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COVID-19

Diagnosing herpes simplex-1 encephalitis at the time of COVID-19 pandemic

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Abstract
Case report We describe the case of a 73-year-old woman who was diagnosed with herpes simplex virus-1 encephalitis during the COVID-19 pandemic. The diagnosis was somehow delayed because relatives were initially cautious in bringing the patient to the hospital and, here, the work-up focus was on coronavirusrelated aspects as the patient was initially reputed to be infected with COVID-19.
Conclusions During the current viral outbreak, physicians should not neglect the possibility of other diseases that represent neurological emergencies and require immediate recognition and treatment.

Keywords COVID-19 pandemic · Herpes simplex-1 · Valproic acid

Introduction

The current COVID-19 pandemic is nowadays heavily affecting each person's life and also the everyday work of many doctors. The outbreak has had a dramatic impact on neurology practice with effects at various levels, from the treatment of acute neurological patients, such as those with stroke, to the care of patients with chronic neurological diseases [1], but also in terms of training of medical students and residents, and even considering the way the usual neurological patients are approached.

Only a few days before the COVID-19 outbreak, a certain clinical presentation would have been interpreted in a quite standardized way on the basis of history, symptoms, and signs, and it would have led to ask for a series of radiological and laboratory investigations. Based on clinical elements and results of investigations, a diagnosis would have been generated and appropriate therapy introduced. Today, in the COVID-19 era, a patient can be at risk of receiving a misdiagnosis, especially in the emergency setting, because symptoms like fever, tachypnea, and consciousness alteration may be interpreted as solely related to a COVID-19 infection with the consequent primary target of excluding it, for example for decreasing the risk of contagion. This approach, induced by the fear and high-level stress induced by the pandemic on the health care personnel, can generate some delay in the correct diagnosis and therapy initiation, or even a misdiagnosis with all the possible consequences.

Case report

A 73-year-old woman arrived at the emergency room (ER) because in the morning she was found unresponsive and febrile in the bed. The patient has had a fever for the 3 previous days and, in the afternoon before hospitalization, she had been seen clumsy in movement and slowed in reasoning and speech. Her sister had attributed this condition to the febrile state and a possible, yet non-testified, epileptic event, because the patient had a history of epilepsy since the age of 62; consequently, she decided not to carry the patient to ER or to call her family practitioner. The patient had been on valproic acid (VPA) 300 mg b.i.d. for the last 5 years with incomplete control of crises (a couple of episodes of generalized seizure/year). Laboratory exams, including liver function markers and VPA levels, had always been within the range of normality since then.

On ER admission, the first diagnostic hypothesis was a possible COVID-19 infection, also supported by a reduced oxygen saturation (90%) that required oxygen treatment. A

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nasopharyngeal swab was taken. A brain CT scan showed diffuse hypodensity of the left cerebral hemisphere (Fig. 1a) that was reported as a possible ischemic lesion. As a consequence, the patient underwent an angio-CT scan of the neck vessels and intracranial arteries which did not show any significant alteration.

Only at this time, a neurological evaluation was requested to evaluate what was advanced to be a "cerebral ischemic stroke in a possibly COVID-19 positive patient." On the ER neurological examination, the Glasgow Coma Scale was 7 (E2, V1, M4): the patient had a response with facial grimaces to painful neck stimulus on both sides of the body. A normal flexion of lower limbs was obtained after a painful fingertip stimulus, prevalent on the left. The patient maintained her eyes opened after a painful stimulus for 20–25 s without exploring the surrounding environment. No audible verbal response was present. No difference was shown in pupil diameter and response to light. Corneal reflex was symmetrically present.

The progressive worsening of vigilance in the last 36 h before hospitalization, the absence of a manifest sudden onset, the presence of fever for a few days, the history of epilepsy, and the antiepileptic therapy currently below the therapeutic range (VPA plasmatic levels 20.8 mg/L; therapeutic range 50–100 mg/L) did not sustain the diagnosis of an acute cerebral ischemic event, while they seemed to support the hypothesis of epileptic status or, secondly, of an encephalitic process.

The electroencephalogram (EEG) showed diffuse slow activity and continuous epileptic activity on the left centrotemporal regions (Fig. 2a). A rapid, i.e., infusion of 8 mg of lorazepam induced a rapid change of EEG with the disappearance of the continuous epileptic activity, and the appearance of bilateral synchronous periodic discharges, with the highest amplitude on the left hemisphere, at about 0.2–0.3 cps, suggestive for possible limbic encephalitis, most likely herpetic (Fig. 2b). A lumbar puncture was then performed in the ER. The cerebrospinal fluid (CSF) was slightly hematic. The CSF analysis showed a high protein concentration (3380 mg/L) and an increased amount of white blood cells (108 cells/mL, of which 42%

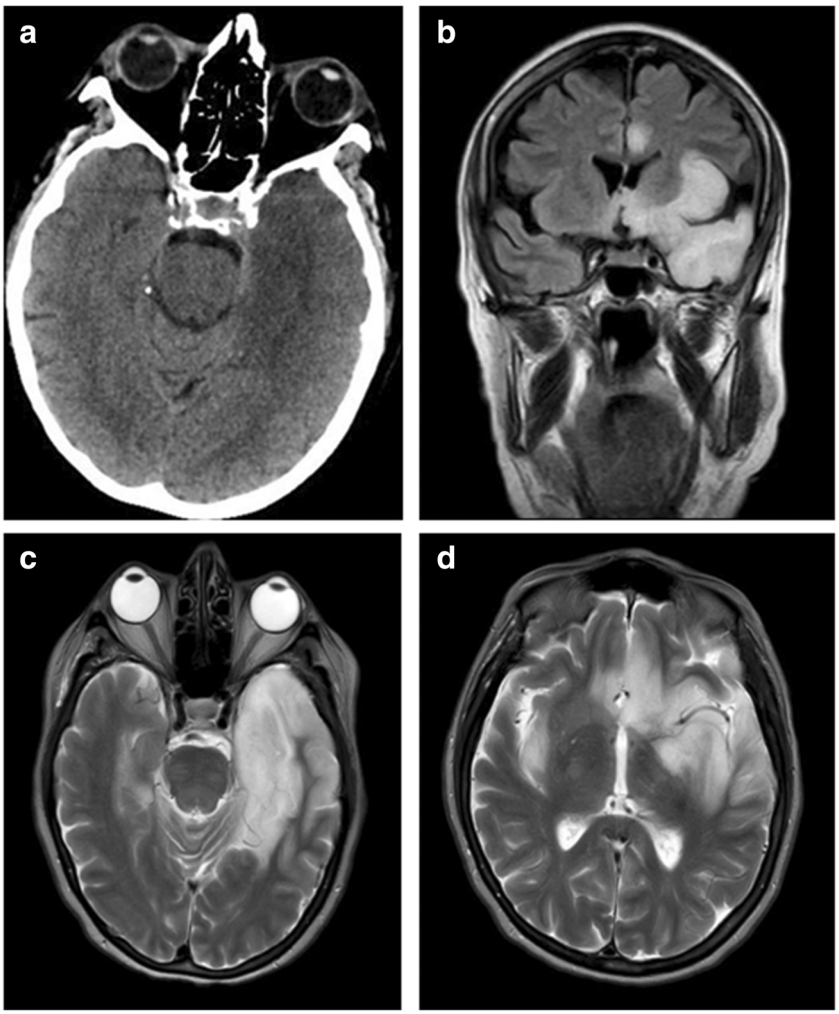

Fig 1 **a** Computed tomography scan in the emergency room showing diffuse hypodensity of the left temporal lobe. **b**–**d** Brain magnetic resonance imaging 5 days after hospitalization. **b** Coronal FLAIR (fluid-attenuated inversion recovery). **c** and **d** Axial T2 weighted. The MRI shows fronto-basal, temporo-occipital, and insular lesions in the left hemisphere and temporo-insular lesions of the right hemisphere

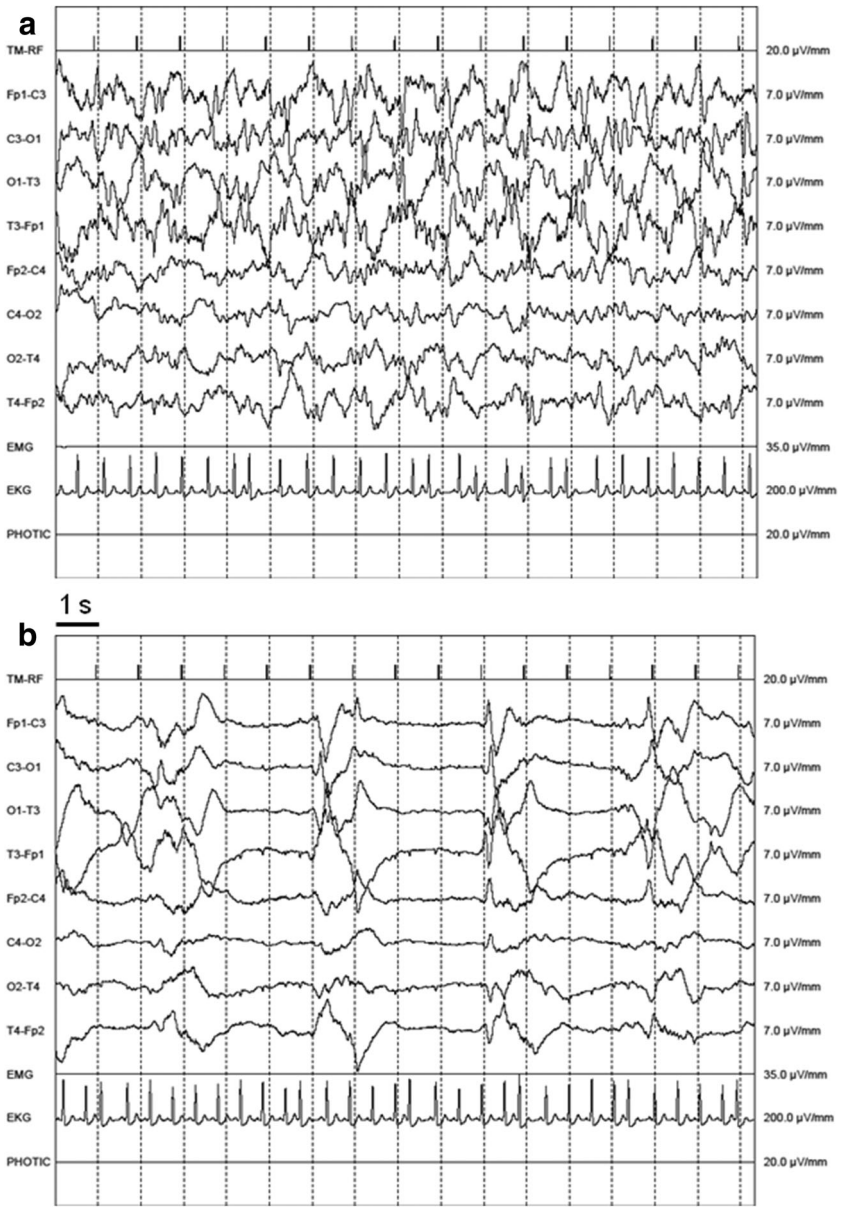

Fig. 2 EEG recordings in the emergency room. **a** Continuous epileptic activity on the left centrotemporal regions. **b** After IV lorazepam 8 mg, bilateral synchronous periodic discharges, with highest amplitude on the left hemisphere, at about 0.2–0.3 cps

mononuclear cells and 58% polymorphonuclear cells. Herpes simplex virus-1 (HSV-1) DNA was found in CSF in large amount (142,387 copies/mL; normal < 250). The COVID-19 RT-PCR test was negative in both the CSF and the nasopharyngeal swab.

The diagnosis was that of an epileptic status caused by HSV-1 encephalitis. Therapy with intravenous acyclovir was started, and the VPA daily dose was incremented to 1300 mg/day. The patient became afebrile and partial neurological recovery was obtained after 3 days.

A few days after hospitalization, the patient underwent an MRI study which showed the extension of the cerebral damage and confirmed a distribution typical for herpetic encephalitis (Fig. 1 b, c, and d).

Discussion

This case report highlights a few issues that need to be considered in this time of COVID-19 outbreak, particularly the fact that other emergencies are not disappeared and should be considered in the differential diagnosis, today as in the past. The diagnosis of HSV-1 encephalitis was somehow delayed in this patient for a number of reasons. The first one was a possible delay in the delivery of this patient to the ER, possibly because relatives were scared of bringing the patient to an environment reputed at high risk of COVID-19 contagion. In fact, while the general Italian population has been invited to stay home in the case of fever and to call the general practitioner to reduce the patient burden of ER, many people do

not know about the presence of differentiated COVID+ and COVID-free pathways in the ER. Second and perhaps more relevant, the fact that in the ER, each patient is today first hypothesized to have a COVID-19-related condition, a conviction that forces many colleagues to first working to exclude it, before of hypothesizing other diseases, on the basis of symptoms and history. Even the presence of a possible ischemic lesions, and therefore the diagnosis of stroke, was related in the ER to an underlying COVID-19 infection, perhaps in relation to the emerging news about the supposed presence of a thrombophilia induced by the COVID-19 [2, 3].

All the above issues might have led to a delay in starting the therapy and therefore to an increased risk of incomplete recovery from the HSV-1 infection. Thus, the COVID-19 pandemic poses everybody at a higher risk of making a certain amount of indirect victims related to COVID-induced misdiagnosis. In this regard, it should be noted that despite the involvement of the central nervous system in COVID-19 infection has been frequently mentioned, only 2 cases of encephalitis caused by this infection have been reported [4, 5]. In one of these reports, however, the virus was not detected in the CSF and an immune-mediated mechanism of injury was postulated [4]. Therefore, in case of signs and symptoms of encephalitis in COVID-19 patients, also other causes of damage to the nervous systems should be carefully considered.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

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