Myeloencephalitis as the only presentation of Omicron SARS-CoV-2 infection

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SUMMARY
SARS-CoV-2 is now a major global health issue and manifests mainly as a respiratory disorder. Several other complications involving hypercoagulability, cardiovascular system and central nervous system have been described in the literature. Among these atypical presentations, encephalopathy associated with SARS-CoV-2 is a rare entity with heterogenous clinical and radiological findings. The direct presence of SARS-CoV-2 in cerebrospinal fluid (CSF) was rarely found in encephalopathy patients with acute SARS-CoV-2 infection. Here, we report a case of myeloencephalitis with positive real-time PCR for SARS-CoV-2 in CSF in a young woman presenting exclusively with neurological symptoms. Other differential diagnosis were extensively pursued by a comprehensive aetiological workup. To our knowledge, this is the first case report in the Omicron era. In the context of recent global explosion of SARS-CoV-2 infections, clinicians should consider this pathogen among other possible neurotropic agents and be familiar with its radiological and clinical presentations.

BACKGROUND
It is projected that about 0.04%–0.2% of all SARS-CoV-2 patients would present with central nervous system (CNS) disease. With the number of daily cases averaging 1 million and 582 423 377 total cases globally at the time of writing, it could be estimated that approximately 400–2000 patients would present with SARS-CoV-2 associated encephalopathy everyday. For comparison, the annual incidence of herpes simplex virus (HSV) encephalitis is 2–4 per 1 000 000 population, translating into around 80 new cases daily worldwide. It is therefore reasonable, on an epidemiological basis, to search for SARS-CoV-2 in all cases of acute or subacute encephalopathy, despite the fact that the presence of viral particles in cerebrospinal fluid (CSF) can be only found in a small number of cases, unlike in the case definition of HSV encephalitis. We present a case of MRI-proven isolated myeloencephalitis with positive real-time-PCR (RT-PCR) for SARS-CoV-2 in CSF in a young patient with no prior history. A temporal relationship between neuroimaging, clinical features and CSF characteristics is also outlined.

CASE PRESENTATION
A previously healthy woman in her late 20s presented at our institution for a sensation of paresthesia of her 2 feet appearing 2 weeks prior, which ascended to lower abdomen and upper limbs associated with tetraparesis within 10 days. Her prior vaccination record included three doses of Pfizer Comirnaty, the last of which was 1 month before the onset of symptom. There was no history of SARS-CoV-2 infection.

At admission, a quick COVID-19 entry screening test per protocol at our hospital was positive. There was absence of respiratory symptoms such as coughing, sore throat nor fever. No anosmia or headache was reported by the patient. The patient was completely eupneic on room air and no abnormalities were found during pulmonary auscultation. Nasal swab RT-PCR revealed a cycle threshold of 20.02 at day 15 since the start of paresthesia.

On neurological examination, the patient was alert, well oriented and afebrile. There were moderate weakness of lower limbs (3/5) and mild weakness of upper limbs (4/5), with a slight asymmetry predominant on the right side. Bilateral hyperreflexia with Babinski signs and ankle clonus were observed. Vibration sensation and joint position sense were reduced in lower left limb and lost in right lower limb. Cerebellar signs such as nystagmus or truncal ataxia were absent. Slight nuchal rigidity was also noted. Neither cranial nerve impairment nor important cognitive dysfunctions were present. Initial diagnostic hypothesis included an acute myeloencephalitis on the basis of a clinically suggestive pyramidal and sensory syndrome with rapid progression.

INVESTIGATIONS
Her first brain and spinal cord MRI with gadolinium (figure 1) was obtained at day 15 of symptoms. A lumbar puncture was then performed revealing a moderate pleocytosis at 74 cells/μL and a slightly elevated proteinorrachia. Other parameters are summarised in table 1. The diagnosis of acute myeloencephalitis was established. RT-PCR for SARS-CoV-2 in CSF was tested and returned positive at a CT of 20.52. An extensive diagnostic workup to rule out other known causes of acute or subacute encephalitis was pursued and returned negative (table 2).

Further investigation by nerve conduction study and electromyography showed no involvement of the peripheral nervous system, ruling out the possibility of a concomitant neuropathy. A 30 min conventional electroencephalography was unremarkable. A thoracoabdominopelvic CT scan later revealed mild bilateral pleural effusion with no pulmonary parenchymal opacities (figure 2). Genome sequencing eventually identified a B.1.1.529 variant (Omicron) in nasal sample.
TREATMENT

A course of high-dose methylprednisolone (1000 mg daily for 5 days) were started immediately after the diagnosis of acute myeloencephalitis was established with exclusion of bacterial and tuberculous causes on CSF analysis. Given a positive nasal swab RT-PCR, intravenous antiviral treatment with remdesivir (loading dose of 200 mg, followed by 100 mg daily) was added on suspicion of SARS-CoV-2 as a possible aetiology. The result of RT-PCR in CSF only came back positive 2 days after antiviral initiation. By day 18 of symptoms, she began developing urinary incontinence and required bladder catheterisation.

A second lumbar puncture was performed at the end of 5-day pulse corticotherapy showing a recession of pleocytosis down to 16 cells/µL and a persistent elevated proteinorrachia (Table 1). Her second SARS-CoV-2 RT-PCR in CSF and subsequent nasal swabs also turned negative. A second brain MRI was obtained 7 days after the first revealing a reduction of contrast enhancement (Figure 3). Other parameters (liver and renal function, ionogram, coagulation) and systemic inflammatory markers related to SARS-CoV-2 infection (C-reactive protein, Interleukin-6) were within normal ranges.

OUTCOME AND FOLLOW-UP

Her clinical status started to recover at day 20 of onset with gradual improvement of paresthesia and limb motor function. Remdesivir was stopped after 9 days and she was later discharged at day 25 of symptoms with very little distal paresthesia, a complete resolution of her urinary incontinence and a slight

Table 1 CSF cytology and biochemistry characteristics

| Days since symptom start | Reference values |
|-------------------------|------------------|
| Day 18                  | Day 23           |
| Appearance              | Colourless, atraumatic tap Colourless, atraumatic tap Colourless |
| Direct fungal examination| Negative Negative Negative |
| Leucocyte counts        | 74 cells/µL 16 cells/µL 0–5 cells/µL |
| % Lymphocyte            | 97% 100%         |
| % Neutrophil            | 3% 0%            |
| Protein                 | 65.748 mg/dL 69.067 mg/dL < 45 mg/dL |
| Glucose                 | 6.09 mmol/L 3.47 mmol/L 2.2–3.9 mmol/L |
| Glycaemia (Ratio of glycorrachia and glycaemia) | 12.9 mmol/L (0.47) 3.4 mmol/L (1.02) 3.9–6.4 mmol/L (> 0.50) |
| Lactate                 | 2.3 mmol/L 1.668 mmol/L 1.1–2.4 mmol/L |
| Adenosine deaminase     | 2.5 U/L – ≤ 33 U/L |
| Chlor                   | 130.1 mmol/L 124.5 mmol/L 120–130 mmol/L |
| RT-PCR for SARS-CoV-2 and cycle threshold | Positive, CT of 20.52 Negative Negative |

Table 2 List of differential diagnostics investigated

| Serum markers | Results |
|---------------|---------|
| Treponema pallidum hemagglutination assay | Negative |
| Anti-nuclear antibodies, anti-dsDNA | Negative |
| Homocysteine and Vitamin B₁₂ | Normal |
| Anti-HIV antibody | Negative |
| Tumour markers (CEA, CA 15–3, CA 125, CA 19–9, cyfra 21–1) | Negative |
| Neuronal antibodies (anti-Yo, anti-Hu, anti-Ri, anti-Amphiphysin, anti-Ma2, anti-CV2) | Negative |
| Anti-NMO (anti-aquaporin 4 antibody) | Negative |
| Anti-NMDA receptor antibody | Negative |
| Anti-VGKC antibody | Negative |

CSF and serum markers

| Oligoclonal band | Negative |
|------------------|---------|

CSF markers

| RT-PCR panel for HSV-1, HSV-2, Influenza, VZV, HHV-6 | Negative |
| Serology for Cysticercus cellulosae, Toxocara canis, Strongyloides stercoralis, Gnathostoma spinigerum, Angiostrongylus cantonensis | Negative |

CSF, cerebrospinal fluid; RT-PCR, real-time PCR.
tetraparesis at 4+/5. At 2-week follow-up visit, there was a near-complete neurological recovery with minimal pronator drift in upper limbs and no paresthesia.

DISCUSSION
To our knowledge, this is the first encephalitis case identified with the Omicron strain and positive RT-PCR in CSF. The emergence of this variant is associated with an increase in infection rate but whether this new variant would result in different neurological involvements remains unknown. Another case presenting with conscious disturbance and myoclonus was reported by Kato et al, although her CSF RT-PCR was negative.6 In the pre-Omicron era, factors commonly associated with SARS-CoV-2-related encephalopathy include older age, critical illness with delirium, seizures, impaired consciousness and mechanical ventilation, none of which was present in our case.7 SARS-CoV-2 encephalitis manifests most frequently with decreased level of consciousness (77%) and around a quarter present without systemic symptoms like fever or headache.8 Motor weakness is even rarer and only present in around 15% of cases.9 The symptoms in our patient are therefore atypical, although given the extreme rarity and novelty, it is not yet possible to define a clear clinical picture of this condition.

Our case met the confirmed diagnostic criteria set for SARS-CoV-2-associated encephalopathy/encephalitis proposed by Ellul et al, with evidence of myeloencephalitis based on CSF pleocytosis, MRI findings, presence of the virus in CSF and absence of other explanatory pathogens or causes.1 Specific intrathecal antibodies for SARS-CoV2 were not tested. The negative diagnostic workup further suggests SARS-CoV-2 as the primary causative agent. The simultaneous documentation of SARS-CoV2 virus in both CSF and nasal swab and the temporal relationship between clinical and virological progression supports a direct mechanism as well (figure 4). The topography of lesions in our case predominates in the grey matter of the paramedian cortex suggesting a viral encephalitis. A similar pattern can be observed in the distribution of ACE2 receptors, which were highly expressed in the frontal cortex and brainstem.9 Recent postmortem studies show that SARS-CoV2 RNA was also most frequently detected in brainstem region.10 Demirci Otluoglu et al described a case with lesions in the posterior medial temporal cortex and upper cervical spinal cord and a documented positive RT-PCR in CSF, although there were noticeable respiratory symptoms.11

There is currently no proven therapeutic strategy for SARS-CoV-2 viral encephalitis. A regimen of corticosteroid, intravenous immunoglobulin or plasma exchange is suggested regardless of mechanism.12 In case of an active systemic infection, antiviral could be considered for at least 5–10 days.12 Agents such as remdesivir or favipiravir were used in several case reports, however, their efficacy in encephalitis is uncertain.11 13 In our case, a regimen of corticosteroid and intravenous Remdesivir was used for the first time in a SARS-CoV-2 encephalitis patient.
institution, remdesivir is the only viable option despite a penetration rate in CSF of less than 5% in animal models.14

The absence of respiratory symptoms and risk factors for CNS involvement in an otherwise healthy young patient is noteworthy. The classical view that SARS-CoV-2 is an airborne virus with predilection for respiratory system could narrow neurologists’ suspicion in the aetiological workup of an acutely presenting encephalopathy. The variant identified is the Omicron strain, the dominant variant responsible for more than 90% of cases worldwide.15 As the number of cases grows exponentially on a global scale, SARS-CoV-2 encephalitis or myelitis could be encountered more frequently and investigations should be directed toward this pathogen regardless of respiratory presentations. Appropriate and timely testing by either intrathecal antibodies or RT-PCR in CSF could be contributory to the diagnosis of this under-recognised pathogen.

**Learning points**

- On an epidemiological basis, SARS-CoV-2 should be considered in the aetiological workups of acute viral myeloneuropathy.
- Acute myeloneuropathy could be the only presentation of Omicron SARS-CoV-2 infection without respiratory prodrome.
- Efficacy of antiviral and corticosteroid are uncertain due to the lack of high-quality evidence and agent with good cerebrospinal fluid bioavailability.

**Correction notice** This article has been corrected since it was published online.
The international official name of the affiliation has been updated from “University of Medicine and Pharmacy Ho Chi Minh City Hospital” to “University Medical Center Ho Chi Minh City”.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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