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ORIGINAL ARTICLE

Electrophysiological features of acute inflammatory demyelinating polyneuropathy associated with SARS-CoV-2 infection

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KEYWORDS
Acute inflammatory demyelinating polyradiculoneuropathy;
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Summary
Objective. — To assess whether patients with acute inflammatory demyelinating polyneuropathy (AIDP) associated with SARS-CoV-2 show characteristic electrophysiological features.
Methods. — Clinical and electrophysiological findings of 24 patients with SARS-CoV-2 infection and AIDP (S-AIDP) and of 48 control AIDP (C-AIDP) without SARS-CoV-2 infection were compared.
Results. — S-AIDP patients more frequently developed respiratory failure (83.3% vs. 25%, $P = 0.000$) and required intensive care unit (ICU) hospitalization (58.3% vs. 31.3%, $P = 0.000$).

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Distal compound muscle action potential duration;
Distal motor latency;
F-wave;
SARS-CoV-2 infection

In C-AIDP, distal motor latencies (DMLs) were more frequently prolonged (70.9% vs. 26.2%, $P = 0.000$) whereas in S-AIDP distal compound muscle action potential (dCMAP) durations were more frequently increased (49.5% vs. 32.4%, $P = 0.002$) and F waves were more often absent (45.6% vs. 31.8%, $P = 0.011$). Presence of nerves with increased dCMAP duration and normal or slightly prolonged DML was elevenfold higher in S-AIDP (31.1% vs. 2.8%, $P = 0.000$);11 S-AIDP patients showed this pattern in 2 nerves.

Conclusion. — Increased dCMAP duration, thought to be a marker of acquired demyelination, can also be oserved in critical illness myopathy. In S-AIDP patients, an increased dCMAP duration dissociated from prolonged DML, suggests additional muscle fiber conduction slowing, possibly due to a COVID-19-related hyperinflammatory state. Absent F waves, at least in some S-AIDP patients, may reflect α-motor neuron hypoexcitability because of immobilization during the ICU stay. These features should be considered in the electrodiagnosis of SARS-CoV-2 patients with weakness, to avoid misdiagnosis.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and its associated coronavirus disease 19 (COVID-19) were reported to originate in December 2019 in Wuhan (China), spreading rapidly around the world. On January 30th 2020, the World Health Organization (WHO) declared COVID-19 to be a public health emergency of international concern, and on March 11th 2020 as a pandemic. COVID-19 is a systemic disorder typically presenting with fever and respiratory symptoms but neurological manifestations such as ischemic stroke, encephalopathies, encephalitis, ageusia, anosmia and skeletal muscle involvement have been also described [4]. Regarding the peripheral nervous system, in the first six pandemic months, 42 patients with SARS-CoV-2 infection and Guillain-Barré syndrome (GBS) were reported [25], totaling, 139 cases by November 19th, 2020 (of which 38.1% were from Italy). The classical GBS clinical sensorimotor presentation with hyporeflexia or areflexia, with or without cranial nerve involvement, was the most frequent but virtually all GBS variants and subtypes were described. A great majority of patients were diagnosed as having acute inflammatory demyelinating polyneuropathy (AIDP) although the electrodiagnostic criteria employed were often not reported. An observational multicenter study in two regions of Northern Italy showed that the incidence of GBS in March and April 2020 was increased 2.6 fold compared with the same months of 2019 and that 88.2% of patients had associated SARS-CoV-2 infection, suggesting a pathogenic link [5].

The aim of this study was to report the electrophysiological features of patients with AIDP and SARS-CoV-2 infection, and to investigate whether they were in any way different compared with a control group of AIDP patients without SARS-CoV-2 infection.

Methods

Patients

We enrolled 24 patients with GBS and confirmed SARS-CoV-2 infection, according to WHO COVID-19 case definitions [27,28] admitted to tertiary hospitals of four cities of the Lombardy region (Bergamo, Brescia, Pavia, Milano) in North Italy during the pandemic peak in March and April 2020. The patients were classified as having AIDP according to recently reported electrodiagnostic criteria [22] (denominated S-AIDP). Controls were 48 consecutive patients diagnosed as having AIDP, according to the same criteria, at the University Hospital of Chieti in the years preceding 2019 (denominated C-AIDP). The diagnosis of GBS was based in both groups on the Brighton Collaboration GBS Working Group criteria [20]. Level 1 of the Brighton criteria indicates the highest degree of diagnostic certainty supported by nerve-conduction studies and the presence of albumin-cytologic dissociation in CSF. A level 2 diagnosis is supported by either a CSF white-cell count of less than 50 cells/μl (with or without an elevated protein level) or nerve-conduction studies consistent with the Guillain—Barré syndrome (if the CSF white-cell count is unavailable). A level 3 diagnosis is based on clinical features without support from nerve-conduction or CSF studies.

Electrophysiological studies and electrodiagnostic criteria

Nerve conduction studies were performed according to standardized techniques [22]. In median, ulnar, peroneal and tibial motor nerves the following parameters were measured: distal motor latency (DML), amplitude of the negative peak of compound muscle action potential (CMAP), duration of CMAP, conduction velocity (CV), and minimal F wave latency. CMAP duration was measured manually at a sensitivity of 500 μV/division from the onset of the first negative phase to return to baseline of the last negative deflection [2,14]. Proximal/distal (p/d) amplitude and duration ratios of CMAPs from different stimulation sites were also assessed.

Electrophysiological findings were normalized as percentages of upper and lower limits of normal (ULN, LLN) according to the reference values of each participating laboratory. The ULNs for distal CMAP (dCMAP) duration were determined using the control duration values reported for 2 Hz low frequency filter +2SD [14]. Distal CMAP duration was considered to be in the demyelinating range when this attained >120% of the ULN i.e.: 9.5 ms for the median, 10.2 ms for the ulnar, 9.5 ms for the peroneal, and 8.9 ms for the tibial nerve [22].

Sensory studies were performed antidromically in median, ulnar and sural nerves and amplitude of sensory nerve action potential (SNAP) was measured from baseline to negative peak.

The criteria set used here for electrodiagnosis of GBS subtypes was originally devised on the basis of two serial electrophysiological studies but also showed highest diagnostic accuracy in the first study compared with two other criteria sets, in a cohort with a balanced number of AIDP and axonal GBS patients. This approach has already been employed in the electrodiagnosis of GBS associated with Zika virus infection (table, supplementary material) [22,23]. This criteria set is mainly characterized by the following features: (1) cut-off values for demyelination are quite stringent (DML > 130% ULN, motor CV <70% LLN); (2) duration of dCMAP is evaluated because it has been shown that increased duration is a sensitive and specific indicator of acquired demyelination [2,16]; (3) because of the recognition that conduction failure (even completely reversible) can be an expression of axonal pathology, p/d CMAP amplitude ratio <0.7 is considered only for axonal GBS subtypes, whereas an increased (>130%) p/d CMAP duration is considered indicative of demyelination [22,24]; (4) isolated F-wave absence, defined as unrecordable or markedly reduced persistence (<20%) of F wave with otherwise normal conductions, is introduced as a parameter suggestive of axonal pathology [12,22]; (5) sural sparing, defined as abnormal ulnar and normal sural SNAP amplitude, is also taken into account [3].

Statistical methods

The clinical characteristics and electrophysiological data between the two groups were compared using standard (unpaired) statistical t-test procedures to assess differences between means and proportions [9]. For the electrophysiological parameters in which the samples were small we also employed permutation tests to compare the mean of two populations [15]. Because of their flexibility and minimal assumptions, results from this non-parametric approach are compared with the standard statistical t-test which requires more restrictive distributional assumptions for the data. For statistical comparisons we considered the following test specifications: (1) the null hypothesis represents the ''no difference'' situation and the alternative represents an ''upper tailed'' specification, i.e. it is assumed that the mean/proportion in the C-AIDP group is greater than the mean/proportion of S-AIDP; (2) the null hypothesis represents the ''no difference'' situation and the alternative represents a ''lower tailed'' specification, i.e. it is assumed that the mean/proportion in the C-AIDP group is smaller than the mean/proportion of S-AIDP; (3) no upper or lower tailed version of the test is assumed and we simply assume that the population means are different. Finally, as for test interpretation, when the two-sided *P*-value is less than the conventional 0.05 the conclusion is that there is a significant difference between the means/proportions. Similarly, values smaller than 0.05 for the one-sided test, also represent statistically significant results.

Ethical committee and informed consent

This study is part of a project approved by Ethical Committee of the University and Spedali Civili of Brescia. All C-AIDP patients provided informed signed consent for the utilization of personal data for research purposes. Regarding the S-AIDP patients, given the difficulty in systematically obtaining informed consent and given the public interest of the project, the research was conducted in the context of the authorizations guaranteed by Article 89 of the GDPR EU Regulation 2016/679.

Results

Patients and clinical features

The data set consisted of 24 S-AIDP and 48 C-AIDP patients. The demographic and clinical characteristics are reported in Table 1. The S-AIDP group consisted of 7 females (age: median 69 years, [IQR 51—74.8], range 42—81) and 17 males (age: median 58 years, [IQR 49—62.3], range 35—76). The control group was composed of 21 females (age: median 56 years [IQR 36.8—64.8], range 16—80) and 27 males (age: median 49, [IQR 28.5—58.5], range 13—74). The median age between the two groups was not significantly different (Kruskal—Wallis test $P = 0.19$). Three S-AIDP patients had type-2 diabetes and arterial hypertension; five additional patients had arterial hypertension. Three C-AIDP patients had type-2 diabetes and arterial hypertension, two had only diabetes and four only arterial hypertension. The diagnosis of SARS-CoV-2 infection was made by positive RT-PCR of nasopharyngeal swab in 83.3% patients and by serology in 16.7%. Most frequent presenting symptoms of COVID-19 were fever (70.8%), cough (70.8%) and dyspnea (58.3%). Hypo-ageusia and hypo-anosmia were reported in 33% and 29.2% of patients, respectively. Interstitial pneumonia was documented by chest RX or CT in 79.2% of patients. In all S-AIDP patients the neuropathic symptoms followed the onset of COVID-19 with a median interval of 28.5 days. All S-AIDP and C-AIDP patients had the classical GBS sensorimotor form with ascending weakness and hypo-areflexia [26]. Cranial nerves were involved in 14 (58.3%) patients. Oculomotor nerves were involved in one patient, facial nerve was involved in ten patients (in seven bilaterally), bulbar nerves were involved in 7 patients. Antibodies to gangliosides GM1, GD1a, GD1b and GQ1b were searched in 11(45.8%) patients and were negative in all.

Significantly more C-AIDP patients fulfilled the Brighton level 1 of diagnostic certainty. This difference was due to the fact that CSF examination was performed in all C-AIDP patients whereas it was performed in only 15 (62.5%) S-AIDP patients. In the remaining nine patients CSF was not examined because of anticoagulant therapy or because of difficulties connected with the ongoing severe health emergency. However, considering that all patients of both groups belonged to the Brighton level 1 or 2 the overall diagnostic certainty is fairly high.

Twenty (83.3%) S-AIDP and 12 (25%) C-AIDP patients developed respiratory failure. Fourteen (58.3%) S-AIDP and 15 (31.3%) C-AIDP were admitted to the intensive care unit (ICU).

Table 1 Demographic and clinical characteristics of patients with AIDP and SARS-CoV-2 infection (S-AIDP) and of control AIDP (C-AIDP).

	S-AIDP 24 patients No (%)	C-AIDP 48 patients No (%)	*P*
Gender	7 F (29%)/17 M (71%)	21 F (44%)/27 M (56%)	—
Age (median years, [IQR], range)	59, [49—70], 35—81	50 [32—64],13— 80	0.19
Diagnosis of SARS-CoV-2 infection			—
NPS	20 (83.3)	NA	
Serology	4 (16.7)		
Interstitial pneumonia	19 (79.2)	NA	—
Interval be**tween onset of COVID-19 and GBS symptoms** (median days, [IQR], range)	28.5, [16—36], 5—46	NA	—
Brighton criteria			0.009* 0.009*
Level 1	7 (29.2)	30 (62.5)	
Level 2	17 (70.8)	18 (37.5)	
Respiratory failure	20 (83.3)	12 (25)	0.000*
ICU admission	14 (58.3)	15 (31.3)	0.031*

ICU, intensive care unit; NA, not applicable; NPS, nasopharyngeal swab.

Electrophysiological findings

The median interval between GBS onset and the electrophysiological test in 21 S-AIDP patient was 7 days, [IQR 6—11], range 3—21. In three patients it was not possible to establish with certainty when the neuropathic symptoms developed. In C-AIDP the median interval between the GBS onset and the electrophysiological test was 10 days, [IQR 6—11.5], range 2—20. The intervals were not significantly different ($P = 0.73$).

In S-AIDP patients a total of 103 motor nerves (mean 4.3 per patient) were studied, 6 peroneal nerves were unexcitable. In C-AIDP a total of 179 motor nerves (mean 3.7 per patient) were studied, 9 peroneal and two tibial nerves were unexcitable.

Table 2 shows the descriptive statistics of five electrophysiological parameters measured in median, ulnar, peroneal and tibial nerves of both groups. In the S-AIDP group, only six median nerves were studied and in all of them F waves were not recordable; comparison with the median nerves of C-AIDP showed no significant differences for all the electrophysiological parameters even employing the permutation test. In ulnar, peroneal, and tibial nerves, the mean dCMAP amplitudes were not significantly different in the two groups. Mean DMLs were significantly more prolonged in the ulnar, tibial and peroneal nerves of C-AIDP whereas in S-AIDP, mean dCMAP durations were significantly increased in the ulnar nerve at the level of 5% and in the tibial at 10% level. Regarding the other parameters, the mean values of CV was significantly lower in C-AIDP ulnar nerves and higher in the peroneal nerves. Mean minimal F latency was significantly prolonged in tibial nerves of S- AIDP. Overall the results from the permutation test were consistent with the t-test in the case of large samples and provided robust results in cases of small samples. Table 3 shows the occurrence of abnormal motor conduction parameters, according to the cut-offs of the electrodiagnostic criteria set employed, in the nerves of the two groups. Apart from the prevalence of decreased CV, the statistical test strongly indicates that the proportion of nerves with abnormal parameters is significantly different in the two cohorts. Specifically, the presence of nerves with prolonged minimal F wave was significantly higher in C-AIDP whereas nerves with no recordable F wave were more frequently observed in S-AIDP. DML was more frequently prolonged in C-AIDP whereas dCMAP duration was more often increased in S-AIDP. When we examined the relationship between DML and dCMAP duration in the individual nerves, the proportion of nerves that presented both pronged DML and increased dCMAP duration was higher in the C-AIDP nerves. Interestingly, dCMAP duration was prolonged in the presence of normal or slightly increased (not reaching the cut-offs for demyelination) DML at a much higher percentage in S-AIDP nerves (Fig. 1B—D), whereas prolonged DML in the presence of normal or slightly increased (not reaching the cut-offs for demyelination) dCMAP duration was more frequent in C-AIDP. Thirty-two S-AIDP nerves presented normal or slightly prolonged DML in the presence of an increased dCMAP duration (mean: 14.0 ms ±4.17, range 9.5—28.6 ms) and 11 S-AIDP patients (45.8%) had this pattern in at least two nerves. Regarding sensory conductions, 30 ulnar and 37 sural nerves were studied in S-AIDP and 47 ulnar and 46 sural nerves in C-AIDP cohort. The mean amplitude of ulnar SNAP was significantly lower, and the frequency of abnormal ulnar SNAPs (reduced amplitude or not recordable) was higher in the C-AIDP group. Conversely, the mean amplitude of sural SNAP and the frequency of abnormal sural SNAPs were comparable in the two groups (Table 4). Consequently sural sparing was more frequent in C-AIDP than in S-AIDP. Concentric needle EMG of at least one proximal and distal muscle was performed in 21 (87.5%) S-AIDP patients. Variable degrees of spontaneous activity (fibrillation potential and positive sharp waves) at rest were found in at least one muscles in 8 (38.1%) patients. The voluntary activity was impossible to evaluate in four patients hospitalized in ICU

Table 2 Motor conduction findings in AIDP patients with SARS-CoV-2 infection (S-AIDP) and in control AIDP (C-AIDP) patients.

	DML					CV					dCMAP amplitude					dCMAP duration					F latency				
	Mean	SD	Min	Max	No	Mean	SD	Min	Max	No	Mean	SD	Min	Max	No	Mean		Min	Max	No	SD	SD	Min	Max	No
Uln S-AIDP	3.6	1.4	2.2	8.8	31	51.9	11.0	25.1	69.2	31	4.5	2.8	0.8	9.5	31	10.7	4.7	5.0	26.0	31	36.9	8.9	30.1	59.4	18
Uln C-AIDP	5.2	2.8	2.8	22.0	48	46.7	9.9	17.0	61.0	48	4.5	2.9	0.6	12.4	48	8.9	2.8	5.3	19.3	47	38.1	8.3	26.6	64.0	29
	P Perm. test		P t-test			P Perm. test		P t-est			P Perm. test		P t-test			P Perm. test		P t-test			P Perm. test		P t-test		
	0.003*		0.000*			0.031*		0.035*			0.989		0.989			0.021*		0.025*			0.635		0.638		
	Mean	SD	Min	Max	No	Mean	SD	Min	Max	No	Mean	SD	Min	Max	No	Mean	SD	Min	Max	No	Mean	SD	Min	Max	No
Tib S-AIDP	6.2	3.5	3.4	20.7	41	38.0	10.8	6.9	56.0	39	3.3	3.0	0.3	12.1	41	13.0	10.1	4.4	58.0	41	68.9	10.9	57.0	89.3	6
Tib-C-AIDP	9.4	5.8	3.5	34.0	33	38.3	9.6	20.0	67.0	31	3.3	2.7	0.10	11.1	33	9.8	9.1	4.7	57.1	32	48.7	4.6	43.9	54.6	6
	P Perm. test		P t-test			P Perm. test		P t-est			P Perm. test		P t-test			P Perm. test		P t-test			P Perm. test		P t-test		
	0.002*		0.002*			0.911		0.913			0.973		0.974			0.088**		0.083**			0.000*		0.002*		
	Mean	SD	Min	Max	No	Mean	SD	Min	Max	No	Mean	SD	Min	Max	No	Mean	SD	Min	Max	No	Mean	SD	Min	Max	No
Per S-AIDP	7.7	2.5	3.7	12.6	16	34.4	5.6	27.0	43.4	13	2.2	1.9	0.2	6.3	16	11.4	4.7	5.4	19.3	16	64.2	10.8	56.5	71.8	2
Per C-AIDP	10.8	4.5	5.8	25.5	39	39.5	7.3	26.0	55.0	38	1.9	1.6	0.2	6.1	39	10.7	5.9	4.8	35.2	39	60.7	9.4	50.7	80.0	12
	P Perm. test		P t-test			P Perm. test		P t-est			P Perm. test		P t-test			P Perm. test		P t-test			P Perm. test		P t-test		
	0.003*		0.006*			0.028*		0.025*			0.473		0.470			0.332		0.338			0.753		0.643		
	Mean	SD	Min	Max	No	Mean	SD	Min	Max	No	Mean	SD	Min	Max	No	Mean	SD	Min	Max	No	Mean	SD	Min	Max	No
Med S-AIDP	10.0	4.9	5.9	18.9	6	40.8	12.4	17.9	50.0	6	2.1	1.2	0.6	3.5	6	10.4	3.1	7.1	15.0	6	—	—	—	—	—
Med C-AIDP	10.6	4.8	4.10	22.3	48	43.7	11.3	19.0	66.0	48	3.4	2.8	0.1	12.1	48	10.3	5.0	5.8	36.0	47	41.3	10.2	24.5	64.0	32
	P Perm. test		P t-test			P Perm. test		P t-est			P Perm. test		P t-test			P Perm. test		P t-test			P Perm. test		P t-test		
	0.403		0.390			0.565		0.556			0.264		0.267			0.395		0.490			—		—		

CV, conduction velocity; dCMAP, distal compound muscle action potential; DML, distal motor latency; No, number of nerves; Perm, permutation; Uln, ulnar; Tib, tibial; Per, peroneal; Med, Median.

* Significant at the 5% level.

** Significant at the 10% level.

Table 3 Frequency of abnormal motor conduction parameters in nerves of AIDP patients with SARS-CoV-2 infection (S-AIDP) and in control AIDP (C-AIDP).

	S-AIDP 103 nerves No (%)	C-AIDP 179 nerves No (%)	*P*
Prolonged DML	27 (26.2)	127 (70.9)	0.000*
Increased dCMAP duration	51 (49.5)	58 (32.4)	0.002*
Increased p/d CMAP duration	14 (13.6)	11 (6.1)	0.016*
Decreased CV	10 (9.7)	24 (13.4)	0.179
Prolonged F latency	9 (8.7)	34 (19.0)	0.001*
F not recordable	47 (45.6)	57 (31.8)	0.011*
Prolonged DML and increased dCMAP duration	19 (18.4)	54 (30.2)	0.015*
Prolonged DML and normal^ dCMAP duration	9 (8.7)	74 (41.3)	0.000*
Normal^ DML and increased dCMAP duration	32 (31.1)	5 (2.8)	0.000*

CMAP, compound muscle action potential; CV, conduction velocity; DML, distal motor latency; d, distal; p, proximal; ^, normal or slightly increased but not reaching the employed cut-offs for demyelination.

Table 4 Sensory action potential amplitudes and sural sparing in AIDP patients with SARS-CoV-2 infection (S-AIDP) and in control AIDP (C-AIDP).

	Ulnar SNAP (μV)			Sural SNAP (μV)			Sural sparing (%)
	Mean (SD) [range] No	NR (%)	Reduced/NR (%)	Mean (SD) [range] No	NR (%)	Reduced/NR (%)	
S-AIDP	10.9 (6.1) [0.9—25.0] 27	3/30 (10)	15/30 (50)	12.5 (7.3) [0.6—26.2] 30	7/37 (18.9)	10/30 (30)	7/23 (30.4)
C-AIDP	7.4 (6.2) [1.0—23.8] 26	21/47 (44.7)	41/47 (87.2)	13.6(8.6) [3.8—38.0] 38	8/46 (17.4)	13/46 (28.3)	26/46 (56.5)
P t-test	0.041*	0.001*	0.000*	0.606	0.430	0.437	0.022*

No, number of nerves; NR, no response; SNAP, sensory nerve action potential.

because of sedation or coma. In the remaining 17 patients the recruitment pattern was reduced and at a qualitative evaluation the amplitude of motor unit action potentials (MUAPs) was described as reduced with an excess of polyphasic potential in 6 (35.3%) patients.

Discussion

All patients with GBS associated with SARS-CoV-2 infection fulfilled the employed electrodiagnostic criteria for the diagnosis of AIDP, but when compared with C-AIDP showed significant differences. Notably, S-AIDP nerves showed less prolonged mean values of DML and DML less frequently reached the cut-offs for demyelination, whereas mean dCMAP duration was increased in the ulnar nerve and dCMAP duration values more frequently reached the cut-offs for demyelination. In S-AIDP nerves, DML was normal or slightly prolonged, but not reaching the employed cut-offs for demyelination, with increased dCMAP duration occurring eleven times more commonly than in C-AIDP. Increased dCMAP duration is considered a specific marker of demyelination that improves the sensitivity of criteria employed in the electrodiagnosis of AIDP [2,16]. CMAP is the summation of many MUAPs, and CMAP amplitude, duration, and morphology are mainly determined by: (1) the distribution of conduction velocities of individual axons; (2) the distance between stimulating and recording electrodes; (3) the conduction velocity of the muscle fibers; (4) phase cancelation between individual MUAPs. Normally the individual MUAP has a negative peak duration of 5—6 ms overlapping that of the negative phase of dCMAP. Indeed, with distal nerve stimulation most MUAPs arrive at the recording electrodes in phase with each other and the resulting CMAP is quite compact because of the restricted range of conduction velocities of axons (around 10 m/sec) and the short distance between the stimulating and recording electrodes. In the nerves of S-AIDP patients with normal DML and increased dCMAP duration at least some large diameter fast fibers conduct normally and the increased dCMAP duration could be explained by preferential demyelination of slower conducting nerve fibers or by conduction slowing of muscle fibers. Interestingly in critical illness myopathy (CIM), besides reduced dCMAP amplitudes, prolonged dCMAP durations (comparable to those found in S-AIDP nerves with normal or slightly prolonged DML) have been reported [1,10,11]. Reduced muscle fiber excitability can

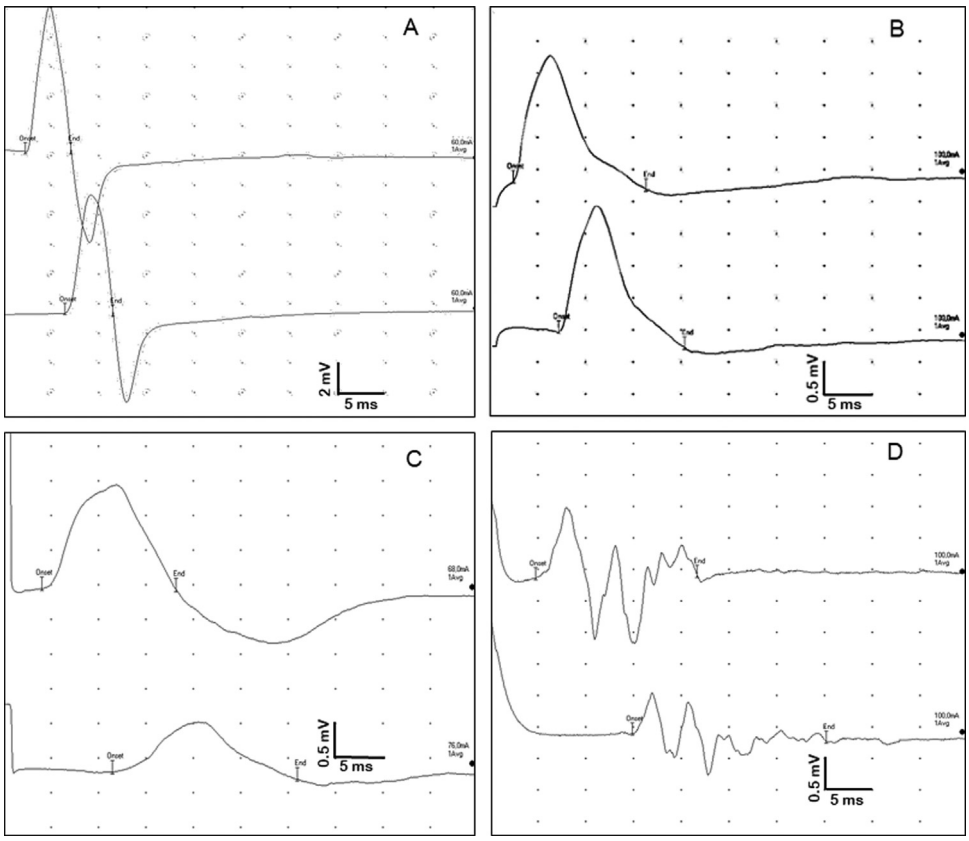

Fig. 1 Motor nerve conduction studies in a normal control and in patients with AIDP and SARS-COV-2 infection (S-AIDP). (A) ulnar nerve of a normal control: distal CMAP (dCMAP) amplitude is 10.8 mV, distal motor latency (DML) is 2.3 ms, dCMAP duration is 4.7 ms, conduction velocity (CV) is 61.9 m/s, p/d CMAP amplitude is 0.9, p/d CMAP duration is 1; (B) ulnar nerve of a S-AIDP patient: dCMAP amplitude is reduced (2 mV), DML is normal (2.4 ms), dCMAP duration is increased (13.9 ms, 136% upper limit of normal), CV is 46.8 m/s, p/d CMAP amplitude is 1, p/d CMAP duration is 1 indicating that CMAP duration did not change between proximal and distal stimulation. Note, compared to A, the prolonged negative phase with a long tail and the absence of the following positive phase of CMAPs; (C) ulnar nerve of a S-AIDP patient: DML is prolonged (3.8 ms) but not reaching the cut-off for demyelination (130% upper limit of normal =4.3 ms), dCMAP amplitude is reduced (1.6 mV), dCMAP duration is increased (15.3 ms, 150% upper limit of normal), CV is 35.1 m/s, p/d CMAP amplitude is reduced (0.56), p/d CMAP duration is increased (1.4) indicating an additional temporal dispersion in the elbow-wrist nerve segment: (D) tibial nerve of a S-AIDP patient: DML is normal (4.8 ms), dCMAP amplitude is reduced in (0.9 mV) with polyphasic morphology, dCMAP duration is increased (16.9 ms, 190% upper limit of normal), CV is 45.3 m/s, p/d CMAP amplitude is reduced (0.53), p/d CMAP duration is increased (1.2) but not reaching the required cut-off for temporal dispersion (>1.3).

explain low CMAP amplitudes in humans with CIM and in animal models [17—19]. In an in vitro model, serum from CIM patients applied to single muscle fibers induced depolarization of resting membrane potential, reduced the action potential rise time, and increased inward sodium current peak amplitude [7]. In patients with CIM, mean muscle fiber conduction velocity was halved, the conduction velocity ratio between fastest and slowest fibers doubled, and an inverse relationship between conduction velocity of muscle fibers and CMAP durations was demonstrated [1]. It can be hypothesized that in CIM associated with sepsis and systemic inflammatory response syndrome, a depolarizing shift of muscle membrane potential, possibly caused by inflammatory cytokines, may induce sodium-channel inactivation, slowing of conduction velocity or even membrane inexcitability, and eventually muscle damage [7,8]. Some COVID-19 patients present a so-called ''cytokine storm'', an uncontrolled over-production of soluble inflammatory markers which, in turn, sustains an aberrant systemic inflammatory response [13]. In the cohorts reported here, patients with S-AIDP had more frequent respiratory failure and were more frequently admitted to ICU compared to C-AIDP, probably because of summation of the effects of COVID-19 and GBS. Specifically, all 11 patients with normal or slightly prolonged DML and increased dCMAP duration in at least two nerves had pneumonia with respiratory insufficiency and 72.7% were hospitalized in ICU. We hypothesize that in these patients the increased dCMAP duration with normal or slightly prolonged DMLs indicates an additional involvement of muscle fiber excitability, similar to that described in CIM and likely due to the COVID-19 hyperinflammatory state. If increased dCMAP duration is not, as previously thought, specific of demyelination[16] but may also be due to muscle conduction slowing, it is important to establish how much this abnormality might have influenced electrodiagnosis in the S-AIDP group. As a matter of fact in three (12.5%)

patients, increased dCMAP duration in at least two nerves was decisive for the diagnosis. When the increased dCMAP durations were excluded, the electrodiagnosis changed in two patients to equivocal: in one patient who had one prolonged F wave and two slow CVs not reaching the demyelinating cut-off; in the other who had one increased p/d CMAP duration. However, in the latter patient, a control study after 17 days showed two increased p/d CMAP duration, one prolonged F wave and one slow CV confirming the AIDP diagnosis. The third patient, a 47-year-old man, had severe COVID-19 pneumonia and very high titers of IL6 (6152 pg/ml, normal <3.4) at ICU admission when severe muscle weakness was noted. Five days later, the patient was in a coma and electrophysiology showed: normal DMLs, slightly reduced dCMAP amplitudes in the ulnar (5.2 mV) and tibial (5.4 mV), increased dCMAP durations in the tibial nerves (163% and 204% ULN), three unrecordable F waves, normal ulnar and sural SNAP. EMG did not show spontaneous activity and voluntary recruitment was not possible. CSF examination was not performed because of anticoagulant therapy. The patient was treated with three courses of intravenous immunoglobulins and five plasma exchanges without any improvement and died 46 days after ICU admission. In this patient, if we exclude increased dCMAP durations, there remain absent F waves that are usually considered an expression of a proximal conduction block in the early stage of AIDP or acute motor axonal neuropathy [6,12]. However, absent F waves that re-emerged soon after a short bust of repetitive stimulation have been recently described in two patients with CIM (one with COVID-19) and thought to be due to hypo-excitability of α-motor neurons because of reduced mobility [21,29]. For the above considerations, it is likely that increased dCMAP durations and absent F waves could be alternatively explained by reduced muscle excitability due to systemic hyperinflammation and immobility. Therefore the diagnosis should be changed to that of CIM. Indeed, the frequency of unrecordable F-waves was higher in S-AIDP patients and it is conceivable that the greater disease severity and the higher ICU hospitalization rate with immobilization may at least in part contribute to F-wave absence.

This study has some limitations inherent to all studies conducted in an epidemic setting. EMG was not performed in all patients and was evaluated only qualitatively. MUAP analysis, although often difficult to accomplish in weak, sedated, ICU patients, could have helped to better assess muscular involvement. Moreover the very recently described technique to investigate the reemergence of F-wave after short burst stimulation was not employed.

Conclusions

Patients with S-AIDP frequently present increased dCMAP durations and absent F waves.

Increased dCMAP duration, thought to be specific for acquired demyelinating neuropathies, can be also found in CIM; at least in some S-AIDP patients, this can be due to muscle fiber conduction slowing because of the hyperinflammatory state of COVID-19.

Unrecordable F waves does not necessarily imply proximal conduction failure in severe COVID-19 patients and may be due to prolonged immobilization because of ICU stay with consequent α-motor neuron hypoexcitability.

The above considerations should be taken into account when examining patients with COVID-19 and weakness, to avoid misdiagnoses.

Declarations of interest

None declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.neucli.2021.02.001.

Declaration of Competing Interest

The authors report no declarations of interest.

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