CASO CLÍNICO/CASE REPORT

COVID-19 Associated Longitudinal Extensive Transverse Myelitis with Cerebral Spinal Fluid SARS-CoV-2 Detection

Mielite Transversa Longitudinalmente Extensa Associada a COVID-19 com Deteção de SARS-CoV-2 no Líquido Cefalorraquidiano

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DOI: https://doi.org/10.46531/sinapse/CC/230058/2023

Informações/Informations:
Caso Clínico, publicado em Sinapse, Volume 23, Número 4, outubro-dezembro 2023. Versão eletrónica em www.sinapse.pt;
Case Report, published in Sinapse, Volume 23, Number 4, October-December 2023. Electronic version in www.sinapse.pt

Keywords:
COVID-19;
Myelitis, Transverse;
RNA, Viral/cerebrospinal fluid;
SARS-CoV-2.

Palavras-chave:
COVID-19;
Mielite Transversa;
RNA, Viral/líquido cefalorraquidiano;
SARS-CoV-2.

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Recebido / Received: *2023-08-02*
Aceite / Accepted: *2023-11-11*
Publicado / Published: *2024-01-22*

Abstract

There have been multiple reports of COVID-19 associated neurological symptoms, including several cases of para-infectious myelitis.

We report a case of an 84-year-old male patient presenting with acute paraparesis coinciding with active mild COVID-19 pneumonia. Spinal cord magnetic resonance imaging (MRI) showed longitudinally extensive transverse myelitis (LETM) affecting the entire cervical cord to the tenth thoracic level, and cerebral spinal fluid (CSF) was positive for SARS-CoV-2. The patient was evaluated for other causes of LETM, which were convincingly excluded. He was treated with steroid pulses and plasmapheresis, with significant imaging improvement. The patient has since made a good recovery, being now able to walk unassisted.

Although several instances of COVID-19 associated myelitis have been reported, positive identification of the virus in CSF is rare. The identification of viral material may support the hypothesis of direct spinal cord infection in co-occurrence with a para-infectious inflammatory reaction.

Resumo

Têm-se registado múltiplos relatos de sintomas neurológicos associados à COVID-19, incluindo vários casos de mielite para-infecciosa. Relatamos o caso de um doente do sexo masculino, de 84 anos de idade, que apresentou um quadro de paraparésia aguda simultaneamente a uma pneumonia ligeira por COVID-19. A ressonância magnética da medula espinhal revelou uma mielite transversa longitudinalmente extensa (LETM) com atingimento de toda a medula cervical até ao décimo nível torácico, e com deteção de SARS-CoV-2 no líquido cefalorraquidiano (LCR). O doente foi avaliado para outras possíveis causas de LETM, que foram excluídas de forma convincente. Foi tratado com pulsos de corticoterapia e plasmaferese, com melhoria significativa a nível imagiológico. Desde então, o doente tem tido uma boa recuperação, sendo agora capaz de caminhar sem ajuda. Conclusões: Embora tenham sido relatados vários casos de mielite associada à COVID-19, a identificação positiva do vírus no LCR é rara. A identificação de material viral pode apoiar a hipótese de infeção direta da medula espinhal em simultâneo com uma reação inflamatória para-infecciosa.

Introduction

The neurological complications of SARS-CoV-2 infection were recognized early in the COVID-19 pandemic. While the neuropathogenesis of COVID-19 is still controversial, several mechanisms have been proposed, such as direct invasion of the central nervous system (CNS) via the nasal epithelium or vagus nerve,[1,2] and interaction between the virus and the ACE2 receptors expressed on the membrane of spinal cord neurons.[3,4] Other possible mechanism is a post-viral immunological reaction to COVID-19, resulting in a hyper-inflammatory state causing myelin damage.[5]

The range of neurological manifestations reported in COVID-19 disease is broad, mostly consisting of mild or nonspecific symptoms.[6,7] However, serious complications such as stroke, Guillain-Barré syndrome, and encephalopathy, have been reported.[8] Myelitis is one potential severe complication of SARS-CoV-2. In most cases, causality was assumed due to the temporal coincidence of flu-like symptoms due to COVID-19 infection and acute flaccid paralysis.[9] Several cases of COVID-19 associated CNS disease with viral RNA identified in the cerebral spinal fluid (CSF) have been reported.[10] In the case of myelitis, there is, however, to our knowledge, a small number of case reports with direct identification of the virus in the CSF.[11,12]

We present a case of longitudinally extensive transverse myelitis (LETM) in a patient with COVID-19 pneumonia and the detection of SARS-CoV-2 RNA in CSF.

Case Report

An 84-year-old male patient was observed in the emergency department for urinary retention, paresthesia and progressive lower limb weakness, which evolved over 72 hours. His medical history was relevant for a neuroendocrine stomach tumor with pulmonary metastasis, in remission for the past 5 years after partial gastrectomy and right pulmonary upper lobectomy. The patient was diagnosed ten days earlier with SARS-CoV-2 infection, after three days of fever and myalgia. The neurological symptoms started with acute urinary retention. He then developed ascending lower limb paresthesia which rapidly evolved into complete sensory abolition from the waist down. He also noticed progressive lower limb (LL) weakness. He was febrile, with no signs of respiratory distress. The neurological examination showed

Table 1. Summary of CSF and blood analysis findings on presentation.

CSF	Value	Flag
Protein (mg/dL)	**90**	High
WBC (/mm³)	**27**	High
Mononuclear		
RBC (/mm³)	**56**	High
Glycosis (mg/dL)	50	Normal
Gram stain	Negative	—
Culture	Negative	
PCR multitest (*HSV1-2, Enterovirus, VZV, HHV 6, HPeV, CMV, N.meningitidis, S. Pneumoniae, H. Influenzae, E. Coli K1, S, Agalactiae, L. Monocytogenes, C. Neoformans*)	Negative	
SARS-CoV-2	**Positive**	**SARS-CoV-2 detected**
Arterial blood gas		
pH	7,.8	Normal
pCO2 (mmHg)	38	Mild type 1 respiratory failure
pO2 (mmHg)	67	
Blood		
WBC (x10^9/L)	7.7	Normal
Neutrophiles	6.07	Normal
Lymphocytes	0.51	Low
Monocytes	0.63	Normal
Eosinophyles	0.16	Normal
Basophyles	0.03	Normal
RBC (x10^9/mL)	4.83	Normal
Hemoglobin (g/dL)	14.4	Normal
Mean corpuscular volume (fL)	84.5	Normal
Mean corpuscular hemoglobin (pg)	29.8	Normal
Mean corpuscular hemoglobin concentration (g/dL)	35.3	Normal
Platelet (x10^9/L)	276	Normal
Prothrombin time (s)	12.2	Normal
aPTT (s)	24.1	Normal
Creatinine (mg/dL)	0.81	Normal
BUN (mg/dL)	15	Normal
Glycosis (mg/dL)	81	Normal
Na (mmol/L)	134	Normal
K (mmol/L)	5.1	Normal
Protein (g/dL)	7.2	Normal
Albumin (g/dL)	3.8	Normal
LDH (U/L)	**425**	High
ALT (U/L)	38	Normal
AST (U/L)	36	Normal
GGT (U/L)	**113**	High
Bilirubin total (mg/dL)	0.6	Normal
Creatinine kinase (u/L)	93	Normal
C-reactive protein (mg/dL)	**10.4**	High

severe asymmetric paraparesis (muscle strength 0/5 on right, 2/5 on left). Both LL were hypotonic and ankle reflexes could not be elicited. The remainder deep tendon reflexes were otherwise brisk, with bilateral Babinsky sign. Both upper and lower superficial abdominal reflexes were abolished. Superficial sensation was completely abolished below the T4-5 level, as were positional and vibrational senses. The patient required continuous urinary catheterization.

Workup

Routine blood laboratory tests showed mild type I respiratory failure, elevated CRP and mild lymphopenia (**Table 1**). Chest X-ray showed a diffuse interstitial reticular pattern. Cervical and thoracic spine computed tomography (CT) scan was performed to exclude a compressive lesion and was normal except for the diffuse bilateral pulmonary opacities. A lumbar puncture was performed, and CSF analysis showed mild mononuclear pleocytosis with elevated protein (**Table 1**). The CSF sample was analyzed for the presence of several pathogens using a multiplex PCR assay (FilmArray Meningitis/Encephalitis Panel; bioMérieuxÆ), and for Epstein-Barr virus using a commercially available PCR assay (RealStar EBV PCR Kit; Altona DiagnosticsÆ), which were not detected (**Table 1**).

Further CSF investigation was performed, with detection of SARS-CoV-2 RNA (**Table 1**). To perform this analysis, viral nucleic acid was extracted from the primary CSF sample using the EMAG automated extraction platform (bioMérieuxÆ). The detection of SARS-CoV-2 RNA was performed using a multiplex real-time reverse transcription PCR assay targeting regions of the nucleocapsid, spike protein, and RNA-dependent RNA polymerase genes (Allplex SARS-CoV-2/FluA/FluB/RSV Assay; SeegeneÆ). This same assay also allowed exclusion of influenza A and B virus and respiratory syncytial virus. The spinal cord magnetic resonance imaging (MRI) obtained on the second-day post-admission showed a longitudinally extensive, non-gadolinium-enhancing centromedullary lesion ranging from C1 to D7 (**Fig. 1**). Brain MRI was normal. Extensive diagnostic workup was performed and excluded other possible causes (**Table 2**).

Treatment

The patient started daily 1000 mg iv methylprednisolone. Given the severity of his symptoms, he was also started remdesivir (200 mg loading dose on day 1, followed by a 100 mg maintenance dose administered daily for 4 days). He remained on steroid pulses for 7 days, with only mild neurological improvement. He then underwent 7 sessions of plasma exchange (PLEX) on alternate days over the following two weeks, with partial clinical and imagiological improvement.

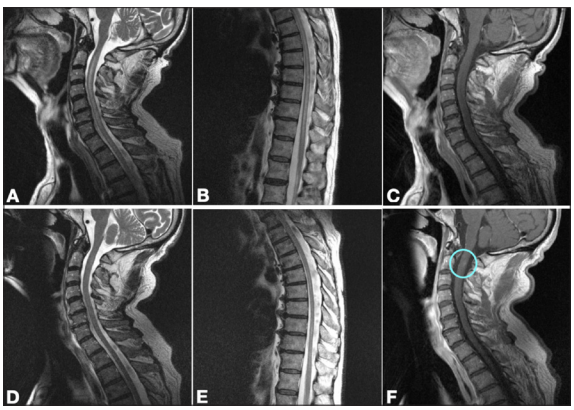

Figure 1. Initial cervical and thoracic MRI showing extensive centromedullary T2 hyperintensity (A, B) with no gadolinium enhancement (C). Follow-up cervical and thoracic MRI showing reduction in lesion size centromedullary T2 hyperintensity (D,E) but with evidence of slight gadolinium enhancement (F)

Outcome

Spinal cord MRI performed after 4 PLEX sessions, showed significant reduction in lesion size and perilesional edema, although some segments showed slight gadolinium enhancement (**Fig. 1**). Upon discharge, there was improvement in superficial sensibility, however, he was still incapable of unassisted standing due to paraparesis (proximal strength 3/5 and distal strength 4/5), and needed permanent urinary catheterization. The patient began a rehabilitation program while in hospital and was then discharged to a rehabilitation facility. Over the next six months, there was a remarkable recovery, and the patient is now capable of unassisted gait, with normal LL strength.

Discussion and Conclusion

While COVID-19 is foremost a lower respiratory illness, several cases of neurological manifestations have been reported. Acute myelitis is an often-incapacitating disease resulting from spinal cord inflammation. There are myriad possible causes, requiring extensive workup. Among the possible etiologies, immune-mediated diseases are predominant. Inflammatory myelitis is well known to occur in post or para-infectious contexts.

Table 2. Summary of diagnostic workup performed during hospitalization.

Serology	IgG	IgM	Notes
CMV	Negative	Negative	
EBV	Reactive	Negative	Previous infection
Borrelia burgdorferi	Negative	Negative	
VZV	Reactive	Negative	Previous infection
SARS-CoV-2	**Reactive (5380)**	**Reactive (22070)**	**Active infection**
Syphilis screening	Negative	Negative	
HIV	Negative		
Hepatitis B/C/E	Negative		
Quantiferon TB	Negative		
Vitamin B12 (pg/mL)	427	Normal	
Folic Acid (ng/mL)	5.6	Normal	
Interleukin-6	2.9	Normal	
Systemic autoimmune & inflammatory disease markers		No evidence of systemic autoimmune or inflammatory disease	
Anti-DS-DNA	Negative		
Antinuclear and anti-cytoplasm antibodies	Negative		
anti-SSA60,SSB,Sm,RNP,Scl70, JO1	Negative		
Antiphospholipid antibodies	Negative		
Anti-cardiolipin antibodies	Negative		
Angiotensin converting enzyme (mcg/L)	6	Normal	
Neurologic autoimmune disease markers & antineuron antibodies		No evidence of primary neurological inflammatory disease (namely NMO-SD) or paraneoplastic neurological syndrome	
Anti-Aquaporin 4 Ab	Negative		
Anti-MOG Ab	Negative		
Autoimmune encephalitis (anti-NMDAR, AMPA 1/2, DPPX,CASPR2, LGI1 and GABABr)	Negative		
Anti-Hu, anti-Ri, anti-Yo, anti-ampyphisin, anti-Ma2,, anti-CV2, anti-recovering, anti-SOX1, anti-Titine, anti-Zic4, anti-GAD65, anti-Tr(DNER)	Negative		
Brain CT scan	Normal		
Brain MRI	Normal		
Nerve conduction study (EMG)	Normal	No evidence of polyneuropathy or radiculopathy	

More rarely, direct infection of the spinal cord occurs.[13,14] The underlying pathophysiology of SARS-CoV-2 associated myelitis is still not fully understood and presumed to result from a combination of immune-mediated responses, direct cellular infection, and induction of a prothrombotic state. Identification of SARS-CoV-2 in the CSF is rare even in the presence of neurological symptoms.[15]

In recent years, several case series of myelopathy associated with SARS-CoV-2 have been published. In a systematic review of transverse myelitis associated with COVID-19 infection conducted in 2022, 76 reported cases were identified.[16] To date, there are few reported cases of identification of SARS-CoV-2 material in the CSF in myelitis; we found one case of an adult patient and another in a child with associated ADEM.[11,12]

Several treatments were tried in patients with COVID-19 associated LETM, including steroid pulses, IgIV, and/or plasmapheresis in most patients, as well as antivirals.[9,16] The majority of patients exhibited partial clinical recovery. However, severe cases with no response to treatment and cases resulting in patient death have been reported.[16] There are also descriptions of severe cases where additional drugs such as rituximab and infliximab were added after the initial corticosteroid and IgIV regimen, with associated clinical improvement.[16,17] In a patient with an acute ascending necrotizing myelitis following COVID-19 infection, cyclophosphamide was administered, followed by eculizumab, leading to clinical stabilization at the time of discharge.[17]

We believe that the identification of viral material in the CSF supports the possibility of direct spinal cord infection co-occuring with a para-infectious inflammatory reaction. Sharing cumulative experience will hopefully contribute to a better understanding of COVID-19 associated neurological disease. ■

Contributorship Statement / Declaração de Contribuição

FG, CL: Manuscript elaboration.
CV, JV, LC, IC: Manuscript review.
All authors approved the final version to be published.

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.

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