Radiology

Imaging of Neurologic Disease in Hospitalized Patients with COVID-19: An Italian Multicenter Retrospective Observational Study

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Conflicts of interest are listed at the end of this article.

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An outbreak of coronavirus disease 2019 (COVID-19) began in Wuhan, China, in December 2019 and has rapidly spread around the world to become a pandemic (1). Italy was the second epicenter of the spread of the disease, and at the time of writing has a total of 222 104 cases and 31 106 deaths (1). Several studies have described the spectrum of chest imaging features of COVID-19 (2). However, to date, only a few case reports have described COVID-19–associated neurologic imaging findings (3–8). The purpose of our study was to systematically characterize neurologic symptoms and neuroimaging features in hospitalized patients with COVID-19 from multiple institutions in Italy.

Materials and Methods

Study Design and Patient Population

We used a retrospective, multicenter study design from three major institutions in Italy (University of Brescia, Brescia; University of Eastern Piemonte, Novara; and University of Sassari, Sassari). Institutional review board approval and waivers for informed consent were obtained at all institutions. Our inclusion criteria included *(a)* hospitalized patients who were positive for COVID-19 by means of real-time reverse-transcriptase polymerase chain reaction testing (Sentinel Diagnostics, Milan, Italy) of respiratory secretions obtained by means of bronchoalveolar lavage, endotracheal aspirate, nasopharyngeal swab, or oropharyngeal swab from February 29 to April 4, 2020; *(b)* presence of acute neurologic symptoms during hospital stay; and *(c)* any neurologic imaging studies, including brain or spine imaging. We reviewed the electronic medical records to extract clinical, laboratory, and demographic data.

Image Acquisition

All images were obtained as per standard of care protocols. MRI scans of brain and spine were obtained with 1.5-T scanners with standardized protocols. Gadopentetate dimeglumine (0.1 mmol/kg gadobutrol [Gadovist; Bayer, Berlin, Germany]) was used for contrast material–enhanced studies.

Image Interpretation

The neurologic imaging characteristics that were evaluated are listed in Table 1. All scans were initially analyzed by the institution's own neuroradiologists. Subsequently, all images were reviewed by three neuroradiologists in consensus (R.G., L.S., and A.C., with 30, 14, and 32 years of neuroradiology experience, respectively).

Statistical Analysis

Continuous variables are presented as means ± standard deviations and were compared between patients with altered mental status by using the Student *t* test; categoric variables are presented as frequencies with percentages. All statistical analyses were performed by using software (Stata, version 15; StataCorp, College Station, Tex). $P < .05$ was indicative of a statistically significant difference.

Results

A total of 725 consecutive hospitalized patients with COVID-19 were reviewed. Of these 725 patients, 108 (15%) met the eligibility criteria (Fig 1). Of the 108 patients, 107 (99%) were examined with unenhanced brain CT, 17 (16%) with head and neck CT angiography, and 20 (18%) with brain MRI. Of the 20 patients who underwent brain MRI, 10 (50%) underwent MRI with and without intravenous contrast material, 10 (50%) underwent head and neck MR angiography, and three underwent additional MRI of the whole spine for evaluation of lower extremity weakness. Table 2 summarizes the demographic characteristics, medical history, and neurologic characteristics. The most common neurologic symptoms were altered mental status in 64 of the 108 patients (59%) and ischemic stroke in 34

Table 1: Neuroimaging Characteristics of Hospitalized Patients with New Onset of Neurologic Symptoms after COVID-19

Neuroimaging Characteristics	CT or MRI Finding
Acute ischemic infarcts	34/108 (31)
Large vascular territory	19/108 (18)
Small infarcts	11/108 (10)
Basal ganglia	7/108 (6)
Watershed zone	4/108 (4)
Cardioembolic	3/108 (3)
Hypoxic-ischemic encephalopathy	1/108 (1)
Intracranial hemorrhages	6/108 (6)
Large	2/108 (2)
Small	1/108 (1)
Subarachnoid	3/108 (3)
Enhancement (MRI with and without IV contrast material)	
Cranial nerves*	1/10 (10)
Cauda equina*	2/10 (20)
Leptomeningeal	0/10 (0)
Parenchymal	0/10 (0)
Acute encephalopathy†	1/20 (5)
PRES	1/20 (5)
Nonspecific encephalopathy	2/20 (10)
MS plaque exacerbation‡	2/20 (10)
T2/FLAIR hyperintensity	
Nonspecific but likely chronic	7/20 (35)
White matter disease	
Basal ganglia	2/20 (10)
Subcortical	3/20 (15)
Cerebral venous thrombosis (CT angiography)	2/17 (12)

Note.—Numbers are numbers of patients (numerator/denominator), with percentages in parentheses. FLAIR = fluid-attenuated inversion recovery, IV = intravenous, MS = multiple sclerosis, PRES = posterior reversible encephalopathy syndrome.

* One patient with Miller-Fisher syndrome, a regional variant of Guillain-Barré syndrome, had both cranial nerve and cauda equina enhancement. A 62-year-old man presented with bilateral facial nerve palsy, ophthalmoplegia, areflexia, and polyradiculopathy. Results of real-time reverse-transcriptase polymerase chain reaction assay of the cerebrospinal fluid were negative for severe acute respiratory syndrome coronavirus 2.

† A 60-year-old man without history of seizures presented with first time convulsion (Fig 2). Real-time reverse transcriptase polymerase chain reaction assay of the cerebrospinal fluid was negative for severe acute respiratory syndrome coronavirus 2.

‡ One patient, a 53-year-old woman, presented with seizures and altered mental status.

Table 2: Characteristics of Hospitalized Patients with COVID-19

Characteristic	Value
Sex	
M	69 (64)
F	39 (36)
Age	
Mean (y)*	69 ± 15
<50 y	11 (10)
≥50 y	97 (90)
Median (y)†	71 (60.5–79)
Past medical history	
Hypertension	55 (51)
Diabetes	30 (28)
Coronary artery disease	25 (23)
Cerebrovascular disease	15 (14)
Malignancy	13 (12)
Multiple sclerosis	1 (1)
HIV	1 (1)
Behçet disease	1 (1)
Hemoglobinopathy	1 (1)
Neurologic signs	
Altered mental status	64 (59)
Ischemic stroke	34 (31)
Headache	13 (12)
Myalgias	13 (12)
Seizure	10 (9)
Dizziness	4 (4)
Neuralgia	3 (3)
Ataxia	2 (2)
Hyposmia	2 (2)

Note.—Except where indicated, data are numbers of patients (n = 108), with percentages in parentheses. COVID-19 = coronavirus disease 2019, HIV = human immunodeficiency virus.

* Data are means ± standard deviations.

† Numbers in parentheses are the interquartile range.

(31%). Of the 108 patients, 31 (29%) had no known past medical history and 77 (71%) had at least one of the following chronic disorders: coronary artery disease (n = 25, 23%), cerebrovascular disease (n = 15, 14%), hypertension (n = 55, 51%), and diabetes (n = 30, 28%). Of the 31 patients without known past medical history (age range, 16–62 years) (29%), 10 had acute ischemic infarcts and two had intracranial hemorrhage. Seventy-one of the 108 patients (66%) had no acute findings on brain CT scans; seven of the 20 patients who underwent MRI (35%) had acute abnormalities on brain MRI scans. There was a statistically significant association between the prevalence of altered mental status and patient age (mean age, 72 years ± 11 vs 64 years ± 18; P = .007).

The main neurologic imaging hallmark was acute ischemic infarcts, which were present in 34 of the 108 patients (31%) (30 [28%] on CT scans and four [20%] on MRI scans). Of these infarcts, 19 (18%) were large (15 in the middle cerebral artery territory, two in the posterior cerebral artery territory, two in the anterior cerebral artery territory), 11 (10%) were small, three (3%) were cardioembolic, and one (1%) had an hypoxic-ischemic encephalopathy pattern. Six of the 108 patients (6%) had intracranial hemorrhages, with subarachnoid hemorrhage being the most common (n = 3, 3%). Additional neurologic imaging findings are shown in Table 1.

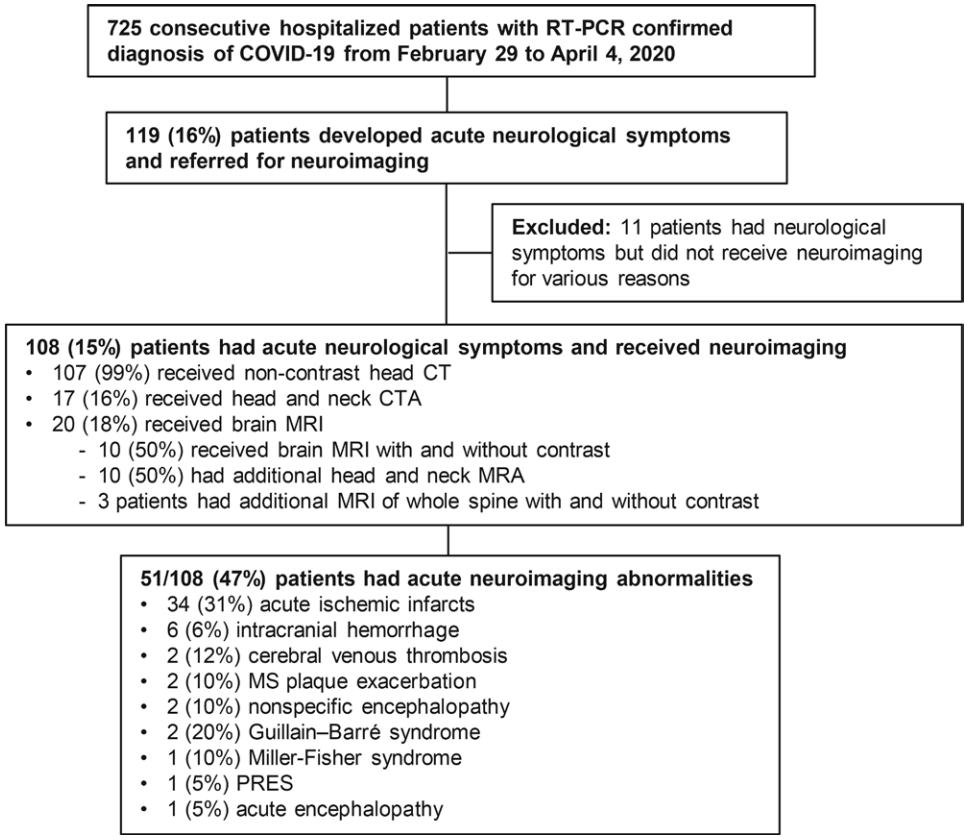

Figure 1: Study flowchart. COVID-19 = coronavirus disease 2019, CTA = CT angiography, MRA = MR angiography, MS = multiple sclerosis, PRES = posterior reversible encephalopathy syndrome, RT-PCR = real-time reverse-transcriptase polymerase chain reaction.

Discussion

Our study demonstrated that the neurologic imaging features of hospitalized patients with COVID-19 were variable, without a specific pattern but dominated by acute ischemic infarcts and intracranial hemorrhages. We also showed that the neurologic MRI spectrum may include posterior reversible encephalopathy syndrome, hypoxic-ischemic encephalopathy, exacerbation of demyelinating disease, and nonspecific cortical pattern of T2 fluid-attenuated inversion-recovery hyperintense signal with associated restriction diffusion that may be caused by systemic toxemia, viremia, and/or hypoxic effects (9). Currently, we have a poor mechanistic understanding of the neurologic symptoms in patients with COVID-19, whether these are arising from critical illness or from direct central nervous system invasion of severe acute respiratory syndrome coronavirus 2 (10). Accumulating evidence suggests that a subgroup of patients with severe COVID-19 might have a cytokine storm syndrome that could be a trigger for ischemic strokes, probably related to the prothrombotic effect of the inflammatory response (3,11).

Our results showed a lower prevalence of central nervous system symptoms than the Wuhan experience (8) (15% vs 25%, respectively); however, the prevalence of ischemic strokes was higher in our study (31% vs 11%). Furthermore, our findings also support the suggested potential for COVID-19–associated Guillain-Barré syndrome and variants (12). None of our patients showed abnormal parenchymal or leptomeningeal enhancement. In conclusion, neurologists and neuroradiologists should be familiar with the broad spectrum of neurologic imaging patterns associated with COVID-19.

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Author contributions: Guarantors of integrity of entire study, A.M., R.G.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, A.M., L.S., A.V., A.R., S.S., S.B., P.C., E.P., A. Padovani, R.G.; clinical studies, A.M., M.L., A.C., P.C., A. Paschè, E.P., A. Padovani; experimental studies, A.C., P.C., A. Paschè; statistical analysis, A.M., L.S., B.Z., P.C., R.G.; and manuscript editing, A.M., L.S., A.V., A.R., M.G., S.S., B.Z., S.B., P.C., E.P., A. Padovani, R.G.

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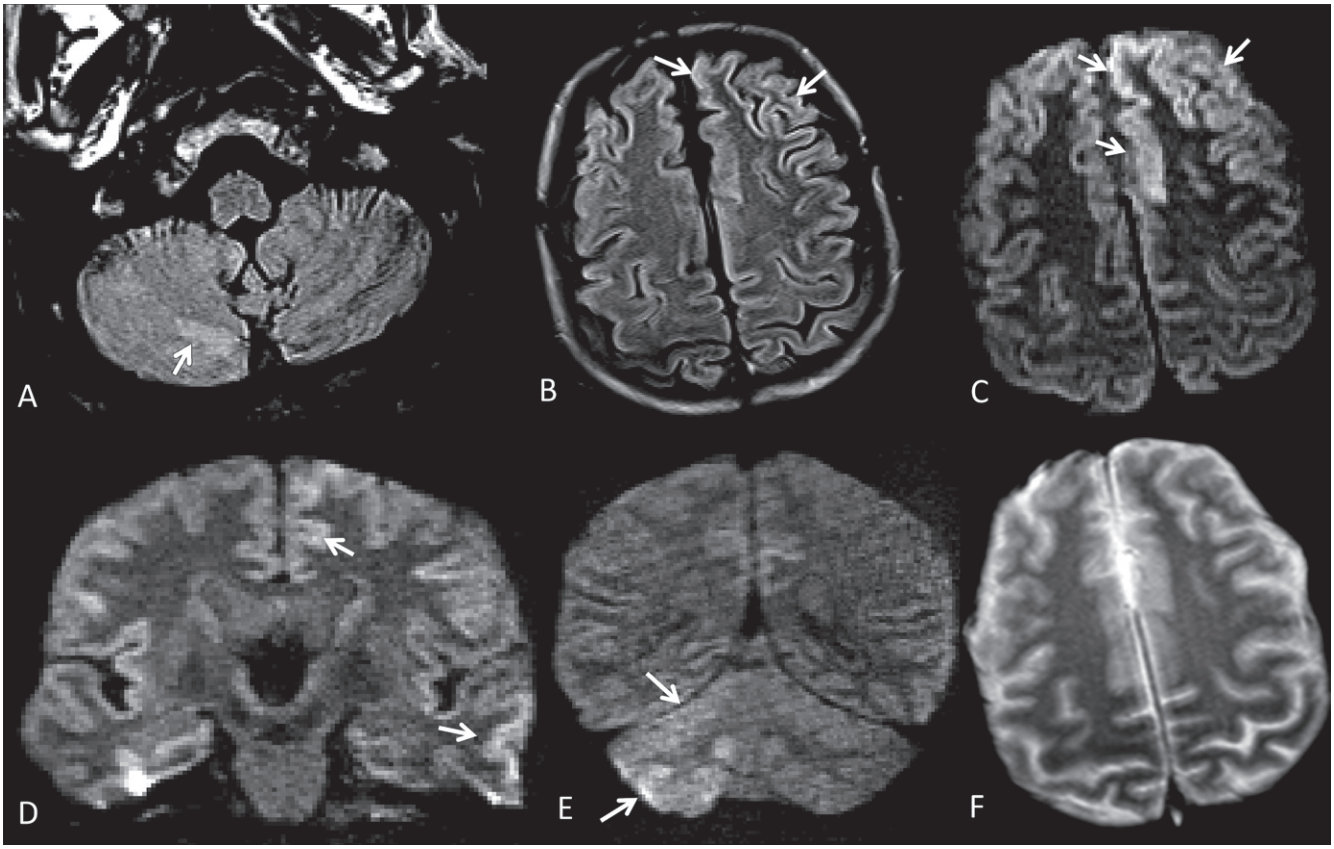

Figure 2: Images of acute encephalopathy in a 60-year-old-man without history of seizures who presented with convulsion. *A, B,* Fluid-attenuated inversion-recovery images show multifocal areas of hyperintensity in the right cerebellum (arrow in *A*), left anterior cingular cortex, and superior frontal gyrus (arrows in *B*). *C–E,* Diffusion-weighted images show restricted diffusion in the left anterior cingulate cortex and superior frontal gyrus (arrows in *C*), superior frontal and middle temporal gyrus (arrows in *D*), and right cerebellum (arrows in *E*), consistent with cerebellar diaschisis. *F,* MRI scan obtained with gradient-echo sequence shows no hemosiderin deposits.

relevant relationships. **P.C.** disclosed no relevant relationships. **A. Paschè** disclosed no relevant relationships. **E.P.** disclosed no relevant relationships. **A. Padovani** disclosed no relevant relationships. **R.G.** disclosed no relevant relationships.

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