Neurology and neuropsychiatry of COVID-19: a systematic review and meta-analysis of the early literature reveals frequent CNS manifestations and key emerging narratives

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ABSTRACT

There is accumulating evidence of the neurological and neuropsychiatric features of infection with SARS-CoV-2. In this systematic review and meta-analysis, we aimed to describe the characteristics of the early literature and estimate point prevalences for neurological and neuropsychiatric manifestations. We searched MEDLINE, Embase, PsycINFO and CINAHL up to 18 July 2020 for randomised controlled trials, cohort studies, case-control studies, cross-sectional studies and case series. Studies reporting prevalences of neurological or neuropsychiatric symptoms were synthesised into meta-analyses to estimate pooled prevalence. 13 292 records were screened by at least two authors to identify 215 included studies, of which there were 37 cohort studies, 15 case-control studies, 80 cross-sectional studies and 83 case series from 30 countries. 147 studies were included in the meta-analysis. The symptoms with the highest prevalence were anosmia (43.1% (95% CI 35.2% to 51.3%), n=15 795, 63 studies), weakness (40.0% (95% CI 27.9% to 53.5%), n=221, 3 studies), fatigue (37.8% (95% CI 31.6% to 44.4%), n=21 101, 67 studies), dysgeusia (37.2% (95% CI 29.8% to 45.3%), n=13 686, 52 studies), myalgia (25.1% (95% CI 19.8% to 31.3%), n=66 268, 76 studies), depression (23.0% (95% CI 11.8% to 40.2%), n=43 128, 10 studies), headache (20.7% (95% CI 16.1% to 26.1%), n=64 613, 84 studies), anxiety (15.9% (5.6% to 37.7%), n=42 566, 9 studies) and altered mental status (8.2% (95% CI 4.4% to 14.8%), n=49 326, 19 studies). Heterogeneity for most clinical manifestations was high. Neurological and neuropsychiatric symptoms of COVID-19 in the pandemic’s early phase are varied and common. The neurological and psychiatric academic communities should develop systems to facilitate high-quality methodologies, including more rapid estimation of the longitudinal course of neuropsychiatric complications of newly emerging diseases and their relationship to neuroimaging and inflammatory biomarkers.

INTRODUCTION

COVID-19 stimulated a global academic response to examine the clinical sequelae and biology of the SARS-CoV-2 virus, including its neurological and neuropsychiatric impact.1 2 Although the earliest reports naturally highlighted respiratory symptoms,1 it was quickly recognised that SARS-CoV-2, like other coronaviruses,7 can affect the central and peripheral nervous system.14 Many of the very earliest studies of the neurological and neuropsychiatric complications of SARS-CoV-2 infection were small retrospective case reports or series.3 6 These initial studies were feasible to deliver quickly in the context of a new and poorly understood disease. Case reports7 8 were superseded by case series,6 36 then case-control9 and cohort studies,10 11 which suggested significant morbidity and mortality from neurological or neuropsychiatric complications.12 Currently, large multicentre prospective studies are underway13 and already reporting.14 We anticipate that the quality of evidence, and our knowledge, will improve considerably as these data continue to emerge rapidly.

In response to these signals, we aimed to develop a novel, sustainable platform to evaluate emerging knowledge of the neurology and neuropsychiatry of COVID-19. This also served to assist colleagues in keeping up to date with the literature relevant to their specialty, given the extraordinary volume of research and pace with which research is being published. In May 2020, we started logging literature on relevant symptoms, clinical associations and putative underlying mechanisms in our blog, ‘The neurology
RESULTS

We included 38 studies, comprising 11,774 cases, with details available from 215 abstracts.

Methodological characteristics of the studies and risk of bias were assessed using the Newcastle–Ottawa Scale, including its adaptation for cross-sectional studies. The most common study type was a case-series (83%), followed by cohort (12%), case-control (7%) and cross-sectional (7%) studies. The overall strategy was to combine synonyms for COVID-19 with neurological or neuropsychiatric manifestations in PubMed, Scopus, CINAHL, Medline, PsycINFO and Embase databases.

We included control, case-control, cross-sectional case–control studies in our meta-analysis.

Four studies were included in our meta-analysis.

The prevalence of neurological and neuropsychiatric manifestations reported by the included studies and risk of bias were assessed using the Newcastle–Ottawa Scale.
report of the outbreak in Wuhan by the Chinese authorities (31
December 2019) to the first group of cohort studies.

Studies were written by a primary author affiliated with an
institution from a total of 30 countries globally (figure 3). The
most frequent contributors were China (n=50 studies), USA
(n=32 studies), Italy (n=28 studies) and France (n=23 studies).
All but three studies starting recruitment in January 2020 were
located in China. Globally, most studies (138, 64.2%) were single
centre without a significant shift towards multicentre studies as
the pandemic accelerated: where collection date was clear, 44 of
65 (67.7%) of earlier studies were single centre, compared with
72 of 115 (62.6%) of later studies (p=0.49).

Studies were predominantly in hospitalised patients (118
studies, 54.9%) and during the acute illness (144, 67.0%). There
were a total of 105638 subjects. Number of subjects in each
study varied between 10 and 40469 (median 101, IQR 196).
There were 18 studies with 1000 or more subjects.

There was evidence for ethical approval and informed consent
in most studies, but this was waived in a minority, frequently
because of the particular circumstances of the pandemic.

Quality assessment found only 23 (10.7%) studies to be
of high quality, 98 (45.6%) were of moderate quality and 94
(43.7%) were of low quality.

Prevalence of neuropsychiatric and neurological
manifestations

Twenty neurological or neuropsychiatric manifestations were esti-
mated by at least three studies, such that we included 147 studies
(reporting on 99905 infected patients) in the meta-analysis.
Overall prevalences are shown in table 2 with forest plots available in figure 4 and online supplemental figures 1–20. The most often studied symptoms were headache (examined in 84 studies, n=64613), myalgia (76 studies, n=66268), fatigue (67 studies, n=21101), anosmia (63 studies, 15975) and dysgeusia (52 studies, n=13686). The most prevalent symptoms were anosmia (43.1% (35.2% to 51.3%), n=15975 in 63 studies), weakness (40.0% (27.9% to 53.5%), n=221 in 3 studies), fatigue (37.8% (31.6% to 44.4%), n=21101 in 67 studies), dysgeusia (37.2% (29.8% to 45.3%), n=13686 in 52 studies) and myalgia (25.1% (19.8% to 31.3%), n=66268 in 76 studies). Sleep disorder was a broad term that was used in a number of studies; of the eight studies reporting a sleep problem, two specified insomnia, one sleep impairment and the remainder an unspecified sleep disorder.

Between-study heterogeneity was mostly high with I^2 ≥90% for 13 manifestations, ≥50% and <90% for 2 manifestations, and <50% for 5 manifestations. Most symptoms were recorded merely as ‘present’ or ‘absent’ by study authors. The robustness of the main analyses was assessed by repeating the analyses on headache, myalgia, anosmia, fatigue and dysgeusia using the standard random-effects model for meta-analysis with the Freeman-Tukey double arc sine transformation. The results were in line with the main analysis (see online supplemental table 4).

Subgroup analyses

Subgroup analysis was conducted by study design (prospective and retrospective; table 3), case severity (outpatient, mixed non-severe, non-severe inpatients, severe but not admitted to intensive therapy unit (ITU) and admitted to ITU; table 4) and country of origin (online supplemental table 5). For headache, myalgia, anosmia and dysgeusia, there were significantly higher reported rates in prospective studies than in retrospective studies. In the severity subgroup analysis, compared with the ITU group, headache was more common in mixed non-severe and outpatient populations (p<0.001); myalgia was more common in mixed non-severe and outpatient populations (p=0.04 and <0.001, respectively); anosmia was more common in mixed non-severe and outpatient populations (p=0.05 and 0.04, respectively), and dysgeusia was more common in mixed non-severe populations (p=0.02); there were no significant differences between groups for fatigue.

DISCUSSION

To our knowledge, this is the largest and most comprehensive systematic review of the neurological and neuropsychiatric manifestations of COVID-19. We identified 215 studies, published between January and July 2020, with a total population of 105638, containing a large variation in the size of studies. We uncovered some general findings about the methodological characteristics of the early evolving literature in response to a novel pathogen. Studies varied substantially in design, geographical location, treatment setting, illness stage, sample size, diagnostic method and clinical manifestations studied. More studies were retrospective than prospective and case series comprised a significant minority of the early literature. In terms of country of origin, after the first few weeks of the pandemic, in which the literature was dominated by studies from China, a wide range of research was produced from 30 countries, among which less economically developed countries were mostly absent. Most studies confirmed formal ethical review and most required informed consent, but these requirements were waived in a subset of cases.

In our review, we summarise point prevalence of 20 neurological and neuropsychiatric complications of COVID-19. The most frequently studied symptoms were heavily weighted towards non-specific features of systemic illness, such as headache, myalgia, fatigue, anosmia and dysgeusia, which are unlikely to be ‘primary’ neurological symptoms. It was predominantly these more non-specific symptoms that were found to have the highest prevalences, ranging from 20.7% (16.1% to 26.1%) to 43.1%
(35.2% to 51.3%) (headache and anosmia, respectively). Of note, more specific neurological and neuropsychiatric symptoms such as altered mental status, depression, anxiety, sleep disorder, stroke and seizures were less frequently studied. However, the core psychiatric disorders of depression (23.0% (11.8% to 40.2%)) and anxiety (15.9% (5.6% to 37.7%)) appeared to be highly prevalent. The reported prevalence of major neurological disorders such as ischaemic stroke (1.9% (1.3% to 2.8%)), haemorrhagic stroke (0.4% (0.3% to 0.7%)) and seizure (0.06% (0.06% to 0.07%)) were substantially lower. Subgroup analyses suggested that study design (prospective vs retrospective), severity of illness and country of origin of a study affected the prevalence figures obtained. Importantly, for myalgia, fatigue, anosmia and dysgeusia, prevalences were substantially higher in prospective studies compared with retrospective studies.

There are several limitations to our study, relating both to the quality of the underlying evidence and to the data synthesis. Major limitations in the study design were the frequent absence
of comparison groups, limiting conclusions about the specificity of symptoms to COVID-19; retrospective study designs, which meant that only those symptoms that happened to be enquired about were included; and small sample sizes, which risk reporting bias. In terms of populations, the frequent use of hospital inpatients is unrepresentative of the majority of patients with COVID-19, who are not admitted to hospital. Regarding clinical manifestations, the main limitations were reliance on self-report measures, which risks recall biases; lack of baseline assessment, which prevents estimation of incidence; and a focus on non-specific neuropsychiatric symptoms rather than on major neurological and neuropsychiatric disorders. In addition, some of the most commonly studied symptoms (such as weakness and fatigue) have some conceptual overlap, so it is possible that the prevalences found in this review may be underestimated. Terminology connoting altered mental status varied, with terms such as delirium and encephalopathy chosen in different studies, despite existing recommendations on standardisation of the nomenclature. The finding that only 10.7% of the studies were of high quality limits the strength of any conclusions that can be drawn. In terms of the data synthesis, we were limited by excluding studies not published in English, which may particularly have reduced the number of important studies included from China, and the generalisability of our results may be limited by the geographical scope of the studies. The rapidly evolving literature means that any review on this subject risks becoming out of date. Furthermore, the high heterogeneity between studies, even after subgroup analyses, suggests that variation in populations, outcomes and measurement techniques might account for much of the differences between studies. Finally, the cross-sectional nature and the focus on acute presentations of most studies reported to date limit our ability to draw conclusions about the long-term impact of neuropsychiatric post-COVID-19 symptom burden. Future well-designed prospective cohorts, such as the UK-based Post-hospitalisation COVID-19 Study (https://www.phosp.org/), may be able to address this gap in the knowledge.

There are several implications of this review for future research. First, while retrospective studies are important in identifying associations in large patient populations, they are likely to underestimate the prevalence of important symptoms. This may particularly be the case with some neuropsychiatric disorders such as depression and delirium, which are known to be generally under-recognised. Therefore, even in the context of a pandemic, there is a need to improve the speed with which the academic community can produce prospectively designed studies, which are based on registered protocols and use validated and objective measures. Standardised case definitions and record forms for common neurological manifestations of viral infections were produced by the Brain Infections Global Network from early in the pandemic and made freely available. These have been modified by other international groups, and are being incorporated into the WHO case report forms. More studies are required of those not admitted to hospital and the timing of neurological and neuropsychiatric symptoms relative to diagnosis must be specified. In terms of the clinical manifestations, many of the common and debilitating neurological symptoms (such as headache, myalgia and anosmia) were assessed systematically by a large number of studies, allowing for meaningful prevalence estimates and subgroup analyses. However, some severe neurological and neuropsychiatric disorders, such as depression, stroke and seizures, received comparatively scant attention and would benefit from similar study. Finally, the occasional waivers of ethical review and the more frequent waivers of informed consent in these studies illustrate that some aspects of study review may be overly burdensome—and therefore potentially neglected—during a pandemic. While we acknowledge the need for proper ethical and institutional oversight, COVID-19 may be an opportunity for this process to be streamlined across the field, especially for non-interventional studies, where the risks to participants are minimal, so that studies during a pandemic (and beyond) can start quickly and inform urgent policy needs.

![Table 2 Overall meta-analytical estimates of point prevalence of neurological or neuropsychiatric symptoms](image-url)

Table 2 Overall meta-analytical estimates of point prevalence of neurological or neuropsychiatric symptoms

<table>
<thead>
<tr>
<th>Symptom/syndrome</th>
<th>Studies</th>
<th>n</th>
<th>Point prevalence (%)</th>
<th>95% CI</th>
<th>I²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>84</td>
<td>64613</td>
<td>20.7</td>
<td>16.1 to 26.1</td>
<td>99.0%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>76</td>
<td>66268</td>
<td>25.1</td>
<td>19.8 to 31.3</td>
<td>99.1%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>67</td>
<td>21101</td>
<td>37.8</td>
<td>31.6 to 44.4</td>
<td>98.7%</td>
</tr>
<tr>
<td>Anosmia</td>
<td>63</td>
<td>15975</td>
<td>43.1</td>
<td>35.2 to 51.3</td>
<td>98.8%</td>
</tr>
<tr>
<td>Dysgeusia/vertigo</td>
<td>52</td>
<td>13686</td>
<td>37.2</td>
<td>29.8 to 45.3</td>
<td>96.6%</td>
</tr>
<tr>
<td>Dizziness/vertigo</td>
<td>26</td>
<td>47619</td>
<td>6.4</td>
<td>4.0 to 10.0</td>
<td>97.1%</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>19</td>
<td>49326</td>
<td>8.2</td>
<td>4.4 to 14.8</td>
<td>99.0%</td>
</tr>
<tr>
<td>Anosmia at follow-up</td>
<td>11</td>
<td>3182</td>
<td>11.8</td>
<td>5.5 to 23.5</td>
<td>98.5%</td>
</tr>
<tr>
<td>Depression</td>
<td>10</td>
<td>43128</td>
<td>23.0</td>
<td>11.8 to 40.2</td>
<td>99.3%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>9</td>
<td>42566</td>
<td>15.9</td>
<td>5.6 to 37.7</td>
<td>99.5%</td>
</tr>
<tr>
<td>Sleep disorder</td>
<td>8</td>
<td>42221</td>
<td>23.5</td>
<td>12.0 to 40.9</td>
<td>98.9%</td>
</tr>
<tr>
<td>Ichaemic stroke</td>
<td>8</td>
<td>5258</td>
<td>1.9</td>
<td>1.3 to 2.8</td>
<td>61.7%</td>
</tr>
<tr>
<td>Other CVD</td>
<td>6</td>
<td>43701</td>
<td>1.6</td>
<td>0.3 to 7.9</td>
<td>98.7%</td>
</tr>
<tr>
<td>Dysgeusia at follow-up</td>
<td>6</td>
<td>2065</td>
<td>11.7</td>
<td>5.1 to 25.0</td>
<td>96.7%</td>
</tr>
<tr>
<td>Seizure</td>
<td>5</td>
<td>41929</td>
<td>0.06</td>
<td>0.06 to 0.07</td>
<td>0.0%</td>
</tr>
<tr>
<td>Haemorrhagic stroke</td>
<td>5</td>
<td>3074</td>
<td>0.4</td>
<td>0.3 to 0.7</td>
<td>0.0%</td>
</tr>
<tr>
<td>Visual defect</td>
<td>5</td>
<td>678</td>
<td>3.0</td>
<td>1.9 to 4.5</td>
<td>0.0%</td>
</tr>
<tr>
<td>Hearing impairment</td>
<td>4</td>
<td>557</td>
<td>2.0</td>
<td>1.1 to 3.5</td>
<td>0.0%</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>4</td>
<td>455</td>
<td>3.5</td>
<td>1.7 to 7.4</td>
<td>51.8%</td>
</tr>
<tr>
<td>Weakness</td>
<td>3</td>
<td>221</td>
<td>40.0</td>
<td>27.9 to 53.5</td>
<td>45.4%</td>
</tr>
</tbody>
</table>

CVD, cardiovascular disease.

Neuropsychiatry

There are several clinical implications of our study. First, practitioners should be aware that neurological and neuropsychiatric symptoms are very common with four (anosmia, weakness, dysgeusia and fatigue) estimated to occur in more than 30% of patients. Second, these non-specific neurological and neuropsychiatric symptoms appear to be the most common. Neuropsychiatric disorders such as anxiety and depression occupy an intermediate space with prevalence of between 15.9% (5.6% to 37.7%) and 23.0% (11.8% to 40.2%), while major neurological disorders such as stroke and seizures are much rarer. However, because of the very high number of individuals infected with SARS-CoV-2 worldwide, even less frequent symptoms may still result in a substantial increase in the burden of disease. This means that services for those with common mental illnesses and

Table 3  Subgroup analysis by study design for five most commonly studied clinical manifestations

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Retrospective</th>
<th>Prospective</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Studies</td>
<td>Prevalence (95% CI)</td>
</tr>
<tr>
<td>Headache</td>
<td>46</td>
<td>11.1 (8.0 to 15.3)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>42</td>
<td>16.8 (11.8 to 23.1)</td>
</tr>
<tr>
<td>Anosmia</td>
<td>16</td>
<td>22.3 (11.4 to 39.0)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>13</td>
<td>22.3 (11.0 to 40.2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>41</td>
<td>33.5 (26.1 to 41.8)</td>
</tr>
</tbody>
</table>
neurological rehabilitation should be resourced and equipped for an increase in case numbers. Many of these disorders can become chronic, so the neurological and psychiatric impact of the pandemic may substantially outlast the current phase. Third, given the multitude of symptoms reported, neurological and neuropsychiatric comorbidity is likely to be the norm rather than the exception in COVID-19, so there must be accessible advice and input from these specialties for patients who are acutely unwell. Finally, although there is a relative lack of data on non-hospitalised patients, the data available suggest that several symptoms, such as anosmia, dysgeusia, fatigue, headache, and myalgia, are common even among those with milder illness. Although long-term evidence from this earliest literature was sparse, it gives some initial indication that the symptoms described in ‘long COVID’ may be a continuation of some of those experienced in the acute phase of the illness. Long COVID is, however, likely to be a heterogeneous entity with a multifactorial aetiology, including viral persistence, inflammatory changes, physical deconditioning and psychological factors. Our finding that the most frequently reported neurological symptoms actually occurred more frequently in those with less severe COVID-19 suggests that neurological symptoms are not necessarily correlated with systemic or respiratory symptoms, implying that different mechanisms or timing of mechanisms may be involved.

In conclusion, COVID-19 is accompanied by a wide range of neurological and neuropsychiatric symptoms from the common, such as fatigue and anosmia, to the more infrequent but severe, such as stroke and seizure. There is substantial psychiatric morbidity, but a lack of control groups limits to what extent causality can be attributed.

Table 4

Subgroup analysis by case severity for five most commonly studied clinical manifestations

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Outpatients</th>
<th>Mixed non-severe</th>
<th>Severe non-ITU</th>
<th>Includes ITU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>14</td>
<td>44.0 (32.8 to 55.8)</td>
<td>96.7</td>
<td>16</td>
</tr>
<tr>
<td>Myalgia</td>
<td>14</td>
<td>44.0 (32.8 to 55.8)</td>
<td>96.7</td>
<td>16</td>
</tr>
<tr>
<td>Anosmia</td>
<td>17</td>
<td>51.7 (42.2 to 61.6)</td>
<td>97.1</td>
<td>16</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>17</td>
<td>45.2 (34.1 to 61.6)</td>
<td>97.1</td>
<td>16</td>
</tr>
<tr>
<td>Fatigue</td>
<td>10</td>
<td>42.2 (29.3 to 65.8)</td>
<td>97.1</td>
<td>16</td>
</tr>
</tbody>
</table>

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Contributors TRN and AR conceived the study. AR and JPR led and coordinated the study. MB compared the work with other systematic reviews. CW, BC, MB, JS, DH, ERR, LT, AR, MFL and JB screened studies for eligibility. AR, JPR, JS and MB consulted on study inclusion. CW, BC, DH, HM, ERR, LT, SR, RDS and JB extracted the data. JB, MB, JS, DH, HM, ERR, LT, SR, A S, RDS, CKH, MFL, DFA, AR and BC checked data extraction. AR conducted OCEBM ratings. JPR calculated descriptive statistics. CW and KJ conducted the meta-analysis, supported by HH. CW and DH created figures. JPR, BC, MB, JS, DH, HM, LT, SR, A S, RDS, CKH, MFL, VS, ZH, SC, EB, DW, TAP, ME, IK, TRN, and AR conducted quality assurance. JPR and AS supervised and arbitrated quality assessment. JB made the PRISMA flow chart. JPR, MB and JPR used reference management software to adhere to PRISMA guidelines. AR, JPR, ERR, VS and MB drafted the manuscript. JPR, MB, JS and JB checked the completed manuscript. ERR and ZH created tables. MFL sorted funding statements. JPR and EB formatted the manuscript. DW, ME, IK, TS, BDM, TRN, AR and TAP provided senior review of the manuscript. JPR and AR are responsible for the overall content of the study.

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