Journal of Iranian Medical Council, Volume 7, Issue no. 2
http://dx.doi.org/10.18502/jimc.v7i2.15051

Case Report

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COVID-19 and Neuromuscular Involvement: A Case Series and Brief Review of Literature

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Abstract

Background: Tough COVID-19 predominantly affects the respiratory tract, and extra-pulmonary manifestations, including neuromuscular complaints have been associated with this disorder. It is vital to monitor COVID-19 cases for the occurrence of Neuromuscular Disorders (NMDs), which could be overshadowed by severe respiratory and cardiovascular symptoms. In this study, we reported electrophysiological findings of a series of COVID-19 patients with complaints of paresthesia and weakness.

Methods: In this case series, the Electrodiagnostic studies (EDX) of 36 patients with recent complaints of weakness or paresthesia and a history of COVID-19 before symptoms were reported.

Results: 12 cases (33.3%) had abnormal EDX, five males and seven females, with a mean age of 51.42±11.49 years, history of hospitalization in five cases (41.7%), and ICU admission in four (33.3%). Seven cases were concluded as having a predominantly axonal type polyneuropathy (five sensory-motor and two sensory polyneuropathies). Of these seven, one was suggestive of Critical Illness Neuropathy (CIN). Three cases demonstrated a myopathic pattern with a history of ICU admission, hence the impression of Critical Illness Myopathy (CIM). In addition, one of these three, developed both myopathy and neuropathy and thus, is considered as having CIM/N. One case was diagnosed with Chronic Inflammatory Demyelinating Polyneuropathy (CIDP). The last case demonstrated an inflammatory involvement of lumbosacral roots (COVID-19-related radiculitis).

Conclusion: COVID-19 could be associated with a wide range of NMDs. In this study, the presence of axonal polyneuropathy, CIDP, and myopathy was demonstrated following SAR-COV-2 infection. Also, CIN/M was observed in COVID-19 patients with a history of ICU admission.

Keywords: COVID-19, Critical illness, Muscular diseases, Polyneuropathies, Polyradiculoneuropathy

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Received: Apr 25 2023
Accepted: Sept 20 2023

Citation to this article:
Moradi K, Forogh B, Sadeghi Sh, Khabbaz MS, Attari A, Taghizadeh FS, et al. COVID-19 and Neuromuscular Involvement: A Case Series and Brief Review of Literature. *J Iran Med Counc*. 2024;7(2):377-88.

Introduction

Since December 2019, several cases of viral pneumonia of an unknown origin had been identified in Wuhan, China. Later, it was determined that this pneumonia is caused by a novel beta-coronavirus virus that was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the World Health Organization (WHO) (1). SARS-CoV-2 shares up to 80% of its structural and genetic properties with SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), but with a higher person-to-person transition potential, longer incubation period, shorter serial interval, and lower mortality rate (2). Currently, coronavirus disease 2019 (COVID-19), a set of disorders caused by this virus, has spread worldwide, rapidly and a pandemic was officially declared on March 11, 2020, with more than 140 million diagnosed cases globally (3).

COVID-19 predominantly affects the respiratory tract, causing a range of respiratory problems, ranging from a simple cold to Acute Respiratory Distress Syndrome (ARDS) (4-6). Patients typically presented with cough, fever, sore throat, dyspnea, fatigue, and myalgia (4). However, extra-pulmonary manifestations of the disease also have become evident, including thrombotic complications, cardiac dysfunction, acute renal injury, gastrointestinal manifestations, neurologic and musculoskeletal symptoms, and dermatologic complications (7,8).

Several neuromuscular complaints have been directly or indirectly associated with COVID-19, including anosmia and ageusia, headaches, dizziness, acute Cerebrovascular Accident (CVA), Acute Disseminated Encephalomyelitis (ADEM), encephalopathy, Critical Illness polyneuropathy and Myopathy (CIN/M), symmetrical neuropathy, and Guillain-Barré Syndrome (GBS) (9-11).

It is vital to monitor COVID-19 cases for the occurrence of these Neuromuscular Disorders (NMD), which could be overshadowed by severe respiratory and cardiovascular manifestations of SARS-CoV-2 (12). As was demonstrated in a study by Guidon *et al* (13), the COVID-19 pandemic has the potential to affect a large portion of patients with NMDs with lasting consequences, thus, it is vital to assess potential neuromuscular complications of COVID-19, its risk factors, and developing practical guidelines for proper diagnosis and treatment of these disorders.

The electrodiagnostic examination (EDX) [including Nerve Conduction Study (NCS) and electromyography (EMG)] is a powerful tool for the identification and localization of pathologies within the lower motor neuron system and remains an important diagnostic technique to assist in the diagnosis and differentiation of acquired NMDs (14,15). In addition, EMG and NCS help to guide further assessments, such as molecular genetic studies and muscle biopsies, and contribute to choosing the proper management and treatment protocols (15).

Based on the above-mentioned notes, an EDX examination could help distinguish the neurologic symptoms following COVID-19. In this study, we reported electrophysiological findings of a series of COVID-19 patients with complaints of new-onset paresthesia and weakness.

Materials and Methods

In the present study, patients with recent complaints of weakness or paresthesia and a history of COVID-19 before symptoms, referred to physical medicine and rehabilitation outpatient clinic for EDX exam, were included. The study was approved by the Ethics Committee of Iran University of Medical Sciences (IUMS), under number IR.IUMS.REC.1399.622. The participants underwent EDX and the report of EDX was collected. For inclusion, definite documentation of SARS-CoV-2 infection was required [positive Polymerase Chain Reaction (PCR) test for SARS-CoV-2 from either nasal, oro-pharyngeal, or saliva swab sample]. The NMD symptoms had to be manifested after the diagnosis of COVID-19, and thus, not be a pre-existing condition. Patients with a previous history of neuromuscular disorders (*e.g.*, neuropathy, myopathy, *etc.*) were excluded.

The electrodiagnostic evaluation included a Nerve Conduction Study (NCS) and needle Electromyography (EMG). It was performed using a Natus Synergy Ultrapro S100 instrument. During NCS, sensory and motor responses of bilateral upper (*i.e.*, median, ulnar, and radial nerves) and lower (*i.e.*, peroneal, tibial, and sural nerves) extremities were recorded, using the techniques provided by Dumitru and Amato (16). The reference values for each

nerve were according to Preston and Shapiro (17). The needle EMG was performed using disposable concentric needles. Distal and proximal muscles were evaluated in the either upper or lower limb, most commonly First Dorsal Interosseous (FDI), Extensor Digitorum Communis (EDC), Flexor Carpi Radialis (FCR), biceps brachialis, and posterior deltoid muscles in the upper limbs; and quadriceps (vastus lateralis and medialis), Tibialis Anterior (TA), Peroneus Longus (PL), and gastrocnemius muscles in the lower limbs. In either case, the muscle selection for EMG was individualized, based on physical exam, NCS findings, and the physician's experience, and in addition to the mentioned muscles, other muscles were also tested, if required. In each subject, the presence of Spontaneous Activity (SA) [including Positive Sharp Wave (PSW) and Fibrillation Potential (FP)] was assessed at rest. Furthermore, during muscle activation, amplitude and duration of Motor Unit Action Potentials (MUAP), the percentage of polyphasic MUAPs, and muscle volition and recruitment pattern were evaluated and the presence of neurogenic MUAPs (*i.e.*, long-duration, high-amplitude, and polyphasic MUAPs with decreased recruitment) and myogenic MUAPs (*i.e.*, short, small, and polyphasic MUAPs with early recruitment) were reported.

Data were analyzed using SPSS software V22. Mean and standard deviation were used for quantitative variables and relative frequency was used for qualitative variables.

Results

During the present study, 36 patients were included. Of these, 12 (33.3%) had abnormal electrodiagnostic studies. Of the participants with normal EDX reports, 12 were male and 12 were female, with a mean age of 45.00 ± 10.56 years. Of these 24, 10 were hospitalized with a mean hospital stay of 5.70 ± 1.83 days. History of Intensive Care Unit (ICU) admission was observed in none of the cases with normal EDX.

In 12 cases with abnormal EDX, there were five males and seven females, with a mean age of 51.42 ± 11.49 years. History of hospitalization and ICU admission following COVID-19 was observed in 5 and 4 of these 12 cases, respectively. The clinical characteristics of these cases are demonstrated in table 1. As it is shown, patients presented with either hypoesthesia/paresthesia or weakness.

The NCS and EMG findings of cases with abnormal EDX are summarized in tables 2 and 3 and the EDX conclusion is demonstrated in table 4.

Table 1. Summary of patients' clinical data

Patient ID	sex	Age	Symptoms	ICU admission
Patient 1	M	31	Hypoesthesia, distal weakness	
Patient 2	F	57	Paresthesia, absent DTRs	No
Patient 3	F	55	Paresthesia, absent DTRs, lower limb weakness	Yes
Patient 4	M	42	Paresthesia, hypo/absent DTRs	No
Patient 5	M	71	Paresthesia, hypo/absent DTRs	No
Patient 6	F	35	Lower>upper limb weakness	Yes
Patient 7	F	57	Lower>upper limb weakness, absent DTRs	Yes
Patient 8	F	57	Lower>upper limb weakness, absent DTRs	No
Patient 9	F	55	lower limb weakness	Yes
Patient 10	M	42	Lower>upper limb weakness, absent DTRs	No
Patient 11	M	60	Hypoesthesia	No
Patient 12	M	55	Lower limb pain	No

ICU: Intensive Care Unit; M: Male; F: Female; DTR: Deep Tendon Reflex.

Table 2. Summary of NCS data

Patient ID	NCS Parameters	Median (SNAP)		Median (CMAP)		Ulnar (SNAP)		Ulnar (CMAP)		Radial (SNAP)		Peroneal (CMAP)		Tibial		Sural		Upper F response	Lower F response
		Rt	Lt	Rt	Lt	Rt	Lt	Rt	Lt	Rt	Lt	Rt	Lt	Rt	Lt	Rt	Lt		
1	Latency	Ab	Ab	32	29	Ab	Ab	9	12	3	3.1	10.4	19.1	10.9	9.1	2.8	2.8		
	Amplitude	Ab	Ab	4.8	1.3	Ab	Ab	1.1	1	9	8	3.4	1.3	VL	1	17	16	Prolonged	Ab
	Velocity	Ab	Ab	56	46	Ab	Ab	43	33	-	-	38	44	-	-	-	-		
Patient 2	Latency	Ab	Ab	5	5.8	Ab	Ab	3.9	3.3	3	3.1			5.8	6.4	3.5	3.3		
	Amplitude	Ab	Ab	4.6	3.9	Ab	Ab	8.4	8.7	9	8	VL	VL	6.5	6	5	4	Ab	Ab
	Velocity	Ab	Ab	42	45	Ab	Ab	42	43	-	-			38	38				
Patient 3	Latency	Ab	Ab	4.6	4.5	Ab	Ab	3.5	3.4	Ab	Ab	5.1	Ab	5.3	5.6	Ab	Ab		
	Amplitude	Ab	Ab	2.8	3.4	Ab	Ab	6.1	5.6	Ab	Ab	1.5	Ab	2.1	2.8	Ab	Ab	Normal	Ab
	Velocity	Ab	Ab	47	48	Ab	Ab	50	51	Ab	Ab	40	Ab	38	37	Ab	Ab		
Patient 4	Latency	Ab	Ab	4.9	4.8	Ab	Ab	3.8	3.7	Ab	Ab	4.1				Ab	Ab		
	Amplitude	Ab	Ab	4.9	5.1	Ab	Ab	4.7	5.4	Ab	Ab	2.1	VL	VL	VL	Ab	Ab	Ab	Ab
	Velocity	Ab	Ab	40	39	Ab	Ab	43	41	Ab	Ab	41				Ab	Ab		
Patient 5	Latency	3.5	3.5	3.9	4.1	3.4	3.1	3.1	3	3.1	3	-	-	5.7	5.6	3.2	3.2		
	Amplitude	11	10	6.6	7.8	11	8	5.8	6	9	8	-	-	3.9	4.3	5	5	Normal	Normal
	Velocity	-	-	51	50	-	-	50	52	-	-	-	-	42	40	-	-		
Patient 6	Latency	3.5	3.4	3.7	3.4	3.2	3.1	3.4	3.4	3.3	3.1	4.9	4.9	5.3	5.1	3.1	3.0		
	Amplitude	38	39	11.2	12.9	39	36	10.9	11.3	29	27	5.6	5.8	7.3	7.8	18	19		
	Velocity	-	-	53	51	-	-	56	51	-	-	43	41	43	45	-			
Patient 7	Latency	3.4	3.3	3.7	3.8	3.3	3.1	3.9	3.3	3	3.1			5.8	6.4	3.1	2.9		
	Amplitude	9	8	4.6	3.9	8	8	5.4	5.7	7	8	VL	VL	2.5	2.1	5	4	Normal	Normal
	Velocity	-	-	49	48	-	-	51	49	-	-			38	38	-	-		
Patient 8	Latency	3.6	3.1	3.6	3.5	3.1	3.2	3.7	3.3	3.2	3.1	4.2	4.3	5.6	5.9	3.0	2.9		
	Amplitude	8	9	4.4	4.6	7	8	4.8	5.1	7	7	1.2	1.3	2.3	2.6	6	5	Normal	Normal
	Velocity	-	-	52	51	-	-	51	50	-	-	42	40	40	39	-	-		
Patient 9	Latency	3.4	3.1	3.7	3.6	3.1	3.0	3.2	3.3	3.1	3.5	4.8	4.6	5.5	5.4	2.8	3.0		
	Amplitude	42	44	12.2	12.8	38	38	12.7	12.1	28	31	5.5	5.1	7.5	7.1	17	19	Normal	Normal
	Velocity	-	-	53	54	-	-	56	53	-	-	43	45	41	44	-	-		
Patient 10	Latency	3.5	3.4	3.1	3.4	3.4	3.3	3.7	3.5	3.0	3.1	4.5	4.6	5.4	5.3	3.3	2.8		
	Amplitude	9	8	5.7	5.3	9	11	5.4	5.6	8	7	2.1	2.3	3.3	3.6	6	7	Normal	Normal
	Velocity	-	-	56	55	-	-	53	51	-	-	42	43	42	44	-	-		
Patient 11	Latency	3.2	3.1	3.5	3.7	3.0	3.2	3.4	3.6	3.2	3.5	4.9	4.8	5.8	5.4	3.1	3.0		
	Amplitude	8	9	12.9	12.1	7	7	11.2	11.1	7	6	5.5	5.1	7.1	7.2	5	5	Normal	Normal
	Velocity	-	-	53	50	-	-	52	53	-	-	41	43	41	42	-	-		
Patient 12	Latency	-	-	-	-	-	-	-	-	-	-	5.1	5.0	5.8	5.9	2.4	3.0		
	Amplitude	-	-	-	-	-	-	-	-	-	-	4.5	4.9	6.5	6.7	19	17	Prolonged	Prolonged
	Velocity	-	-	-	-	-	-	-	-	-	-	43	41	41	42	-	-		

NCS: Neve Conduction Study; SNAP: Sensory Nerve Action Potential; CMAP: Compound Muscle Action Potential; Rt: Right; Lt: Left; Ab: Absent; VL: Very Low; –: not performed.

Normal Values [according to Preston DC, Shapiro BE. Electromyography and neuromuscular disorders e-book: clinical-electrophysiologic correlations (Expert Consult-Online). Elsevier Health Sciences; 2012 Nov 1]:

- Median SNAP: Distal Peak Latency ≤ 3.5 ms, Amplitude ≥ 20 μV, Conduction Velocity ≥ 50 ms
- Median CMAP: Distal Latency ≤ 4.4 ms, Amplitude ≥ 4.0 *mV*, Conduction Velocity ≥ 49 *ms*, F-Latency ≤ 31 *ms*
- Ulnar SNAP: Distal Peak Latency ≤ 3.1 *ms*, Amplitude ≥ 17 *μV*, Conduction Velocity ≥ 50 *ms*
- Ulnar CMAP: Distal Latency ≤ 3.3 ms, Amplitude ≥ 6.0 *mV*, Conduction Velocity ≥ 49 *ms*, F-Latency ≤ 32 *ms*
- Radial SNAP: Distal Peak Latency ≤ 2.9 *ms*, Amplitude ≥ 15 *μV*, Conduction Velocity ≥ 50 *ms*
- Peroneal CMAP: Distal Latency ≤ 6.5 *ms*, Amplitude ≥ 2.0 *mV*, Conduction Velocity ≥ 44 *ms*, F-Latency ≤ 56 *ms*
- Tibial CMAP: Distal Latency ≤ 5.8 *ms*, Amplitude ≥ 4.0 *mV*, Conduction Velocity ≥ 41 *ms*, F-Latency ≤ 56 *ms*
- Sural SNAP: Distal Peak Latency ≤ 4.4 *ms*, Amplitude ≥ 6 *μV*, Conduction Velocity ≥ 40 *ms*

Table 3. Summary of EMG data

Patient ID	EMG Parameters	Upper limb		Lower limb	
		Proximal*	Distal**	Proximal***	Distal****
Patient 1	SA	No	No	No	No
	MUAP	Normal	Normal	Normal	Normal
	IP	Decreased	Decreased	Decreased	Decreased
Patient 2	SA	No	No	No	Few: PSW, Fib
	MUAP	Polyphasic	↑amp, polyphasic	Normal	↑amp, polyphasic
	IP	Decreased	Decreased	Decreased	Decreased
Patient 3	SA	No	No	No	No
	MUAP	Polyphasic	↓amp, polyphasic	↓amp, polyphasic	↓amp, polyphasic
	IP	Increased	Increased	Increased	Increased
Patient 4	SA	No	No	No	Few: PSW, Fib
	MUAP	Polyphasic	↑amp, polyphasic	↑amp, polyphasic	↑amp, polyphasic
	IP	Decreased	Decreased	Decreased	Decreased
Patient 5	SA	No	No	No	No
	MUAP	↑amp, polyphasic	Normal	Normal	Normal
	IP	Decreased	Full	Full	Full
Patient 6	SA	No	No	No	No
	MUAP	Polyphasic	Polyphasic	↓amp, polyphasic	↓amp, polyphasic
	IP	Increased	Increased	Increased	Increased
Patient 7	SA	No	Few: PSW, Fib	No	Some: PSW, Fib
	MUAP	Polyphasic	↑amp, polyphasic	↑amp, polyphasic	↑amp, polyphasic
	IP	Decreased	Decreased	Decreased	Decreased
Patient 8	SA	No	Few: PSW, Fib	No	Some: PSW, Fib
	MUAP	Polyphasic	↑amp, polyphasic	↑amp, polyphasic	↑amp, polyphasic
	IP	Decreased	Decreased	Decreased	Decreased
Patient 9	SA	No	No	No	No
	MUAP	Polyphasic	Polyphasic	↓amp, polyphasic	polyphasic
	IP	Increased	Increased	Increased	Increased
Patient 10	SA	No	No	No	Few: PSW, Fib
	MUAP	Polyphasic	↑amp, polyphasic	↑amp, polyphasic	↑amp, polyphasic
	IP	Decreased	Decreased	Decreased	Decreased
Patient 11	SA	No	No	No	No
	MUAP	↑amp, polyphasic	Normal	Normal	Normal
	IP	Decreased	Full	Full	Full
Patient 12	SA	-	-	Some: PSW, Fib	Some: PSW, Fib
	MUAP	-	-	↑amp, polyphasic	↑amp, polyphasic
	IP	-	-	Decreased	Decreased

EMG: Electromyography; SA: Spontaneous Activity; MUAP: Motor Unit Potentials; IP: Interference Pattern; PSW: Positive Sharp Waves. Fib: Fibrillation Potentials; amp: Amplitude; –: not performed.

* First Dorsal Interosseous, Extensor Digitorum Communis, Flexor Carpi Radialis

** Biceps Brachialis, Posterior Deltoid

*** Tibialis Anterior, Peroneus Longus, Gastrocnemius

**** Quadriceps (Vastus Lateralis And Medialis),

Table 4. Summary of patients' EDX impression

Patient ID	Impression
Patient 1	Acquired neurogenic process, involving multiple peripheral nerves, almost in symmetric pattern, with segmental demyelination, suggestive of chronic inflammatory demyelinating radiculopolyneuropathy, probably due to COVID-19
Patient 2	Acquired symmetric sensorimotor peripheral polyneuropathy, mostly axonal type, involving all limb, distal > proximal
Patient 3	Myopathic process, involving all limb, mostly proximal lower limbs, without spontaneous activity. Symmetric mild mixed sensorimotor peripheral polyneuropathy. The EDX findings are suggestive of Critical Illness Neuropathy/Myopathy
Patient 4	Chronic symmetric sensorimotor peripheral polyneuropathy, mostly axonal type, involving all limbs, distal > proximal, lower > upper
Patient 5	Mild symmetric axonal sensory peripheral polyneuropathy, involving all limbs
Patient 6	Severe myopathic process in upper and lower limbs, more prominent in lower limbs, without spontaneous activity
Patient 7	Subacute symmetric axonal sensorimotor peripheral polyneuropathy, more prominent in lower limbs, suggestive of Critical Illness Neuropathy
Patient 8	Subacute symmetric axonal sensorimotor peripheral polyneuropathy, more prominent in lower limbs, suggestive of subacute inflammatory neuropathy
Patient 9	Severe myopathic process in upper and lower limbs, more prominent in proximal and lower limbs, without spontaneous activity, suggestive of Critical Illness Myopathy
Patient 10	Chronic symmetric axonal sensorimotor peripheral polyneuropathy, more prominent in lower limbs
Patient 11	Mild symmetric axonal sensory peripheral polyneuropathy
Patient 12	Subacute mild to moderate bilateral L4-L5>S1 roots involvement with some evidence of active axon loss, suggestive of post-COVID-19 radiculitis

EDX: Electrodiagnostic Study.

In 5 of 12 cases (patients #2, #4, #7, #8, and #10) decreased/absent amplitude of either sensory or motor responses were observed, with nearly normal conduction velocity and distal latency. During the needle EMG, polyphasic, high amplitude MUAPs were observed in distal > proximal muscles with the presence of SA predominantly in the distal lower limb muscles. The EDX of these 5 cases was concluded as symmetric sensorimotor peripheral polyneuropathy, predominantly axonal type, involving all limbs, with distal > proximal, and lower > upper extremities. Due to the history of ICU admission, the EDX finding was suggestive of CIN in patient #7.

In patient #1, very low amplitude/absent sensory and motor responses with prolonged distal latency and decreased velocity were observed. In needle EMG, normal MUAPs with decreased interference patterns were recorded. In this patient, symptoms [hypoesthesia, distal weakness, and generalized decreased reflexes] started one month after COVID-19 and progressed for three months [at the time of EDX]. Lab tests including Complete Blood Test (CBC), routine chemistries, ANA, serum and urine immunoglobulin studies, and Human Immunodeficiency Virus (HIV) and hepatitis serology, were normal. This patient was concluded as having an acquired neurogenic process, involving multiple peripheral nerves, almost in a symmetric pattern, with segmental demyelination, suggestive of Chronic Inflammatory Demyelinating radiculopolyneuropathy (CIDP) according to criteria provided by Dumitru *et al* (16), probably due to COVID-19.

In two cases (patients #5 and #11), low amplitude sensory response, with normal latency and velocity and normal or near-normal motor conduction study and needle EMG was observed. A sensory axonal polyneuropathy was reported in either case.

In three cases (patients #3, #6, and #9), short MUAPs with decreased amplitude and duration and generalized easy recruitment (increased interference pattern),

Table 5. Summary of some studies showing EDX abnormality in patients with COVID-19

Author year	Type of article	Demographic			Admission to ICU	Mechanical ventilation	EDX impression						Treatment	Treatment outcome
		Cases	Sex M/F	Age			AIDP	Axonal (AMAN/ AMSAN)	Mixed	Neuropathy (Not GBS)	CIN/ CIM	N/A		
Hasan *et al*, 2020	Meta-analysis	61	42/19	57	23/56	14/56	40/61	11(6/5) /61	2/61	N/A	N/A	8/61	IVIg 51/55 PE 4/55	65.3% with good outcome
Paliwal *et al*, 2020	Review of article	45 (39 GBS 6 non-GBS)	31/14	60.55	N/A	N/A	24/32	7/32	N/A	6	N/A	7/39	N/A	65.8% with good outcome
Abu-Rumeileh *et al*, 2021	Systematic review	73	50/23	55	N/A	15/70	48/62	9/62	5/62	N/A	N/A	11/73	IVIg 60/70 PE 10/70	72.1% with partial or complete remission
Desai *et al*, 2020	Review of article	73	N/A	N/A	N/A	N/A	81.8%	12.7% /5.4%	N/A	N/A	N/A	N/A	N/A	>70% with good outcome
Soliman *et al*, 2020	Case report	2	2/0	60	2/2	2/2	N/A	N/A	N/A	2/2	N/A	N/A	N/A	N/A
Versace *et al*, 2021	Case report	2	2/0	67.5	2/2	2/2	N/A	N/A	N/A	N/A	0/2	N/A	Rehabi-litation	Improved progressively
Nasuelli *et al*, 2020	Case report	4	3/1	69.5	4/4	4/4	N/A	N/A	N/A	N/A	4 CIN /M	N/A	Rehabi-litation	1/4 showed good outcomes
Cabañes Martínez *et al*, 2021	Case report	12	10/2	65	12/12	12/12	N/A	N/A	N/A	N/A	4/7	N/A	N/A	N/A
Madia *et al*, 2020	Case report	6	5/1	51 to 72	6/6	6/6	N/A	N/A	N/A	N/A	0/6	N/A	N/A	All with good outcome

M/F: Male/Female; ICU: Intensive Care Unit; AIDP: Acute inflammatory demyelinating polyneuropathy; EDX: Electrodiagnosis study; AMAN: acute motor axonal neuropathy; AMSAN: acute motor-sensory axonal neuropathy; GBS: Guillain-Barré syndrome; CIN: Critical illness neuropathy; CIM: Critical illness myopathy; N/A: Not available; IVIg: Intravenous immunoglobulin; PE: Plasma exchange

predominantly in lower limbs (proximal>distal) were found during needle EMG. The NCS was normal in two of them (patients #6 and #9) and the EDX was concluded as a myopathic process in the upper and lower limbs, more prominent in the lower limbs. Furthermore, due to a history of ICU admission before weakness, the EDX finding was suggestive of CIM. In patient #3 who also had an ICU admission history, absent sensory and low amplitude motor responses, with normal latency and velocity were observed. The EDX report of this patient was concluded as having CIM/N.

During the EDX of patient #12, normal NCS and polyphasic and high amplitude MUAPs with the presence of some SA in the lower limb were observed. An impression of subacute bilateral L4-L5>S1 roots involvement was concluded for this patient, and with a nearly normal lumbosacral MRI only a small bulging at L5-S1 without significant cord compression and no history of previous signs and symptoms of radiculopathy, a possible diagnosis of post-COVID-19 radiculitis was suggested in this patient.

Discussion

In the present study, we presented the EDX findings

of 36 cases with neuromuscular manifestations, following SARS-CoV-2 infection. Of these cases, 12 cases (33.3%) had abnormal EDX findings. Majority of the observed abnormal EDX were predominantly axonal-type polyneuropathy (7 of 12 abnormal EDX, 5 cases with sensory-motor, and 2 with pure sensory polyneuropathy). Of these seven cases, one case was CIN (due to a history of ICU stay). A myopathic process was observed in three cases, all with a history of ICU stay, thus the impression of CIM. Also, one of these three developed both myopathy and neuropathy; therefore, it is considered as having CIM/N. One case was diagnosed with chronic demyelinating neuropathy, well known as CIDP following COVID-19. In the last abnormal case, an inflammatory irritation of lumbosacral roots was observed (COVID-19-related radiculitis).

SARS-CoV-2 is an RNA virus with a surface spike (S) protein that has a high affinity for the Angiotensin-Converting Enzyme 2 (ACE2) receptor, thus binds to this receptor to enter host cells (1). The ACE2 receptor is highly expressed in multiple human tissues, including respiratory epithelial cells, the gastrointestinal system, the heart, kidney (18,19), as well as in the central and peripheral nervous systems (*e.g.*, neurons, astrocytes, and oligodendrocytes) and skeletal muscle (20,21). Although the exact pathogenesis of SARS-CoV-2- related NMDs is not fully understood, several mechanisms have been described for neuromuscular involvement following COVID-19 (1). Hypothetically, SARS-CoV-2 could invade peripheral nerves and skeletal muscles via the ACE2 receptor (20-23). Furthermore, due to the resemblance of the surface glycoproteins of the virus to the human Glycans, COVID-19 could prompt the cross-activation of autoreactive T or B cells, *i.e.*, 'the molecular mimicry' (20,21). Direct cytotoxic effects of SARS-CoV-2 and a post-infectious classical immune-mediated mechanism have also been suggested (9,20).

Regardless of the pathogenesis mechanism, several NMDs have been associated with SARS-CoV-2 in the recent pandemic. The complete neurological involvement of COVID-19 is yet to be described (3). A summary of several studies on NMDs following COVID-19 and their EDX manifestations is demonstrated in table 5. The most common peripheral nervous system (PNS) involvement following COVID-19 is GBS, a serious autoimmune disorder in which the immune system attacks healthy nerve cells in PNS. Multiple cases of GBS following SARS-CoV-2 infection have been described in recent months. Hasan *et al* (9) described 61 patients (68.9% males, mean age of 57 years) with COVID-19-associated GBS in their meta-analysis of 45 studies (between January 1st and August 5th, 2020). The demyelinating subtype of GBS was observed in majority of the cases (75.5%). The patients were treated using either intravenous immunoglobulin (IVIG) (92.7%) or plasmapheresis (7.3%) with a favorable outcome in 65.3% of the cases (GBS-disability score ≤ 2). According to Paliwal *et al* (20) review of articles, among published reports on COVID-19-related NMDs up to July 2nd, 2020, 39 cases with GBS were published. According to this review, SARS-CoV-2-associated GBS was observed more frequently in elderly subjects. The majority of patients had the demyelinating type of neuropathy and the GBS was initiated 3 days to 4 weeks after the onset of COVID-19 symptoms. Among these patients, severe respiratory disorders and old age were associated with poor outcomes. Five patients presented with Miller-Fisher Syndrome (MFS) (three males, aged 36-74) with good improvement following IVIG administration. Abu- Abu-Rumeileh *et al* (24) included patients with COVID-19-associated GBS from 52 publications up to July 20th, 2020. These were 73 cases, with a mean age of 55 ±17 years and a male predominance (68.5%). Most of the patients demonstrated a sensorimotor and acute inflammatory demyelinating polyneuropathy pattern. Albuminocytological dissociation was observed in the Cerebrospinal Fluid (CSF) of 71% of the cases and CSF SARS-CoV-2 RNA was absent in all the subjects. The COVID-19-related GBS was associated with a good result in the majority of the cases and a less favorable outcome was observed in older cases. According to Desai *et al* (2), up to November 15th, 2020, at least 73 cases of COVID-19-related GBS and its variants have been reported. The most common type was acute inflammatory demyelinating polyneuropathy (AIDP) (81.8% of the cases) followed by acute motor-sensory axonal neuropathy (AMSAN) (12.7% of the cases) and acute motor axonal neuropathy (AMAN) (5.4% of the cases). More than

70% of the patients showed a good prognosis, mostly after treatment with IVIG.

Paliwal *et al* (20) also described 6 patients with non-GBS neuropathy. Of these, the EDX was not performed in two cases (due to the patient's death). The other four cases were all males, aged 52 to 72, with quadriparesis following mechanical ventilation. Three were diagnosed with demyelinating polyradiculoneuropathy whereas the other's EDX was suggestive of axonal neuropathy. All the patients had autonomic dysfunction and action myoclonus; a feature not seen in CIN. Soliman *et al* (25) reported two cases (66- and 54-years old males) with peripheral axonal polyneuropathy following COVID-19. They both had a history of severe respiratory dysfunction, leading to intubation. The first case was presented four months after discharge, with a preserved right foot drop, generalized paresthesia, and left hand-grip weakness. Ultrasound (US) assessment revealed an abnormality in the left ulnar and right common peroneal nerve. The second case was presented two months after discharge with bilateral lower limb weakness, left leg paresthesia, and a persistent left foot drop. The US findings were correlated with left peroneal neuropathy. Both cases underwent EDX and concluded as having an asymmetric, axonal sensorimotor polyneuropathy.

In addition to the above-mentioned disorders, patients with COVID-19 who required ICU stay and prolonged intensive care treatment with ventilation, and immobilization, are vulnerable to the development of CIN/M (26). In the present study, out of 36 cases, four had a history of ICU stay following COVID-19. We observed either CIM, CIN, or both in these cases. CIM, a primary myopathic process with unknown pathophysiology, and CIN, a symmetric length-dependent sensory-motor, predominantly axonal polyneuropathy, both occur in patients with prolonged hospitalization/ICU stay and either are associated with duration of ICU stay (3). CIN/M could dramatically affect the patient's functional capacity and lead to a worse respiratory outcome and failure of the weaning from ventilator support (27). Up to November 2020, EDX-confirmed CIM was observed in 20 patients with COVID-19 (26). The exact incidence of the CIN/M could not be calculated; since firstly, some of the suspicious patients died without performing diagnostic studies, and secondly, non-essential studies were delayed or even canceled (3).

Madia *et al* (28) described the occurrence of CIM in 6 patients following COVID-19 and ICU admission. All the patients described having generalized weakness, mildly elevated creatine kinase (CK), and a myopathic pattern during EMG examination. The authors reposted that all had a good outcome. Versace *et al* (26) described two male cases with CIM following prolonged ICU stay and ventilator support. Both patients demonstrated proximal muscle weakness and elevated CK levels after weaning from the mechanical ventilator. The patients underwent EDX four weeks after discharge. Normal sensory responses and decreased CMAP amplitude with normal distal latency and velocity in NCS and spontaneous activity and polyphasic, easy recruitment MUAPs in needle EMG of proximal muscles were observed in both cases. Clinical condition and CK level improved progressively in both patients after several weeks of rehabilitation programs. Nasuelli *et al* (27) described four cases with focal hypotrophy of the shoulder girdle and in the bilateral peroneal territory, following a prolonged ICU stay. The lab tests revealed elevated LDH levels and negative antiganglioside antibodies. The EDX was suggestive of CIN/M (a symmetrical axonal polyneuropathy in distal muscles combined with a myopathic pattern in bilateral deltoids). Only one of four showed good outcomes following rehabilitation programs. The authors suggested early electrostimulation programs in patients with COVID-19 requiring mechanical ventilation to prevent CIN/M. Cabañes-Martínez *et al* (3) reported 12 SARS-CoV-2-positive patients with ICU admission, suspicious of CIN/M. The EDX result was compatible with sensory-motor axonal polyneuropathy in four (36.6%) and myopathy in seven cases (63.6%). Of the three performed muscle biopsies, one demonstrated scattered necrotic and regenerative fibers without inflammatory signs, while the other two showed non-specific myopathic findings.

The exact mechanisms of CIN/M are not well understood (3). It appears that the same pathogenic mechanism causing interstitial respiratory damage following COVID-19, *i.e.*, the inflammatory cytokine storm together with coagulopathy and macrophage

activation are responsible for nerve and muscle damage in patients requiring prolonged intensive care, *i.e.*, CIN/M (29). Furthermore, several risk factors have been described for the development of CIN/M, including administration of corticosteroids, neuromuscular blocking drugs, and some antibiotics, prone positioning (3).

In addition, an important note is to distinguish between GBS and CIN or CIM which is vital for treatment consideration. The key points for differential diagnosis between ICU-acquired weakness and GBS are:

(1) The rapid and monophasic course of GBS

(2) The history of administration of neuromuscular blockade agents is crucial in the development of CIN/M.

(3) Involvement of cranial nerves pathologies in GBS

(4) Albuminocytological dissociation in CSF analysis of patients with GBS

(5) The presence of serum antiganglioside antibodies in GBS (12)

Finally, COVID-19 could be associated with a wide range of NMDs. Familiarity with their incidence, etiology, and EDX manifestations is vital for physicians to optimize patient care. These disorders can lead to important short and long-term consequences and could be managed with timely diagnosis and proper treatment. Furthermore, in some reports, the neurological disorders, namely stroke, and GBS, were the initial presentation of COVID-19 (24,30). Due to the importance of NMDs, further studies are vital to provide the required clinical data and develop awareness regarding neuromuscular manifestations of COVID-19, and establish proper treatment guidelines.

The present study had several limitations. As our data was collected mainly from EDX reports cards, several information were not available. Although patients with a previous history of neuromuscular disorders were not included in this study, a thorough history of participants including risk factors for peripheral nerve/muscular disorders (*e.g.*, medical comorbidities, including vascular events, metabolic disorders [*e.g.*, diabetes], smoking, *etc.*) was not available. Furthermore, the mean time from symptoms' onset/infection and EDX, course of symptoms, COVID-19 management, treatment options and its outcome were not recorded. Additionally, the correlation between COVID-19 severity and EDX alterations was not evaluated.

Conclusion

COVID-19 could be associated with a wide range of NMDs. In the present study, the presence of axonal polyneuropathy, CIDP, and myopathy was demonstrated following SAR-COV-2 infection. Also, CIN/M was observed in COVID-19 patients with a history of ICU admission. Familiarity with the incidence, etiology, and EDX manifestations of these disorders is vital for physicians to optimize patient care and treatment management.

Acknowledgements

The study was approved by the ethics committee of Iran University of Medical Sciences (IUMS), under number IR.IUMS.REC.1399.622. This study did not receive any financial support.

Conflict of Interest

No conflicts are declared.

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