Headache and impaired consciousness level associated with SARS-CoV-2 in CSF

A case report

José Cebrián, MD,* Alicia Gonzalez-Martinez, MD,* María J. García-Blanco, MD, Diego Celdrán-Vivancos, MD, Eduardo López Palacios, MD, Gemma Reig-Roselló, MD, Laura Casado-Fernández, MD, José Vivancos, MD, PhD, and Ana Beatriz Gago-Veiga, MD, PhD

Neurology® 2020;95:266-268. doi:10.1212/WNL.00000000000010213

Correspondence

Dr. Gonzalez-Martinez
alicia.gonzalez.martinez@live.com

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) main clinical features include fever, cough, and dyspnea; however, in a recent series, diarrhea (19.2%), headache (13.1%), and impaired consciousness (7.5%) were also frequent symptoms.¹ Rare associations like Miller-Fisher syndrome² or encephalitis³ have been recently reported. However, to date, there are few studies demonstrating the presence of SARS-CoV-2 in CSF and neurologic symptoms.³

We report a patient presenting with gastrointestinal manifestations followed by headache and impaired consciousness with positive CSF qualitative real-time reverse-transcriptase-PCR (qRT-PCR) coronavirus disease 2019 (COVID-19) test, in the absence of inflammatory CSF.

Case report

A 74-year-old woman with previous history of hypertension and low-frequency episodic migraine with typical aura presented to the emergency department with severe headache with photophobia, vomiting, and progressive confusion. She reported a 10-hour visual aura before the headache, with progressive blurred binocular vision causing reading trouble, similar to her typical shorter auras.

She had diarrhea, hyporexia, myalgias, nausea, and vomiting over the past 10 days. Along the clinical course, she did not develop fever, cough, anosmia, hypogeusia, or respiratory or urinary symptoms. There was no history of recent toxic exposure.

At arrival, she showed stable vital signs (oxygen saturation: 100%) with tachypnea, with no fever or signs of dehydration. Physical evaluation including cardiopulmonary and abdominal examination was normal. Neurologic examination revealed impaired level of consciousness, photophobic appearance, confusion, and incoherent speech (Glasgow Coma Scale: Eye: 3, Verbal: 3, Motor: 6, and Total: 12). Pupils were equal and reactive to light. Eye movements were normal. She demonstrated spontaneous antigravity symmetrical limb movement and bilateral flexor plantar reflex. Meningeal irritation signs were absent.

Routine laboratory studies indicated leukocytosis ($16 \times 10^9/\text{mm}^3$). Urine drug test was negative, and arterial blood gas analysis showed lactic acid of 4.6 mmol/L. ECG showed sinus rhythm without repolarization disturbances. Chest x-ray and noncontrast CT were normal. Nasopharyngeal and CSF qRT-PCR tests for SARS-CoV-2 were both positive. SARS-CoV-2 qRT-PCR in CSF was performed using the approved FDA kit ([fda.gov/media/137651/download](https://www.fda.gov/media/137651/download)), with ≥ 200 copies/mL detection limit, without cross-reactions with other respiratory pathogens. CSF analysis yielded noninflammatory findings (white blood cell [WBC]/ mm^3 : 1, red blood cell

*These authors contributed equally to this work.

From the Department of Neurology (J.C., A.G.-M., G.R.-R., L.C.-F., J.V., A.B.G.-V.), Hospital Universitario de La Princesa & Instituto de Investigación Sanitaria de La Princesa; Faculty of Medicine (A.G.-M., J.V., A.B.G.-V.), Universidad Autónoma de Madrid; Department of Internal Medicine (M.J.G.-B.), Hospital Universitario de La Princesa; and Department of Ophthalmology (D.C.-V., E.L.P.), Hospital Universitario de La Princesa, Madrid, Spain.

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Figure Brain MRI performed 48 hours after headache onset showing small ischemic stroke

MRI axial DWI (A) showing a 3-mm area of restricted diffusion that is also seen as hyperintense on MRI axial FLAIR (B) sequence in the right parieto-occipital cortex compatible with acute ischemic lesion. DWI = diffusion-weighted imaging; FLAIR = fluid-attenuated inversion recovery.

[RBC]/mm³: 1, protein: 30 mg/dL, glucose: 82 mg/dL, and opening pressure: 10 cmH₂O). Microarrays for herpesviruses (1-2-6-7-8), varicella-zoster, Epstein-Barr, cytomegalovirus, and enterovirus were performed. Acid-fast bacilli (AFB) and bacterial cultures and stains were negative.

In the absence of fever, inflammatory CSF, or meningeal signs, encephalitis was excluded. Treatment was largely supportive, including pain drugs, fluid replacement, oxygen therapy, ceftriaxone—until CSF negative results arrival—hydroxychloroquine, and lopinavir/ritonavir with progressive improvement of confusion within the first 24 hours. Headache with intense photophobia and phonophobia persisted for the next 5 days despite IV acetaminophen and dextropropofol treatment.

A brain MRI obtained 48 hours after admission showed a 3-mm area of restricted diffusion that was also seen as hyperintense on a FLAIR sequence on right parietal corticosubcortical location (figure), without signs of venous thrombosis. Acetylsalicylic acid was initiated.

During hospitalization, blood tests showed a mild transient increase of inflammatory markers (C-reactive protein: 2.95 mg/L, ferritin: 295 ng/mL, D-dimer: 0.70 mcg/mL) without other alterations or respiratory manifestations. After 7 days, the patient was completely recovered and therefore discharged home.

Discussion

This case report provides further evidence of SARS-CoV-2 potential neuroinvasive ability. Notably, this case reports positive qRT-PCR in CSF in the absence of neuroinflammatory response, with headache and impaired consciousness as the main neurologic symptoms.

Although headache is one of the most common neurologic symptoms in patients with SARS-CoV-2,¹ aura has not been

previously reported. It is unknown whether the presence of SARS-CoV-2 might act as a trigger of intense migraine-like headache with prolonged aura in susceptible patients, and more studies are needed to examine the effects of COVID-19 in patients with preexisting migraine.

Altered consciousness usually occurs in severe patients¹ and represents either the result of hypoxemia, dehydration, or inflammatory systemic response that drives to an impaired consciousness level or encephalitis with inflammatory parenchymal lesion and high CSF WBC count, none of them present in our patient. Viral tropism to the thalamus and brainstem has been reported.⁴ Consequently, we hypothesize that neuroinvasion itself might be related to impaired consciousness.

After vascular neurologist evaluation, the small acute ischemic lesion would not explain consciousness impairment. Its etiology might be related to SARS-CoV-2 infection⁵ or migrainous infarction, being CNS vasculitis unlikely. Nonetheless, further vascular and hypercoagulability studies need to be performed to rule out other common causes.

It has been suggested that neuroinvasion of SARS-CoV-2 might occur through peripheral nerve terminals via the olfactory nerves using angiotensin-converting enzyme 2 receptor expressed in the respiratory system, intestinal epithelium, and nervous system.⁴ Based on the present case report, with gastrointestinal manifestations at onset and absence of hyposmia, we suggest the presence of another potential spreading pathway through peripheral nerve terminals such as the vagus nerve.^{6,7} Further research in this regard needs to be performed.

Acknowledgment

The authors thank the patient and her family, the physicians and nurses involved in the care of this patient, and the microbiology and core laboratory staff.

Study funding

No targeted funding reported.

Disclosure

The authors report no disclosures relevant to the manuscript. Go to [Neurology.org/N](#) for full disclosures.

Publication history

Received by *Neurology* April 27, 2020. Accepted in final form June 18, 2020.

Appendix Authors

Name	Location	Contribution
José Cebrián, MD	Department of Neurology & Instituto de Investigación Sanitaria de La Princesa, Hospital Universitario de La Princesa, Madrid, Spain	Designed and conceptualized the study; analyzed the data; and drafted the manuscript for intellectual content
Alicia Gonzalez-Martinez, MD	Department of Neurology & Instituto de Investigación Sanitaria de La Princesa, Hospital Universitario de La Princesa, Madrid, Spain; Faculty of Medicine, Universidad Autónoma de Madrid, Madrid, Spain	Designed and conceptualized the study; analyzed the data; and drafted the manuscript for intellectual content
María J. García Blanco, MD	Department of Internal Medicine, Hospital Universitario de La Princesa, Madrid, Spain	Major role in the acquisition of data
Diego Celdrán-Vivancos, MD	Department of Ophthalmology, Hospital Universitario de La Princesa, Madrid, Spain	Major role in the acquisition of data
Eduardo López Palacios, MD	Department of Ophthalmology, Hospital Universitario de La Princesa, Madrid, Spain	Major role in the acquisition of data
Gemma Reig Roselló, MD	Department of Neurology & Instituto de Investigación Sanitaria de La Princesa, Hospital Universitario de La Princesa, Madrid, Spain	Interpreted the data and revised the manuscript for intellectual content

Appendix (continued)

Name	Location	Contribution
Laura Casado Fernández, MD	Department of Neurology & Instituto de Investigación Sanitaria de La Princesa, Hospital Universitario de La Princesa, Madrid, Spain	Interpreted the data and revised the manuscript for intellectual content
José Vivancos, MD, PhD	Department of Neurology & Instituto de Investigación Sanitaria de La Princesa, Hospital Universitario de La Princesa, Madrid, Spain; Faculty of Medicine, Universidad Autónoma de Madrid, Madrid, Spain	Interpreted the data and revised the manuscript for intellectual content
Ana Beatriz Gago-Veiga, MD, PhD	Department of Neurology & Instituto de Investigación Sanitaria de La Princesa, Hospital Universitario de La Princesa, Madrid, Spain; Faculty of Medicine, Universidad Autónoma de Madrid, Madrid, Spain	Interpreted the data and revised the manuscript for intellectual content

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Neurology 2020;95:266-268 Published Online before print July 8, 2020
DOI 10.1212/WNL.00000000000010213

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