Neuroradiological Features of Mild and Severe SARS-CoV-2 Infection.

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INTRODUCTION

In 2019, the novel SARS-CoV-2 coronavirus was first reported in Wuhan, China and commenced a global pandemic that has resulted in over 21 million confirmed cases and 762,997 deaths as of August 2020 (1). Although the major cause of morbidity and mortality in COVID-19 infection is acute respiratory distress syndrome (ARDS) and subsequent respiratory failure, a surprising number of patients have been reported to exhibit neurological symptoms, ranging from acute cerebrovascular insults, encephalitis, inflammatory demyelination, to isolated sensorineural deficits—in particular, anosmia and dysgeusia (2). Therefore, it is of critical importance for healthcare providers to be aware of the spectrum of neurological and neuroradiological manifestations that can either present as an incidental finding or initial symptom of COVID-19 infection, or as potential sequelae to a primary COVID-19 pneumonia. In particular, it is poorly understood how presentation of neurological symptoms can vary in patients with different severities of COVID-19 infection. Towards this end, a systematic review was conducted on the current literature thus far on neuroradiological findings in the setting of mild and severe SARS-CoV-2 infection.

METHODS

Literature Search

A systematic search was conducted via query of the Pubmed and Embase electronic databases with the following search terms: “[(brain or neurological or neurology or neuropsychiatric or neuroimaging or anosmia or neuropsychological or neuroradiology) AND (MRI or magnetic resonance imaging or CT or computerized tomography or radiology or radiological or imaging) AND (COVID-19 or novel coronavirus or SARS-COV-2 or 2019-nCoV)].” Duplicate records between the two databases and studies without sufficient abstract and title relevance were excluded in an initial screen. Screening based on the full-text of the article was then performed on the remaining studies.
excluding any that met the following predetermined criteria: (1) the study did not contain CT or MRI findings of the brain, (2) the study did not involve patients with confirmed COVID-19 infection, (3) the study was a review, editorial, or commentary (Fig 1). Literature search and study screening were performed by a single investigator and was completed by July 17, 2020. The quality of included studies was examined based on the nine item National Institutes of Health (NIH) Quality Assessment Tool for Case Series, which assesses the quality of data in a study based on the following nine questions: (1) Was the study question or objective clearly stated? (2) Was the study population clearly and fully described, including a case definition? (3) Were the cases consecutive? (4) Were the subjects comparable? (5) Was the intervention clearly described? (6) Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants? (7) Was the length of follow-up adequate? (8) Were the statistical methods well-described? and (9) Were the results well-described? an overall rating of “good,” “fair,” or “poor” was then assigned (3). Studies Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklists were utilized for the study selection process (4). No institutional review board approval was required for this study.

**Results**

Overview of included studies

In total, 536 records were identified from Pubmed and Embase and 89 nonduplicate studies were screened based on title and abstract relevance. Twenty-eight studies were then excluded from this pool, primarily those that reported neurological symptoms in patients but did not include radiological findings. Because the SARS-COV-2 pandemic has been a rapidly emergent phenomenon, there is a relatively low number of large-scale retrospective and observational studies reporting neuroradiological findings currently represented in the literature. Consequently, we decided to include 51 case reports and case series in this review for a total of 61 studies (5–65) comprising 711 patients. All of these studies used a combination of CT and MRI, with the exception of a singular instance of PET-CT to evaluate orbitofrontal function in a patient with anosmia (41). The methodological quality of the included studies as determined by the NIH quality assessment tool are detailed in Table 1 and were generally rated as “fair” and “good.”

**Synopsis of retrospective studies**

Ten observational or retrospective studies with study cohort >10 patients describing 628 patients of median age 66 were identified and screened for inclusion in the current study (Table 2, Fig 2) (5–14). The vast majority of these patients (579, 92.2%) were admitted to the ICU, intubated and placed on mechanical ventilation, or were reported to have ARDS, and thus were classified as having severe COVID-19 infection. The predominant neuroradiological findings in this population of 628 patients were nonspecific white matter abnormalities (162, 25.8%), ischemic infarct (141, 22.5%), and cerebral hemorrhage (78, 12.4%). Less commonly reported findings included leptomeningeal enhancement (13, 2.1%), venous thrombosis (3, 0.48%), posterior reversible encephalopathy syndrome (3, 0.48%), olfactory bulb abnormalities (3, 0.48%), encephalitis (1, 0.16%). Study-specific neuroradiological findings for each of the 10 retrospective studies are detailed in Supplementary Table 1.

**Synopsis of case reports and series**

Fifty-one case reports and case series describing 83 patients of median age 54 years were included in the current study,
| Citation            | NIH Quality Assessment Tool Criteria | Overall Rating |
|---------------------|--------------------------------------|----------------|
| Radmanesh, 2020 (5) | Yes Yes NR Yes NA Yes NA Yes Yes   | Fair           |
| Helms, 2020 (6)     | Yes Yes CD Yes NA Yes NA Yes Yes   | Good           |
| Giorgianni, 2020 (7)| Yes Yes Yes Yes NA Yes NA Yes Yes   | Fair           |
| Jain, 2020 (8)      | Yes Yes CD Yes NA Yes NA Yes Yes   | Good           |
| Kandemirli, 2020 (9)| Yes Yes CD Yes NA Yes NA Yes Yes   | Fair           |
| Kremer, 2020 (10)   | Yes Yes CD Yes NA Yes NA Yes Yes   | Fair           |
| Coolen, 2020 (11)   | Yes Yes Yes Yes NA Yes NA Yes Yes   | Good           |
| Mahammedi, 2020 (12)| Yes Yes CD Yes NA Yes NA Yes Yes   | Good           |
| Radmanesh, 2020 (13)| Yes Yes Yes Yes NA Yes NA Yes Yes   | Good           |
| Chougar, 2020 (14)  | Yes Yes Yes Yes NA Yes NA Yes Yes   | Good           |
| Falcone, 2020 (15)  | Yes Yes NA NA NA NA NA Yes Yes     | Fair           |
| Abdi, 2020 (16)     | Yes Yes NA NA NA NA NA Yes Yes     | Fair           |
| Hutchins, 2020 (17) | Yes Yes NA NA NA NA NA Yes Yes     | Fair           |
| Virhammar, 2020 (18)| Yes Yes NA NA NA NA NA Yes Yes     | Fair           |
| Li, 2020 (19)       | Yes Yes NA NA NA NA NA Yes Yes     | Fair           |
| Pinto, 2020 (20)    | Yes Yes NA NA NA NA NA Yes Yes     | Fair           |
| Sancho-Saldana, 2020(21)| Yes Yes NA NA NA NA NA Yes Yes     | Fair           |
| Oguz – Akarsu, 2020 (22)| Yes Yes NA NA NA NA NA Yes Yes     | Fair           |
| Zhang, 2020 (23)    | Yes Yes NA NA NA NA NA Yes Yes     | Fair           |
| Mirzaee, 2020 (24)  | Yes Yes NA NA NA NA NA Yes Yes     | Fair           |
| Novi, 2020 (25)     | Yes Yes NA NA NA NA NA Yes Yes     | Fair           |
| Efe, 2020 (26)      | Yes Yes NA NA NA NA NA Yes Yes     | Fair           |
| Hayashi, 2020 (27)  | Yes Yes NA NA NA NA NA Yes Yes     | Fair           |
| Politii, 2020 (28)  | Yes Yes NA NA NA NA NA Yes Yes     | Fair           |
| Laurenson, 2020 (29)| Yes Yes NA NA NA NA NA Yes Yes     | Fair           |
| Garaci, 2020 (30)   | Yes Yes NA NA NA NA NA Yes Yes     | Fair           |
| Hemasian, 2020 (31) | Yes Yes NA NA NA NA NA Yes Yes     | Fair           |
| Wong, 2020 (32)     | Yes Yes NA NA NA NA NA Yes Yes     | Fair           |
| Vollono, 2020 (33)  | Yes Yes NA NA NA NA NA Yes Yes     | Fair           |
| Galougahi, 2020 (34)| Yes Yes NA NA NA NA NA Yes Yes     | Fair           |
| Moriguchi, 2020 (35)| Yes Yes NA NA NA NA NA Yes Yes     | Fair           |
| Alberti, 2020 (36)  | Yes Yes NA NA NA NA NA Yes Yes     | Fair           |
| Lantos, 2020 (37)   | Yes Yes NA NA NA NA NA Yes Yes     | Fair           |
| Yin, 2020 (38)      | Yes Yes NA NA NA NA NA Yes Yes     | Fair           |
| Al-olama, 2020 (39) | Yes Yes NA NA NA NA NA Yes Yes     | Fair           |
| Farhadian, 2020 (40)| Yes Yes NA NA NA NA NA Yes Yes     | Fair           |
| Karimi-Galougahi, 2020 (41)| Yes Yes NA NA NA NA NA Yes Yes     | Good           |
| Dinkin, 2020 (42)   | Yes Yes NA NA NA NA NA Yes Yes     | Fair           |
| Franceschi, 2020 (43)| Yes Yes NA NA NA NA NA Yes Yes     | Fair           |
| Aragao, 2020 (44)   | Yes Yes CD Yes NA Yes NA Yes Yes   | Good           |
| Kulick-Soper, 2020 (45)| Yes Yes NA NA NA NA NA Yes Yes     | Fair           |
| Cariddi, 2020 (46)  | Yes Yes NA NA NA NA NA Yes Yes     | Fair           |
| Hanafi, 2020 (47)   | Yes Yes NA NA NA NA NA Yes Yes     | Fair           |
| Li, 2020 (48)       | Yes Yes NA NA NA NA NA Yes Yes     | Fair           |
| Espinosa, 2020 (49) | Yes Yes NA NA NA NA NA Yes Yes     | Fair           |
| Haddadi, 2020 (50)  | Yes Yes NA NA NA NA NA Yes Yes     | Fair           |
| Radmanesh, 2020 (51)| Yes Yes NA NA NA NA NA Yes Yes     | Fair           |
| Parsons, 2020 (52)  | Yes Yes NA NA NA NA NA Yes Yes     | Fair           |
| Afshar, 2020 (53)   | Yes Yes NA NA NA NA NA Yes Yes     | Fair           |
| Dixon, 2020 (54)    | Yes Yes NA NA NA NA NA Yes Yes     | Fair           |
| Sachs, 2020 (55)    | Yes Yes NA NA NA NA NA Yes Yes     | Fair           |
| Zanin, 2020 (56)    | Yes Yes NA NA NA NA NA Yes Yes     | Fair           |
| Kaya, 2020 (57)     | Yes Yes NA NA NA NA NA Yes Yes     | Fair           |
| Poyiadji, 2020 (58) | Yes Yes NA NA NA NA NA Yes Yes     | Fair           |

(continued)
summarized in (Table 3, Fig 3) (15–65). The severity of COVID-19 patients in this pool was more diverse, with 41 patients (49.4%) classified as mild and 42 patients (50.6%) classified as severe. As there is a large variation in both the neurological presentation and severity of respiratory symptoms in COVID-19 patients, we listed the prevalence of major neuroradiological findings in mild and severe COVID-19 patients separately. Amongst the 41 mild patients, the most prevalent radiological findings were cranial nerve abnormalities (13, 31.7%), many of which were abnormalities in the olfactory tract (9, 30.0%), followed closely by cerebral infarction (12, 29.3%) and white matter abnormalities (8, 19.5%). Leptomeningeal enhancement (3, 7.3%), myelopathy (2, 4.9%), cerebral hemorrhage (1, 2.4%), venous thrombosis (1, 2.4%), peripheral nerve abnormalities (1, 2.4%), and normal imaging (3, 7.3%) were less commonly reported findings. Amongst the 42 severe patients, the most prevalent radiological findings were white matter abnormalities (21, 50%), followed by cerebral infarct (13, 33.3%) and cerebral hemorrhage (13, 33.3%). Posterior reversible encephalopathy syndrome (4, 9.5%) and venous thrombosis (1, 2.4%) were less commonly reported findings. Study-specific radiological findings and neurological symptoms are detailed for mild patients in Supplementary Table 2 and severe patients in Supplementary Table 3.

**DISCUSSION**

In this study, the range of potential neuroradiological findings that have been reported in patients with SARS-CoV-2 infection were systematically tabulated according to severity of the primary respiratory infection. To the best of our knowledge, this is the first systematic review on neuroradiological findings in COVID-19 performed in this manner. Surprisingly, cerebral infarction was commonly reported in cases of both mild and severe COVID-19 infection, suggesting that ischemic stroke may be a result of a virally-induced hypercoagulable state and not merely a consequence of severe systemic disease. Hemorrhagic events are also a commonly reported finding, but in contrast to ischemic infarction, the prevalence of hemorrhage appears to be more specific for severe COVID-19 patients. Although the majority of retrospective cohorts analyzed consisted solely of severe patients, one recently published study examined a comparable amount of ICU and non-ICU patients and similarly concluded that ischemic lesions were equally present across both populations while hemorrhages were limited to those with severe disease (14).

In contrast, isolated cranial nerve abnormalities were exclusively reported in patients with mild infection, with a high degree of olfactory tract involvement. These structural findings are corroborated by 18FDG PET/CT imaging of an otherwise asymptomatic COVID-19 patient with anosmia demonstrating hypometabolism in the orbitofrontal cortex (41). These data suggests that cranial nerve abnormalities and anosmia could present as the initial or sole indicator of COVID-19 infection.

Many pathophysiological mechanisms of nervous system involvement in COVID-19 infection have been proposed.
These include a hypercoagulable state leading to thromboembolic events, endothelial cell and neurovascular injury via ACE2-mediated tropism and subsequent hemorrhage, hypoxic ischemia secondary to acute respiratory failure, direct neurotropism and access to the brain via hematogenous spread or retrograde migration along the olfactory nerve, and inflammatory injury secondary to cytokine storms (2,66). Although anosmia can conceivably be caused by rhinitis or mucus plugging as in influenza and other viral infections, these are not typical symptoms of COVID-19 infection nor would this explanation be consistent with the length of anosmia and central localization of reported structural and functional brain abnormalities (2,8,41). The prevalence of these findings in patients with mild or asymptomatic infection further argue against a conductive anosmia and more supports a sensorineural etiology. Although some coronaviruses can invade the olfactory bulb via the cribriform plate (67), a lack of evidence for Ace2 expression in murine neurons (68) argues against direct neurotropism of SARS-CoV-2, although a recent study reported Ace2 expression in mitral cells of the olfactory bulb (69). Rather, SARS-CoV-2 may indirectly influence olfactory neural circuits via infection of non-neuronal Ace2-positive cells such as oligodendrocytes.

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**TABLE 3. Summary of Case Reports and Series**

| Total number of case reports and series | 42 case reports, 9 case series |
| Total number of patients | 83 patients |
| Median age | 54 years |
| Severity of respiratory symptoms | 41 mild patients (49.4%) in 30 (57.7%) studies |
| | 42 severe patients (50.6%) in 21 (42.3%) studies |

**Neuroradiological findings in mild COVID-19 infection (41 patients)**

- Cranial nerve abnormalities: 13 (31.7%)
- Ischemic infarct: 12 (29.3%)
- White matter abnormalities: 8 (19.5%)
- Normal imaging: 3 (7.3%)
- Leptomeningeal enhancement: 2 (4.9%)
- Myelopathy: 2 (4.9%)
- Cerebral hemorrhage: 1 (2.4%)
- Venous thrombosis: 1 (2.4%)

**Neuroradiological findings in severe COVID-19 infection (42 patients)**

- White matter abnormalities: 21 (50%)
- Ischemic infarct: 13 (33.3%)
- Cerebral hemorrhage: 13 (31.0%)
- Posterior reversible encephalopathy syndrome: 4 (9.5%)
- Venous thrombosis: 1 (2.4%)

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**Fig. 2.** Neuroimaging findings in patients with severe COVID-19 infection. Head CT depicting (a) extensive acute intracranial hemorrhage in a 74-year-old man with absent brainstem reflexes following uncal, subfalcine, and transtentorial herniation and (b) left parietal intraparenchymal hemorrhage with surrounding vasogenic edema in a 61-year-old woman with right-sided weakness and numbness (13). (c,d) Noncontrast head CT showing two different ischemic lesions in the left occipital and right frontal lobes of a 64-year-old man with elevated coagulation tests (65). (e,f) Axial susceptibility weighted imaging of extensive microhemorrhages in a 57-year-old man, primarily in the subcortical white matter, corpus callosum, internal capsule and cerebellar peduncles (10). (g,h) White matter abnormalities that are hyperintense on axial T2 FLAIR imaging (g) and show perivascular enhancement on postcontrast T1-weighted images (h) in a 37-year-old male who developed ARDS and multiple organ failure (14). Panels a and b reproduced from Radmanesh et al. (13) with permission from the American Society of Neuroradiology, panels c and d reproduced from Morassi et al. (65) with permission from Springer Nature (COVID-19 PMC Open Access Subset), Panels e and f reproduced from Kremer et al. (10) and panels g and h reproduced from Chougar et al. (14) with permission from the Radiological Society of North America (COVID-19 PMC Open Access Subset).
astrocytes, and endothelial cells by pathologically altering axonal conduction velocity, metabolic and neurotransmitter homeostasis, and/or cerebral perfusion (68,70,71). The high prevalence of white matter abnormalities, ischemic infarction, and hemorrhage found on neuroimaging of COVID-19 patients support these disease mechanisms. Given the wide range of potential neurological symptoms reported in COVID-19 patients, it is likely that many or all of these mechanisms are involved to some degree across the patient population.

There are several limitations to this study. It is difficult to standardize reporting of radiological data, which can be in the
form of objective observations or presumptive diagnoses that may be subject to clinical bias. Reporting standards also varied for MRI sequence details, clinical neurological symptoms, and descriptions of findings. A subset of neuroimaging abnormalities, particularly in the population of elderly, ill patients with severe infection, may be incidental findings unrelated to acute COVID-19 infection. Routine neuroimaging represents an unnecessary viral exposure risk and is not indicated in most COVID-19 patients, and so brain imaging studies are likely to be selectively done in patients with significant neurological symptoms, underreporting potential findings in patients with mild disease. Conversely, there is a high probability of publication bias in the reviewed case reports as COVID-19 patients with unremarkable neuroimaging findings are unlikely to be published.

Concluding remarks
We suggest that the findings of this systematic review provide public health utility in that incidental neuroimaging findings or unexplained neurological symptoms can prompt evaluation for mild COVID-19 infection and prevention of asymptomatic spread, as well as clinical utility in aiding surveillance and management of potential life-threatening neurological sequelae in the setting of severe COVID-19 infection such as cerebral infarction and hemorrhage. Amidst a global pandemic, dissemination of information to the medical community at all levels—from case reports to retrospective studies to meta-analyses—will be required for clinicians to make informed decisions when caring for patients with SARS-CoV-2. From a pathophysiological perspective, lateral integration of clinical data, neuroimaging findings, pathology reports, animal models, and molecular studies will be necessary to fully understand the effects of COVID-19 infection on the nervous system.

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