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# Brain abnormalities in COVID-19 acute/subacute phase: A rapid systematic review

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ABSTRACT

*Objective:* This systematic review aimed to synthesize early data on typology and topography of brain abnormalities in adults with COVID-19 in acute/subacute phase.
*Methods:* We performed systematic literature search via PubMed, Google Scholar and ScienceDirect on articles published between January 1 and July 05, 2020, using the following strategy and key words: ((covid[Title/Abstract]) OR (sars-cov-2[Title/Abstract]) OR (coronavirus[Title/Abstract])) AND (brain[Title/Abstract]). A total of 286 non-duplicate matches were screened for original contributions reporting brain imaging data related to SARS-Cov-2 presentation in adults.
*Results:* The selection criteria were met by 26 articles (including 21 case reports, and 5 cohort studies). The data analysis in a total of 361 patients revealed that brain abnormalities were noted in 124/361 (34%) reviewed cases. Neurologic symptoms were the primary reason for referral for neuroimaging across the studies. Modalities included CT (-angiogram, -perfusion, -venogram), EEG, MRI (-angiogram, functional), and PET. The most frequently reported brain abnormalities were brain white matter (WM) hyperintensities on MRI 66/124 (53% affected cases) and hypodensities on CT (additional 23% affected cases), followed by microhemorrhages, hemorrhages and infarcts, while other types were found in < 5% affected cases. WM abnormalities were most frequently noted in bilateral anterior and posterior cerebral WM (50% affected cases).
*Conclusion:* About a third of acute/subacute COVID-19 patients referred for neuroimaging show brain abnormalities suggestive of COVID-19-related etiology. The predominant neuroimaging features were diffuse cerebral WM hypodensities / hyperintensities attributable to leukoencephalopathy, leukoaraiosis or rarefield WM.

## 1. Introduction

Over 12 million individuals worldwide have tested positive for Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) coronavirus 19 (COVID-19) up to date (Coronavirus disease (COVID-19) Pandemic. Geneva: World Health Organization, 2020). The pandemic has triggered massive quantities of scientific publications reporting data on COVID-19 of clinical- and scientific-relevance. The typical presentation of SARS-CoV-2 involves fever and respiratory symptoms. However, the recognition of neuroinvolvement of COVID-19 is increasing daily since the initial indications in February 2020 (Li et al., 2020). Currently, PubMed database search alone for the keywords "covid"/"sars-cov-2"/"coronavirus" and "neurologic"/"CNS" results in over 120,000 matches. Cohort studies and case reports describe various brain manifestations suggestive of COVID-19 etiology. At the time of "flattening the epidemic curve", this growing body of research characterizing acute/subacute phase of infection calls for a synthesis.

The aim of this systematic review is to provide a synthesis of early evidence of brain abnormalities in patients with COVID-19 in acute/subacute phase, with the focus on (1) frequency of particular brain abnormality types, and (2) topographical distribution of registered brain abnormalities.

## 2. Methods

### 2.1. Search strategy and study selection

A systematic search of literature was performed in line with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Hutton et al., 2015;

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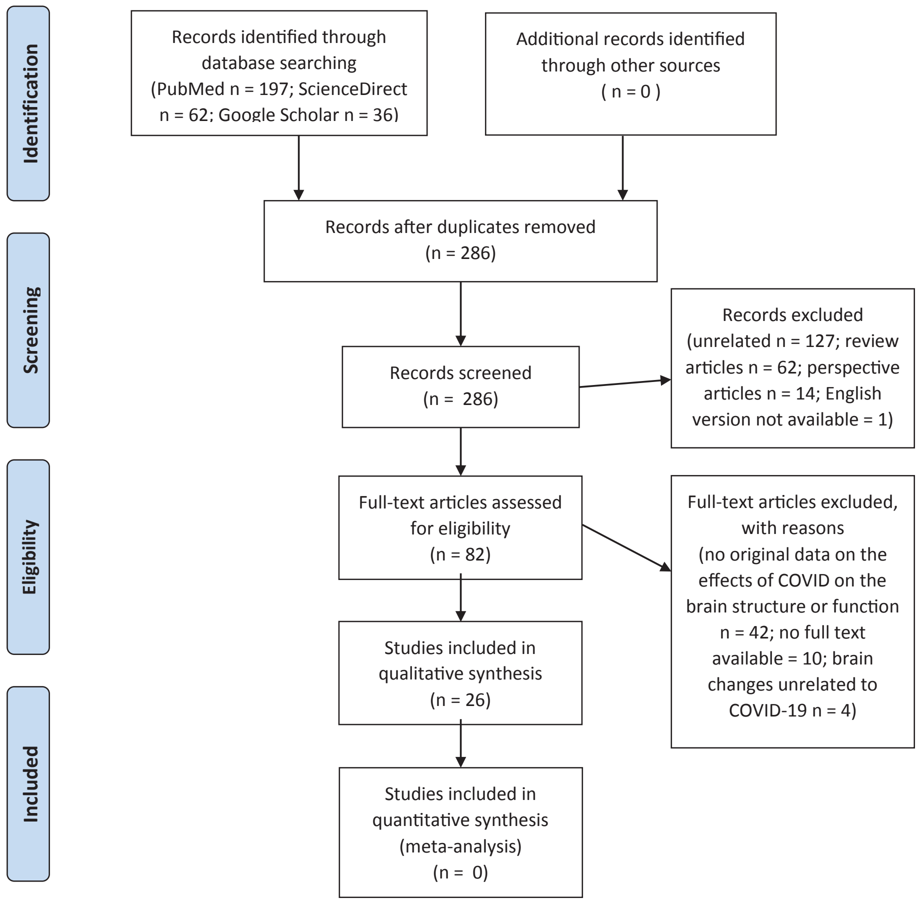


**Fig. 1.** PRISMA (2009) flow diagram of the study.

Moher et al., 2009) (Fig. 1). Search was implemented for PubMed, GoogleScholar, and ScienceDirect databases. The search strategy and keywords was as follows: ((covid[Title/Abstract]) OR (sars-cov-2[Title/Abstract]) OR (coronavirus[Title/Abstract])) AND (brain[Title/Abstract]). Search was limited to articles published between January 01 and July 05, 2020. The review protocol was not previously registered. Initial search was screened for duplicates. Then, two independent authors (ARE and SC) identified potential articles through (1) screening titles and abstracts, and (2) screening full text using inclusion and exclusion criteria (below). Search was finalized on July 06, 2020.

### 2.2. Inclusion and exclusion criteria

Original contributions, which presented data on brain structural and/or functional abnormalities (or absence of such) suggestive of COVID-19 etiology, were included in the current systematic review. Articles were excluded in case of no original neuroimaging data, no full text, no available English version of the article, or in case of reviews, letters to editor, correspondence, perspective, and opinion not containing original data of interest.

### 2.3. Data extraction

Data was extracted by two independent authors (ARE and SC) with the use of standardized form where rows contained information about the authors and year of publication, while columns indicated the following: study type (i.e., case report or cohort study), number of patients who completed at least one brain scanning session, age, sex, survival status, pre-existing medical conditions, RNA PCR fluid (CSF) status for SARS-CoV-2, early symptoms of COVID-19 (i.e., before hospital admission), symptoms of COVID-19 at/after hospital admission, symptoms of COVID-19 the day of brain scan (separately for 1st brain imaging and follow-ups), brain imaging interpretation, procedures performed on the brain during that hospital visit/stay, brain imaging modality, brain imaging results (separately for each scanning session in case of follow-ups).

## 3. Results

### 3.1. Study selection and characteristics

Initial search resulted in a collection of 295 records. Duplicates were removed, leaving 286 original contributions. Screening titles and abstracts excluded unrelated articles (n = 127); review articles (n = 62); perspective articles (n = 14); articles with English version not available (n = 1). The remaining 82 potential articles were entered into full text screening using inclusion and exclusion criteria. This step excluded articles with no original data on the brain structure or function with suggested relevance to COVID-19 (n = 42); no full text available (n = 10). Out of the identified 30 eligible articles, one article was excluded from the synthesis as patient SARS-CoV-2+ status was not confirmed neither in the swab specimen nor real-time polymerase chain reaction in the cerebrospinal fluid (Haddadi et al., 2020). Additional three article were excluded as the relationship between brain abnormalities and COVID-19 infection was noted by the authors as improbable. In detail, the authors attributed reported brain abnormalities rather to other/pre-existing medical conditions, previous pathological situations or interpreted them as potentially coincidental with COVID-19 (Morrasi et al., 2020; Degeneffe et al., 2020; Petrescu et al., 2020). Therefore, we entered a total of 26 articles (including 21 case reports, and 5 cohort studies) into the final synthesis. All 361 participants from 26 studies were patients with confirmed COVID-19 infection (with swab

**Table 1**
Characteristics of the included studies.

| Study | Study type | Number of patients with CT/MRI scan | Case ID for this review | Age | Sex | Survival | Pre-existing medical conditions | SARS-CoV-2 status | Early COVID-19 symptoms (before hospital admission) | Early COVID-19 symptoms (at/after hospital admission) | COVID-19 symptoms the day of the 1st CT/MRI scan | COVID-19 symptoms the day of the 2nd CT/MRI scan | COVID-19 symptoms the day of the 3rd CT/MRI scan | COVID-19 symptoms the day of the 4th CT/MRI scan | Surgical procedures on the CNS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Abdi et al. (2020) [6]** | Case study (n = 1) | 1 | A | 58 | M | Died probably due to status epilepticus | Missing data | Positive on RS-PCR but negative in the CSF | Slowly progressive gait disturbance around one month before admission; consciousness profoundly deteriorated two days before the admission | Decreased level of consciousness and the inability to walk; no complaints of pulmonary symptoms such as cough or dyspnea; drowsy but could obey simple tasks, and speaking consisted of short, simple words; could move all limbs but the left upper limb moved less; deep tendon reflexes were brisk and plantar reflexes were upgoing. | Missing data | N/A | NA | NA | NA |
| **Al-olama et al. (2020) [7]** | Case study (n = 1) | 1 | B | 36 | M | Missing data | Unremarkable past medical history | Positive | 2 days history of fever, headache, body pain, cough, diarrhea, vomiting | GCS=13/15; drowsiness and appeared mildly confused | N/A | N/A | N/A | N/A | Evacuation of the chronic subdural hematoma was performed on 5/5 via burr hole after CT 2-week follow-up |
| **Anzalone et al. (2020) [8]** | Cohort study (n = 4 described out of 21 scanned) | 21 | C | 46-63 | 2 males, 2 females | Missing data | No relevant clinical history or previous treatment or hypertension | Positive in nasopharyngeal swab specimen | Missing data | Present, not specified | Intubated in the first week from onset of ARDS and presented neurological signs of agitation and spatial disorientation after weaning from mechanical ventilation. One patient had a generalized seizure. The time interval from onset of neurological symptoms to MRI was 2–6 days | Missing data | N/A | N/A | N/A |
| **Asfar et al. (2020) [9]** | Case study (n = 1) | 1 | D | 39 | F | Missing data | Insignificant | Positive | Fever and myalgias had been present for nine days; she did not experience any improvement with rest and anti-inflammatory drug (NSAIDS) | Fever, myalgias, anorexia, drowsiness and dry cough | Decreased level of consciousness | N/A | N/A | N/A | N/A |
| **Cariddi et al. (2020) [10]** | Case study (n = 1) | 1 | E | 64 | F | Missing data | Hypertension, gastroesophageal reflux disease, hyperuricemia, dyslipidemia, obstructive sleep apnea and paroxysmal atrial fibrillation | Positive on nasopharyngeal swab | 10-day history of fever and dyspnea | Febrile (39 °C) with marked dyspnea. Unremarkable neurological examination. | After 25 days under sedation and ventilation, she was weaned, woke up and complained of blurred vision drowsy, showed an altered mental status, a decreased left nasolabial fold, the tone and the strength were slightly decreased in the legs, and all deep tendon reflexes were reduced symmetrically | Missing data | N/A | N/A | N/A |
| **Dixon et al. (2020) [12]** | Case study (n = 1) | 1 | F | 59 | F | Died after the withdrawal of ventilatory support | Aplastic anemia treated with intermittent red blood cell and platelet transfusions | Positive on nasopharyngeal swab | 3 weeks history of transient abdominal pain and diarrhea; 10 days history of persistent cough, sore throat, shivering, and headache, with subsequent shortness of breath and myalgia | GCS=11/15; recurrent fleeting episodes of vacant staring and speech arrest associated with flexion of both shoulders and a brief witnessed generalized tonic-clonic seizure (GTCS),vomiting, followed by postictal reduced consciousness; no focal deficits | [CT at the time of admission] | GCS fell to 5 (E1, V1, and M3), with associated development of an extensor left plantar response and an unreactive left pupil | Neurologic examination after withdrawal of sedation showed intact corneal reflexes and normal pupillary responses to light. Doll's eye response reduced; coughed on suction and initiated breathing but required pressure support mechanical ventilation; displayed no response to verbal command or painful stimuli | N/A | N/A |
| **Espinosa et al. (2020) [13]** | Case study (n=1) | 1 | G | 72 | M | Missing data | Hypertension, hyperlipidemia and type 2 diabetes mellitus | Positive on PCR | About 6 days history of fever and dry cough | His chest x-ray revealed multifocal consolidations concerning for multifocal pneumonia. The patient continued to decompensate and was ultimately intubated for acute hypoxemic respiratory failure. | [EEG 72h after sedation was discontinued] Not responsive to verbal command or reactive to noxious painful stimuli; brainstem reflexes remained intact by grimace | N/A | N/A | N/A | N/A |
| | | | | | | | | | | He did not respond to verbal command or react to noxious painful stimuli, only his brainstem reflexes remained intact by grimace | | | | | |
| **Fischer et al. (2020) [14]** | Case study (n=1) | 1 | H | 47 | M | Survived | Hypertension and asthma | Positive | Several days of fevers and dyspnea; hypoxic. | Day 1: developed progressive respiratory failure, requiring intubation and transfer to the intensive care unit. Acute respiratory distress syndrome requiring mechanical ventilation for over 40 days, shock, renal failure, and pneumomediastinum. Day 20: sedation was weaned. Next several weeks: he fluctuated between coma and the minimally conscious state, in which he intermittently visually tracked an examiner but did not otherwise demonstrate purposeful behaviors. | Missing data | N/A | N/A | N/A | N/A |
| **Franceschi et al. (2020) [15]** | Case study (n = 2) | 2 | I | 48 | M | Recovered | Obesity | Positive PCR | Fever and cough | GSC=missing data; Fever progressed to 105°F and he developed difficulty breathing ; then: shock with widely varying blood pressures | Diagnosed with inflammatory cytokine release syndrome (high D-dimer, lactate dehydrogenase, C-reactive protein, and ferritin values) and developed an altered mental status | N/A | N/A | N/A | N/A |
| | | | J | 67 | F | Discharged | Multiple comorbidities and past medical history of hypertension, diabetes, coronary artery disease, gout, and asthma | Positive PCR | Altered mental status, including lethargy and confusion | GSC=missing data; 2 days before CT and MRI: afebrile, denied cough, chest pain, and shortness of breath; presented variations in blood pressure | Missing data | N/A | N/A | N/A | N/A |
| **Guennec et al. (2020) [16]** | Case study (n=1) | 1 | K | 69 | M | Improved | Diabetes mellitus, hypertension, and a single seizure (1 year earlier; related to hyperglycaemia and uncontrolled diabetes) | Positive RT-PCR assay of a tracheal aspirate; negative on RT-PCR assay of the CSF | 5-day history of cough, fever, and anosmia | The patient improved after one week, allowing for weaning from mechanical ventilation, but he presented signs of frontal lobe syndrome including verbal perseverations and imitation behavior, and was drowsy for several days after extubation | Missing data | Missing data | Missing data | Missing data | N/A |
| **Hayashi et al. (2020) [18]** | Case study (n=1) | 1 | L | 75 | M | Died due to respiratory failure (day 12 after admission) | Mild Alzheimer's disease | Positive on throat swab RT-PCR test | A few days history of left-dominant kinetic tremor in his hands, walking instability and urinary incontinence; plus diarrhea but denied cough, breathing discomfort or fever. He denied headache or loss of taste or smell, or convulsion | Day 1: Body temperature = 36.7°C, pulse rate =93 beats/min; mild ataxic gait; alerted consciousness and normal eye movement, but the finger-to-nose test showed bilateral marked dysmetria. No muscle weakness or abnormal tendon reflexes of extremities. Developed fever = 39.3°C; rapidly developed severe hypoxemia. Day 2: disoriented in time and place, but his neurological deficit and cerebellar ataxia had resolved. Day 3: became alert, coherent and oriented. | N/A | N/A | N/A | N/A | N/A |
| **Hepburn et al. (2020) [19]** | Case study (n = 2) | 2 | M | 76 | M | In a long-term acute care hospital for further ventilator management | Chronic asthma on benralizumab, hypertension, chronic kidney disease, hyperlipidemia, left bundle branch block, diastolic dysfunction, and cervical fusion | Positive on PCR on post-operative day 4 | Severe right lower extremity pain, fever and encephalopathy | GSC=14/15, was oriented to name only, and exhibited exaggerated deep tendon reflexes but had no other focal neurological deficits | Post-operative day 1 symptoms: high-grade fevers and acute hypoxemic respiratory failure; Post-operative day 2 symptoms: patient suffered several episodes of left upper extremity clonic activity and worsening encephalopathy with decline in level of consciousness as evidenced by increased drowsiness and inability to follow commands | Missing data | N/A | N/A | Surgical drainage was performed, and the patient was started empirically on vancomycin and piperacillin–tazobactam |
| | | | N | 82 | M | Patient remained on the ventilator, and after 20 days of ICU stay, the family opted for withdrawal of life-sustaining support. | Chronic obstructive pulmonary disease, venous thromboembolic disease, complete heart block, and chronic kidney disease | Positive on nasopharyngeal swab PCR | 10-day history of progressive dyspnea, altered mental status, and generalized weakness | GSC=missing data; hypoxic, febrile, tachycardic | Right eyelid and facial twitching | N/A | N/A | N/A | N/A |

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**Table 1** (*continued*)

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Kadono et al. (2020) [20]** | Case study (n=1) | 1 | O | 44 | M | Improved and discharged | 6 months earlier: symptomatic epilepsy following cerebral venous thrombosis with acute hemorrhagic infarction because of nephrosis. A right front-temporal decompression surgery was performed. Seizure-free after surgery. | Positive on RT-PCR | One week before admission: felt bulging of a scalp flap. On the morning of admission: numbness in left hand and face. | A seizure during admission (starting from jerking of his left hand and then the entire body). | After the seizure, he claimed anosmia. Day 1: developed a fever of 38.5 °C and hypoxia. | Missing data | N/A | N/A | N/A |
| **Kandemirli et al. (2020) [21]** | Cohort study (n = 50) | 27 | P | Mdn=63; range=34-87 | 21 males | Missing data | Hypertension (n=16), diabetes mellitus (n=11), cerebrovascular accident (n=2), coronary artery disease (n=3), atrial fibrillation (n= 1), congestive heart failure (n=2), chronic kidney disease (n=4), lung cancer (n= 1), Addison's disease (n=1) | Cerebrospinal fluid (CSF) was obtained in 5/10 patients with cortical signal abnormalities (total protein elevated in 4/5). CSF checked in 2/15 cases which did not show COVID-19 related or acute intracranial findings on MRI, and showed elevated CSF protein. | Missing data | Missing data | Missing data | N/A | N/A | N/A | N/A |
| **Kremer et al. (2020) [22]** | Cohort study (n=190) | 37 | Q | M=61, SD=12 | 30 males | 5 (14%) patients died | History of stroke was in 7 (19%) patients, seizures in 1 (3%) and another neurological history was in 8 (22%) patients. | Positive on nasopharyngeal or lower RT-PCR. Positive on RT-PCR CNS in 1/28 patient. | 32/37 (87%) admitted because of acute respiratory failure; 4 (11%) patients had headaches and 5 (14%) had seizures. The most frequent neurologic manifestations: altered consciousness (27/32, 73%), pathological wakefulness after | Missing data | Missing data | N/A | N/A | N/A | N/A |
| | | | | | | | | | sedation (15/37, 41%), confusion (12/37, 32%), agitation (7/37, 19%). | | | | | | |
| **Li et al. (2020) [23]** | Case report (n=1) | 1 | R | 21 | M | Discharged after 23-day of hospitalization with partial recovery of sense of smell | Without past medical history | Positive on RT-PCR in nasopharyngeal swab | Five-day of loss of smell without other respiratory tract discomfort or fever. At the quarantine station of the hospital: fever up to 38 C, infiltration over left lower lung near the cardiac apex on chest X-ray film | Missing data | N/A | N/A | N/A | N/A | N/A |
| **Moriguchi et al. (2020) [24]** | Case report (n = 1) | 1 | S | 24 | M | Missing data | Paranasal sinusitis | Positive in CSF, but negative in nasopharyngeal swab | Headache, generalized fatigue, fever; then: worsening headache, sore throat | GSC=6/15 (E4 V1 M1)with hemodynamic stability, neck stiffness; consciousness disturbance; transient generalized seizures (~1 min) | [CT at the time of admission] | Missing data | N/A | N/A | N/A |
| **Muhammad et al. (2020) [25]** | Case report (n = 1) | 1 | T | 60 | F | Recovered | Missing data | Positive in oropharyngeal swab PCR | Loss of consciousness | GCS=reduced; respiratory insufficiency | [CT at the time of admission] | Missing data | Until last imaging on day 12-post ictus no delayed cerebral ischemia was detected | N/A | Aneurysm was clipped microsurgically immediately after admission |
| **Parsons et al. (2020) [26]** | Case report (n=1) | 1 | U | 51 | F | Missing data | Had no pertinent neurological hist ory | Positive on PCR from a na sopharyngeal swab. There w ere four oligoc lonal bands, p resent in both serum and CS F. SARS-CoV-2 was not detec ted by qualitat ive PCR | Dyspnea, fever, and vomiting | Febrile, tachycardic, and hypoxic. Around 2.5 weeks after admission (during which intubated and maintained on sedative drip): neurological exam was notable for unresponsiveness (GC S 3). Pupils were equal and reactive to light, corneal resp onses were intact, and the oculocephalic response to the left was impaired. Muscle tone was faccid throughout, and the ex tremities did not move. Deep tendon refexes were depressed, and plantar resp onses were mute. | Missing data | Missing data | Missing data | Missing data | N/A |

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**Table 1** (*continued*)

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Politi et al. (2020) [28]** | Case report (n=1) | 1 | V | 25 | F | Not specified, but recovered from anosmia | No significant medical history. | Positive on swab test and RT-PCR | Mild dry cough that lasted for 1 day, followed by persistent severe anosmia and dysgeusia. No fever. No trauma, seizure, or hypoglycemic event. | Three days later, nasal fibroscopic evaluation results were unremarkable, and noncontrast chest and maxillofacial computed tomography results were negative. | Missing data | Missing data | N/A | N/A | N/A |
| **Radmanesh et al. (2020) [29]** | Cohort (n=27) | 27: of those data provided for 11 patients* | W | M=53; range=38-64 | 9 males | 6 of 11 died (3 had leuoencephalophathy, 1 microhemmorhages, 2 both); 5 currently in critical care | Missing data | Positive on RT-PCR in nasopharyngeal swab, and one positive in the CSF | Missing data | Missing data | Missing data | N/A | N/A | N/A | N/A |
| **Radmanesh et al. (2020) [30]** | Cohort (n=3661) | 242** | X | M=68.7, SD=16.5 | 150 males | 2-week follow-up period:, 63 patients died or were transitioned to hospice or comfort care and 179 showed improvement or stability. | Of patients imaged for altered mental status, 42 (41.2%) had white matter microangiopathic changes, 29 (28.4%) had chronic infarcts, and 1 patient had an incidental meningioma. | Positive on PCR in nasal swab | Missing data | The 3 most common clinical indications for brain imaging: 1) altered mental status (102 patients, 42.1%, all were inpatients), 2) syncope/fall (79 patients, 32.6%, including 4 outpatients), and 3) focal neurologic deficit (30 patients, 12.4%, all were inpatients); 5 outpatients were imaged for nonacute headache, and 2 were imaged for generalized weakness | Missing data | Missing data | Missing data | N/A | All 3 patients with anterior circulation large-vessel occlusions underwent mechanical thrombectomy with TICI 3, 2a, and 2b revascularizations, respectively. |
| **De Stefano et al. (2020) [31]** | Case report (n=1) | 1 | Y | 56 | F | Cognition and vigilance improved after 10 days from the first EEG with normalization of orientation and language, but persistent slight executive dysfunction | Tobacco smoking induced pulmonary emphysema and hypothyroidism | Positive on PCR nasopharyngeal swab | Cough and fever | Antibiotics were administered and patient recovered at home. After ten days, she developed a respiratory failure. On admission, she was febrile (39.6C) and presented clinical and imaging signs of pneumonia. Otherwise physical examination was normal, in particular the neurological examination did not show any abnormalities. Conscious and orientated, with no sensory or motor deficits. | No clinical or electroencephalographic improvement | Awake during this period of record but unresponsive (eyes open, exploring the space, not speaking, not following simple verbal orders) | Missing data | Missing data | N/A |
| **Virhammar et al. (2020) [32]** | Case report (n=1) | 1 | Z | 55 | F | Extubated on day 35 and discharged to rehabilitation | Previously healthy | First and second CFS sample was negative but third sample was positive | Fever and myalgia | Lethargic and had difficulty managing the stairs. Found unresponsive in bed. At readmission, her temperature was 37.6 °C. She was hemodynamically stable and had no respiratory problems. She was stuporous and had multifocal myoclonus. | She was stuporous and had multifocal myoclonus. | Neurological status deteriorated and she was intubated and transferred to the intensive care unit. | Her neurological symptoms had by then worsened with impaired brain stem reflexes. | A scant improvement was noted with increased level of consciousness and normalization of brain stem reflexes. | N/A |
| **Zanin et al. (2020) [33]** | Case report (n = 1) | 1 | α | 54 | F | Recovered | History of anterior communicating artery (AComA) aneurysm treated surgically 20 years before | Positive on RT-PCR | Found unconscious | GCS=12/15 (E3 M6 V3), without focal sensorimotor deficits. No signs of both tongue biting and incontinence were reported by the familiars. Anosmia and ageusia were referred by several days | [CT at the time of admission] | [Follow-up a few hours later] | N/A | N/A | N/A |
| **Zoghi et al. (2020) [34]** | Case report (n = 1) | 1 | β | 21 | M | At the end of the second week, the upper limb weakness improved, but the force of the lower limbs was 3+/5 | Missinig data | Two COVID-19 nasopharyngeal swab tests were negative, as was the CSF assay for the genome of the virus. Serologic tests were negative for IgM, but the IgG level was 1.6 (positive >1.1). | Fever with chills, nonproductive cough, and a sore throat 2 weeks before admission, All symptoms decreased in severity within 10 days, after which he developed significant loss of appetite, recurrent vomiting with food intolerance, and generalized malaise. Following 3 days of repeated vomiting, he experienced weakness and paresthesia of the lower limbs, which continued throughout the day. He had urinary retention, increased paraparesis severity and weakness in the upper limbs; he also became drowsy. No headache, vertigo, diplopia, dysphagia, neck pain, or blurred vision. | The patient was lethargic but obeyed simple verbal commands. The patient was lethargic but obeyed simple verbal commands. No evidences of nuchal rigidity, Kernig's or Brudzinski's signs. Pupils equally reactive to light. The muscular strength was 4+/5 in the upper limbs and 2/5 in the lower limbs. Normal deep tendon reflexes in all four limbs and Babinski's sign was absent. The position and light touch sensation were impaired in both lower limbs; additionally, he had a T8 sensory level. The abdominal cutaneous reflex was absent in all directions. | Missing data | N/A | N/A | N/A | N/A |

*Notes*. N/A – non-applicable, M – male, F – female, GCS – Glasgow Coma Score, CT – Computed Tomography, MRI – Magnetic Resonance Imaging, CNS –Cerebrospinal Fluid, CSF – Chemical-physical cerebrospinal fluid, PCR– Polymerase chain reaction, RNA- Ribonucleic acid, RT-PCR – Real-time polymerase chain reaction.

* Authors provided neuroimaging results for 11/27 cases. The inclusion of those 11 cases was based onnoted abnormalities interms of white matter T2 hyper-intensities (more than expected for age-related microangiopathy based on visual qualitative assessment) and/or microhemorrhages (defined as ≤ 4 mm in size). Microhemorrhages confined to any areas of acute/subacute infarcts were excluded.

** 242 out of 3661 patients were MRI scanned. The authors reportthe most common clinical indications for brain imaging in their cohort to be: altered mental status (n = 102), syncope/fall (n = 79), or focal neurologic deficit (n = 30).

and/or CSF test) (Coronavirus disease (COVID-19) Pandemic. Emergency use ICD codes for COVID-19 disease outbreak. Geneva: World Health Organization, 2020). Brain abnormalities suggestive of COVID-19 etiology were present in 124/361 (34%) reported cases. Available demographic and illness characteristics are shown in Table 1.

### 3.2. Typology of brain abnormalities in COVID-19

The most frequent brain abnormalities were brain WM hyper-intensities on MRI and hypodensities on CT, which together accounted for 76% of affected cases (Table 2). Hyperintensities in cerebral WM were reported in 66/124 (53% affected cases). Those abnormalities were noted in bilateral medial temporal lobes [Z] (Virhammar et al., 2020), frontal, occipital, parietal [C (Anzalone et al., 2020): 4/21 cases], all of the above plus temporal lobes [D (Asfar et al., 2020); P (Kandemirli et al., 2020): 12/27; W (Radmanesh et al., 2020): 10/11 cases; Q (Kremer et al., 2020): 16/37]. Changes were also registered in insular cortex [P (Kandemirli et al., 2020): 3/27], subinsular regions [Z] (Virhammar et al., 2020), cingulate gyri [P (Kandemirli et al., 2020): 3/27], cerebral peduncle and internal capsule [β] (Zoghi et al., 2020), thalamus [Z (Virhammar et al., 2020); D (Asfar et al., 2020); H (Fischer et al., 2020), midbrain [Z] (Virhammar et al., 2020), pons [D (Asfar et al., 2020); β (Zoghi et al., 2020), parahippocampal gyri and basal ganglia [H] (Fischer et al., 2020), splenium of corpus callosum [L (Hayashi et al., 2020); β (Zoghi et al., 2020), olfactory nerves/bulb [R (Li et al., 2020), W (Petrescu et al., 2020) and gyrus rectus [W] (Petrescu et al., 2020), or described as diffuse [α (Zanin et al., 2020), W (Radmanesh et al., 2020): 10/11 cases; Q (Kremer et al., 2020): 11/37; U (Parsons et al., 2020). Three patients showed lateralized hyper-intensities: one case of right prefrontal involvement [K] (le Guennec et al., 2020), one case of right temporal lobe, inferior horn of lateral ventricle and hippocampus [S] (Moriguchi et al., 2020), and one case of left WM, cortical and deep gray matter and midbrain [A] (Abdi et al., 2020). Diffuse leukoencephalopathy was further reported in 4/124 (3%) in bilateral cerebellar hemispheres and middle cerebellar ped-uncles [W (Radmanesh et al., 2020): 4/11].

Hypodensities were noted in additional 29/124 (23% affected cases), and were primarily registered as diffuse changes in bilateral WM [E (Cariddi et al., 2020); X (Radmanesh et al., 2020): 26/242 cases]. Two case studies described hypodensities in amygdala [F] (Dixon et al., 2020), supratentorial leptomeningeal [N] (Hepburn et al., 2020), left occipital lobe [F] (Dixon et al., 2020) in WM and gray matter).

Other brain abnormalities were reported as follows. *Microhemorrhages* in WM were noted in 16/124 (13%) with bilateral diffuse presentation [W (Radmanesh et al., 2020): 5/11], in corpus callosum [W (Radmanesh et al., 2020): 4/7; Y (De Stefano et al., 2020), and putamen [F] (Dixon et al., 2020), bilateral juxtacortical WM and internal capsule [Y] (De Stefano et al., 2020); or diffuse [Q (Kremer

**Table 2**
Brain imaging features in patients with COVID-19 in acute/subacute phase.

| Study | | | | Abdi et al. (2020) [6] | Al-olama et al. (2020) [7] | | Anzalone et al. (2020) [8] | | Asfar et al. (2020) [9] | Cariddi (2020) [10] | | Dixon et al. (2020) [12] | | | Espinosa et al. (2020) [13] | Fischer et al. (2020) [14] | Franceschi et al. (2020) [15] | | | Guennec et al. (2020) [16] | | | | Hayashi et al. (2020) [18] | Hepburn et al. (2020) [19] | | | Kadono et al. (2020) [20] | | Kandemirli et al. (2020) [10] | Kremer et al. (2020) [22] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Case ID for this review | | | | A | B | | C | | D | E | | F | | | G | H | I | | J | K | | | | L | M | | N | O | | P | Q |
| Scanning session | | | | Initial | Initial | 14-day follow up | Initial | 1 month follow-up | Initial | Initial (26th day) | Follow-up (56th day) | Initial | 12hours-follow up | 6-day follow up | Initial | Initial | Initial | 12-day follow up | Initial | Initial | 1-day follow-up | 15-day follow-up | 30-day follow-up | Initial | Initial | 2-day follow up | Initial | Initial | 1-month follow-up | March1-April 18, 2020 | Initial |
| CT | | | | | x | x | | | | x | | x | x | | | | x | | x | x | | | | | x | | x | x | x | | |
| CT angiogram | | | | | x | | | | | | | | x | | | | | | | | | | | | | | | | | | |
| CT venogram | | | | | | | | | | | | | | | | | x | | | | | | | | | | | | | | |
| CT perfusion | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| PET | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| EEG | | | | | | | | | | | | | | | x | x | | | | X | x | | | | | x | x | | | | |
| MRI | | | | x | | | x | x | x | | x | | | x | x | x | | x | x | X | | X | x | x | | x | | x | | x | x |
| fMRI (resting state) | | | | | | | | | | | | | | | | x | | | | | | | | | | | | | | | |
| MR angiography | | | | | | | | | | | | | | | | | | | x | | | | | | | | | | | | |
| Lack of acute/subacute abnormalities | | | Unremarkable | | | | X MRI 17/21; MRI-SWI 21/21 | X MRI in 1/1 | | | | | | | X MRI | X ¥¥¥ fMRI | | | X MR-agnio | X CT | | | X MRI | | X CT | X MRI | | | | X 15/27 cases MRI | |
| | | | Lack of T2hyperintensities and/or microhemorrhages | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | Lack of arteriovenous malformation or aneurysms | | X CT-angio | | | | | | | | | | | | | | | | | | | | | | | X MRI | | | |
| | | | Lack of acute vascular occlusion | | | | | | | | | | X CT-angio | | | | | | | | | | | | | | | X MRI | | | |
| **Acute/subacute brain abnormalities** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Hemisphere** | **Area** | **Depth** | **Abnormality** | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Bilateral** | Diffuse or not specified | Periventricular white matter | Hyperintensities without restriction of diffusion nor contrast enhancement | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | Intraventricular | Hemorrhage | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | Juxtacortical white matter | Punctate microhemorrhages | | | | | | | | | | | | | | | | | | | | | | | | | | | | X $ MRI (9/37) |
| | | | Hyperintensity | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | Subcortical white matter | Hypodensity/hyperintensity | | | | | | | X ¥¥ CT | X MRI | | X CT | | | | | | | | | | | | | | | | | | X MRI(11/37) |
| | | | Swelling, restricted diffusion with peripheral enhancement | | | | | | | | | | | X MRI | | | | | | | | | | | | | | | | | |
| | | Deep gray matter | Hypodensity | | | | | | | | | | X CT-angio | | | | | | | | | | | | | | | | | | |
| | | Not specified | Slowing consistent with encephalopathy and no epileptiform abnormalities | | | | | | | | | | | | X EEG | | | | | | | | | | | | | | | | |
| | | | Slowing | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | Disorganized delta-theta slowing but no evidence of seizures or epileptiform discharges | | | | | | | | | | | | | X EEG | | | | | | | | | | | | | | | |
| | Parasagittal | Not specified | Intermittent onset of 4 Hz rhythms in absence of encephalopathy | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Centrum semiovale | Subcortical and deep white matter | Hyperintensities, mild restricted diffusion | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Corona radiata | Subcortical and deep white matter | Hyperintensities, mild restricted diffusion | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Anterior circulation territories | Not specified | Acute/subacute infarct | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Posterior circulation territories | Not specified | Acute/subacute infarct | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Posterior parieto-occipital | Subcortical | Ffocal vasogenic/cytotoxic edema | | | | | | | | | | | | | | X CT | X MRI | X CT†, MRI | | | | | | | | | | | | |
| | | Not specified | Restricted diffusion | | | | | | | | | | | | | | | | X MRI | | | | | | | | | | | | |
| | | Not specified | Hemorrhages | | | | | | | | | | | | | | | | X MRI-SWI | | | | | | | | | | | | |
| | Parietal | Subcortical and deep white matter | Abnormalities (hyperintensities???) | | | | | | | | | | | | | | | | | | | | | | | | | | | X 3/27 cases MRI | |
| | | Cortical | Hyperintensities | | | | X MRI 4/21 | | | | | | | | | | | | | | | | | | | | | | | | |
| | Occipital | Subcortical and deep white matter | Abnormalities (hyperintensities???) | | | | | | | | | | | | | | | | | | | | | | | | | | | X 4/27 cases MRI | |
| | | | Hyperintensities, mild restricted diffusion | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | Juxtacortical white matter | Hyperintensities, mild restricted diffusion | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | Cortical | Hyperintensities | | | | X MRI 4/21 | | | | | | | | | | | | | | | | | | | | | | | | |
| | Frontal | Subcortical and deep white matter | Abnormalities (hyperintensities???) | | | | | | | | | | | | | | | | | | | | | | | | | | | X 4/27 cases MRI | |
| | | Subcortical and juxtacortical white matter (precentral gyrus) | Hyperintensities, mild restricted diffusion | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | Cortical | Hyperintensities | | | | X MRI 4/21 | | | | | | | | | | | | | | | | | | | | | | | | |
| | Temporal | Subcorticaland deep white matter | Abnormalities (hyperintensities???) | | | | | | | | | | | | | | | | | | | | | | | | | | | X 1/27 cases MRI | |
| | | Subcortical and deep white matter | Hyperintensities, mild restricted diffusion | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | Medial | Hyperintensities without restricted diffusion | | | | | | X MRI | | | | | | | | | | | | | | | | | | | | | | X MRI (16/37) |
| | Frontal–temporal regions | Not specified | Seizures | | | | | | | | | | | | | | | | | | | | | | | | X ††† EEG | | | | |
| | Amygdala | Not specified | Hypodensity | | | | | | | | | | X CT-angio | | | | | | | | | | | | | | | | | | |
| | | Not specified | Hemorrhage | | | | | | | | | | | X MRI | | | | | | | | | | | | | | | | | |
| | Putamen (dorsolateral) | N/A | Microhemorrhage | | | | | | | | | | | X MRI | | | | | | | | | | | | | | | | | |
| | Thalamic nuclei (ventrolateral, medial) | N/A | Swelling, restricted diffusion with peripheral enhancement | | | | | | | | | | | X MRI | | | | | | | | | | | | | | | | | |
| | | | Hyperintensities | | | | | | X MRI | | | | | | | X MRI | | | | | | | | | | | | | | | |
| | | | Hypodensities | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Internal capsule | Not specified | Hyperintensities | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | Microbleeds | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Subinsular regions | N/A | Swelling, restricted diffusion with | | | | | | | | | | | X MRI | | | | | | | | | | | | | | | | | |

(continued on next page)

**Table 2** (*continued*)

| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | peripheral enhancement | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | Hyperintensties | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Insular cortex | N/A | Abnormalities (hyperintensities???) | | | | | | | | | | | | | | | | | | | | | | | | | | | X 3/27 cases MRI | |
| | Parahippocampal gyri | N/A | Hyperintensity | | | | | | | | | | | | | X MRI | | | | | | | | | | | | | | | |
| | Basal ganglia | Not specified | Restricted diffusion with associated edema | | | | | | | | | | | | | X MRI | | | X MRI | | | | | | | | | | | | |
| | | | Hyperintensity | | | | | | | | | | | | | X MRI | | | | | | | | | | | | | | | |
| | Cingulate gyri | Not specified | Swelling, restricted diffusion with peripheral enhancement | | | | | | | | | | | X MRI | | | | | | | | | | | | | | | | | |
| | | Not specified | Abnormalities (hyperintensities???) | | | | | | | | | | | | | | | | | | | | | | | | | | | X 3/27 cases MRI | |
| | Cerebellar hemispheres | Not specified | Restricted diffusion with associated edema | | | | | | | | | | | | | | | | X MRI | | | | | | | | | | | | |
| | | Iinfratentorial parenchyma | Diffuse leukoencephalopathy | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Middle cerebellar peduncles | Infratentorial parenchyma | Diffuse leukoencephalopathy | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | Not specified | Hyperintensities | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Cerebral peduncle | Not specified | Hyperintensities | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Olfactory nerves | N/A | hyperintensities | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Supratentorial leptomeningeal | Not specified | Increased enhancement | | X CT-angio | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | White matter | Hypodensities | | | | | | | | | | | | | | | | | | | | | | | X ‡ CT | | | | | |
| **Left** | Diffuse | White matter | Hyperintensity | X MRI FLAIR - weighted | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | Cortical and deep gray matter | Hyperintensity | X MRI FLAIR - weighted | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Occipital | Cortical and subcortical | Hypodensity | | | | | | | | | | X CT | | | | | | | | | | | | | | | | | | |
| | | Subcortical white matter | Parenchymal hemorrhage | | | | | | | X CT | | | | | | | | | | | | | | | | | | | | | |
| | Frontal | Subarachnoid | Aneurysmal hemorrhage | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | Delayed cerebral ischemia | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Right** | | Subdural | Hematoma | | X * CT | X ** CT | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Frontal | Intracerebral | Hematoma | | X* CT | X*** CT | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | Restricted diffusion with associated edema | | | | | | | | | | | | | | | | X MRI | | | | | | | | | | | | |
| | | | Repetitive 1 Hz rhythmic bursts | | | | | | | | | | | | | | | | | X EEG | | | | | | | | | | | |
| | | | persistent short - interval (0.7 -1.2 sec) lateralized periodic discharges | | | | | | | | | | | | | | | | | | X EEG | | | | | | | | | | |
| | | Orbital prefrontal cortex adjacent to the olfactory bulb, spread towards mesial prefrontal cortex and caudate nucleus | Hyperintensity | | | | | | | | | | | | | | | | | X MRI | | | | | | | | | | | |
| | | Gyrus rectus | Hyperintensity | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | Frontal | Hyperintensity | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | Prefrontal cortex | Hyperintensity | | | | | | | | | | | | | | | | | | | X MRI | | | | | | | | | |
| | | Subarachnoid | Hemorrhage | | X CT | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Temporal | Subarachnoid | Hemorrhage | | X CT | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | Not specified | Severe swelling | | | | | | | | | | | | | | | | | | | | | | | | | X CT | X δ CT | | |
| | | | Hypodensity correlated to hemorrhagic process | | | | | | | | X MRI | | | | | | | | | | | | | | | | | | | | |
| | | Mesial lobe | Hyperintensity | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Sylvian fissure | Subarachnoid | Hemorrhage | | X CT | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Posterior parieto-occipital | Not specified | Hemorrhage | | | | | | | | | | | | | | X CT | | | | | | | | | | | | | | |
| | Centroparietal | Not specified | Focal seizures | | | | | | | | | | | | | | | | | | | | | | | X †† EEG | | | | | |
| | Inferior horn of lateral ventricle | N/A | Hyperintensity | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Olfactory bulb | N/A | Reduced volume | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | hippocampus | Not specified | Hyperintensity, atrophy | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Midline structures** | Brainstem | Not specified | Swelling | | | | | | | | | X CT | X CT-angio | X MRI | | | | | | | | | | | | | | | | | |
| | | | Hemorrhage | | | | | | | | | | | X MRI | | | | | | | | | | | | | | | | | |
| | | | Hyperintensities | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | Midbrain | Hyperintensity | X MRI FLAIR - weighted | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | Hypodensity | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | Pons | Hemorrhage | | | | | | | | | | X CT-angio | | | | | | | | | | | | | | | | | | |
| | | | Swelling | | | | | | | | | | | X MRI | | | | | | | | | | | | | | | | | |
| | | | Hyperintensities without restricted diffusion | | | | | | X MRI | | | | | | | | | | | | | | | | | | | | | | |
| | Corpus callosum | Not specified | Petechial hemorrhages | | | | | | | | | | | | | | | X MRI-SWI | | | | | | | | | | | | | |
| | | | Puctiform micsrobleeds | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | Splenium | Punctate microhemorrhages | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | Swelling, restricted diffusion with peripheral enhancement | | | | | | | | | | | X MRI | | | | | | | | | | | | | | | | | |
| | | | Hyperintensity | | | | | | | | | | | | | | | | | | | | | X MRI-DWI | | | | | | | |

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**Table 2** (*continued*)

| Study | | | | Li et al. (2020) [23] | Moriguchi et al. (2020) [24] | | Muhammad et al. (2020) [25] | | | Parsons et al. (2020) [26] | | | | Politi et al. (2020) [28] | | Radmanesh et al. (2020, a) [29] | Radmanesh et al. (2020, b) [30] | De Stefano et al. (2020) [31] | | | | Virhammar et al. (2020) [32] | | | | Zanin et al. (2020) [33] | | Zoghi et al. (2020) [34] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Case ID for this review | | | | R | S | | T | | | U | | | | V | | W | X | Y | | | | Z | | | | α | | β |
| Scanning session | | | | Initial | Initial | 1-day follow-up | Initial | 3, 6, 9-day follow-up | 12-day follow up | Initial (day 24) | Follow-up (29th day) | Follow-up (38th day) | Follow-up (58th day) | Initial | 28-day follow-up | April 5-25,2020 | March 1-31,2020 | Initial | 1-day follow-up | 3-day follow-up | 19-day follow-up | Initial (9th day) | Follow-up (11th day) | Follow-up (12th day) | Follow-up (14th day) | Initial | Few hours follow-up | Initial |
| CT | | | | | x | | x | | | | | | | | | | x | | | | | x | x | | | x | x | |
| CT angiogram | | | | | | | x | | | x | | | | | | | | | | | | | | | | | | |
| CT venogram | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| CT perfusion | | | | | | | | x | x | | | | | | | | | | | | | | | | | | | |
| PET | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| EEG | | | | | | | | | | x | | | | | | | | x | x | x | | | | | x | | x | x |
| MRI | | | | x | | x | | | | x | x | x | x | x | x | x | x | | | | x | | | x | x | | x | x |
| fMRI (resting state) | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| MR angiography | | | | | | | | | | | | | | | | | | | | | X | | | | | | | |
| Lack of acute/subacute abnormalities | | | Unremarkable | | X ‡‡ CT | | | X ‡‡‡ CTP | | | | | | | X $$ MRI | | X ⁋⁋ 205 (not directly reported) / 242 scanned | | | X EEG | X MRI-angio | | | | | X CT | X CT | X EEG |
| | | | Lack of T2hyperintensities and/or microhemorrhages | | | | | | | | | | | | | X 16/27 cases MRI | | | | | | | | | | | | |
| | | | Lack of arteriovenous malformation or aneurysms | | | | | | | X CT-angio | | | | | | | | | | | | | | | | | | |
| | | | Lack of acute vascular occlusion | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Acute/subacute brain abnormalities** | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Hemisphere** | **Area** | **Depth** | **Abnormality** | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Bilateral** | Diffuse or not specified | Periventricular white matter | Hyperintensities without restriction of diffusion nor contrast enhancement | | | | | | | | | | | | | | | | | | | | | | | | X MRI | |
| | | Intraventricular | Hemorrhage | | | | | | | X MRI | | | | | | | | | | | | | | | | | | |
| | | Juxtacortical white matter | Punctate microhemorrhages | | | | | | | | | | | | | X⁋ 5/11 cases MRI | | | | | X MRI-SWI | | | | | | | |
| | | | Hyperintensity | | | | | | | X MRI | X MRI | X MRI | X MRI | | | | | | | | | | | | | | | |
| | | Subcortical white matter | Hypodensity/Hyperintensity | | | | | | | X MRI | X MRI | X MRI | X MRI | | | | | | | | | | | | | | | |
| | | | Swelling, restricted diffusion with peripheral enhancement | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | Hypodensity/hyperintensity | | | | | | | | | | | | | | X 26/242 ¥ cases CT/MRI | | | | | | | | | | | |
| | | Deep gray matter | Hypodensity | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | Not specified | Slowing consistent with encephalopathy and no epileptiform abnormalities | | | | | | | | | | | | | | | | | | | | | | X EEG | | | |
| | | | Slowing | | | | | | | X EEG | | | | | | | | | | | | | | | | | | |
| | | | Disorganized delta-theta slowing but no evidence of seizures or epileptiform discharges | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Parasagittal | Not specified | Intermittent onset of 4 Hz rhythms in absence of encephalopathy | | | | | | | | | | | | | | | X EEG | X EEG | | | | | | | | | |
| | Centrum semiovale | Subcortical and deep white matter | Hyperintensities, mild restricted diffusion | | | | | | | | | | | | | X 10/11 cases MRI | | | | | | | | | | | | |
| | Corona radiata | Subcortical and deep white matter | Hyperintensities, mild restricted diffusion | | | | | | | | | | | | | X 10/11 cases MRI | | | | | | | | | | | | |
| | Anterior circulation territories | Not specified | Acute/subacute infarct | | | | | | | | | | | | | | X 9/242 cases CT | | | | | | | | | | | |
| | Posterior circulation territories | Not specified | Acute/subacute infarct | | | | | | | | | | | | | | X 4/242 cases CT | | | | | | | | | | | |
| | Posterior parieto-occipital | Subcortical | Ffocal vasogenic/cytotoxic edema | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | Not specified | Restricted diffusion | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | Not specified | Hemorrhages | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Parietal | Subcortical and deep white matter | Abnormalities (hyperintensities⁋⁋⁋) | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | Cortical | Hyperintensities | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Occipital | Subcortical and deep white matter | Abnormalities (hyperintensities⁋⁋⁋) | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | Hyperintensities, mild restricted diffusion | | | | | | | | | | | | | X 10/11 cases MRI | | | | | | | | | | | | |
| | | Juxtacortical white matter | Hyperintensities, mild restricted diffusion | | | | | | | | | | | | | X 7/11 cases MRI | | | | | | | | | | | | |
| | | Cortical | Hyperintensities | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Frontal | Subcortical and deep white matter | Abnormalities (hyperintensities⁋⁋⁋) | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | juxtacortical white matter (precentral gyrus) | Hyperintensities, mild restricted diffusion | | | | | | | | | | | | | X 10/11 cases MRI | | | | | | | | | | | | |
| | | Cortical | Hyperintensities | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Temporal | Subcorticaland deep white matter | Abnormalities (hyperintensities⁋⁋⁋) | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | Subcortical and deep white matter | Hyperintensities, mild restricted diffusion | | | | | | | | | | | | | X 10/11 cases MRI | | | | | | | | | | | | |
| | | Medial | Hyperintensities without restricted diffusion | | | | | | | | | | | | | | | | | | | | | | X MRI | | | |
| | Frontal–temporal regions | Not specified | Seizures | | | | | | | | | | | | | | | | | | | | | | | | X EEG | |
| | Amygdala | Not specified | Hypodensity | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | Not specified | Hemorrhage | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Putamen (dorsolateral) | N/A | Microhemorrhage | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Thalamic nuclei (ventrolateral, medial) | N/A | Swelling, restricted diffusion with peripheral enhancement | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | Hyperintensities | | | | | | | | | | | | | | | | | | | | | X MRI | X MRI | | | |
| | | | Hypodensities | | | | | | | | | | | | | | | | | | | X CT | X CT | | | | | |
| | Internal capsule | Not specified | Hyperintensities | | | | | | | | | | | | | | | | | | | | | | | | | X MRI |
| | | | Microbleeds | | | | | | | | | | | | | | | | | | X MRI-SWI | | | | | | | |
| | Subinsular regions | N/A | Swelling, restricted diffusion with | | | | | | | | | | | | | | | | | | | | | | | | | |

(continued on next page)

**Table 2** (*continued*)

| | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | peripheral enhancement | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | Hyperintensities | | | | | | | | | | | | | | | | | | | | | X MRI | | | | |
| | Insular cortex | N/A | Abnormalities (hyperintensities‽‽‽) | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Parahippocampal gyri | N/A | Hyperintensity | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Basal ganglia | Not specified | Restricted diffusion with associated edema | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | Hyperintensity | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Cingulate gyri | Not specified | Swelling, restricted diffusion with peripheral enhancement | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | Not specified | Abnormalities (hyperintensities‽‽‽) | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Cerebellar hemispheres | Not specified | Restricted diffusion with associated edema | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | Iinfratentorial parenchyma | Diffuse leukoencephalopathy | | | | | | | | | | | | | X 4/11 cases MRI | | | | | | | | | | | | |
| | Middle cerebellar peduncles | Infratentorial parenchyma | Diffuse leukoencephalopathy | | | | | | | | | | | | | X 4/11 cases MRI | | | | | | | | | | | | |
| | | Not specified | Hyperintensities | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Cerebral peduncle | Not specified | Hyperintensities | | | | | | | | | | | | | | | | | | | | | | | | | X MRI |
| | Olfactory nerves/bulb | N/A | Hyperintensities | X MRI | | | | | | | | | | X MRI | X $$$ MRI | | | | | | | | | | | | | |
| | Supratentorial leptomeningeal | Not specified | Increased enhancement | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | White matter | Hypodensities | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Left** | Diffuse | White matter | Hyperintensity | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | Cortical and deep gray matter | Hyperintensity | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Occipital | Cortical and subcortical | Hypodensity | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | Subcortical white matter | Parenchymal hemorrhage | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Frontal | Subarachnoid | Aneurysmal hemorrhage | | | | X CT+CT-angio | | | | | | | | | | | | | | | | | | | | | |
| | | | Delayed cerebral ischemia | | | | | | X CTP | | | | | | | | | | | | | | | | | | | |
| **Right** | | Subdural | Hematoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Frontal | Intracerebral | Hematoma | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | Restricted diffusion with associated edema | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | Repetitive 1 Hz rhythmic bursts | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | persistent short -interval (0.7 -1.2 sec) lateralized periodic discharges | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | Hyperintensity | | | | | | | | X MRI | X MRI | X MRI | | | | | | | | | | | | | | | |
| | | Orbital prefrontal cortex adjacent to the olfactory bulb, spread towards mesial prefrontal cortex and caudate nucleus | Hyperintensity | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | Gyrus rectus | Hyperintensity | | | | | | | | | | | X MRI | | | | | | | | | | | | | | |
| | | Prefrontal cortex | Hyperintensity | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | Subarachnoid | Hemorrhage | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Temporal | Subarachnoid | Hemorrhage | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | Not specified | Severe swelling | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | Hypodensity correlated to hemorrhagic process | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | Mesial lobe | Hyperintensity | | | X FLAIR | | | | | | | | | | | | | | | | | | | | | | |
| | Sylvian fissure | Subarachnoid | Hemorrhage | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Posterior parieto-occipital | Not specified | Hemorrhage | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Centroparietal | Not specified | Focal seizures | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Inferior horn of lateral ventricle | N/A | Hyperintensity | | | X MR-DWI | | | | | | | | | | | | | | | | | | | | | | |
| | Olfactory bulb | N/A | Decreased volume | X MRI | | | | | | | | | | | | | | | | | | | | | | | | |
| | Hippocampus | Not specified | Hyperintensity, atrophy | | | X FLAIR | | | | | | | | | | | | | | | | | | | | | | |
| **Midline structures** | Brainstem | Not specified | Swelling | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | Hemorrhage | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | Hyperintensities | | | | | | | | | | | | | | | | | | | | | X MRI | | | | |
| | | Midbrain | Hyperintensity | | | | | | | | | | | | | | | | | | | | X MRI | | | | | |
| | | | Hypodendsity | | | | | | | | | | | | | | | | | | | X CT | | | | | | |
| | | Pons | Hemorrhage | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | Swelling | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | Hyperintensities without restricted diffusion | | | | | | | | | | | | | | | | | | | | | | | | | X MRI |
| | Corpus callosum | Not specified | Petechial hemorrhages | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | Puctiform microbleeds | | | | | | | | | | | | | | | | | X MRI-SWI | | | | | | | | |
| | | Splenium | Punctate microhemorrhages | | | | | | | | | | | | | X ‽ 4/7 MRI | | | | | | | | | | | | |
| | | | Swelling, restricted diffusion with peripheral enhancement | | | | | | | | | | | | | | | | | | | | | | | | | |
| | | | Hyperintensity | | | | | | | | | | | | | | | | | | | | | | | | | X MRI |

*Notes*. “x” indicates the presence of abnormality on brain scan, CT – Computed Tomography; MRI – Magnetic Resonance Imaging, EEG – Electroencephalography, N/A – non-applicable, * acute, surrounded by edema and caused midline shift
** became chronic
*** re-reabsorbing with persistent perilesional brain edema and midline shift
†with associated mass effect and cortical sulcal effacement
†† three focal seizures lasting approximately 30 s each
††† focal status epilepticus
‡consistent with mild microvascular disease but without acute intracranial lesion
‡‡ no evidence of brain edema
‡‡‡ no signs of cerebral vasospasm
**microhemorrhages varied between 5 and 6 to innumerable. Predominantly punctate, smaller than 3-mm in size. no concomitant larger intracranial hemorrhage. One patient with microhemorrhages has a prior brain MRI available (7 days before current hospital admission), which revealed that all hemorrhages were new. 4 in 7 patients had CT 3–7 days before MRI - no punctate microhemorrhages shown.
**No patients with altered mental status as the indication for brain imaging demonstrated acute or subacute infarct or acute intracranial hemorrhage
***the authors did not clearly state if hyperintensities comprised all cases of abnormalities.
¥ White matter microangiopathy was more than expected for age in 26 patients and in additional 108 patients as much as expected for age.
¥¥ posterior frontal and temporo-parieto-occipital symmetric bilateral hypodensity of the subcortical white matter.
¥¥¥ Default Mode Network was studied based on four nodes: the medial prefrontal cortex, the posterior cingulate cortex, and bilateral inferior parietal lobules
$ extensive and isolated WM microhemorrhages
$$ the signal alteration in the cortex completely disappeared
$$$ the olfactory bulbs were thinner and slightly less hyperintense
δ improved brain swelling

et al., 2020): 9/37]. *Infarct* was reported in 13/124 (10%) and involved bilateral anterior [X (Radmanesh et al., 2020): 9/242] and posterior [X (Radmanesh et al., 2020): 4/242] circulation territories. *Hemorrhages* were noted in 7/124 (6%) and included: bilateral posterior parieto-occipital area (J) (Franceschi et al., 2020) and amygdala [F] (Dixon et al., 2020); as well as left frontal [T] (Muhammad et al., 2020) and occipital areas [E] (Cariddi et al., 2020); right temporal area [E] (Cariddi et al., 2020); temporal plus frontal lobes and Sylvian fissure [B] (Al-olama et al., 2020); and right posterior parieto-occipital area [I] (Franceschi et al., 2020); brain stem and pons [F] (Dixon et al., 2020); and corpus callosum [I] (Franceschi et al., 2020); and intraventricular layering in the occipital horns of lateral ventricles [U] (Parsons et al., 2020). *Swelling/edema, restricted diffusion* was reported in 4/124 (3%) in bilateral WM with diffuse presentation [F] (Dixon et al., 2020), in posterior parieto-occipital regions [I (Franceschi et al., 2020), J (Franceschi et al., 2020), thalamic nuclei [F] (Dixon et al., 2020), subinsular regions [F] (Dixon et al., 2020), basal ganglia [J] (Franceschi et al., 2020), cingulate gyri [F] (Dixon et al., 2020), cerebellar hemispheres [J] (Franceschi et al., 2020), right frontal lobe [J] (Franceschi et al., 2020), and right temporal lobe [O] (Kadono et al., 2020), as well as brain stem, pons and splenium [F] (Dixon et al., 2020). *Seizures* were noted in 4/124 (3%) in bilateral fronto-temporal regions [N (Hepburn et al., 2020); α (Zanin et al., 2020)], right frontal [K] (le Guennec et al., 2020) and right centropatieral area [M] (Hepburn et al., 2020). EEG demonstrated *wave slowing* in 4/124 (3%) patient cases [G (Espinosa et al., 2020), H (Fischer et al., 2020), U (Parsons et al., 2020) Z (Virhammar et al., 2020). CT-angio revealed *increased enhancement* in 1/124 (1%) patient case bilateral supratentorial leptomeningeal [B] (Al-olama et al., 2020). *Ischemia* was characterized in another patient case (1/124 (1%) in left frontal lobe [T] (Muhammad et al., 2020). *Hematoma* was also identified in one case report (1/124 (1%) and located in right subdural and frontal area [B] (Al-olama et al., 2020). *Smaller olfactory bulb* was noted in one case report 1/124 (1%). One report on spontaneous brain activity revealed no abnormalities in the Default Mode Network [H] (Fischer et al., 2020).

### 3.3. Topography of brain abnormalities in COVID-19

Diffuse subcortical and deep WM abnormalities were the most prominent. A cumulative of 62/124 (50%) of cases presented brain abnormality in either anterior areas [D (Asfar et al., 2020); N (Hepburn et al., 2020); α (Zanin et al., 2020), X (Radmanesh et al., 2020): 9/242 cases, Z (Virhammar et al., 2020) or posterior regions [I (Franceschi et al., 2020), J (Franceschi et al., 2020), X (Radmanesh et al., 2020): 4/242 cases] or anterior-posterior regions [C (Anzalone et al., 2020): 4/21 cases; E (Cariddi et al., 2020); P (Kandemirli et al., 2020): 4/27 cases; W (Radmanesh et al., 2020): 10/11 cases; Q (Kremer et al., 2020): 20/37]. Of those, several patients additionally presented brain abnormalities which were lateralized [I (Franceschi et al., 2020); E (Cariddi et al., 2020); J (Franceschi et al., 2020), cerebellar (W (Radmanesh et al., 2020): 4/11 cases], located in cortex [C (Anzalone et al., 2020): 4/21 cases], deep brain structures [D (Asfar et al., 2020); P (Kandemirli et al., 2020): 3/27 cases], scattered in juxtacortical WM [Y] (De Stefano et al., 2020), or diffuse [α] (Zanin et al., 2020). Unspecified brain location for brain waves slowing on EEG recording was reported in four cases [G (Espinosa et al., 2020); H (Fischer et al., 2020); U (Parsons et al., 2020); Z (Virhammar et al., 2020).

Anterior brain regions were affected bilaterally in 45/124, i.e., 36% of patients with brain abnormalities. Those primarily involved juxta/subcortical and deep white matter (WM) hyperintensities in medial temporal lobe [Z] (Virhammar et al., 2020), frontal and temporal lobes [W (Radmanesh et al., 2020): 10/11 cases], frontal lobe [P (Kandemirli et al., 2020): 4/27 cases, including 1/27 also in temporal lobe], or temporal lobe (D (Asfar et al., 2020), Q (Kremer et al., 2020): 16/37; R (Li et al., 2020), or gyrus rectus and olfactory bulb (V) (Politi et al., 2020). Seizures were noted with the EEG in fronto-temporal regions for two patients [N (Hepburn et al., 2020); α (Zanin et al., 2020)]. One study reported infarcts in anterior circulation territories [X (Radmanesh et al., 2020): 9/242 cases].

Posterior brain regions presented bilateral abnormalities in 22/124 (18% of patients with brain abnormalities). One patient showed subcortical WM hypodensities reaching from occipito-parieto-temporal reaching toward posterior frontal tracts [E] (Cariddi et al., 2020). Subcortical and deep WM hyperintensities were diffuse [U] (Parsons et al., 2020), included occipital and parietal regions [P (Kandemirli et al., 2020): 4/27 and 3/27 cases respectively], or were accompanied by mild restricted diffusion in subcortical and deep WM in occipital lobe [W (Radmanesh et al., 2020): 10/11 cases, including 7 cases with additional abnormalities in juxtacortical WM]. Two other cases showed focal vasogenic/cytotoxic edema [I (Franceschi et al., 2020), J (Franceschi et al., 2020)] in posterior parieto-occipital regions, while one was further accompanied by restricted diffusion and hemorrhages [J] (Franceschi et al., 2020). Another study reported infarcts in posterior circulation territories [X (Radmanesh et al., 2020): 4/242 cases].

Exclusively right cerebral hemisphere abnormalities were noted in 8/124 (6%) affected cases and were not specific to any one particular location or type of abnormality. Hyperintensities were noted in temporal mesial lobe, inferior horn of lateral ventricle and hippocampus in one patient [S] (Moriguchi et al., 2020)). One case report showed restricted diffusion with associated edema in frontal lobe [J] (Franceschi et al., 2020). Another patient showed subdural and frontal intracerebral hematoma, accompanied by subarachnoid hemorrhage in frontal, temporal regions and Sylvian fissure [B] (Al-olama et al., 2020). Intraventrivular hemorrhage was noted in one case [U] (Parsons et al., 2020). Focal seizures in centroparietal regions were noted in another two case reports [M (Hepburn et al., 2020); K (le Guennec et al., 2020)]. One case report revealed hemorrhage in posterior parieto-occipital region [I] (Franceschi et al., 2020). Another case reported severe brain swelling in the right temporal lobe, which was previously injured by hemorrhagic infarction [O] (Kadono et al., 2020).

Exclusively left cerebral hemisphere abnormalities were reported in 3/124 (2%) affected cases. Those included diffuse hyperintensities in WM, cortical and deep gray matter [A] (Abdi et al., 2020), hypodensity in occipital cortex and WM [F] (Dixon et al., 2020), and aneurysmal hemorrhage with delayed cerebral ischemia in frontal lobe [T] (Muhammad et al., 2020).

Cerebellar abnormalities were evident in 7/124 (6%) affected cases, and involved white matter hypodensity [N] (Hepburn et al., 2020) or diffuse leukoencephalopathy [W (Radmanesh et al., 2020): 4/11 cases], restricted diffusion with associated edema [J] (Franceschi et al., 2020), and increased enhancement on CT-angio [B] (Al-olama et al., 2020).

Deep brain structures were affected in 9/124 (7%) affected cases, out of which 4 comprised insula and cingulate gyri abnormalities [P (Kandemirli et al., 2020): 3/27 cases], and swelling and restricted diffusion with peripheral enhancement [F] (Dixon et al., 2020). The same patient [F] (Dixon et al., 2020) also showed swelling and restricted diffusion with peripheral enhancement in thalamus and putamen, as well as hypodensity/hemorrhage in amygdala [F] (Dixon et al., 2020). Four cases showed internal capsul hyperintensities [β] (Zoghi et al., 2020) or microbleeds [Y] (De Stefano et al., 2020), hyperintensities in thalamic nuclei [D (Asfar et al., 2020); Z (Virhammar et al., 2020)] and subinsula [Z] (Virhammar et al., 2020), or cerebral peduncle [β] (Zoghi et al., 2020). Additionally, restricted diffusion with edema was noted in basal ganglia (no details available) in one patient [J] (Franceschi et al., 2020).

The midline structures of the brain were affected in 12/124 (10%) affected cases and mainly included abnormalities in the corpus callosum, i.e., hyperintensities [L (Hayashi et al., 2020); β (Zoghi et al., 2020)], hemorrhage [I] (Franceschi et al., 2020), microhemorrhages [W (Radmanesh et al., 2020)]: 4/7 cases; Y (De Stefano et al., 2020), and swelling and restricted diffusion [F] (Dixon et al., 2020).

Additionally, one of those patients [F] (Dixon et al., 2020) showed signs of swelling and hemorrhage in brain stem and hemorrhage in pons. Hyperintensities were noted in midbrain [A (Abdi et al., 2020); Z (Virhammar et al., 2020)] and pons [D (Asfar et al., 2020); β (Zoghi et al., 2020)].

Only 6/361 patients were scanned with CTP, CT-/MR-angio. In 4 of those 6 cases, the results were not showing arteriovenous malformation or aneurysms or acute vascular occlusion, or were unremarkable. Two patients showed frontal subarachnoid hemorrhage or ischemia, one of them only on the follow-up scan.

In the majority of reviewed cases 237/361 (66%), CT/MRI did not reveal any acute/subacute brain abnormalities that were attributed to COVID-19 as the most probable cause. Those included 17/21 patients [C] (Anzalone et al., 2020), 15/27 [P] (Kandemirli et al., 2020), and 205/242 [X] (Radmanesh et al., 2020). Additionally, one study did not report neuroimaging results for 16/27 patients as they did not show white matter T2 hyperintensities and/or microhemorrhages W (Radmanesh et al., 2020). However, such description does not allow to uniformly determine whether brain scans in those 16 patients were unremarkable.

Finally, three case reports showed brain abnormalities (in the form of cortical hyperintensities) on the initial scan, but a complete resolution of lesions at 1-month follow-up scan [C (Anzalone et al., 2020); K (le Guennec et al., 2020)]; V (Politi et al., 2020). Additionally, one case showed EEG signal abnormalities that were no longer present at around two weeks after Sars-CoV-2 detection [Y] (De Stefano et al., 2020).

## 4. Discussion

This systematic review provides a synthesis of early evidence on brain abnormalities suggestive of COVID-19 etiology in patients in acute/subacute phase. Collectively, published reports show that out of patients with available brain imaging, 66% patients do not present brain manifestations of presumed COVID-19 etiology. Various brain abnormalities were present in the remaining 34% reviewed cases. Together, this suggests that early neurologic symptoms, which were the reason for referral for brain imaging, may appear earlier than the brain structural changes can be detected with the available technology. Future studies should consider employing myelin imaging or WM tractography based on diffusion-weighted imaging data to provide additional description of more intricate brain WM changes in COVID-19. Alternatively, transient neurologic symptoms may also be related to acute/subacute brain alterations at the level of functional networks. This hypothesis can be examined for example with the use of resting state functional MRI sequences. This methodology may be especially useful considering the respiratory complications in COVID-19.

The primary neuroimaging feature involved WM hyperintensities on or MRI hypodensities on CT, which was observed in 76% of the affected cases. These changes were primarily diffuse in the cerebral WM, however, the provided examples of brain scans for cohort studies [W (Radmanesh et al., 2020), X (Radmanesh et al., 2020)] also reveal the increased density of WM changes in close proximity to the ventricles. As the brain images were not provided for all reported cases, we cannot verify whether the increased periventricular presentation is a common characteristics. At the same time, the involvement of cerebellar, midline- or deep brain structures was reported infrequently. Together, the exhibited topographical pattern of the WM abnormalities allows us to speculate about attributing these changes to leukoencephalopathy, leukoaraiosis (LA) or rarefield WM not restricted to periventricular area. This interpretation is in line with the notion made by the Authors of the original articles [F (Dixon et al., 2020), W (Radmanesh et al., 2020)]. LA is one of the most prominent characteristics of the aging brain, often asymptomatic and only revealed with neuroimaging. However, the analyzed data further suggest that the prevalence of LA is higher in this patient population than expected for age. Other possible interpretations may include encephalitis as suggested in several reports (Anzalone et al., 2020; Asfar et al., 2020; Espinosa et al., 2020; Hayashi et al., 2020; Kremer et al., 2020), acute necrotizing encephalitis (Virhammar et al., 2020), encephalomyelitis (Abdi et al., 2020; Zoghi et al., 2020), demyelination (Zanin et al., 2020; Parsons et al., 2020; Zoghi et al., 2020), or microangiopathy (Fischer et al., 2020). Therefore, we encourage future studies to report more detailed description of the WM changes in order to establish differential characteristics of COVID-19-related vs. age-related changes in WM. One way to address this as well as to enable future meta-analyses, is to report the scores on the Fazekas scale (Fazekas et al., 1987).

The potential neuropathological associations of LA may include hypoxia, hypoperfusion, as well as demyelination or axonal loss, with consequent disconnection syndromes. However, the potential pathogeneses of brain abnormalities in COVID-19 patients remain unclear and are beyond the scope of this systematic review. We restricted the analyses to the synthesis of available evidence regarding types and topography of registered brain abnormalities. Future longitudinal studies are needed to address the mechanisms of brain manifestations, neurologic sequelae in COVID-19, and the directional relationship between neuroinvasive actions of SARS-CoV-2 and respiratory failure.

Other types of brain abnormalities were less frequently observed and included aneurysm, hematoma, hemorrhage and seizure. These brain abnormalities were reported infrequently as compared to LA cases. Thus, it can be hypothesized, that if the presentation of these conditions is related to COVID-19, than perhaps it may be enhanced or accelerated with systemic inflammation rather than directly triggered by the infection. The neuropathological associations of these brain abnormalities should be examined in the future studies.

Importantly, in three patient cases with cortical hyperintensities, there was a resolution of lesions noted on a 30-day follow-up. Comparisons with other reports are limited as only two more research teams presented an extensive follow-up brain scan in one patient [F (Dixon et al., 2020); U (Parsons et al., 2020)]. Also, one of the patients with EEG showed resolution of signal abnormalities at around 2-week mark following Sars-CoV-2+ detection [Y] (De Stefano et al., 2020). The hypothesis on transient character of brain abnormalities should be assessed in future research.

This systematic review has limitations. It is based on the available evidence with the assumption that the original contributions report all evident brain abnormalities and their proposed interpretation of the relationship with COVID-19 is accurate. Neuroimaging findings were excluded from the current review and analysis in cases where the authors reported them to be unrelated to the COVID-19, coincidental, or where the authors provided a different explanation for the findings. For example, one study reported 134/242 patients to show WM hypodensities/hyperintensities, out of which in 108 changes were “as much as expected for age” (Radmanesh et al., 2020). Importantly, as the relationship between brain structure/function and COVID-19 infection is not clear yet, such interpretations may lead to underreporting brain issues in this patient population and the current results should be treated with caution. Furthermore, our literature search only included articles with title and/or abstract containing the word “brain” and at least one of the following “covid”/“sars-cov-2”/“coronavirus”. As this holds a potential of missing original contributions of interest, we checked the results of the following extended search strategies: ((covid [Title/Abstract]) OR (sars-cov-2[Title/Abstract]) OR (coronavirus [Title/Abstract])) AND (brain[Title/Abstract]) OR (CNS[Title/Abstract]), which yielded 106,581 results; and ((covid[Title/Abstract]) OR (sars-cov-2[Title/Abstract]) OR (coronavirus[Title/Abstract])) AND (brain[Title/Abstract]) OR (neurologic[Title/Abstract]), which yielded 83,533 results as of July 06, 2020. However, for the purpose of a timely contribution on early evidence of abnormalities due to COVID-19 only in the brain and not other parts of the CNS, we analyzed the data from the initial, more narrow and precise search. Our future research plans involve a more holistic literature search employing the above extended the search strategies. Another limitation is posed by the reasons for referral to CT/MRI/EEG imaging in the analyzed studies as well as bias related to the case reports, such as the selection of patient cases for presentation. Missing data on neurologic symptoms in original articles did not allow us to analyze the relationships with the revealed brain abnormalities patterns. Due to few published cohort studies, we incorporated case reports into a cumulative synthesis, but we were unable to employ meta-analytic approach. Future systematic reviews should include meta-analysis of larger cohort studies once they become available.

## 5. Conclusion

We found that brain images in acute/subacute patients with COVID-19 are predominantly characterized by diffuse cerebral WM hyperintensities/hypodensities. The available evidence allows to speculate about the higher prevalence of leukoencephalopathy, leukoaraiosis or rarefield WM in this patient population than expected for age. Large cohort studies reporting details of registered brain abnormalities are needed in order to establish (1) the incidence of brain abnormalities, (2) neurologic sequelae, and (3) pathophysiological associations of neuroinvasion in COVID-19.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2020.07.014.

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