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## Neuroradiological features in COVID-19 patients: First evidence in a complex scenario

In December 2019, a novel coronavirus, named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was discovered in Wuhan, China, as the infectious agent responsible for coronavirus disease 2019 (COVID-19). The first Italian case of COVID-19 was recorded on February 21, 2020, in the small town of Codogno. From here, the SARS-CoV-2 has quickly diffused in Northern Italy. In a short time, Lombardy has become the first European epicenter of the COVID-19 disease. Lombardy, the most populous region in Italy (10,060,574 inhabitants), has also rapidly achieved the primacy of the highest number of SARS-CoV-2 infected people and COVID-19 deaths. Today, on May 2, 2020, over 3 million SARS-CoV-2 infections have been recorded in the world, with the highest number of cases (1,103,781) and deaths (65,068) in the United States. In Italy, the trend of infections is slightly decreasing, with the number of infected and deaths reaching 207,428 and 28,236, respectively [1].

The rapid and uncontrolled person-to-person transmission of SARS-CoV-2 has progressively led to an oversaturation of the Lombard Regional Health System. Suddenly, most hospitals had to manage a large load of COVID-19 patients in need of health care at various assistance levels (ordinary hospitalization, subintensive care, and intensive regime). The Lombard Regional Government issued on March 8, 2020, the Decree No. XI/2906 [2], with the establishment of a new Hub and Spoke system. In this way, the time-dependent emergencies were centralized in the Hub hospitals, while the Spoke satellites were mainly dedicated to the management of COVID-19 patients [3]. It should be emphasized that several COVID-19 cases have also been concentrated in the Hub structures to guarantee a complete buffer of care needs. Indeed, our institution, Di Circolo and Fondazione Macchi Hospital in Varese, at least recovered 1000 patients for SARS-CoV-2 infection since the start of the COVID-19 outbreak in Italy.

We report the neuroradiological features in an observational series of 26 SARS-CoV-2 patients admitted to our Hospital with laboratory diagnosis (i.e. positive pharyngeal swab or bronchial lavage) and neurologic symptoms. The whole cohort underwent an accurate clinical and neurological evaluation and a neuroimaging study with at least one computed tomography (CT) scan. Patients' anamnestic, clinical, and neuroradiological features are described in Table 1. The median age of the patients was 70.6 years, with a range between 21 and 88. Eight patients had previous cerebral neurologic disorders, including stroke, epilepsy, and moderate cognitive impairment. Most of the patients had systemic comorbidities, in particular 5 patients presented with hypertension and 5 others with diabetes. From the neurological point of view, most patients were evaluated for the onset of coma or paresis. In half of our cohort, no acute brain events were recorded. In 5 patients, we found parenchymal hemorrhage (Fig. 1A–D), in detail 2 frontal, 1 hemispheric, 1 cerebellar, and 1 parietal. Of these cases, 4 patients were in coma, 1 patient only reported headache. In 4 cases, hemorrhage was massive and with poor clinical outcomes. In 4 patients, we recorded posterior circle ischemic events (occipital lobe and thalamus); among these, all patients had ictal syndrome. In 1 patient presented with coma, we documented right temporal lobe encephalitis (Fig. 1E and F), as was previously described in a similar case [4].

**Table 1**
Anamnestic, clinical and neuroradiological features of our series of COVID-19 patient.

| Variable | Number of patients $n = 26$ |
|---|---|
| Physiological anamnesis | |
| Mean age and range | 70.6 (21–88) |
| Male | 46.1% (12/26) |
| Comorbidities | |
| Neurological disorders | 30.7% (8/26) |
| Hypertension | 19.2% (5/26) |
| Diabetes | 19.2% (5/26) |
| Hypothyroidism | 11.5% (3/26) |
| Epilepsy | 7.7% (2/26) |
| None | 3.8% (1/26) |
| Other | 34.6% (9/26) |
| Neurological symptoms | |
| Coma | 23.1% (6/26) |
| Confusional state | 15.4% (4/26) |
| Dizziness | 11.5% (3/26) |
| Headache | 3.8% (1/26) |
| Paresis | 23.1% (6/26) |
| Other | 23.1% (6/26) |
| Neuroradiological findings at CT/MRI | |
| Ischemic | 15.4% (4/26) |
| Parenchymal hemorrhage | 19.2% (5/26) |
| Encephalitis | 3.8% (1/26) |
| Non acute events | 61.6% (16/26) |

Today, the scientific community is concerned about the systematic effect of SARS-CoV-2 infections. The neuroinvasive and neurotropism of the virus is suggested by different clinical and biological studies. To date, clinical evidence of neurological involvement by SARS-CoV-2 infection is described by different studies. Ling M. et al. [5] identified neurological involvement in 83 COVID-19 patients, in a cohort of 214 patients. In those patients, neurological symptoms were recorded, highlighting 5 patients with ischemic stroke and 1 case of cerebral hemorrhage. A French study showed the evidence of cerebral perfusion alteration; they evaluated 13 patients with magnetic resonance describing bilateral frontotemporal region hypoperfusion, aspecific leptomeningeal enhancement, and focal acute ischemic stroke in asymptomatic patients [6]. A French case report described the evidence of a middle cerebral artery occlusion with a large intraluminal floating thrombus that occurred on a non-stenosing plaque of the common carotid artery in a 66-year-old man [7]. The rarity of intraluminal floating thrombi in a non-ulcerated plaque of the cervical artery suggests the possible role of SARS-CoV-2 as a pro-thrombotic factor and as instability factor of atheromatous plaque instability. Another study from New York City described acute ischemic stroke in 5 patients younger than 50 years and the higher incidence of ischemic stroke in young patients compared to the past year [8]. In March 2020, a Japanese group [4] described the first case of encephalitis caused by SARS-CoV-2, suggesting the possible neuroinvasive role of the virus as previously describe during the 2002–2003 Severe Acute Respiratory Syndrome (SARS) pandemic.

As other genera of Coronavirus which have shown neurotropic and neuroinvasive abilities, it is believed that SARS-CoV-2 can have neuroinvasive potential [9]. The SARS-CoV-2 neurotropism can be mediated with host receptor angiotensin-converting enzyme 2 (ACE2) [10]. ACE receptors are expressed in different human

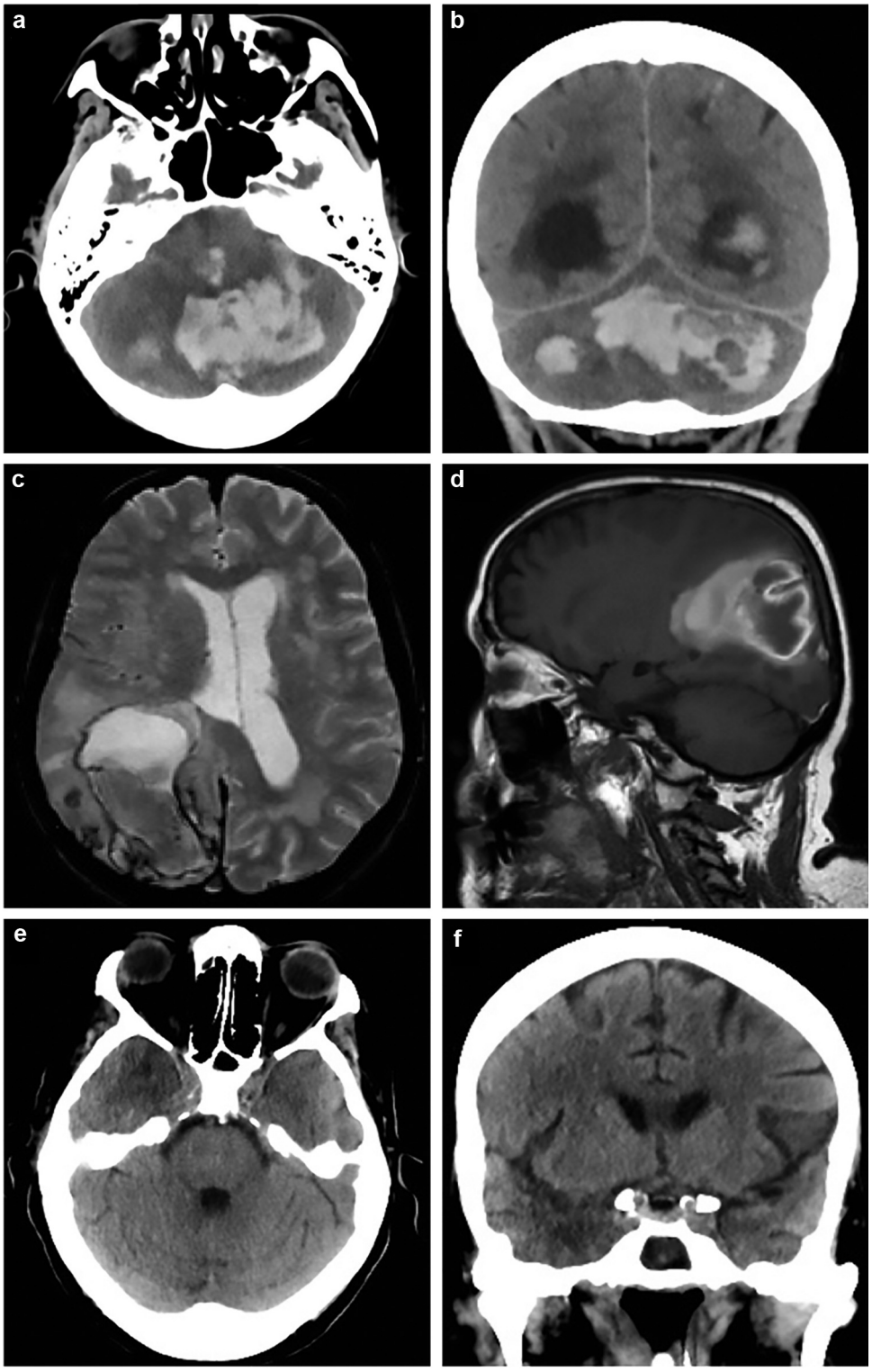


**Fig. 1.** It shows three SARS-CoV-2 patients with cerebral imaging studies. The first case was evaluated with non-contrast CT, A axial and B coronal show massive bilateral cerebellar parenchymal and intraventricular hemorrhage. The second case underwent magnetic resonance imaging brain evaluation and shows: C axial T2 gradient echo and D sagittal T1 spin-echo highlights wide right parieto-occipital hemorrhage. Last patient, evaluated with brain CT, reveals on E axial and F coronal plans right temporal lobe hypodensity; no acute ictal clinical onset, in addition with the isolated involvement of white substance, made us suggest that the lesion could be related to an inflammatory process.

cells, even in capillary endothelium cells. It is speculated that through endothelial cells, SARS-CoV-2 can access the brain and interact with ACE2 receptors expressed in neurons. Once the central nervous system is reached, SARS-CoV-2 can determine the activation of a self-reinforcing inflammatory processes through a "cytokine storm", causing irreversible neuronal damage [11]. Also, the endothelial ruptures in cerebral capillaries can contribute to the pathophysiology of SARS-CoV-2 brain damage [11].

About 70 days from the first case of COVID-19 registered in Italy and 50 days from the first hospitalization of COVID-19 patient in our hospital, some initial assessments of possible neurological and neuroradiological implications of SARS-CoV-2 can be postulated. From

our first observations, it can be assumed that SARS-CoV-2 has a possible promoting and synergistic role in cerebral ischemic, hemorrhagic and inflammatory events, in line with its biological and pathophysiological characteristics. These first evidence, although needing to be supported by more data and scientific studies with statistical solidity, offer a first starting point towards a broader definition of the systemic and not only pulmonary tropism of this virus.

## Disclosure of interest

The authors declare that they have no competing interest.

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