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Journal of the Formosan Medical Association 120 (2021) 2032–2036

Available online at www.sciencedirect.com

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Case Report

Motor demyelinating tibial neuropathy in COVID-19

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Received 14 December 2020; received in revised form 9 April 2021; accepted 11 April 2021

KEYWORDS
COVID-19;
Motor demyelinating neuropathy;
Electrophysiology;
Nerve conduction study;
SARS-CoV-2

Ten patients suffering from residual symptoms after the resolution of COVID-19, which manifested as fatigue in the lower limbs, have been submitted to nerve conduction studies. Motor demyelinating neuropathy features mainly of the tibial nerves but also the peroneal, median, and ulnar nerves were objectified. These findings might be considered as new neurological characteristics of SARS-CoV-2 infection.

Introduction

The medical practice in the context of the COVID-19 pandemic pushes us, as researchers and physicians, to identify new weapons in the fight against SARS-CoV-2. We already know that the virus affects a variety of human systems, being responsible for respiratory,[1] digestive,[2] cardio-vascular,[3] cutaneous,[4] but also neurological manifestations such as ageusia, anosmia, amnesic changes, myalgia, and paresthesia.[5]

The neurophysiological investigation provides important data to support the diagnosis of polyneuropathy and might also be relevant in establishing the correct prognosis and treatment of these patients.[6] The nerve conduction study (NCS) is regarded as the gold standard for diagnosing

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https://doi.org/10.1016/j.jfma.2021.04.011

neuropathy due to its objective nature as well as the reproducible and dependable results obtained in the evaluation of peripheral nerve function.[6] Our paper aims to objectify the specific effects of SARS-CoV-2 on peripherical nerves using NCS.

Case series

Ten medical employees of the Clinical Emergency Hospital "Bagdasar Arseni" reported residual symptoms after recovering from the COVID-19 infection, most importantly fatigue in their lower limbs. We mention that the analyzed patients did not receive any medication for their residual symptoms or any neurological treatment. On their return to work, the subjects were submitted to NCS following the recommendation of the occupational health physician.

The patients (6 female and 4 male) aged 38—55 years old (median = 43.5) suffered from a wide range of symptoms during their SARS-CoV-2 disease evolution, which ran its course between 14th of July and 9th of November 2020, for all patients. Infection status was established by RNA testing and the patients were considered disease-free after a negative test, which according to the protocol is performed 2 weeks after the positive diagnosis. The demographic data of the patients, as well as their reported clinical symptoms and sequelae, are presented in Table 1.

The patients included in this study were submitted to a complete sensory and motor NCS analysis, on both upper and lower limbs. None of the patients had previously performed NCS investigations. Regarding the NCS data, only the abnormal findings were reported in this paper. The NCS investigation of the tibial nerves showed slight prolonged distal latency, partial or total conduction block, and rare or absent F-waves, suggesting a motor demyelinating bilateral tibial neuropathy. One patient also showed a low compound muscle action potential amplitude associating axonal features of a motor tibial neuropathy (Tables 2 and 3). Additionally, 8 patients presented with motor demyelinating bilateral peroneal neuropathy, all with axonal features. Four patients developed motor demyelinating median neuropathy, and one added motor demyelinating ulnar neuropathy (Table 3). Following the NCS examination, all patients were referred to a neurologist.

Our study has been carried out in accordance with the Declaration of Helsinki and an informed consent was obtained from all patients.

Discussion

Literature data regarding SARS-CoV-2-induced neuropathy is scarce, consisting of several case reports, some of them objectified by NCS,[7] and some not.[8] In this case series presentation, we have used a specific diagnostic tool, NCS, to sustain the peripheral motor neuropathy features induced by SARS-CoV-2 mostly in the lower limbs. This paper continues previous observations of our study group where using NCS we advanced the supposition that COVID-19 may cause polyneuropathy and myopathy.[9]

By using NCS we have been able to objectify the demyelinating nature of the motor nerve changes, for the majority of studied nerves: tibial, median, and ulnar. This suggests a potentially reversible neuropathy, however, some of the patients showed additional axonal features, mainly on the peroneal nerves, which implies a poor prognosis for nerve rehabilitation.[10]

Also, we have identified the main location of the COVID-19 neuropathy which is the tibial nerves. Some other nerves were also affected by motor demyelinating neuropathy, especially the peroneal nerve, and for some cases, the median and ulnar. This data provides the paraclinical correspondence of the patients' common clinical complaints of fatigability, especially in the lower legs. Needle electromyography can bring additional data in this manner, this being the reason why a chronic radiculopathy cannot be excluded in patient 2 because only NCS was performed.

For the analyzed patients, no sensory nerve abnormality was observed, so it is assumable that COVID-19 generates a motor demyelinating neuropathy. The two patients suffering from diabetes mellitus might have associated various types of polyneuropathy.[11] However, these patients did not have any history of associated polyneuropathy, so, presumably, COVID-19 generated the motor demyelinating tibial neuropathy, without sensory component involvement, in these cases as well. In diabetes mellitus, single fiber EMG can demonstrate a small fiber polyneuropathy.[12] Additional tests may also be performed, but the elements of demyelinating motor neuropathy demonstrated by NCS cannot be excluded. However, a diabetic polyneuropathy of small fibers cannot be ruled out in patients 1 and 7.

To date, few acquired polyneuropathies are known to associate demyelination as a primary pathological phenomenon, namely: Guillain-Barré syndrome (in which acute inflammatory demyelinating polyneuropathy, AIDP, is the most common variant of the syndrome), chronic inflammatory demyelinating polyneuropathy (CIDP), multifocal motor neuropathy (MMN), toxic-induced polyneuropathy, polyneuropathy associated with antibodies (monoclonal gammopathy of undetermined significance, anti-myelin-associated glycoprotein), polyneuropathy associated with osteosclerotic myeloma, or with Waldenstrom macroglobulinemia, and last but not least, polyneuropathy associated with human immunodeficiency virus. Therefore, there is a precedent where a virus can generate a specific motor demyelinating polyneuropathy by itself.[13]

Guillain-Barré is a syndrome including acute demyelinating inflammatory polyneuropathy, an immune-mediated predominantly motor polyneuropathy. NCS findings suggest distal prolonged latencies and slow conduction velocities on two or more nerves, as well as prolonged F-waves and conduction block on one or more nerves. The common NCS features with those identified in our patients may suggest a possible Guillain-Barré syndrome. Summarizing the reported data, Zhao et al. described an associated or SARS-CoV-2-induced Guillain-Barré syndrome due to the constant absence of F-waves on several nerves, associated with prolonged distal latency and slow motor conduction velocity.[14] However, Guillain-Barré syndrome is rarely purely motor, in which case it presents as an axonal form known as acute motor axonal neuropathy. Furthermore, the

Table 1 Demographic data and symptoms of the study lot.

Case No.	Gender	Age (years)	Comorbidities	COVID-19 onset symptoms	Disease course[a]	Sequelae
1	F	55	Diabetes mellitus	fatigability, teary and painful eyes, dry throat, cold ears	14 days	fatigability, painful legs, myalgia
2	M	39	Lumbar disc hernia	ageusia, anosmia, dry cough	16 days	fatigability
3	F	51	Hypertension	dizziness, generalized myalgia	14 days	fatigability
4	M	38	None	fatigability, cervical and thoracal pain, generalized myalgia	14 days	fatigability
5	F	45	None	fatigability	14 days	fatigability
6	M	40	None	dry cough, fever, sleepiness, generalized myalgia, headache	14 days	Fatigability, transient memory loss
7	F	57	Diabetes mellitus	dry cough, fever, generalized myalgia and numbness, eye pain, nausea, vomiting	12 days	generalized myalgia and numbness, fatigability
8	F	42	Hypertension	dry cough, fever, stuffy nose, generalized myalgia	17 days	fatigability, transient memory loss
9	M	53	None	dry cough, fatigability	14 days	fatigability
10	F	38	None	flu like state, headache, dry cough, fatigability, generalized myalgia, fever	30 days	generalized myalgia, especially in lower legs, fatigability

[a] Interval between first positive and first negative PCR testing during the course of the disease.

Table 2 Nerve conduction study results on tibial nerves, for the studied cases.

Case No.		1	2	3	4	5	6	7	8	9	10
Nerve	Parameters										
Right tibial nerve	DL (ms)	**5.2**	**5.8**	**5.9**	**8.0**	**4.8**	**4.8**	**4.4**	**4.3**	**7.5**	**6.9**
	CMAP amplitude (mV)	5.9	3.5	2.9	6.1	7.4	4.8	5.6	10.4	**1.1**	10.6
	MCV (m/s)	42	47	44	47	41	42	**32**	50	40	41
	CB (%)	**40**	19	28	4	**34**	7	**80**	**36**	**53**	**46**
	F-wave (ms)	49 **Rare waves**	**A**	45	**A**	51.7	**A**	**A**	44	51.2	**53**
Left tibial nerve	DL (ms)	**4.6**	**4.8**	**5.1**	**6.4**	**4.5**	**5.5**	**6.0**	**4.4**	**6.0**	**5.1**
	CMAP amplitude (mV)	8.9	6.6	4.3	2.9	8.1	5.1	3.3	5.1	3.6	3.7
	MCV (m/s)	50	49	**15**	54	54	**38**	43	**28**	**38**	49
	CB (%)	30	**38**	**46**	**32**	**56**	**96**	22	**82**	3	**56**
	F-wave (ms)	48 **Rare waves**	**A**	**A**	**A**	**52.5**	**A**	**A**	**A**	**A**	**53** **Rare waves**

Abbreviations: A = absent, CB = conduction block, CMAP = compound muscle action potential, DL = distal latency, MCV = Motor conduction velocity. Note: Abnormal values are marked with bold characters. Normal ranges of NCS: DL < 4 ms, CMAP amplitude >2 mV, MCV >40 m/s.

classical Guillain-Barré form of AIDP induced by SARS-CoV-2 can also be excluded due to the lack of sensory component involvement in COVID-19 infection.

Our patients performed NCS at least 30 days from the onset of SARS-CoV-2, so it is presumable that if patients have a COVID-19-induced demyelinating motor neuropathy then they were in the chronic phase. CIDP is also a chronic acquired demyelinating polyneuropathy with motor but also sensory implication, so it does not correspond with our NCS findings.[13]

MMN might be a clinical diagnostic for our NCS findings. Also, a specific form of motor demyelinating neuropathy induced by SARS-CoV-2 cannot be excluded, as other virus-induced specific motor demyelinating polyneuropathies were described.

Mononeuritis multiplex is a length-dependent dying-back, axonal polyneuropathy. The specific feature of SARS-CoV-2 is demyelinating polyneuropathy with axonal features, therefore a possible form of mononeuropathy multiplex due to SARS-CoV-2 was not considered.[15]

A possible connection between vasculitis and polyneuropathy in COVID-19 should also be investigated. Generalized polyneuropathy is the most common presentation of nerve vasculitis, while SARS-CoV-2 reveals macro- and microvascular thrombosis involving blood vessels of all major organs, associated with abnormal molecular patterns and endothelial direct or indirect, cell injury, caused by oxidative stress, chemokines, cytokines, or other factors.[15–17] Additionally, Pinto et al. reported a case of central nervous system vasculopathy with anti-myelin oligodendrocyte

Table 3 Nerve conduction studies abnormal findings and impression.

Case No.	Abnormal NCS findings	NCS impression
1	*Tibial nerves*: bilateral prolonged DL, right partial CB, rare bilateral F-wave.	Motor demyelinating tibial neuropathy.
2	*Tibial nerves*: bilateral prolonged DL, left partial CB, bilateral F-wave is absent.	Motor demyelinating tibial neuropathy.
3	*Peroneal nerves:* bilateral prolonged DL, bilateral partial CB, bilateral F-wave is absent, and bilateral CMAP amplitude is low. *Tibial nerves*: bilateral prolonged DL, left partial CB, left F-wave is absent, low left MCV.	Motor demyelinating neuropathy: bilateral tibial and peroneal with axonal elements on peroneal nerves.
4	*Median nerves:* bilateral total CB, bilateral F-wave is absent. *Peroneal nerves:* bilateral prolonged DL, bilateral F-wave is absent, and bilateral CMAP amplitude is low. *Tibial nerves*: bilateral prolonged DL, left partial CB, bilateral F-wave is absent.	Motor demyelinating neuropathy: bilateral median, tibial, and peroneal with axonal elements on bilateral peroneal nerves.
5	*Peroneal nerves:* bilateral prolonged DL, left partial CB, and right total CB, right F-wave is absent, and left CMAP amplitude is low. *Tibial nerves*: bilateral prolonged DL, left total CB, right partial CB, left F-wave is slightly prolonged.	Motor demyelinating neuropathy: bilateral tibial and peroneal nerves with axonal elements on the left peroneal nerve.
6	*Median nerves:* bilateral prolonged DL, bilateral total CB, rare bilateral F-wave. *Peroneal nerves:* bilateral prolonged DL, bilateral partial CB, right F-wave is absent, and right CMAP amplitude is low. *Tibial nerves*: bilateral prolonged DL, left total CB, bilateral F-wave is absent.	Motor demyelinating neuropathy: bilateral median, tibial and peroneal nerves with axonal elements on the right peroneal nerve.
7	*Median nerves:* rare bilateral F-wave. *Ulnar nerves:* rare bilateral F-wave. *Peroneal nerves:* bilateral prolonged DL, bilateral partial CB, bilateral F-wave is absent, bilateral CMAP amplitude is low. *Tibial nerves:* bilateral prolonged DL, right total CB, low right MCV, bilateral F-wave is absent.	Motor demyelinating neuropathy: median, ulnar, peroneal, tibial with axonal element on peroneal nerves.
8	*Peroneal nerves:* bilateral prolonged DL, bilateral total CB, left F-wave is absent, left MCV is prolonged and left CMAP amplitude is low. *Tibial nerves*: bilateral prolonged DL, right partial CB and left total CB, left F-wave is absent.	Motor demyelinating neuropathy: bilateral peroneal and tibial nerves with axonal elements on peroneal nerves.
9	*Median nerves:* bilateral prolonged DL. *Peroneal nerves:* bilateral prolonged DL, partial CB, and low CMAP amplitude; bilateral F-wave is absent. *Tibial nerves:* bilateral prolonged DL, left F-wave absent; right total CB and right low CMAP amplitude.	Motor demyelinating neuropathy: bilateral median, tibial, and peroneal nerves with axonal elements. on right tibial and peroneal bilateral nerves.
10	*Peroneal nerves:* bilateral prolonged DL, total CB on the right side, low CMAP amplitude on the left side, rare bilateral F-wave. *Tibial nerves:* bilateral prolonged DL, F-wave slight prolonged; left total CB and right partial CB, bilateral F-wave close to physiological limits.	Motor demyelinating neuropathy: bilateral tibial and peroneal nerves with axonal elements on the left peroneal nerve.

Abbreviations: CB = conduction block, CMAP = compound muscle action potential, DL = distal latency, MCV = Motor conduction velocity, NCS = nerve conduction study, SNAP = sensory nerve action potential, SCV = Sensory conduction velocity.

glycoprotein antibodies in a patient with COVID-19 launching the hypothesis of vascular and neurogenic inflammation working together through an unbalanced immune system to produce vasculitis associated with nerve demyelination. These complex interconnections need further observation and dedicated studies in order to reveal the actual impact and implications of this disease.

A neurological evaluation is recommended in these patients, as well as a follow-up NCS investigation after 6—12 months.

Conclusion

Motor demyelinating peripheral neuropathy features of the tibial and other nerves, might be regarded as new neurological characteristics of COVID-19. The elements of demyelinating motor neuropathy may be the paraclinical expression of a focal motor neuropathy or a specific SARS-CoV-2-induced motor demyelinating neuropathy. These diagnoses require additional paraclinical investigations for confirmation, including needle EMG. Larger studies and follow-up examinations are necessary for revealing the pathogenesis and evolution of these specific SARS-CoV-2 neurological complications.

Ethical statement

This case series presentation has been approved by the Ethics Commission of the "Bagdasar Arseni" Clinical Emergency Hospital, Bucharest, Romania, No. 39310/18.11.2020; all patients signed an informed consent.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jfma.2021.04.011.

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