

Neurological, Neuromuscular, and Autonomic Manifestations of COVID-19: A Retrospective Study

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Abstract

Background

Neurovascular, neuromuscular, and autonomic complications of COVID-19 have rarely been characterized within a single cohort.

Objective

To compare the clinical, electrodiagnostic, and autonomic profiles of COVID-19 patients across these three domains.

Methods

This retrospective study included 72 adults with COVID-19 and neurological findings evaluated at Cleveland Clinic Florida from January 2020 through February 2023, grouped as neurovascular (NV; n = 29), neuromuscular (NM; n = 12), or autonomic dysfunction (AD; n = 31). Chi-square, Fisher's exact tests, and ANOVA were used.

Results

Mean age differed across groups (NV 69.7, NM 61.4, AD 45.8 years; $p < .0001$). Males predominated in the NV (62.1%) and NM (66.7%) groups, and females in the AD group (74.2%; $p = .0064$). Ischemic stroke accounted for 79.3% of NV cases, 47.8% of undetermined etiology by TOAST criteria. NV in-hospital mortality was 13.8% (4/29); deceased patients had higher NIHSS scores (16.3 vs. 6.5), higher D-dimer levels (11,440 vs. 6,965 ng/mL), and frequent bilateral strokes (50.0%). In the NM group, EMG was abnormal in 83.3% and nerve conduction studies in 58.3%. In the AD group, postural orthostatic tachycardia syndrome (POTS) was diagnosed in 36.7% and cardiovagal failure in 26.7%, and QSART showed a length-dependent sudomotor pattern. Unvaccinated status was most frequent in the NM group (91.7%; $p = .0014$).

Conclusions

COVID-19 is associated with distinct neurovascular, neuromuscular, and autonomic phenotypes. The frequency of POTS, electrodiagnostic abnormalities, and the association of elevated D-dimer with stroke mortality support comprehensive neurological evaluation of patients with COVID-19.

Introduction

Long COVID-19, also known as post-acute sequelae of SARS-CoV-2 infection (PASC), is characterized by persistent symptoms following acute COVID-19. The World Health Organization defines it as a condition occurring usually within three months of SARS-CoV-2 infection, with symptoms lasting at least two months that cannot be explained by an alternative diagnosis.[1] The European Centre for Disease Prevention and Control and European Respiratory Society recognize it as a multisystem condition with symptoms persisting beyond four weeks, while the Centers for Disease Control and Prevention similarly defines it as symptoms lasting four or more weeks after initial infection [2–4]. The National Academies and the RECOVER consortium have proposed further definitions [5, 6]. Despite slight definitional variations, these organizations agree that Long COVID is a complex, multisystem condition, and the absence of a universally accepted definition underscores the necessity for standardized criteria.[2, 3, 5, 6]

Estimates of the proportion of infected individuals who develop persistent symptoms vary widely across studies, definitions and viral variants, and are higher in hospitalized cohorts.[7–9] Neurological symptoms, including cognitive disturbances, headache, anosmia and sleep disturbances, are among the most frequent manifestations of Long COVID.[7, 10, 11] Neuromuscular symptoms, including myalgia, fatigue and muscle weakness, are common,[12] while autonomic dysfunction, including postural orthostatic tachycardia syndrome (POTS) and orthostatic hypotension, is increasingly recognized as a common component [13–15]. Females and middle-aged adults appear more susceptible to persistent symptoms, particularly neurological and autonomic disturbances.[8, 16]

The pathophysiology of Long COVID neurological manifestations involves multiple interacting mechanisms. SARS-CoV-2 can induce neuroinflammation through systemic cytokine storm and blood-brain barrier disruption, with elevated pro-inflammatory cytokines detected in cerebrospinal fluid of affected patients.[17, 18] Autoimmune mechanisms, including molecular mimicry and autoantibody production targeting G-protein-coupled receptors, have been implicated in autonomic dysfunction.[19, 20] Mitochondrial dysfunction contributes to fatigue and exercise intolerance, while immune-mediated damage to autonomic nerve fibers and small fiber neuropathy underlie dysautonomia.[12, 21, 22] Electrophysiological studies have demonstrated small fiber neuropathy and neuromuscular junction dysfunction in Long COVID patients.[12, 22]

Despite growing recognition of these manifestations, comprehensive characterization of neurovascular, neuromuscular, and autonomic presentations within a single cohort remains limited. This study aims to characterize the demographic, clinical, electrodiagnostic, and autonomic profiles of COVID-19 patients presenting with neurological findings and to compare outcomes across these three domains.

Methods

This retrospective study included 72 COVID-19 positive patients aged 18 years and older with neurological findings admitted at Cleveland Clinic Florida from January 2020 through February 2023.

Patients were categorized into three groups based on their primary neurological manifestation: neurovascular disorders (NV), neuromuscular disorders (NM), and autonomic dysfunction (AD).

Descriptive analytic techniques were performed to assess the study population. Means, medians, standard deviations, and inter-quartile ranges were calculated for continuous variables. Frequencies and counts, as well as chi-square and Fisher exact tests, were conducted for categorical variables. ANOVA was used for comparison of continuous variables across groups. Statistical significance was set at $p < .05$.

Results

Demographics and Clinical Characteristics (Table 1). Seventy-two patients were categorized into NV ($n = 29$, 40.3%), AD ($n = 31$, 43.1%), and NM ($n = 12$, 16.7%) groups. The overall mean age was 58.0 years ($SD = 18.4$), with significant differences across groups (NV: 69.7, NM: 61.4, AD: 45.8; $p < .0001$). Mean BMI did not differ significantly ($p = .2758$). The NM group had markedly longer hospitalizations (median = 19.0 days) compared to NV (3.0 days) and AD (4.0 days; $p = .0322$).

Gender distribution differed significantly ($p = .0064$): the AD group was predominantly female (74.2%), while males predominated in NV (62.1%) and NM (66.7%). Racial distribution also differed ($p = .0132$), with the AD group having the highest proportion of White patients (93.3%) and the NM group the highest proportion of Black/African American patients (33.4%).

All patients had at least one comorbidity. Cardiac comorbidities were most prevalent in the NV group (89.7% vs. 66.7% NM vs. 35.5% AD; $p < .0001$). COVID-19 respiratory symptoms were present in 54.2% overall, highest in the NM group (75.0%; $p = .0187$). Most patients (87.5%) had mild disease; the NM group had the highest ICU admission rate (33.3%), though this did not reach significance ($p = .0636$).

Vaccination status differed significantly ($p = .0014$): 91.7% of NM patients were unvaccinated with no fully vaccinated patients, compared to 55.2% fully vaccinated in the NV group and 29.0% in the AD group.

Diagnostic Procedures (Table 2). Carotid imaging was performed in 96.6% of NV patients versus 20.0% NM and 23.3% AD ($p < .0001$), with CTA as the predominant modality (83.8%). Carotid obstruction was identified exclusively in NV patients (left: 30.8%; right: 23.1%). Echocardiography was performed in 71.0% overall with no group differences ($p = .9765$). Mean ejection fraction was preserved across all groups (61.0%, $SD = 7.4$; $p = .6952$). Transesophageal echocardiography was performed exclusively in NV (15.8%) and NM (14.3%) groups ($p = .0455$).

Neurovascular Findings (Tables 3a, 3b). Among the 29 NV patients, mean D-dimer was markedly elevated at 6,965 ng/mL ($SD = 8,971.9$, $N = 4$). Mean NIHSS at admission was 6.5 ($SD = 6.8$), with minimal change at discharge (6.6, $SD = 7.8$). Functional status deteriorated substantially: at admission, 72.4% had mRS 0, but by discharge, 34.5% had mRS 4–6 (moderately severe disability to death).

Ischemic stroke predominated (79.3%), followed by hemorrhagic stroke (13.8%) and TIA (6.9%). Anterior circulation strokes accounted for 65.4% of cases, with the middle cerebral artery most commonly affected (56.0%). The parietal lobe (51.7%) and frontal lobe (41.4%) were the most frequently involved regions. TOAST classification revealed undetermined etiology in 47.8%, small vessel occlusion in 26.1%, cardioembolism in 17.4%, and large artery atherosclerosis in 8.7%. Cerebral vasculitis was identified in 11.1%. Among 16 patients with echocardiographic data, the relationship between left atrial size and TOAST classification did not reach significance ($p = .2371$). Tenecteplase was administered in 8.7% and mechanical thrombectomy in 4.3%.

Neuromuscular Findings (Table 4). All 12 NM patients underwent EMG, compared to 53.3% of AD patients ($p = .0034$). Concentric needle EMG abnormalities were significantly more frequent in the NM group (83.3% vs. 13.3% AD; $p = .0003$), as were EMG muscle testing abnormalities (75.0% vs. 6.7%; $p = .0008$). NCS abnormalities were present in 58.3% of NM and 33.3% of AD patients ($p = .1939$). Nerve conduction studies were performed only in the NM and AD groups; the highly significant three-group differences for individual nerves ($p < .0001$ for most comparisons) therefore largely reflect the absence of testing in the NV group rather than differences in nerve function. MRI brain abnormalities were found in 60.0% of NM patients who underwent imaging ($p = .0275$), and MRI spine abnormalities in 85.7% ($p = .2222$).

Autonomic Dysfunction Findings (Table 5). QSART testing revealed a pattern suggestive of length-dependent sudomotor neuropathy, with reduced sweat output at distal sites (distal leg ratio 0.3, proximal foot ratio 0.4) relative to proximal sites (forearm ratio 0.9). HRDB testing showed a mean heart rate variance of 12.9 bpm (SD = 9.5), with a subset demonstrating reduced cardiovagal function. The mean Valsalva ratio was 1.7 (SD = 0.8).

Tilt table testing ($N = 30$) demonstrated SBP decrease in 76.7% and HR increase in 90.0% of patients. Symptoms included dizziness (29.0%), lightheadedness (12.9%), malaise (12.9%), and presyncope (9.7%); no syncope occurred. POTS was diagnosed in 36.7% (11/30), cardiovagal failure in 26.7% (8/30), and autonomic failure in 9.7% (3/31; 2 mild, 1 moderate). MRI brain was normal in 94.4% of AD patients.

Mortality Analysis (Table 6). All 4 deaths occurred in the NV group (mortality rate: 13.8% NV, 5.6% overall). Deceased patients were older (median 79.5 years), predominantly male (75.0%), and had substantially higher NIHSS scores at admission (16.3 vs. 6.5) that worsened at discharge (21.5). D-dimer levels were markedly elevated (mean 11,440 ng/mL vs. 6,965 ng/mL overall NV). All had ischemic strokes, with bilateral involvement in 50.0% (vs. 17.2% overall NV) and equal anterior-posterior distribution (50/50 vs. 65/35). TOAST classification showed undetermined etiology in 75.0%. Notably, 75.0% of deceased patients were fully vaccinated, likely reflecting higher vaccination rates and baseline stroke risk in older adults. All 4 patients had an mRS score of 6 at discharge.

Discussion

This retrospective study of 72 COVID-19 patients with neurological findings at Cleveland Clinic Florida reveals distinct demographic and clinical profiles across neurovascular, neuromuscular, and autonomic dysfunction subgroups, reinforcing the multifaceted neurological impact of SARS-CoV-2.

The NV group comprised older patients (mean 69.7 years) with high rates of cardiac comorbidities (89.7%), consistent with established cerebrovascular risk profiles in COVID-19.[23, 24] The male predominance (62.1%) aligns with reports of sex-based differences in COVID-19 thrombotic complications.[25] Ischemic strokes predominated (79.3%), with the high rate of undetermined TOAST etiology (47.8%) suggesting COVID-19-specific prothrombotic mechanisms beyond traditional stroke etiologies.[23, 26, 27] Elevated D-dimer levels, particularly in the mortality subgroup (11,440 ng/mL), support the role of hypercoagulability.[28] The mortality analysis identified several potential prognostic markers: higher NIHSS scores (16.3 vs. 6.5), bilateral stroke involvement (50.0% vs. 17.2%), and markedly elevated D-dimer levels. Cerebral vasculitis in 11.1% of evaluated patients further supports immune-mediated vascular inflammation in COVID-19-associated cerebrovascular disease.

The NM group demonstrated the most severe disease course, with the longest hospitalizations (median 19.0 days), highest ICU admission rate (33.3%), and most extensive electrodiagnostic abnormalities (83.3% abnormal EMG). These findings, suggestive of Guillain-Barré syndrome, critical illness neuropathy, and myopathic changes, are consistent with prior reports of immune-mediated peripheral nerve involvement.[29, 30] The striking finding that 91.7% of NM patients were unvaccinated, with no fully vaccinated patients in this subgroup, suggests a potential protective effect of vaccination against severe neuromuscular complications, consistent with emerging data on vaccines reducing COVID-19-associated neurological events, though prospective studies are needed to establish causality.[31] MRI abnormalities in 60.0% of brain and 85.7% of spinal imaging further support inflammatory processes.

The AD group represented the largest subgroup (43.1%) with a distinct profile: younger age (mean 45.8 years), female predominance (74.2%), and lower cardiac comorbidity rates (35.5%). This demographic pattern mirrors the well-established predilection of POTS and dysautonomias for younger females.[13, 16] POTS was the most common specific diagnosis (36.7%), consistent with emerging literature on post-COVID dysautonomia.[13–15] QSART testing revealed a length-dependent sudomotor neuropathy pattern, consistent with small fiber neuropathy increasingly recognized in post-COVID autonomic dysfunction.[22] The near-normal MRI brain findings (94.4%) suggest primarily peripheral rather than central autonomic involvement. Notably, NCS abnormalities in 33.3% of AD patients indicate subclinical peripheral nerve involvement, supporting a shared pathophysiological continuum between neuromuscular and autonomic manifestations.

The finding that 75.0% of the mortality group was fully vaccinated likely reflects the older age of these patients (median 79.5 years), as older adults had higher vaccination rates and higher baseline stroke risk, rather than evidence against vaccine efficacy.

Limitations. The retrospective design limits causal inferences, and the small sample size (N = 72) with unequal group sizes restricts generalizability and statistical power. Selection bias toward hospitalized

patients may overrepresent certain manifestations. D-dimer values were available for only 4 NV patients. The single-center design and lack of long-term follow-up are additional limitations.

Conclusions

COVID-19 is associated with diverse neurological manifestations spanning neurovascular, neuromuscular, and autonomic domains, each with distinct demographic and clinical profiles. Key findings include the high prevalence of POTS (36.7%) predominantly in younger females, significant electrodiagnostic abnormalities in the NM group (83.3% abnormal EMG), the predominance of undetermined stroke etiology (47.8%) suggesting COVID-19-specific prothrombotic mechanisms, and the association of elevated D-dimer, bilateral strokes, and higher NIHSS scores with mortality. The striking association between unvaccinated status and neuromuscular complications warrants further investigation. Longitudinal studies are needed to assess the persistence of neurological deficits, identify predictive biomarkers (particularly D-dimer for stroke prognosis) and evaluate targeted immunomodulatory and anticoagulant therapies.

Declarations

Funding:

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Conflicts of Interest: None

Ethics Approval: This study was approved by the Cleveland Clinic Florida Institutional Review Board IRB (FLA 22–023). The study was conducted in accordance with the Declaration of Helsinki.

Consent to Participate: Informed consent was waived due to the study's retrospective design.

Data Availability: The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

AUTHOR CONTRIBUTIONS

Raphael Bastianon Santiago, MD (Research Neuroscience Fellow, Braathen Neurosciences Institute, Cleveland Clinic Florida, at the time of the study; currently Lyerly Neurosurgery, Baptist Neurological Institute, Jacksonville, FL): collected data, built the REDCap database, and performed the statistical analysis, discussed jointly with N. Galvez-Jimenez, A. Cvetkovska, O. Delgado, and E. Veliz.

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