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Neurological presentations of COVID-19: Findings from the Spanish Society of Neurology neuroCOVID-19 registry

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ABSTRACT

Objective: We report the findings from the Spanish Society of Neurology's NeuroCOVID-19 Registry.

Methods: We performed a multicentre study of patients with neurological manifestations of COVID-19. Participating physicians reported demographic, clinical, and paraclinical data and judged the involvement of COVID-19 in causing neurological symptoms.

Results: A total of 233 cases were submitted, including 74 different combinations of manifestations. The most frequently reported were stroke (27%), neuromuscular symptoms (23.6%), altered mental status (23.6%), anosmia (17.6%), headache (12.9%), and seizures (11.6%). The mean age of patients was 61.1 years, with 42.1% being women; a higher proportion of women was recorded among patients with altered mental status, anosmia, and headache. The onset of symptoms differed within categories. Onset of anosmia occurred a mean (standard deviation) of 2.9 (2.5) days after the first general symptom, whereas neuromuscular symptoms appeared after 13.9 (10.1) days. Neurological symptoms were persistent in 33% of patients. General symptoms were present in 97.7% of patients, and results from general laboratory studies were abnormal in 99.4% of patients. Cerebrospinal fluid analysis findings were abnormal in 62.7% of the cases in which this test was performed ($n = 51$), but positive results for SARS-CoV-2 were only found in one case.

Conclusions: The neurological manifestations of COVID-19 are diverse. Anosmia, myalgia, and headache occur earlier in the course of the disease. Altered mental status, neuromuscular symptoms, and stroke are associated with greater severity. COVID-19 must be incorporated into most clinical and radiological differential diagnoses. COVID-19 may cause persistent and disabling neurological symptoms.

1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic has challenged healthcare systems worldwide. Clinicians and neurologists have been obliged to familiarise themselves with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in record time [1]. Spain has been one of the most severely affected countries worldwide, having been struck since the very onset of the pandemic [2]. The Spanish Society of Neurology (SEN) created a task force to review the existing evidence about previous coronaviruses and the exponentially increasing evidence about COVID-19 [3].

The first large series described a relatively low frequency of mostly non-specific neurological symptoms, including myalgia, headache, anosmia, and altered mental status [4–7]. However, since the publication of the initial neurological series and cases, the number and frequency of neurological manifestations have significantly increased [8,9]. The SEN created a nation-wide registry of COVID-19 cases with neurological manifestations [10]. The main objectives were to raise awareness about the different neurological presentations and to report weekly to SEN members about the collected data. The purpose of this study is to present the findings from the registry and to discuss the clinical implications for the management of neuroCOVID-19.

2. Material and methods

We performed an observational, descriptive, multicentre study of a series of patients with COVID-19 presenting neurological manifestations during the course of the disease. Hospital admission was not a requisite for inclusion in the registry, and both inpatients and outpatients were included. All neurologists belonging to the SEN were informed about the registry and were invited to participate, both by personal e-mail and through the official SEN website. Weekly reminders were sent from the SEN's head office. The registry was created on March 16th, 2020, and the information gathered in this study includes all consecutive cases recorded until July 9th, 2020. Lockdown was implemented in Spain on March 15th, and by July 9th, the number of cases had multiplied by 28, when compared with March 16th. On April 6th, Spain surpassed Italy as the European country with the most COVID-19 cases.

2.1. Variables

Information was collected by using a pre-established, standardised questionnaire hosted on Google Forms. The registry included information about the physician reporting the case (name, hospital, region, and type of SEN membership [resident or full member]), demographical data, patient's history, general COVID-19 symptoms, neurological signs and symptoms, and complementary test results.

Participants were asked to report the neurological presentation using a pre-defined list of neurological manifestations, which included anosmia, headache, meningeal syndromes, altered mental status, seizures, movement disorders, ataxia, myelopathy, radiculopathy, polyradiculopathy, plexopathy, optic neuropathy, oculomotor nerve palsy, vestibular neuropathy, other cranial nerve syndromes, rhabdomyolysis, and dysautonomia. We also included clinico-radiological syndromes, such as ischaemic stroke, intracranial haemorrhage, acute disseminated encephalomyelitis, and others. Finally, in the event that the presentation was different from those listed, participants were invited to describe it. We studied whether patients presented a single manifestation or a combination of neurological symptoms. The full definition of the main variables studied is provided as supplementary material. We present neurological manifestations according to the different subspecialties of neurology, where appropriate.

Demographic data included age and sex of patients. Information about prior medical history included the presence of general comorbidities (arterial hypertension, diabetes, smoking, chronic heart diseases, chronic pulmonary diseases, cancer, malnutrition, immunosuppression, other diseases, and chronic neurological diseases (stroke, dementia, other neurodegenerative diseases, muscle disorders, multiple sclerosis, other autoimmune diseases, epilepsy, headache). Chronic treatments, including angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), non-steroidal anti-inflammatory drugs (NSAIDS), steroids, and immunosuppressant drugs were also recorded.

Regarding the epidemiology of the contagion, we analysed whether the patient was a healthcare worker and the presumed source of transmission, including workplace-related, close contact with a relative, social exposure (demonstrations, meetings), recent travel, or unknown. We recorded the time from the first general COVID-19 manifestation to onset of the first neurological symptom.

The description of the clinical presentation included general symptoms (arthralgia, asthenia, weakness, diarrhoea, dyspnoea, chest pain, expectoration, fever, light-headedness, odynophagia, skin rash, cough, vomiting, and others). We analysed whether patients also presented headache, anosmia, and/or myalgia, given that these symptoms were commonly reported in clinical series. The severity of COVID-19 disease was classified as mild disease, pneumonia, acute respiratory distress syndrome (ARDS) [11] (supplementary material), and other complications (cardiac insufficiency, acute kidney injury, septic shock, disseminated intravascular coagulation, and others). The need for intensive care unit (ICU) admission was also recorded. Participants indicated whether COVID-19 was diagnosed by polymerase chain reaction (PCR), serological testing, quick tests, or based on clinical signs and symptoms [12]. Due to a shortage of reagents during the peak of the pandemic, some local protocols allowed COVID-19 diagnosis based on the typical clinical picture, prior contact with a patient with COVID-19, and lack of a more plausible explanation for the patient's symptoms. Participants were instructed to report cases without diagnostic confirmation when these were not better accounted for by another diagnosis. Abnormal results from the general laboratory analysis were recorded, including leucocytosis, lymphocytosis, lymphopenia, anaemia, thrombocytopaenia, increased liver enzymes, increased lactate dehydrogenase (LDH), rhabdomyolysis, decreased glomerular filtration rate, and abnormal coagulation parameters.

The results of specific neurological work-up were specifically assessed. We analysed whether cerebrospinal fluid (CSF) was tested and recorded the presence of pleocytosis, increased protein levels, hypoglycorrhachia, and increased CSF opening pressure. Participants reported whether CSF samples were tested for SARS-CoV-2 with PCR. Neurological imaging was assessed, including the type of study (head computed tomography [CT], cranial or spinal magnetic resonance imaging [MRI]), the results, and the interval between symptom onset and study performance. We also evaluated the results of other ancillary studies, including electroencephalography (EEG), electroneurography (ENG), and other tests. The indication of each ancillary study was based on the judgement of the responsible neurologist, and was not a requisite for the inclusion in the registry.

The registry also recorded patients' outcomes, including the treatment administered (lopinavir/ritonavir, interferon beta, hydroxychloroquine, remdesivir, tocilizumab, or other). The duration of the neurological symptoms was reported, and the neurologist reporting the case subjectively judged whether the causality of SARS-CoV-2 infection in the presence of the neurological symptoms was coincidental, probably causal, or definitely causal. Patient management was based on the local standard of care in effect at the time of the report. Patients were included regardless of whether or not they were managed in a specific neuroCOVID-19 unit, since the registry was opened at the very early stage of the pandemic, when information about neurological manifestations of COVID-19 was limited.

2.2. Ethics

The study protocol was approved by the Ethics Review Board of
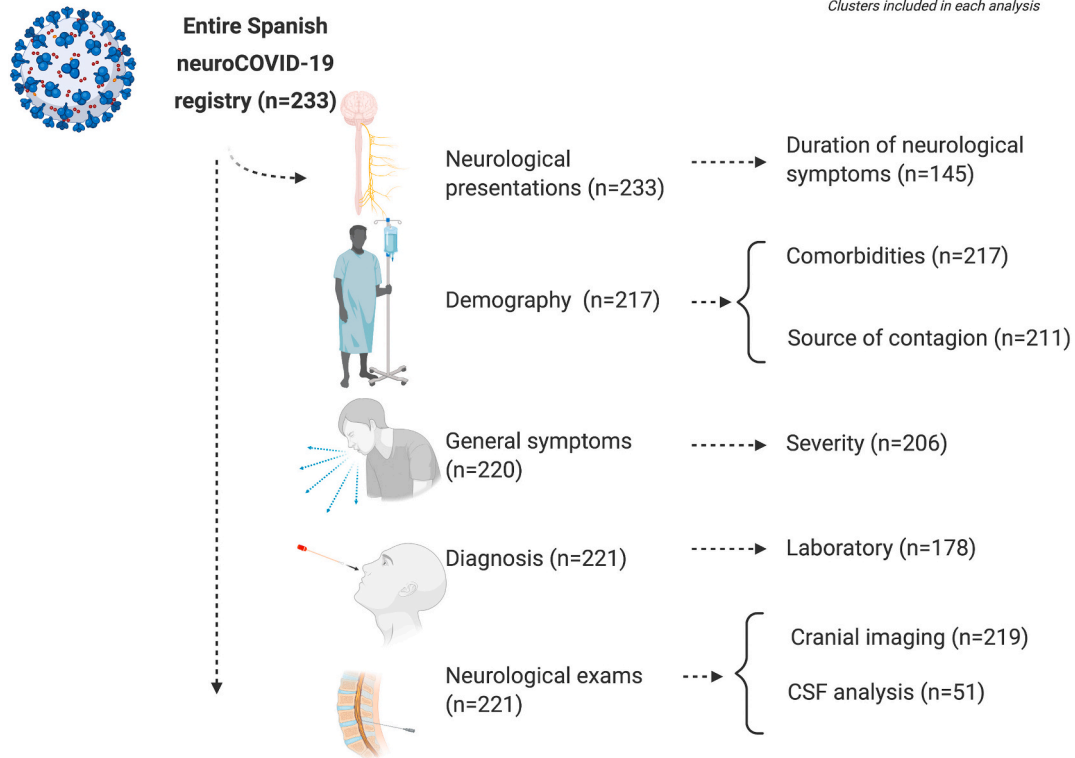
Clusters included in each analysis

Fig. 1. Flow chart of patients who were eligible and included in each analysis.

Hospital Clínico Universitario de Valladolid, Spain (PI 20–1722). Written informed consent was waived due to the nature of the study, the absence of personal data, and the risk of transmission of the virus.

2.3. Statistical analysis

Qualitative and quantitative ordinal variables are expressed as frequency and percentage, with the denominator included for those variables for which the number of valid responses was not the full sample. Continuous quantitative variables are expressed as mean and standard deviation (SD) if they were normally distributed, or median and interquartile range (IQR) if they were not. Normality was evaluated with the Kolmogorov-Smirnov test. We compared qualitative variables with the Fisher exact test and quantitative variables within groups with the ANOVA test when they were normally distributed and their variances were homogeneous according to Levene's test. Patients presenting multiple neurological manifestations were excluded from direct comparisons within groups. The Bonferroni method was used to adjust for multiple comparisons. Missing data were managed by complete case analysis. Statistical analysis was conducted using SPSS v26.0 (IBM Corp.; Armonk, NY, USA) for Mac.

3. Results

During the study period, 233 different cases were submitted by 98 different researchers, who each submitted 1.3 (2.8) cases on average; 188 (80.7%) cases were submitted by full members of the SEN, 43 (18.5%) cases by residents, and one (0.4%) by a non-member; this information was not specified in one case (0.4%). Fourteen of the 17 Spanish autonomous regions were represented, with most cases being reported in Madrid (106 cases; 45.5%), followed by the Basque Country (23; 9.9%), Catalonia (17; 7.3%), and Castile and Leon (17; 7.3%).

A total of 74 different combinations of manifestations were observed; the most frequently reported were stroke (63 cases; 27.0%), neuromuscular symptoms (55; 23.6%), altered mental status (55; 23.6%),

Table 1
Demographic variables and frequency of comorbidities.

Variable	Value	*n*
Age (mean, SD)	61.1 (17.5)	217
Female sex (*n*, %)	93 (42.1%)	221
Comorbidities (*n*, %)	145 (66.8%)	217
Hypertension (*n*, %)	91 (41.9%)	217
Diabetes (*n*, %)	43 (19.8%)	217
Hyperlipidaemia (*n*, %)	21 (9.7%)	217
Smoking (*n*, %)	19 (8.8%)	217
Neurological diseases (*n*, %)	61 (28.1%)	217
• Stroke	14 (6.5%)	217
• Epilepsy	13 (6.0%)	217
• Headache	10 (4.6%)	217
• Dementia	9 (4.1%)	217
• Neuromuscular disorders	5 (2.3%)	217
• Movement disorders	4 (1.8%)	217
• Neuroimmunology	2 (0.9%)	217
• Space-occupying lesions	2 (0.9%)	217
• Neuro-ophthalmological disorders	1 (0.4%)	217
• Other	2 (1.3%)	217
Heart diseases (*n*, %)	33 (15.2%)	217
Pulmonary disorders (*n*, %)	22 (10.1%)	217
Endocrine disorders (*n*, %)	21 (9.7%)	217
Nephro-urological disorders (*n*, %)	13 (6.0%)	217
Psychiatric disorders (*n*, %)	12 (5.5%)	217
Cancer (*n*, %)	11 (5.1%)	217
Gastrointestinal disorders (*n*, %)	5 (2.3%)	217
Haematological diseases (*n*, %)	4 (1.8%)	217
Immunosuppression (*n*, %)	2 (0.9%)	217
Dermatological diseases (*n*, %)	2 (0.9%)	217
Rheumatoid arthritis (*n*, %)	2 (0.9%)	217
Chronic infections (*n*, %)	2 (0.9%)	217
Genetic disorders (*n*, %)	2 (0.9%)	217
Pregnancy (*n*, %)	1 (0.4%)	217

SD: standard deviation.

Table 2

Type and frequency of general symptoms, headache, anosmia, and myalgia in the sample.

Variable	Frequency	n
Fever	150 (68.2%)	220
Cough	110 (50.0%)	220
Asthenia	81 (36.8%)	220
Dyspnoea	72 (32.7%)	220
Weakness	56 (25.4%)	220
Myalgia	55 (25.0%)	220
Anosmia	43 (19.5%)	220
Headache	38 (17.4%)	220
Arthralgia	28 (12.3%)	220
Diarrhoea	25 (11.4%)	220
Chest pain	17 (7.7%)	220
Odynophagia	13 (5.9%)	220
Rhinorrhoea	9 (4.1%)	220
Expectoration	9 (4.1%)	220
Light-headedness	5 (2.3%)	220
Vomiting	5 (2.3%)	220
Skin rash	2 (0.9%)	220
Anorexia	2 (0.9%)	220
Syncope	1 (0.4%)	220
No systemic symptoms	5 (2.3%)	220

anosmia (41; 17.6%), headache (30; 12.9%), seizures (27; 11.6%), cranial neuropathies (14; 6.0%), movement disorders (13; 5.6%), and meningoencephalitis (8; 3.4%). Clinical presentation included a combination of neurological manifestations in 77 (33.0%) patients, with the most frequent symptoms in those combinations being altered mental status in 44/77 (56.1%), headache in 23/77 (29.9%), and anosmia in 19/77 (24.7%). The full list of manifestations is provided as supplementary material. Fig. 1 shows the number of patients that were eligible for each analysis.

3.1. Demographic profile

Patients' mean (SD) age was 61.1 (17.5) years; 128 (54.9%) were men, 93 (42.1%) were women, and sex was not specified in 12 (5.2%) cases. Patients were healthcare workers in 31/233 (13.3%) cases. Information about comorbidities was available in 217 cases, with 145/217 (66.8%) presenting comorbidities, including prior neurological disorders in 61/217 (28.1%). Table 1 shows the main demographic variables and the frequency of comorbidities. Information about the possible source of contagion was available in 221 cases: the source was unknown in 116 (52.5%) cases and attributed to workplace exposure in 40 (18.0%), close contact with a relative in 28 (12.7%), travel in 25 (11.3%), and nursing homes in 12 (5.4%).

3.2. Frequency and type of general symptoms

Information about the general symptoms of COVID-19 was available in 220 (94.4%) cases. The most frequent general symptoms were fever and cough. Five (2.3%) patients had no general symptoms and for two (0.9%) patients this information was not available due to the lack of relatives and hyperacute presentation of the neurological symptoms (basilar artery stroke and left middle cerebral artery stroke). Table 2 summarises the type and frequency of general symptoms, headache, anosmia, and myalgia.

When comparing the six most frequently represented categories of manifestations, statistically significant differences were observed in age; frequency of general comorbidities; frequency of fever, headache, and anosmia; and time between onset of general COVID-19 symptoms and onset of neurological symptoms (Table 3). Fig. 2 shows the one-minus-survival curve of time to the onset of neurological symptoms within those groups.

Information about the severity of COVID-19 was available for 206 (88.4%) patients, corresponding to mild disease in 80 (38.8%) cases, pneumonia in 131 (63.6%), and ARDS in 38 (18.4%). Anosmia and headache were reported in a higher percentage of patients with mild disease; epilepsy, stroke, and altered mental status most frequently presented in patients with pneumonia; and patients with neuromuscular symptoms, altered mental status, and stroke more frequently presented ADRS (corrected $P < 0.001$ for all comparisons, Table 4). Fig. 3 shows the severity of the disease in patients with the main categories of manifestations. Five (2.5%) patients presented pulmonary embolism. Patients were admitted to the ICU in 58/220 (26.4%) cases, with a mean age of 59 (SD: 11.7); 13/58 of these patients (22.4%) were female. A total of 46/220 (20.1%) patients were intubated. Diagnosis was confirmed by PCR in 162/221 (73.3%) cases, anti–SARS-CoV-2 antibodies in 16/221 (7.2%) cases, and with rapid tests in 5/221 (2.3%) cases. Diagnosis was clinical in 38/221 (17.9%) cases, and supported by highly suggestive CT imaging findings in seven of those cases (full details on supplementary material). Laboratory data were available in 178 cases: of 169 patients who underwent laboratory analyses, findings were abnormal in 168 (99.4%) patients and normal in one (0.6%).

3.3. Results of the ancillary neurological studies

Information regarding lumbar puncture (LP) was available in 178 cases. The procedure was performed in 51/178 (28.7%) cases, with abnormal findings in 32/51 (62.7%). The abnormalities observed were increased CSF protein concentration in 26/51 (51.0%) cases, pleocytosis in six (11.8%), and increased intracranial pressure in one (1.9%). Four (7.8%) patients had both increased CSF proteins and pleocytosis. PCR screening for SARS-CoV-2 in CSF samples was performed in 16/51 (31.4%) patients, with positive results in 1/16 (6.2%), a patient with

Table 3

Comparison of demographic variables, frequency of comorbidities, and main clinical variables within the most frequently represented categories of manifestations.

Variable	Anosmia (n = 41)	Altered mental status (n = 55)	Epilepsy (n = 27)	Headache (n = 30)	Neuromuscular symptoms (n = 55)	Stroke (n = 63)	P
Age (mean, SD)	44.6 (14.7)	67.5 (12.4)	72.2 (17.5)	47.5 (17.2)	59.0 (15.3)	66.9 (15.6)	<0.001[a]
Female sex (n, %)	25 (61.0%)	34 (61.8%)	14 (51.9%)	16 (53.3%)	18 (32.7%)	19 (30.2%)	0.130[b]
Presence of comorbidities (n, %)	13 (31.7%)	38 (69.1%)	20 (74.1%)	14 (46.7%)	34 (61.8%)	55 (81.0%)	<0.001[b]
Fever (n, %)	18 (43.9%)	44 (80.0%)	17 (63.0%)	16 (53.3%)	32 (58.2%)	40 (63.5%)	0.026[b]
Cough (n, %)	16 (39.0%)	25 (45.5%)	14 (51.9%)	14 (46.7%)	24 (56.4%)	36 (57.1%)	0.271[b]
Headache (n, %)	23 (56.1%)	5 (9.1%)	3 (11.1%)	30 (100%)	7 (12.7%)	2 (3.2%)	<0.001[b]
Myalgia (n, %)	25 (61.0%)	10 (18.2%)	1 (3.7%)	9 (30.0%)	21 (38.2%)	14 (22.2%)	0.199[b]
Anosmia (n, %)	41 (100%)	3 (5.5%)	2 (7.4%)	15 (50.0%)	2 (3.6%)	5 (7.9%)	<0.001[b]
Days after COVID-19 onset (mean, SD)	2.9 (2.5)	8.2 (8.3)	5.4 (4.9)	3.6 (4.1)	13.9 (10.1)	11.3 (10.0)	<0.001[a]

SD: standard deviation.

[a] Multiple comparisons–adjusted ANOVA.

[b] Multiple comparisons–adjusted Fisher exact test. Percentages are calculated according to the total number of patients per group.
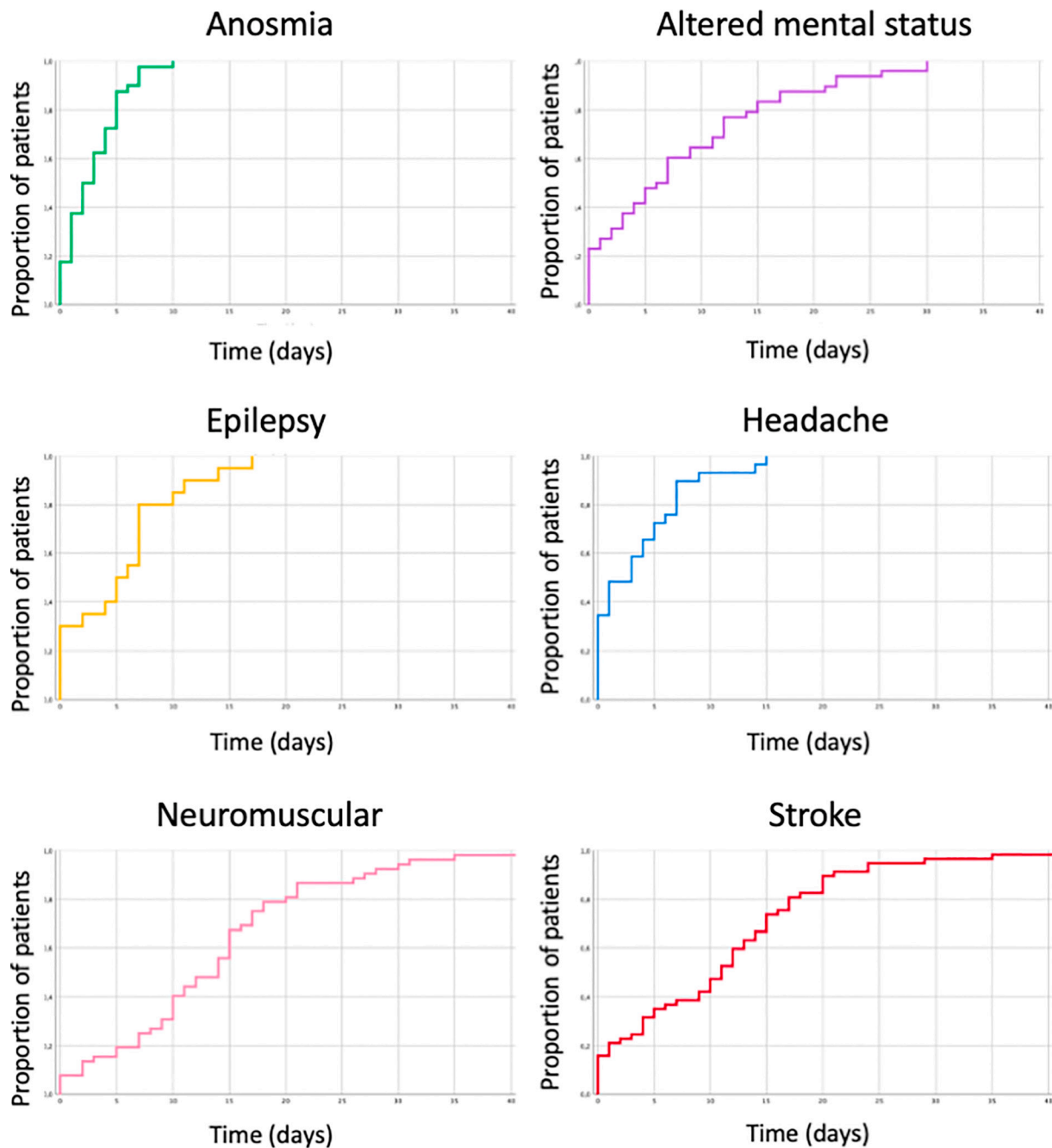
Fig. 2. One-minus-survival curve of time from onset of the first general COVID-19 symptom to the onset of neurological symptoms in the most frequently represented categories of manifestations in the registry.

‡ Multiple comparisons–adjusted Fisher exact test.

Table 4

Severity of the disease within the most frequently represented categories of manifestations.

Variable	Anosmia (*n* = 36)	Altered mental status (*n* = 48)	Epilepsy (*n* = 23)	Headache (*n* = 27)	Neuromuscular symptoms (*n* = 47)	Stroke (*n* = 52)	*P*
Mild disease	33 (91.7%)	10 (20.8%)	4 (17.4%)	19 (70.4%)	8 (17.0%)	4 (7.7%)	<0.001[‡]
Pneumonia	3 (8.3%)	27 (56.2%)	18 (78.3%)	7 (25.9%)	16 (34.0%)	37 (71.2%)	<0.001[‡]
ARDS	0/33 (0%)	11 (22.9%)	1 (3.7%)	1 (3.7%)	23 (48.9%)	11 (21.2%)	<0.001[‡]

Percentages are calculated according to the total number of patients in each group.
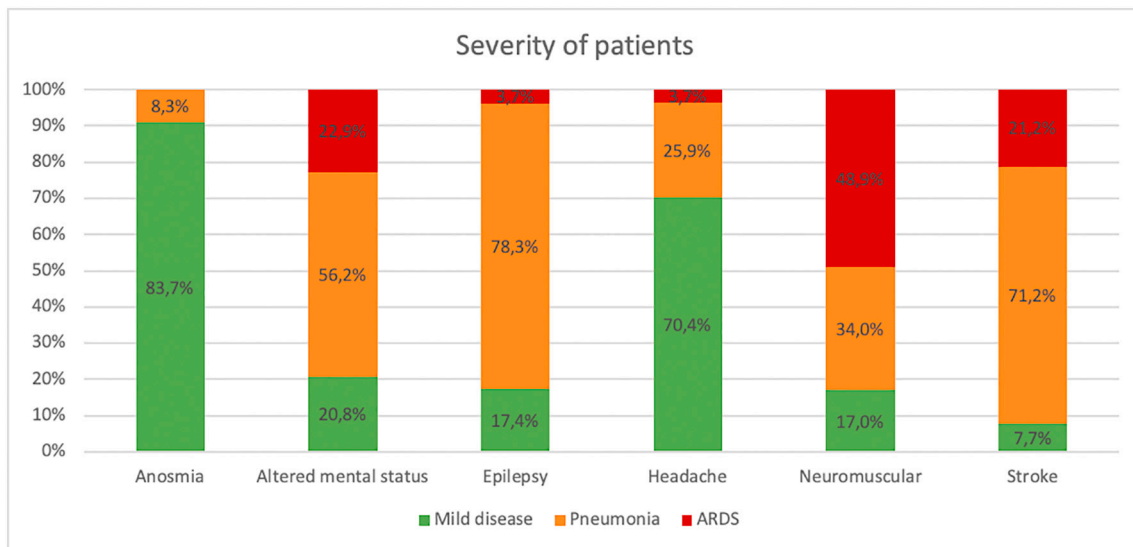
ARDS: acute respiratory distress syndrome.

Fig. 3. Severity of COVID-19 in patients with the most frequently represented neurological complications.
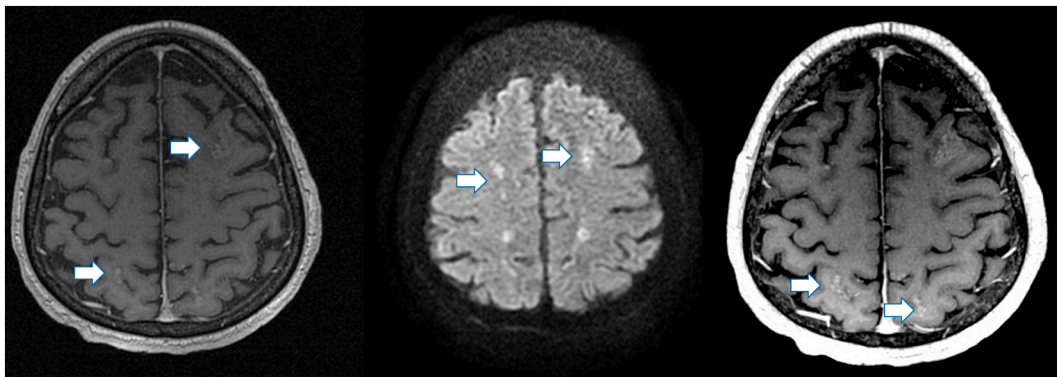

Fig. 4. Brain magnetic resonance imaging study of a 59-year-old man (4A: gadolinium-enhanced T1-weighted sequence, 4B: diffusion-weighted imaging sequence, 4C: FLAIR sequence) showing cortico-subcortical hyperintense lesions, in the convexity of both parietal lobes, suggestive of subacute ischaemic lesions in areas of borderline vascularisation between the middle and anterior cerebral arteries (arrows).

meningoencephalitis. In 10/51 cases, SARS-CoV-2 PCR testing of CSF was not available.

Information about neuroimaging studies was available for 219 patients. CT scans were performed in 123/219 (56.2%), revealing abnormalities in 49/123 (39.8%) cases, including 44 patients with stroke-related changes (Fig. 4), two cases of incidental meningiomas, one patient with findings suggestive of encephalopathy (Fig. 5), one case in which images were suggestive of focal hyper-perfusion not restricted to any vascular territory and in the absence of arterial occlusion, attributed to a recent seizure, and one case of generalised oedema. Mean (SD) time from admission to the CT study was 3.3 (5.6) days. Brain MRI was performed in 57/219 (26.0%) cases, returning abnormal findings in 20/57 (35.7%), including stroke-related findings in 16 cases, 2 patients with changes attributed to encephalitis, and two cases of non-specific white matter lesions. Spinal MRI was performed in 13 patients, showing degenerative signs in 4 cases and meningeal and nerve root enhancement in one case. EEG was conducted in 36 (15.4%) cases: results were normal in 13/36 (36.1%) and revealed diffuse slowing in 14/36 (38.9%) patients, signs compatible with encephalopathy in 6 (16.7%) patients, and focal epileptic activity in 5 (13.9%) cases. The frequency of each ancillary test and the percentage of patients showing abnormal results within the main diagnostic categories are available in the supplementary material.

3.4. Clinical outcomes and causality of the disease

Information about the treatments received was available in 160 cases, with 146 (91.2%) patients being treated. The most frequently used drugs were chloroquine/hydroxychloroquine, which was administered in 130 patients (89.0%), lopinavir/ritonavir in 92 (63.0%), corticosteroids in 54 (37.0%), and azithromycin in 43 (29.4%). The full list of prescribed treatments is available in the supplementary appendix. The duration of neurological symptoms was reported in 145 cases, with a mean (SD) of 17.8 (17.7) days. At the time when the cases were submitted, neurological symptoms persisted in 77 (33.0%) patients, with a mean (SD) age of 58.8 years (16.1); 25 (32.5%) of these patients were women, 44 (57.1%) had prior comorbidities, and 18 (23.4%) had neurological comorbidities. Neuromuscular symptoms were reported in 24 (31.2%) cases, altered mental status in 22 (28.6%), stroke sequelae in 22 (28.6%), anosmia in 18 (23.4%), headache in 11 (14.3%), cranial neuropathies in seven (9.1%), seizures in five (6.5%), movement disorders in two (2.6%), and encephalitis in two (2.6%). Twenty-five (10.7%) patients died, with a mean (SD) age of 74.1 (16.2) years; 14 (56.0%) of these patients were women, all had prior comorbidities, and five (20%) had chronic neurological disorders. Among patients who died, neurological presentations included ischaemic stroke, which was recorded in 12 (48%) cases, altered mental status in six (24%), seizures in three (12%), haemorrhagic stroke in two (8%), and single cases of

Fig. 5. Non-contrast brain CT scan of a 73-year-old woman: decreased generalised cortico-subcortical differentiation with hypodensities in the corpus callosum, and symmetric hyperdensity of the bilateral basal ganglia, suggesting encephalopathy.

polyradiculoneuropathy, myasthenia gravis, and headache. Table 5 compares the duration of neurological symptoms, mortality, and the proportion of patients with sequelae within the main diagnostic categories.

The authors of the cases subjectively judged the causality of the neurological manifestations and SARS-CoV-2 infection as coincidental in 62 (26.7%) cases, whereas this association was reported as probably causal in 140 (60.1%) and definitely causal in 31 (13.3%) cases.

4. Discussion

Since the beginning of the COVID-19 pandemic, neurologists worldwide have been eager to understand the neurotropism of SARS-CoV-2 [10,13]. In this study, we present the results of the national registry of the Spanish Society of Neurology. The main finding of the study is that COVID-19 has a wide range of neurological manifestations, which may coexist and occur early in the course of the disease, and occasionally persist. Until the discovery of an effective treatment or the anticipated vaccine, clinicians must be alert to the neurological symptoms of COVID-19.

Neurological symptoms are the most frequent extra-pulmonary symptoms of the virus. They are described in 36.4%–57.4% of hospitalised patients [5–9] and 84% of patients admitted to intensive care units [14]. Neurological symptoms have been classified according to the anatomical location of the lesion, into symptoms originating in the central nervous system, symptoms originating in the peripheral nervous system, and muscular manifestations [5]. Other authors classify them as non-specific and specific symptoms [15]. In our opinion, the term "non-specific" can be confusing, as no pathognomonic sign or symptom of neuroCOVID-19 has yet been identified. We could classify neurological symptoms into non-focal, generalised symptoms, such as myalgia, headache, anosmia, light-headedness, and altered mental status; and focal symptoms, including stroke, seizures, radiculopathies, cranial nerve syndromes, encephalitis, and movement disorders [8,9].

The present study may not reflect the true epidemiology and frequency of the different neurological symptoms, as other international registries have done [3,10,16]; however, it enables comparison of some other relevant data, such as the time between onset of the disease and onset of neurological symptoms. Indeed, one of our most relevant findings is that non-focal generalised symptoms tend to occur earlier, and frequently co-present, while other symptoms, such as stroke or seizures, may appear later in the course of the disease [16,17]. This is probably associated with the pathophysiology of neuroCOVID-19.

The cause of the neurological symptoms may be related with the host's immune response against the virus [18], as is probably the case with such symptoms as headache [18] or myalgia, which are probably associated with the release of cytokines and inflammatory agents [19–22]. Indeed, some studies report better in-hospital prognosis in patients with headache [18] or anosmia [23], when compared with other patients. The fact that angiotensin-converting enzyme 2 receptor, targeted by the SARS-CoV-2 spike protein [24], is highly expressed in the upper respiratory tract could also explain anosmia and some phenotypic features of headache, such as the frontal predominance and the frequency of cranial autonomic symptoms [25].

The systemic consequences of the infection, such as hypoxaemia, acute kidney injury, hepatic failure, and ionic imbalance [26], as well as the drugs employed in treatment, may play a role in the pathogenesis of such symptoms as altered mental status and seizures in some cases [8,9,27]. Proper work-up of patients with neurological symptoms obliges us to consider and rule out COVID-19 in most cases. In cases with no known cause, complete neurological work-up must be performed, including cranial imaging, EEG, and CSF analysis [10]. These studies frequently return positive results in adequately selected patients [13,14]. Patients with prolonged hospital stays, and particularly those admitted to the ICU, might present complications related to prolonged bed rest and/or superinfection [27].

The neurovirulence of SARS-CoV-2 has been widely discussed. Initially, reported cases of positive PCR results for SARS-CoV-2 in the CSF were exceptional [5–9,11–14,16,28]. Indeed, only one case in our series had positive CSF results for the virus. More recently, the number of reported cases has increased [29,30], and pathological studies have demonstrated the presence of the virus in some samples [31]; however, SARS-CoV-2 does not seem to be highly neurotropic, and after thousands of cases, reports of CSF isolation remain exceptional. As is the case with other pathogens, the immune response against the virus may cause post-viral neurological presentations, such as acute disseminated encephalomyelitis [31–33], Guillain-Barré syndrome [34,35], or Miller Fisher syndrome [36], with relatively good prognosis despite presentation of axonal forms. Another remarkable phenomenon observed during the disease is a prothrombotic state, including cases of venous and arterial

Table 5
Clinical outcome and duration of the disease within the most frequently represented categories of manifestations.

Variable	Anosmia (n = 41)	Altered mental status (n = 55)	Epilepsy (n = 27)	Headache (n = 30)	Neuromuscular symptoms (n = 55)	Stroke (n = 63)	P
Duration of neurological symptoms (days), mean (SD)	25.5 (21.4)	9.9 (11.2)	5.3 (6.7)	17.3 (17.9)	27.3 (17.3)	12.1 (17.3)	<0.001
Mortality, n (%)	0 (0%)	6 (10.9%)	3 (11.1%)	1 (3.3%)	2 (3.6%)	14 (22.2%)	0.002
Sequelae, n (%)	18 (43.9%)	22 (44.9%)	5 (20.8%)	11 (37.9%)	24 (45.3%)	22 (43.1%)	0.265

The percentage of patients with sequelae is calculated according to the total of patients per category minus those who died.
SD: standard deviation.

thrombosis [37–39]. The frequency of ischaemic and haemorrhagic stroke is higher than expected [38].

Neuropathological studies of non-selected patients, some of whom presented headache, anosmia, or myalgia, have shown acute hypoxic changes with loss of neurons but no thrombi or vasculitis. Encephalitis or brain-specific changes attributable to the virus were absent, despite the virus having been observed at low levels in 27.8% of patients [40]. A report of a patient with multiple organ dysfunction but no clear neurological signs or symptoms showed haemorrhagic white matter lesions and a perivascular lesion pattern resembling acute disseminated encephalomyelitis [31]. Recently, some authors correlated MRI diffusion tensor imaging findings with pathological examination findings, reporting moderate parenchymal lymphocytic infiltrate and microglial activation in the brainstem and cerebellar peduncles; perivascular infiltrate of T-lymphocytes in the leptomeninges, cerebral white matter, and basal ganglia; and negative RT-PCR findings for SARS-CoV-2 RNA [41]. This may suggest the involvement of brainstem nuclei involved in arousal. Whether the pathological changes are associated with critical illness-related encephalopathy or are specific to SARS-CoV-2 infection remains to be clarified, as the presence of the virus in the central nervous system may be coincidental.

The neuroinvasion of the virus remains controversial [42–44]. Several routes of entry have been proposed, including the olfactory nerve, the vascular endothelium, migration of leukocytes towards the blood-brain barrier, and trans-synaptic transfer through infected neurons [42–44]. The SARS-CoV-2 spike protein and ACE receptors have been suggested as the key mechanism in the infection of cells, and this receptor is also expressed in the blood-brain barrier [44]. However, further research is needed to clarify the main route and the significance of the presence of the virus in the central nervous system.

Given the frequency of neurological symptoms, many neurologists are concerned about the possibility of patients with COVID-19 being misdiagnosed as not having the infection [45]. Neurological symptoms have frequently been described in international series [4–9]. Some of the neurological manifestations of SARS-CoV-2 may mimic other diseases, and patients with neurological symptoms may coincidentally present SARS-CoV-2 infection. In our series, there were two reports of patients in whom space-occupying lesions with the radiological appearance of meningioma were diagnosed with COVID-19. For this reason, we also analysed the frequency of general symptoms and laboratory abnormalities in patients with neuro-COVID-19. Luckily, we observed that most patients exhibited some alteration of analytic parameters [46]. While imaging abnormalities are frequent, no pathognomonic signs have been established, and COVID-19 must be incorporated into the differential diagnosis lists of many radiological presentations [47,48]. Vascular lesions, leptomeningeal enhancement, and encephalitis have been observed in other series [48]. However, during the pandemic, neurologists must adopt adequate self-protection measures and every patient must be tested and isolated in the event of positive results.

Our registry has some important limitations. The design of the present study prevents us from identifying the patient profile most likely to exhibit neurological symptoms, due to the inherent selection bias of this case series. Other international registries have been designed to overcome this problem [49]. However, we observed that comorbidities were frequent, including both systemic and neurological comorbidities [4–9]. COVID-19 management protocols recommend that patients with heart diseases, pulmonary diseases, oncological diseases, or immunocompromised states be admitted for close monitoring. Little research has been conducted into the role of chronic neurological diseases, although some chronic neurological diseases or treatments might be associated with poorer prognosis [26]. We do not report information on neurological examination as it was freely described by participating physicians. Specific details about the clinical phenotype of some presentations, such as headache, seizures, or neuromuscular disorders were not reported, and should be described in specific series. Neuroimaging studies and CSF analyses were not conducted systematically, and these results should be interpreted with caution, given the high risk of reporting bias. In addition, the causality of the neurological symptoms was judged subjectively. A classification of the type of neurological manifestations, pathophysiology, and causal role of the virus is needed.

5. Conclusion

The neurological manifestations of COVID-19 are diverse. Anosmia, myalgia, and headache are the most frequent symptoms, and occur early in the course of the disease, while other symptoms may present later. COVID-19 must be incorporated into most clinical and radiological differential diagnoses. The cause of the neurological symptoms may be related to the immune response to the virus, the systemic alterations caused by the infection, the neurovirulence of SARS-CoV-2, the prothrombotic state, or the consequences of prolonged hospitalisation. COVID-19 may cause persistent and disabling neurological symptoms.

Data availability

Additional information or datasheets are available for other authors upon reasonable request.

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Appendix B. Supplementary data

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