Encefalopatia com *Delirium* e Convulsões em Doente com COVID-19 Grave

Encephalopathy with Delirium and Generalized Tonic-Clonic Seizure in a Patient with Severe COVID-19

Ana Rita Ramalho[1], Adriana Henriques[1], Helena Rodrigues[1], Ana Carolina Pires[2], Inês Gomes[3], Maja Petrova[1]

Resumo:

As manifestações neurológicas da COVID-19, apesar de menos frequentes que as manifestações respiratórias, têm adquirido cada vez mais importância, apresentando um largo espectro clínico.

Os autores apresentam o caso de um homem de 70 anos com *severe acute respiratory distress syndrome* por SARS-CoV-2. Durante o internamento apresentou irritabilidade, confusão, flutuação do estado de consciência e coma. As serologias e autoimunidade foram negativas. O eletroencefalograma indicou encefalopatia e a ressonância magnética cerebral excluiu lesões inflamatórias ou vasculares. A tomografia computorizada do tórax foi realizada por insuficiência respiratória persistente, identificando pneumonia organizativa, tendo-se iniciado prednisolona com subsequente melhoria respiratória e neurológica.

Os autores pretendem alertar para a encefalopatia associada à COVID-19 grave e para o facto de, apesar de não existir tratamento dirigido, os corticosteroides em alta dose terem demonstrado ser eficazes em casos selecionados, sendo necessários mais estudos para esclarecer o seu efeito e as sequelas neurológicas da COVID-19 grave.

Palavras-chave: COVID-19; Delirium; Encefalopatia; Pneumonia Organizativa; SARS-CoV-2.

Abstract:

Neurological manifestations of COVID-19, despite being far less frequent than respiratory symptoms, are rising in importance, presenting a broad clinical spectrum.

The authors report the case of a 70-year-old man with severe acute respiratory distress syndrome due to SARS-CoV-2 infection. During hospitalisation he presented with irritability, confusion, fluctuating levels of consciousness and coma. Serology and autoimmunity for neurologic diseases were negative. Electroencephalogram indicated encephalopathy and brain magnetic resonance excluded lesions of inflammatory or vascular nature. A thorax computed tomography scan was performed due to persistent respiratory failure and showed organizing pneumonia. Prednisolone was introduced with neurological and respiratory improvement.

The authors aim to raise awareness for severe COVID-19-related encephalopathy and for the fact that, despite having no specific treatment, there is a potential role for high-dose steroids in selected patients. Further studies are needed to understand both the role of steroids and the long-term neurological sequelae of severe COVID-19.

Keywords: COVID-19; Delirium; Encephalopathy; Organizing Pneumonia; SARS-CoV-2.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is predominantly associated with respiratory disease. Nevertheless, despite neurological manifestations being far less frequent, they are rising in importance as the number of patients with SARS-CoV-2 infection continues to increase.[1] These manifestations can occur in the central nervous system (CNS) – as encephalopathy, encephalomyelitis and myelitis –, in the peripheral nervous system (PNS) – as Guillain-Barré syndrome –, or as a cerebrovascular disease – such as stroke. Therefore, early recognition of these conditions, especially in the intensive and intermediate care units, is of a key importance in order to decrease the length of stay and their associated morbimortality, due to their potential to cause lifelong impairment.[1,2]

Case Report

The authors report a case of a 70-year-old man, with past medical history of heavy smoking, hypertension, rectal adenocarcinoma and obstructive sleep apnoea syndrome, who presented to the emergency department 7 days after the diagnosis of SARS-CoV-2 infection, due to resting dyspnoea and persistent fever.

At admission, he was hemodynamically stable and apyretic. He had normal white cell count (4.5x10^9/L;

[1]Serviço de Medicina Interna, Unidade Local de Saúde de Coimbra, Coimbra, Portugal
[2]Centro de Resposta Integrada de Psiquiatria, Unidade Local de Saúde de Coimbra, Coimbra, Portugal
[3]Serviço de Neurologia, Unidade Local de Saúde de Coimbra, Coimbra, Portugal

https://doi.org/10.60591/crspmi.105

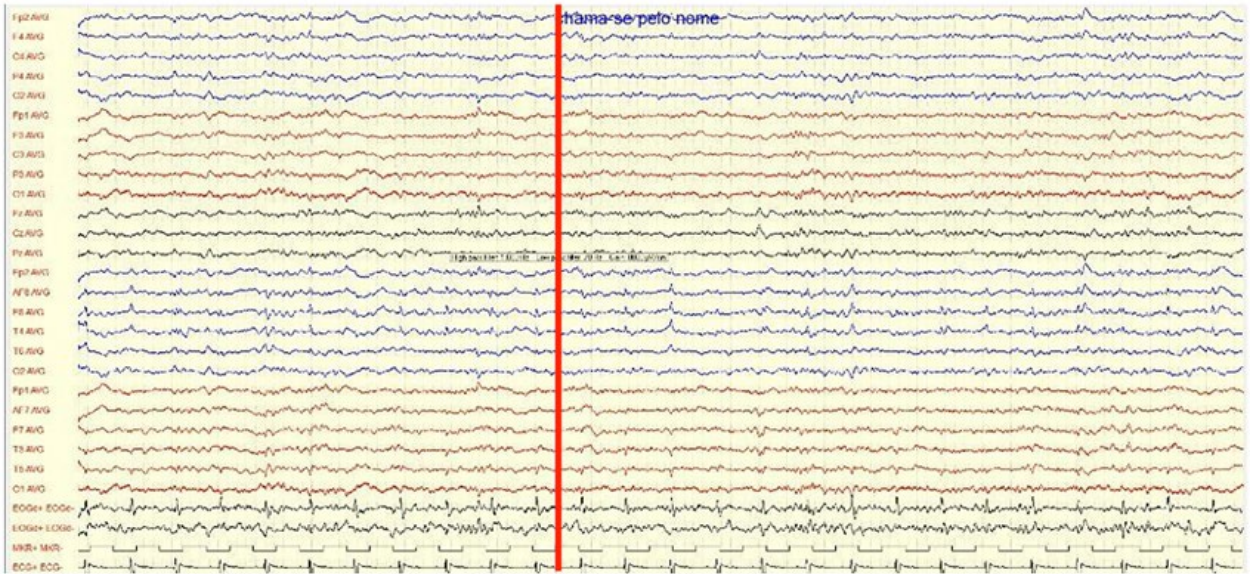

Figure 1: Electroencephalogram showing identification and disorganisation of the base rhythm, with no reactivity to a verbal stimulus (red vertical line).

3.60-10.5x10^9/L) with lymphopenia (0.53x10^9/L; 1.10-4.40x10^9/L), elevation of lactic dehydrogenase (465 U/L; <248U/L), of creatinine kinase (486U/L; <171U/L) and of protein C reactive (5.75 mg/dL; <0.50 mg/dL). His X-ray had bilateral opacities and his arterial blood gas analysis showed respiratory alkalosis, with a P/F ratio of 68, indicating a severe acute respiratory distress syndrome. He was intubated and admitted to the intensive care unit (ICU), where he remained for 32 days.

He was under vasopressor support with norepinephrine for 5 days, sedated with propofol for 21 days, and under dexamethasone for 10 days due to acute respiratory distress syndrome (ARDS), being extubated on the 24th day of hospitalisation, and transferred to the intermediate care unit on the 32nd day.

At first, he presented hypoactive delirium, which was interpreted as being due to prolonged sedation, and had a Glasgow Coma Scale of 11 - E3M6V2. Posteriorly, he presented with hyperactive delirium and had episodes of generalized tonic-clonic seizure, being transferred to the internal medicine ward on the 44th day, where he maintained hyperactive delirium, with no signs or symptoms suggestive of ongoing infection. Despite therapy optimization, the patients' neuropsychiatric state continued to decline, with irritability, confusion, fluctuating levels of consciousness and coma, with posterior cognitive impact.

Blood analysis for reversible causes of dementia and antibodies for autoimmune neurologic diseases were negative. An electroencephalogram (EEG) showed marked slowing and disorganisation of the base rhythm, indicating encephalopathy (grade 3 out of 5), without ictal or interictal epileptic activity (Figs.1 and 2). A brain magnetic resonance image (MRI) did not show any recent lesions of inflammatory or vascular nature (Fig. 3). Therefore, the diagnosis of encephalopathy was made.

Due to persistent need for high fraction of inspired oxygen, a thorax computed tomography (CT) scan was performed and showed signs suggestive of organizing pneumonia (Fig. 4). Prednisolone 40 mg was started, resulting in immediate clinical improvement in both neurological and respiratory symptoms. He was discharged on the 76th day of hospitalisation and was able to collaborate in the provision of basic daily care. One year after discharge, he recovered his previously lost autonomy, without the need for further respiratory rehabilitation or medication. He did not have other episodes of delirium and is able to perform complex tasks such as managing his finances.

Discussion

Encephalitis refers to the acute and diffuse inflammation of the brain parenchyma, presenting with irritability, confusion and fluctuating levels of consciousness, with seizures being less common. It is accompanied by pleocytosis on the cerebrospinal fluid, imaging changes or focal abnormalities on EEG.[1,3] Encephalopathy, on the other hand, can present with changes in behaviour, cognition or consciousness (including delirium and coma), and cortical and subcortical T2/FLAIR signal changes in brain MRI are common neuroimaging abnormalities.[1-3]

The diversity of neurological manifestations reflects the multiple pathogenic pathways of SARS-CoV-2.[6] The mechanism through which SARS-CoV-2 triggers neurological symptoms is still not completely understood, but it is known that it invades human cells by binding to the angiotensin-converting enzyme-2 receptor.[1,3,4] Effects of innate and adaptive immune responses to infection with subsequent cytokine and chemokine

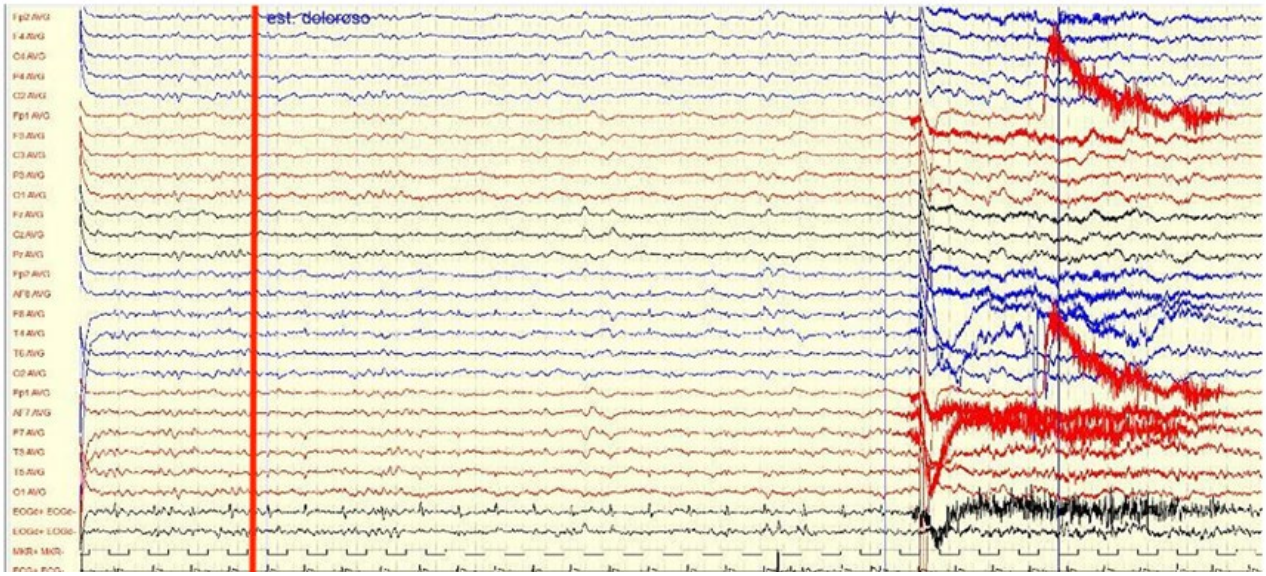

Figure 2: Electroencephalogram showing identification and disorganisation of the base rhythm, with reactivity to a painful stimulus (red vertical line).

storm, damaging the blood-brain barrier and causing a local intensive inflammatory response, or by neurological complications of the systemic effects of COVID-19 are other possible and more probable mechanisms for coronavirus neurological disease, which are supported with the clinical improvement after treatment with high-dose steroid. The direct effect of the virus on the nervous system is a less probable possibility.[1-3,5,6]

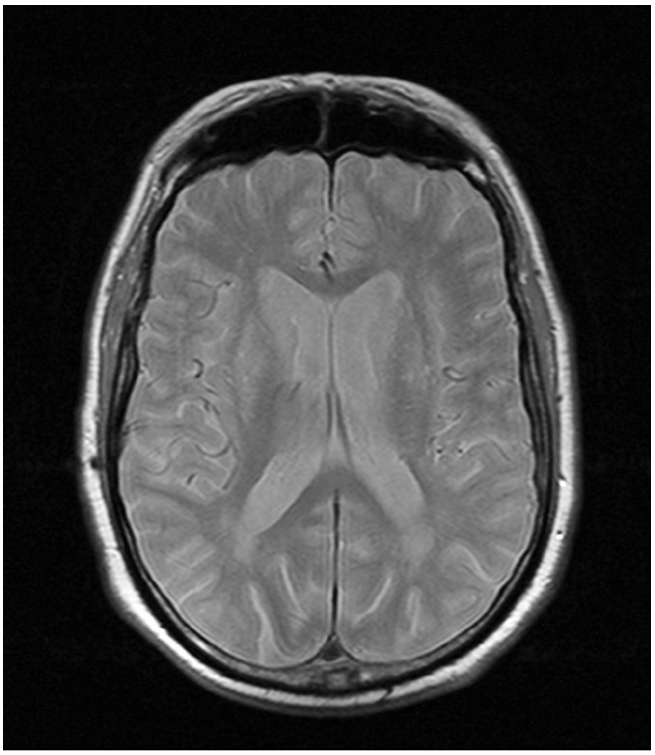

Figure 3: Brain magnetic resonance showing changes of the cerebral white matter signal with changes of several small foci of hyperintensity in FLAIR, without diffusion restriction.

Regarding the contribution of intrinsic and extrinsic factors to the development and severity of neurological symptoms, it is hypothesised that intubation and the use of sedative-hypnotic and anticholinergic agents to which our patient was exposed contribute to the development of encephalopathy.[2,3] One study showed a higher predominance of the male gender and the beginning of neurological symptoms about 21 days after the onset of COVID-19. It showed no association between the severity of pneumonia and encephalopathy, but the group with more severe neurological symptoms had a longer duration of intubation.[2] Another work observed that reduced consciousness occurred in up to 69% of patients with severe COVID-19 requiring intensive care management, being their occurrence associated with the severity of the infection, older age, higher creatinine kinase levels, lower lymphocyte counts and higher

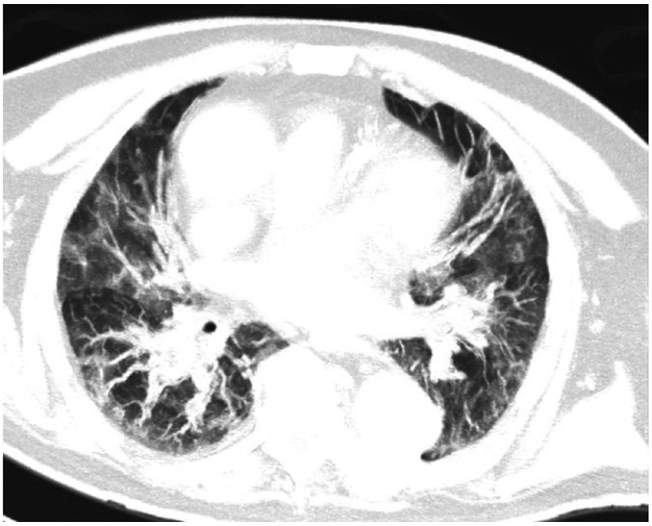

Figure 4: Thorax CT, showing diffuse ground glass densification pattern.

blood urea nitrogen.[6] A complete or partial recovery was observed in more than 50% of patients, either spontaneously or after high-dose steroids or intravenous immunoglobulins, which was what happened with our patient.[6]

One similar work described a case of a 60-year-old man that presented with altered consciousness, irritability, confusion, and akinetic syndrome with mutism. He underwent a brain magnetic resonance that showed neither lesions, nor contrast enhancement, and his EEG presented a generalised slowing with decreased reactivity to verbal stimulus. The diagnosis of COVID-19 encephalitis was assumed, high-dose steroids were started, and there was a complete resolution of symptoms by the 11th day of hospitalisation.[7] Unlike this case, in which the authors identified SARS-CoV-2 as the cause of the encephalitis, in the case we are describing, the neurological condition cannot be attributed solely to COVID-19, as there are other potential contributors, such as sedative-hypnotic agents and admission in the ICU, with their role being previously explored.

Besides the occurrence of neurological symptoms in the acute infection phase, these may persist over time or new ones may develop after the resolution of the acute symptoms. This new condition is named post-COVID-19 syndrome and might occur even after a relatively mild infection and despite the resolution of the acute infection. Its prevalence is estimated to be higher than 30% in patients with asymptomatic or mildly symptomatic SARS-CoV-2 infection, and approximately 80% in patients requiring hospitalisation.[4,8-10] Several studies showed that fatigue and cognitive impairment (brain fog, memory loss and attention deficit) were the most frequent and debilitating neurological manifestations, with approximately one-third of the patients included experiencing persistent fatigue and over one-fifth experiencing cognitive impairment 12 or more weeks following the COVID-19 infection.[5,10-12] Although having no association with hospitalisation during acute infection, they appear to be more likely in patients with more severe acute disease – namely the need for ICU care –, in female and older patients, and patients with preexisting comorbidities.[5,10] Furthermore, these two conditions were shown to represent a major economic burden to healthcare systems worldwide.[10] Therefore, attention must be given to neurological symptoms in both the acute and chronic phases of SARS-CoV-2 infection.

In conclusion, changes in behaviour, cognition, and consciousness in patients with SARS-CoV-2 infection should raise the possibility of severe COVID-19-related encephalitis and encephalopathy, particularly if there are other potential contributors to this involvement of the central nervous system, such as the use of sedative-hypnotic and anticholinergic agents, admission to the ICU and longer intubation. Although there is no specific treatment, high-dose steroids have shown clinical improvement in some selected patients. Further studies are needed to understand both the role of treatment with steroids and the long-term neurological sequelae of COVID-19. ■

Previous Presentations
21st WPA World Congress of Psychiatry

Declaração de Contribuição
ARR – Elaboração, conceção, revisão de literatura e do artigo.
AH, HR – Revisão de literatura e do artigo.
ACP, IG -Conceção e revisão da literatura e do artigo.
MP – Conceção e revisão do artigo.
Todos os autores aprovaram a versão final a ser submetida.

Contributorship Statement
ARR - Elaboration, conception, literature and article review.
AH, HR - Literature and article review.
ACP, IG - Conception and review of literature and article.
MP - Conception and revision of the article.
All authors approved the final draft.

Responsabilidades Éticas
Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.
Fontes de Financiamento: Não existiram fontes externas de financiamento para a realização deste artigo.
Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.
Consentimento: Consentimento do doente para publicação obtido.
Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

Ethical Disclosures
Conflicts of interest: The authors have no conflicts of interest to declare.
Financing Support: This work has not received any contribution, grant or scholarship
Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.
Patient Consent: Consent for publication was obtained.
Provenance and Peer Review: Not commissioned; externally peer reviewed.

Correspondence / Correspondência:
Ana Rita Ramalho - anaritaramalho@ulscoimbra.min-saude.pt
Serviço de Medicina Interna, Unidade Local de Saúde de Coimbra, Coimbra, Portugal
Praceta Professor Mota Pinto, 3004-561 Cimbra

Recebido / Received: 2023/08/09
Aceite / Accepted: 2024/02/26
Publicado online / Published online: 2024/06/17

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