upper limbs preceded by fever and diarrhea diagnosed as acute axonal polyneuropathy, twenty-five patients presented by ascending weakness preceded by fever, dry cough and respiratory distress, electromyography (EMG) and nerve conduction (NC) studies done and confirmed the clinical diagnosis of demyelinating polyneuropathy, while five patients presented by severe fatigue and progressive weakness of both lower and upper limbs, they developed fever and cough 10 days after the neurological symptoms. NC and EMG completed and verified the clinical diagnosis of demyelinating polyneuropathy with a secondary axonal picture [42].

Difference in neuropathy pattern between infection group in our study and others may be due to different viral species which is difficult to be proven due to lack of genomic studies. Unfortunately, due to information scarcity, most of our comparisons regarding the pattern of peripheral neuropathy in our study groups were with case reports.

The results shown that most GBSs following COVID-19 vaccinations fall into the AIDP subtype, which is primarily characterized by sensory involvement and usually develops after the initial dosage of the vaccine. Additionally, bilateral involvement of the seventh cranial nerve is a typical symptom [43].

On the other side, some case reports showed in all tested nerves of the upper and lower limbs, clinical examination and nerve conduction investigations revealed pure motor axonal polyneuropathy with missing compound muscle action potential (CMAP) [44]. Additionally, a different case report revealed post-COVID-19 axonal type sensorimotor peripheral polyneuropathy [45].

Difference in neuropathy pattern between vaccine group in our study and others may be related to the type of vaccine and their mechanism of action and may be due to the small sample size that may affect reliability of results.

Axonal neuropathy predominance in control group may be explained by Preceding diarhea in some cases which may be due to campylobacter jujeni infection followed by axonal injury and also small sample size may affect results of the study.

As regards treatment received, in infection group, 51.9% received plasma exchange, 48.1% received IVIG, while in vaccine group 79.2% of cases were treated by plasma exchage, 20.8% recieved IVIG. In control group, 70% were treated by plasma exchage and 30% recieved IVIG. There is scarcity in reports about superiority of one modality of treatment over the other.

As regards treatment response, there was favorable outcome in 64.3%, 94.7%, 78.6% of patients treated with plasma exchage in infection, vaccine and control groups respectively. While in patients received IVIG, there was favorable outcome in 69.2%, 80%, 83.3% in infection, vaccine and control groups respectively.

Vaccine group showed the most favorable outcome in comparison with infection group may be due to less bulbar involvement in vaccine group, more incidence of multiple systems affection within infection group. Also, Preceding diarrhea may be a reason for poorer prognosis in infection and control group.

Hughes *et al*. reported that Treatment is offered to GBS patients with IVIG or plasma exchange. Treatment with IVIG and plasma exchange have been shown to have similar efficacy in treatment of GBS. Finsterer *et al*. reported in 2022 that since there are no studies about the optimal treatment of SARS COV2-GBS subtypes available, they should be treated empirically in the same way as non-SC2-GBS subtypes [40, 46].

SARS COV2-GBS does not differ from non- SARS COV2-GBS regarding clinical presentation and treatment, but the outcome of SC2-GBS is worse compared to non-CS2-GBS patients [40].

Outcome was favorable in most cases after SARS-CoV-2 vaccinations because long-term characteristics of neurological autoimmunity encountered after SARS-CoV-2 vaccinations are defined [47].

In the same period other COVID positive cases were de novo diagnosed as MG, myopathy and invasive fungal sinusitis. It is not clear if there is casual relationship between COVID and these disorders or just unmasked by the infection or subsequent immune process.

1-A case of MG was COVID positive with severe manifestations required hospitalization 2 weeks before MG symptoms appearance. NCS with slow repetitive supra maximal nerve stimulation showed significant decrement pattern of response, acetylcholine receptors were significantly high, CT chest was done with no thymic hyperplasia or thymoma. Plasma exchange was done with marvelous improvement and thymectomy was done later on. SARS-CoV-2 infection may contribute to the development of a new episode of MG. This unexpected neurological manifestation suggests that the virus could induce the production of antibodies [48].

Up to now, several case reports of COVID-19 infection in pre-existing MG [49] and also new onset post-COVID-19 MG have been reported [50]. The exact mechanism is not fully known, but post-viral autoantibody production due to COVID-19 has been speculated [51].

2-A case had history of 2nd dose AstraZeneca COVID vaccine 3 weeks before onset of myopathy. CPK level initially was 5700 mcg/L, ANA, ANCA, Anti ds DNA Abs: negative, EMG was done showing picture of inflammatory myositis. Patient received 5 days pulse steroids (Methylprednisolone) with partial improvement as regards pain and weakness followed one week later with plasma exchange 6 sessions with nearly total improvement after 4th session. CPK level was repeated in follow up after 2 weeks: 84 mcg/L. CT chest, neck, abdomen with contrast, mammography were done with no significant findings. Routine labs were done including thyroid function tests were normal.

3-Another case of inflammatory myositis was found denovo 3weeks post COVID infection with oral prednisolone intake EMG was done showing inflammaory myopathy, CPK was done initially 2000, ESR 60/90, SGPT 106, SGOT 246.

5. Conclusion

From this study we concluded that:

- Severe COVID-19 infection is associated with higher morbidity and mortality as regards neuromuscular disorders.
- AstraZeneca COVID vaccine is more risky in developing GBS than Sinopharm and Sinovac vaccines.
- There were milder symptoms and better outcome in vaccine group than COVID-19 infection and control groups.
- Higher CSF protein value is associated with poorer outcome as was found in infection and control groups.
- Pattern of neuropathy was predominantly sensorimotor axonal polyneuropathy in COVID-19 infection, vaccine and control groups, however all other patterns were found to a lesser extent.
- Cranial nerves assessment showed that olfacory, bulbar and facial affection were more predominant in infection group than vaccine and control groups.
- There was no difference in response to treatment between IVIG and plasma exchange.

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7. Ethical Approval

As per international standard or university standard, a written ethical approval has been collected and preserved by the authors.

8. Consent

As per international standard or university standard, patient(s) written consent has been collected and preserved by the author(s).

9. Competing Interests

Authors have declared that no competing interests exist.

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