NEUROINFECTIOUS DISEASES - CASE REPORTS COLLECTION 2021

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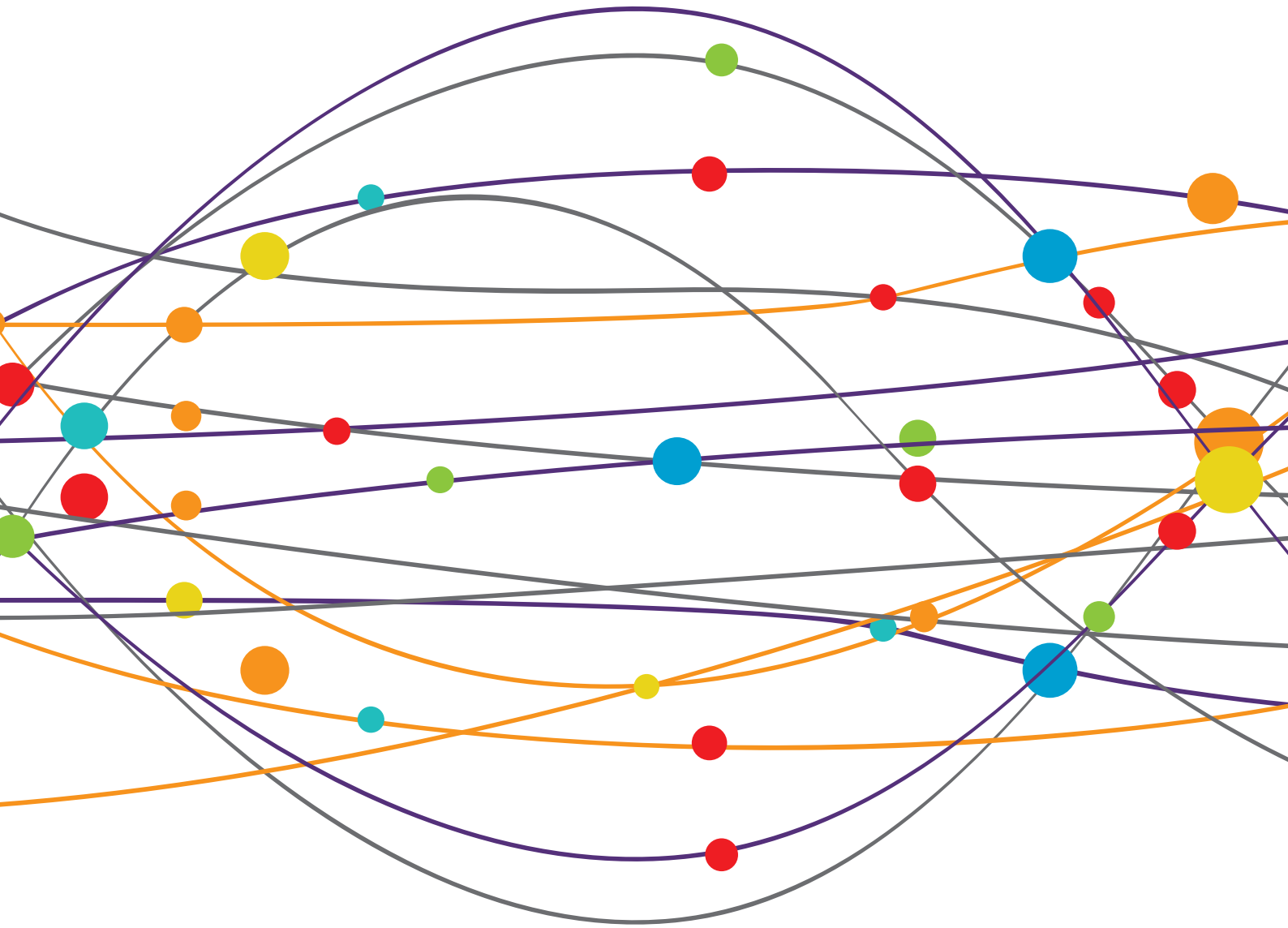

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NEUROINFECTIOUS DISEASES - CASE REPORTS COLLECTION 2021

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CASE REPORT
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Case Report: Guillain–Barré Syndrome Associated With COVID-19

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Guillain–Barré syndrome (GBS) is a potentially fatal, immune-mediated disease of the peripheral nervous system that is usually triggered by infection. Only a small number of cases of GBS associated with COVID-19 infection have been published. We report here five patients with GBS admitted to the Neurology, Psychiatry, and Neurosurgery Hospital, Assiut University/Egypt from July 1 to November 20, 2020. Three of the five patients were positive for SARS-CoV-2 following polymerase chain reaction (PCR) of nasopharyngeal swabs on day of admission and another one had a high level of IgM and IgG; all had bilateral ground-glass opacities with consolidation on CT chest scan (GGO) and lymphopenia. All patients presented with two or more of the following: fever, cough, malaise, vomiting, and diarrhea with variable duration. However, there were some peculiarities in the clinical presentation. First, there were only 3 to 14 days between the onset of COVID-19 symptoms and the first symptoms of GBS, which developed into flaccid areflexic quadriplegia with glove and stocking hypoesthesia. The second peculiarity was that three of the cases had cranial nerve involvement, suggesting that there may be a high incidence of cranial involvement in SARS-CoV-2-associated GBS. Other peculiarities occurred. Case 2 presented with a cerebellar hemorrhage before symptoms of COVID-19 and had a cardiac attack with elevated cardiac enzymes following onset of GBS symptoms. Case 5 was also unusual in that the onset began with bilateral facial palsy, which preceded the sensory and motor manifestations of GBS (descending course). Neurophysiological studies showed evidence of sensorimotor demyelinating polyradiculoneuropathy, suggesting acute inflammatory polyneuropathy (AIDP) in all patients. Three patients received plasmapheresis. All of them had either full recovery or partial recovery. Possible pathophysiological links between GBS and COVID-19 are discussed.

Keywords: COVID-19, SARS-CoV-2, neurological association, Guillain-Barré syndrome, acute inflammatory demyelinating polyradiculoneuropathy, axonal Guillain-Barré syndrome, peripheral neuropathy, polymerase-chain-reaction

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INTRODUCTION

The first cases of COVID-19 reported from Wuhan, China occurred in December 2019, and on March 11, 2020, the World Health Organization (WHO) declared the novel coronavirus (COVID-19) outbreak a global pandemic. COVID-19 can produce a wide spectrum of central and peripheral nervous system disorders. The latter can include anosmia, ageusia, visual impairment,

Guillain–Barré syndrome (GBS) (1–3), and skeletal muscle injury (3). GBS has been recorded after infection with Middle East respiratory syndrome (MERS) virus (4), and recently, a few case reports/series have noted that GBS can be associated with SARS-CoV-2 infection. GBS is an acute immune-mediated polyradiculo-neuropathy that may be triggered by various bacterial and viral infections. Approximately 70% of patients report a recent preceding upper or lower respiratory tract infection or gastrointestinal illness (5). Patients with GBS classically present with progressive symmetrical weakness and numbness of lower limbs that progresses to the upper limbs and is associated with hyporeflexia or areflexia. In severe cases, it can involve respiratory muscles and warrant use of mechanical ventilation (6). Disease progression can be rapid, and most patients with GBS reach their maximum disability within 2 weeks.

The first reported case of GBS associated with COVID-19 infection was of a woman who had just returned from Wuhan on January 19, 2020 (2). A recent review of published cases included 61 patients diagnosed with GBS and laboratory-confirmed preceding/concomitant SARS-CoV-2 (7). Most of the articles included were from high- and upper-middle-income countries according to the World Bank classification. Only one article was reported from Morocco, a lower-middle-income country in Africa.

Here, for the first time in Egypt, we discuss five cases of GBS associated with COVID-19 infection, admitted to the Neurology, Psychiatry, and Neurosurgery Hospital, Assiut University/Egypt during the period from July 1 to November 20, 2020. Clinical and laboratory data are presented in **Table 1** and neurophysiological data are shown in **Table 2**.

Case 1

A 34-year-old male came to the emergency room with a history of cough, expectoration, and fever of 10 days duration followed by numbness of feet and then hands. On admission, polymerase chain reaction (PCR) of nasopharyngeal swab was negative, CT chest showed ground-glass opacities (GGO), and laboratory investigations (↑D-dimer, leukocytosis, anemia, and lymphopenia) suggested probable COVID-19 infection. During admission, he developed weakness of both distal and proximal lower and then upper limbs that progressed rapidly until he became bedridden 1 week later. Two days after this, he developed dysphagia and a nasal tone of speech. The details of the clinical examination, Erasmus GBS Respiratory Insufficiency Score (EGRIS), the medical Research Council (MRC) sum score, the positive laboratory data, and the result of CT chest at the day of admission are illustrated in **Table 1**. The patient was connected to mechanical ventilation.

Neurophysiological study showed evidence of mixed demyelinating and axonal variant of GBS (AIDP); detailed measures are in **Table 2**.

Due to unavailability of intravenous immunoglobulin (IVIG) at that time, the patient received five sessions of plasma exchange (200–250 ml plasma/kg body weight) with no improvement either in motor or in respiratory functions. One month later, the patient received a course of IVIG (0.4 g/kg body weight daily for 5 days). Two weeks later, the patient was weaned from the ventilator and discharged home with motor power grade 1 in proximal and distal muscles of both upper and lower limbs. MRC sum score was 12. Follow-up 2 months after discharge, the patient MRC sum score had increased to 34.

Case 2

A 65-year-old male came to the emergency room with a history of left hemiataxia of 10 days duration; CT brain showed left cerebellar hemorrhage. He received medical treatment and discharged to his home with mild improvement but required mild support to walk. One week later, the patient developed fever, malaise, and cough for 2 days and readmitted again to the hospital and positive PCR was recorded, and then he developed numbness and weakness of all four limbs and within 2 days became bedridden. Details of clinical examinations, EGRIS, MRC sum score, and laboratory findings on admission are shown in **Table 1**. On the third day of admission, the patient had a cardiac attack with elevated liver enzymes for which he received medical treatment and improved.

Blood picture was normal except for the presence of lymphopenia and neutropenia. ABG showed low PaO2 and PaCo2. CT chest showed GGO.

A neurophysiological study showed evidence of a mixed axonal and demyelinating variant of GBS (AIDP); detailed measures are in **Table 2**.

The patient received five sessions of plasmapheresis (one session every other day) and showed marked improvement in motor power such that he could walk with mild support on discharge. MRC sum score was 48.

Case 3

A 49-year-old female had a history of fever and repeated vomiting for 3 days followed by numbness of hands and feet at the time she admitted to the hospital and positive PCR of nasopharyngeal swabs and bilateral GGO of CT chest were recorded; 1 day later, the patient developed rapid progressive symmetrical weakness of both lower and upper limbs, proximal more than distal, and within 2 days, she became bedridden (rapidly evolving). On examination, the patient was fully conscious, with intact cranial nerves. Motor examination showed hypotonia of both upper and lower limbs, reduced muscle strength (MRC grades were 3 for proximal and 4a for distal muscles of both upper limbs; 0 for proximal and 1 for distal muscles of both lower limbs), with four limbs. Sensory examination revealed a glove and stocking hypoesthesia. Three days after admission, the patient developed deviation of the angle of the mouth to the right side and was unable to close her left eye, dysphagia, hoarseness of voice, and an impaired cough reflex. On examination, there was a left lower motor neuron facial palsy and true bulbar palsy with reduced gag reflex. The EGRIS was 5 and the MRC sum score was 24. Details of laboratory findings are in **Table 1**. ABG showed low PaCO2. Otherwise, PT, PC, INR, liver, and renal functions were normal. All electrolytes were normal (Na^+, K^+, and Ca^{2+}).

A neurophysiological study provided evidence of a mixed axonal and demyelinating variant of GBS. Detailed data are given in **Table 2**.

TABLE 1 | Clinical and laboratory data.

Case	Age and sex	COVID-19 related symptoms	Clinical symptoms and signs of GBS MRC at admission and time evolved	EGRIS	Laboratory findings	PCR	CT Chest	Co-morbidities	Treatment and Outcome
1	34 Male	10 days of fever, cough, expectoration	Flaccid areflexic quadriplegiay, stock and glove, hypothesia, bulbar palsy, respiratory failure → mechanical ventilator. MRC sum score: 0. The symptoms evolved over a week.	6	↑D-dimer Leukocytosis, Anemia, Lymphopenia	–ve	Bilateral GGO	None	Five sessions plasmapheresis → no improvement. 1 month later → 5 days IVIG 2 weeks later → weaned from ventilator MRC sum score on discharge: 12 Two months after discharge MRC sum score improved to be 34
2	65 Male	5 days of fever, malaise, cough	Flaccid areflexic quadriplegia, stock & glove hypothesia. MRC sum score: 12. The symptoms evolved over 2 days.	14	Neutropenia, Lymphopenia, ↓ PaCo2 & PaO2	+ve	Bilateral GGO	IHD, Cerebellar hemorrhage	5 sessions of plasmapheresis → improvement MRC sum score on discharge: 48
3	49 Female	3 days of fever and repeated vomiting	Flaccid areflexic quadriplegia, stock & glove hypothesia, Lt LMNL facial palsy, bilateral bulbar palsy, MRC sum score: 24 The symptoms evolved over 2 days.	5	↑D-dimer, Thrombocytosis, Lymphopenia ↓ PaCO2	+ve	Bilateral GGO	None	1 session of plasmapheresis → hypersensitivity reaction. 4 weeks later → 5 days IVIG. 1 week later → started to improve with MRC sum score on discharge: 36. Three weeks after discharge → she can walk with moderate support, MRC sum score 50
4	45 Male	14 days of fever, cough, diarrhea	Flaccid areflexic quadriparesis, stock & glove hypothesia. MRC sum score: 40. The symptoms evolved over 1 day.	4	Anemia, Thrombocytosis, Neutrophilia, Lymphopenia	+ve	Bilateral GGO	DM	Steroids for 2 weeks → marked improvement MRC sum score on discharge: 60 but he still complains from paresethesia of fingers and toes
5	55 Female	14 days of fever, cough, expectoration	Bilateral LMN facial palsy, followed by flaccid areflexic quadriplegia with weakness proximal more than distal, as well as stock and glove hypothesia. MRC sum score: 34. The symptoms evolved over 10 days.	4	Leukocytosis, Neutrophilia, Lymphopenia.	Unavailable High IgG and IgM	Bilateral GGO	None	Received 5 days of IVIG, and showed improvement on discharge that the patient walk with moderate support (MRC = 48). Two months later patient walk without support with the MRC sum score was 60

EGRIS, Erasmus GBS Respiratory Insufficiency Score RF, respiratory failure; LMNL, lower motor neuron lesion; MRC, Medical Research Council; Lap, laboratory results; PaCo2, partial pressure of carbon dioxide; PaO2, partial pressure of oxygen; PCR, Polymerase chain reaction from nasopharyngeal swap; -ve, negative; +ve, positive; CT, computerized tomography; GGO, Ground-glass Opacity; AIDP, acute inflammatory demyelinating polyneuropathy; IHD, Ischemic heart disease; DM, Diabetes mellitus; IVIG, Intravenous immunoglobulin. ↑, increase; ↓, decrease.

TABLE 2 | Neurophysiological data.

	Case 1		Case 2		Case 3		Case 4		Case 5	
	Rt	Lt	Rt	Lt	Rt	Lt	Rt	Lt	Rt	Lt
Median nerve										
Motor DL (ms)	5.40	5.25	3.24	3.12	8.3	7.55	4.9	5.1	4.2	4.3
CMAP amplitude (mV)	9.45	10.3	11.05	9.57	1.76	1.67	17.8	18.7	1.45	1.01
MCV (m/s)	50.0	49.9	59.8	63.7	43.1	51.8	46.7	45.5	55.6	56.5
Sensory DL (ms)	NR	NR	2.46	2.52	NR	NR	NR	NR	3.54	3.64
Sensory amplitude (μV)	NR	NR	32.2	28.2	NR	NR	NR	NR	17.8	18.4
SCV (m/S)	NR	NR	56.9	55.6	NR	NR	NR	NR	39.4	40.5
F-wave (ms)	33.4	34.15	26.6	27.3	35.1	39.5	33.9	34.6	38.4	39.7
Ulnar nerve										
Motor DL (ms)	3.6	3.3	2.07	3.12	8.12	7.55	4.8	5.1	4.6	4.3
CMAP amplitude (mV)	1.4	1.6	7.59	9.57	1.54	1.67	19.5	18.7	1.54	1.01
MCV (m/s)	34.4	44	53.3	63.7	50.8	51.1	43.2	45.5	55.7	56.5
Sensory DL (ms)	3.34	3.42	2.52	3	NR	NR	NR	NR	3.74	3.46
Sensory amplitude (uV)	0.8	1	28.2	31	NR	NR	NR	NR	17.6	18.4
SCV (m/S)	38.6	40.9	55.6	52	NR	NR	NR	NR	38.7	40.5
F-wave (ms)	30.44	31.25	27.3	27.6	40	39	36.4	37	31.4	32.7
Tibial nerve										
Motor DL (ms)	6.7	6.9	6.15	8	9.75	7.15	5.3	5.6	NR	NR
CMAP amplitude (mV)	0.45	0.82	4.71	0.47	1.04	1.52	6.24	5.36	NR	NR
MCV (m/s)	40.4	39.5	43.1	73.4	51	31.7	33.2	31.5	NR	NR
F-wave (ms)	37.6	36.7	33.5	34.4	NR	34	38.5	38.5	NR	NR
Peroneal nerve										
Motor DL (ms)	7.2	7.6	3.05	4.3	6.4	5.75	4.5	4.7	10.5	11.9
CMAP amplitude (mV)	2.51	2.49	0.79	0.77	6.6	6.58	2.23	2.19	0.56	0.45
MCV (m/s)	45.7	44.6	48.2	48.5	39.1	39.8	30.4	38.3	38.1	39.3
F-wave (ms)	NR	NR	41.4	35.7	NR	NR	41.75	40.85	NR	NR

DL, distal latency; MCV, motor conduction velocity; SCV, sensory conduction velocity; NR, no response.

Ten days after admission, the patient received the first session of plasmapheresis, during which she showed a hypersensitivity reaction with respiratory failure. She was admitted to the ICU with an oxygen mask and 40% ventilation. Nasopharyngeal swabs were repeated three times on a weekly basis (firstly at admission) and were positive for COVID-19; the fourth swab was negative. Four weeks later, the patient received 5 days of IVIG, and after 1 week, the motor power of both upper and lower limbs was improved. The MRC sum score was 36. Three weeks after discharge, she could walk with moderate support and had an MRC sum score of 50.

Case 4

A 45-year-old male, known to be diabetic, came to the emergency room complaining of malaise, fatigability, nausea, and vomiting associated with diffuse abdominal pain. A diagnosis of diabetic ketoacidosis was made, and he was admitted for management. Two days later, the patient developed fever, cough, and diarrhea. Chest CT showed bilateral GGO, and he tested positive for COVID-19 following a RT-PCR from a nasopharyngeal swab. The patient was transferred to the isolation hospital for COVID-19 patients (Abo Teg isolation hospital) where he stayed for 5 days and then was discharged home. One week after discharge, the patient complained of paresthesia of the feet and hands, and within a day, he developed bilateral symmetrical weakness of both lower and upper limbs, particularly in proximal muscles. Data of the clinical examination, EGRIS, MRC sum score, laboratory data, and CT chest on admission are given in **Table 1**.

A neurophysiological study showed evidence of a demyelinating variant of GBS. Detailed data are given in **Table 2**.

The patient received steroids for 2 weeks and showed marked improvement. The patient was discharged 2 weeks later with a motor power of 5 proximally and distally of both upper and lower limbs. The MRC sum score was 60, but the patient still complains of paresthesia.

Case 5

A 55-year-old female came to the emergency room with a 2-week history of low-grade fever, cough, and expectoration followed by progressive bilateral facial weakness. Because of the unavailability of PCR of nasopharyngeal swab, CT chest showed bilateral GGO and laboratory investigations were done, revealing leukocytosis, neutrophilia, and lymphopenia (probable

COVID-19). On examination, the patient was fully conscious and was unable to close both her eyes, with reduced blinking, inability to whistle, protrude the lips, or expose the teeth. One week later, after the onset of facial weakness, she developed numbness of both hands and feet, associated with progressive symmetrical weakness of both lower and upper limbs, affecting proximal more than distal muscles and was bedridden by the end of the week. Clinical details, EGRIS, MRC sum score, and CT chest are given in **Table 1**.

Titers of antibodies (IgG and IgM) against the SARS-CoV-2 were elevated 3 weeks after the onset of COVID-19. **Table 1** gives details of laboratory investigations.

Neurophysiological investigation revealed a mixed axonal and demyelinating variant of GBS. Detailed data are given in **Table 2**.

The patient received 5 days of IVIG, after which she started to walk with moderate support after 1 week. Two weeks later, she walked with mild support, and on discharge, the MRC sum score was 48. Two months later, she was walking without support with an MRC sum score of 60.

DISCUSSION

We recruited five cases of GBS-associated COVID-19 over the period from July 1 to November 20, 2020. Three were males and two were female with a mean age of 49.6 ± 11.52 years ranging from 34 to 65. Three of them were younger than 50 years old. In a recent systematic review, Hasan et al. (7) found that of 61 GBS cases associated with COVID-19, two-thirds (68.9%) were male and had a median age of 57 (49–70) years (7). So far, only three children < 18 years have been diagnosed with GBS following a coronavirus infection (8–10).

All our patients had symptoms including fever, malaise, headache, respiratory tract symptoms, and GIT symptoms. None had lost smell or taste. PCR of nasopharyngeal swabs was confirmed positive in three patients and IgM and IgG for corona virus were high in one patient. We did not test for SARS-CoV-2 in CSF since no cerebrospinal fluid samples have tested positive for COVID-19 in any reported cases summarized in systematic reviews of COVID-19 and GBS (11, 12). All patients had decreased lymphocytic count and CT chest with characteristic bilateral (GGO).

In the present study the peculiarities of our cases included the short latent period between the onset of COVID-19 and onset of GBS symptoms (7.2 ± 4.6 days with a range from 3 to 14 days), which is shorter than that reported in the systematic review of Hasan et al. (7). They reported that the median interval between SARS-CoV-2 symptoms and onset of GBS was 14 days with a range of 2 to 33 days (7). The slightly shorter duration in our cases could be explained by an asymptomatic incubation period, denial of early symptoms of COVID-19, or a hyper-inflammatory response as previously suggested by Zhao et al. (2). A similar result was reported by Kajumba et al. (12) in their review of 51 cases of GBS associated with COVID-19: that is, there was only a short time interval between the onset of the COVID-19 and GBS symptoms in comparison to the classic type of GBS. In our study, there was not only a rapid onset of symptoms but also rapid progression (4.4 ± 3.5 days) compared with classic GBS patients who typically reach maximum disability within 2 weeks (13).

The first reported case of GBS linked to COVID-19 was a woman who had returned from Wuhan (the presumed epicenter of the pandemic). She presented with weakness of both lower and both upper limbs and distal hypoesthesia, but had no signs or symptoms of COVID-19 until the eighth day when she developed dry cough and low-grade fever; a PCR was positive for SARS-CoV-2 (2). GBS in this first case followed the pattern of a para-infectious profile similar to GBS associated with Zika virus (14), rather than the classic post-infectious profile of most COVID-19 cases. The time elapsed between the onset of COVID-19 manifestations and GBS symptoms provides clues to the pathogenesis of GBS in SARS-CoV-2. We assume a post-infectious mechanism in the present study likely mediated by immune-mediated damage to peripheral nerve (15, 16). This could be the result of the viral spike protein binding to the receptor of the angiotensin-converting enzyme 2 (17). Alternatively, it could involve T-cell activation and release of inflammatory mediators by macrophages. A recent systematic review found that none of the patients had positive PCR for SARS-CoV-2 in the CSF (18). The absence of evidence for active infection when patients have clinical symptoms of GBS makes an immune-mediated mechanism the most likely cause of GBS associated with SARS-CoV-2.

In the present study, all five patients fulfilled level 2 of the Brighton criteria (6) manifesting with bilateral, flaccid weakness and areflexia in all four limbs. They had a monophasic course, with neurophysiological evidence of AIDP. However, there were some peculiarities in the clinical presentation as three of five cases had cranial nerve affections, suggesting a potential for more cranial nerve involvement of SARS-CoV-2-associated GBS as compared with GBS associated with other infection.

There were other peculiarities in the presentation of cases 2 and 5. Case 2 presented with a cerebellar hemorrhage before symptoms of COVID-19 and had a cardiac attack with elevated cardiac enzymes following onset of GBS symptoms. The association of hemorrhagic strokes with COVID-19 could be related to fluctuations in blood pressure caused by the affinity of SARS-CoV-2 for ACE2 receptors, which are expressed in endothelial and arterial smooth muscle cells in the brain, which, in turn, leads to damage to intracranial blood vessels and wall rupture (19). The same mechanism is probably responsible for myocardial injury, arrhythmia, and acute coronary syndrome that can be associated with SARS-CoV-2 (20).

Case 5 was also unusual in that the onset was associated with bilateral facial palsy that preceded the sensory and motor manifestations of GBS. This is a rare form of GBS as the classic form started usually with the ascending form of acute progressive tetraplegia and simultaneous bilateral facial palsy (21). However, Caamaño and Beato (22) and Chan et al. (23) recorded a case report of facial diplegia associated with COVID-19 but without limb weakness. These different varieties of GBS-associated COVID-19 may be related to the pattern of invasion of the virus to the peripheral nerves.

An important limitation of this case was the elevated IgG and IgM 3 weeks after the onset of symptoms with the possibility

to be related to either IVIG or SARS-CoV-2. However, IVIG has no direct effect on B cell proliferation and immunoglobulin production (24) and did not affect the detection or titers of IgG and IgM. On the other hand, the proportion of IgM-positive sera from the COVID-19 patients was maximal at 83% before 10 days and decreased to 0% after 100 days, while IgG-positive sera tended to plateau between days 11 and 65 at 78–100% and fall to 44% after 100 days (25). So, the elevated IgG and IgM in case 5 might be related to SARS-CoV-2.

Cases 1 and 4 had an uncommon response to treatment. Case 1 failed to respond to plasma exchange but later had a good response from IVIG, whereas IVIG and plasma exchange are usually of similar efficacy in classic GBS (26). In case 4, there was a marked improvement of motor powers after steroid therapy. Although corticosteroids would be expected to be beneficial in reducing inflammation, eight randomized controlled trials on the efficacy of corticosteroids for GBS showed no significant benefit and found that patients treated with oral corticosteroids have poor outcome (27). The positive effect in our cases could be due to the fact that corticosteroids were beneficial in reducing inflammation or were immunomodulatory in patients with COVID-19.

According to neurophysiological subtyping (28), all of our patients had neurophysiological evidence of AIDP. This is the most frequently reported variant of GBS in association with COVID-19 (18).

In the majority of previously published case reports, the outcomes were not clearly described. Here, we were able to present details of the clinical outcome of all five patients (see **Table 1**). All of them had either full recovery or partial recovery.

Although the GBS subtype diagnosis has currently no impact on treatment, we believe that it is important for understanding the underlying pathophysiology. Both IVIG and plasmapheresis are effective treatments for GBS with favorable outcome and a good adverse effect profile. IVIG is considered the first choice treatment because it is relatively easy to administer, is widely available, and has fewer side effects (29). One of our patients received corticosteroids with improvement in motor power within a month.

Early recognition and treatment with IVIG or plasma exchange/plasmapheresis (PLEX), along with supportive care, remains the mainstay of therapy (30–32).

Because we did not test the CSF for SARS-CoV-2 in our cases, there is no proof that COVID caused GBS. Nevertheless, the association between GBS and COVID needs further investigations.

In contrast to the presence of peculiarities of our cases, in a recent epidemiological and cohort study recorded by Keddie et al. (33), they compared COVID-19 (definite or probable)- and non-COVID-19-associated GBS patients and found no significant differences in the pattern of weakness, time to nadir, neurophysiology, or outcome. Two other systematic reviews by Abu-Rumeileh et al. (11) and Sansone et al. (34) showed that the clinical picture of COVID-19-associated GBS seems to resemble that of classic GBS or Zika virus-associated GBS.

Future epidemiological studies are required to evaluate the incidence rate of GBS in COVID-19. Moreover, studies combining treatment interventions with neurophysiological data are needed to investigate the underlying pathophysiological mechanisms.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Faculty of Medicine, Assiut University Hospital, Assiut, Egypt. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

EK: study conception, design of the work, statistical analysis, recruited the cases, critical revision of the manuscript, and prepared final version. KM, AS, and MS: recruited the cases, performed neurophysiological study, drafting the manuscript. AK: revised the manuscript and performed analysis. All authors gave final approval of the version to be published.

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CASE REPORT
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Subacute Cognitive Impairment in Individuals With Mild and Moderate COVID-19: A Case Series

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Background: Previous reported neurologic sequelae associated with SARS-CoV-2 infection have mainly been confined to hospital-based patients in which viral detection was restricted to nasal/throat swabs or to IgM/IgG peripheral blood serology. Here we describe seven cases from Brazil of outpatients with previous mild or moderate COVID-19 who developed subacute cognitive disturbances.

Methods: From June 1 to August 15, 2020, seven individuals 18 to 60 years old, with confirmed mild/moderate COVID-19 and findings consistent with encephalopathy who were observed >7 days after respiratory symptom initiation, were screened for cognitive dysfunction. Paired sera and CSF were tested for SARS-CoV-2 (IgA, IgG ELISA, and RT-PCR). Serum and intrathecal antibody dynamics were evaluated with oligoclonal bands and IgG index. Cognitive dysfunction was assessed by the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), and the Clock Drawing Test (CDT).

Results: All but one of our patients were female, and the mean age was 42.6 years. Neurologic symptoms were first reported a median of 16 days (IQR 15–33) after initial COVID-19 symptoms. All patients had headache and altered behavior. Cognitive dysfunction was observed mainly in phonemic verbal fluency (MoCA) with a median of six words/min (IQR 5.25–10.75) and altered visuospatial construction with a median of four points (IQR 4–9) (CDT). CSF pleocytosis was not detected, and only one patient was positive for SARS-Co

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Conclusions: A subacute cognitive syndrome suggestive of SARS-CoV-2-initiated damage to cortico-subcortical associative pathways that could not be attributed solely to inflammation and hypoxia was present in seven individuals with mild/moderate COVID-19.

Keywords: COVID-19, Encephalopathies, executive function, viral infection, cognitive impairment

INTRODUCTION

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (COVID-19), was first reported in December 2019 in Hubei province, China (1). By May 2021, more than 160 million people were infected by this virus worldwide and over 3.4 million died in the most severe pandemic since the 1918 Spanish Flu (2). From the very beginning, non-specific neurological symptoms such as headache, confusion, and dizziness were reported during the acute phase of COVID-19 (3). Alterations in mental status and behavior were, at first, attributed to a direct infection by SARS-CoV-2 or to the prolonged use of neuromuscular blockers and/or sedative medications (4).

Researchers from the United Kingdom described the first large multicenter investigation of neurologic parameters in SARS-CoV-2 infection (4), followed by studies from France and Italy (5, 6). Altered mental status was the second most frequent manifestation noted. Most reported cases were hospital-based and had severe COVID-19, and SARS-CoV-2 detection was restricted to nasal/throat swabs or to IgM/IgG peripheral blood serology. During the first COVID-19 wave, restricted evidence was presented of neurological manifestations associated with mild or moderate SARS-CoV-2 infection in young patients (4). Viral dynamics in the central nervous system (CNS) was also poorly investigated.

To address the issue of possible neurological manifestations in mild, moderate, severe, and critical COVID-19 infections, the NeuroCovBR study group assembled a multicenter cohort of six neurology reference centers from three different Brazilian administrative regions. After the first included patients, we hypothesized that COVID-19-associated encephalopathic conditions differed from the binomial sepsis—encephalopathy. In support of this possibility, we now describe seven patients from our cohort seen on an outpatient basis who developed encephalopathy and cognitive impairment >7 days after their first mild/moderate manifestations of COVID-19. None had severe illness, were prescribed medications, or exhibited metabolic dysfunctions that could link their clinical presentation to a classic diagnosis of delirium.

METHODS

The NeuroCovBR

A consortium of investigators from six regional SARS-CoV-2 pandemic epicenters located in the Southeast, Northeast, and Federal Districts of Brazil (NeuroCovBR) participates in this prospective cohort neurological study. Included patients must present with possible, probable, or confirmed SARS-CoV-2 meningitis, encephalitis, myelitis, CNS vasculitis, acute disseminated encephalomyelitis, Guillain–Barré syndrome, or other acute neuropathies as defined provisionally by Ellul (7). COVID-19 was defined and classified as mild, moderate, severe, or critical according to the World Health Organization (8, 9).

As a brief description of the study design, patients are referred to the study sites' neurologists by non-specialists (i.e., general practitioners, infectious diseases doctors, intensive care physicians) if any of the above syndromes is suspected as inpatient consultant or outpatient visits. First neurological symptoms must occur within 60 days of the first COVID-19 symptoms, regardless of COVID-19 severity. Demographics, clinics, laboratory, MRI, and electrophysiology tests results are collected and stored at an electronic database designed for this study at REDCap. Additional virology tests are done as described below.

This study is meant to last for 2 years, and the first enrollment occurred by June 1, 2020. It was approved by the Universidade de São Paulo ethics committee (CAAE: 31378820.1.1001.0068) and study site ethics committees. All patients provided written informed consent, and their personal information is protected according to ethical procedures.

Cognitive Impaired Patients

As provisionally defined by Ellul (7) and adopted in our study, SARS-CoV-2 encephalitis is divided into four levels: level 1, encephalitis, level 2, possible encephalitis, level 3, encephalopathy, and level 4, possible encephalopathy. At level 4, we have patients with "suspected encephalopathy (an alteration in consciousness, cognition, personality or behavior) with no other diagnosis apparent, but does not fulfill level 3 criteria," and at level 3 we additionally have "acute or sub-acute (<4 weeks) alteration in consciousness, cognition (including delirium or coma), personality or behavior persisting for more than 24 h" and "absence of an alternative diagnosis for symptoms" (7).

Levels 3 and 4 of SARS-CoV-2 encephalitis (or SARS-CoV-2 encephalopathy) were the main cause of patients' inclusion in the first 45 days of NeuroCovBR enrollment. By that time, we expected this clinical condition to be restricted to patients with severe COVID-19 resembling manifestations of septic encephalopathy similar to other infectious conditions. However, a considerable subset of mild and moderate COVID-19 patients presented this feature. Due to this atypia, here we describe these patients in advance.

SARS-CoV-2 Encephalopathy Patients

We identified seven NeuroCovBR outpatients patients seen from June 1, 2020, to August 15, 2020, with previous confirmed mild or moderate COVID-19, as defined by the World Health Organization (8), who presented with SARS-CoV-2 encephalopathy at least 7 days after manifestation of COVID-19-related symptoms (8).

Exclusion criteria for this report were previous use of medications known to cause cognitive dysfunction (i.e., neuromuscular blockers, sedatives, analgesics, antipsychotics), previous neurologic or psychiatric conditions (i.e., Alzheimer's disease, Parkinson's disease, stroke, epilepsy), and acute metabolic dysfunction (i.e., acute or acute-on-chronic renal failure, altered sodium, altered potassium, hypoglycemia, hyperglycemia).

Cognitive Screening

All subjects included were screened for cognitive dysfunction using the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), and/or Clock Drawing Test (CDT). During this first period of our study, we were only able to perform cognitive screening tests since neuropsychology attendance was suspended by sanitary measures. For the MMSE, the cutoffs for cognitive impairment were 20 points for illiterates, 25 points for 1–4 years of schooling, 26 points for 5–8 years schooling, and 28 points for 9 or more years of schooling, as reported previously for Brazilian subjects (10). For the MoCA test, 25 points was chosen as the cutoff for mild cognitive impairment (11). Patients with <5 schooling years were not submitted to this test due to low accuracy in detecting dementia in this population (12). For the CDT, we used the algorithm method proposed by Mendes-Santos (13), scoring drawn clocks from 1 to 10 points. As an evaluation of visuospatial function, scores lower than 9 were considered as evidence of visuospatial impairment. For each of the three tests, more important than cutoff values was the analysis of the affected cognitive domains. This may be present in cases where the MMSE analysis was normal while the MoCA and CDT results indicated impairments.

Laboratory Procedures

Paired serum and cerebrospinal fluid (CSF) were tested for SARS-CoV-2 IgA and IgG antibodies by a commercial ELISA kit (Euroimmun, Lubeck, Germany) and for SARS-CoV-2-specific RNA by RT-PCR (RealStar RT-PCR kit, Altona Diagnostics, Hamburg, Germany), according to the manufacturers' directions. Blood was tested for cell count, electrolytes, glucose, renal and liver function, C-reactive protein, and D-dimer, by routine laboratory protocols. Routine CSF analyses included cytologic evaluation and biochemical evaluation, lactate measurement, and screening for common local infectious diseases.

Serum and intrathecal samples were analyzed for oligoclonal bands (OCBs), i.e., subfractions of IgG that are encountered in individuals with autoimmune or infectious disorders (14, 15), by isoelectric focusing (Hydragel 9 CSF isofocusing, Sebia, Paris, France). Results were classified as pattern 1—no OCB detected, pattern 2—OCB in CSF only, pattern 3—identical OCBs in CSF and serum with additional OCBs in CSF, pattern 4—identical OCBs in CSF and serum, and pattern 5—ladder OCBs. The IgG index, a measurement of IgG production in serum or CSF, was calculated as [IgG (CSF) × albumin (serum)/IgG (serum) × albumin (CSF)] × 100. Albumin and IgG levels were determined by nephelometry. OCB patterns 2 and 3 and an IgG index >0.7 are indicative of intrathecal antibody production.

Neuroimage and EEG

All patients were submitted either to a brain MRI or to CT scan, based on analysis of the attending physician and hospital availability. The findings were evaluated by a radiologist with training in neuroradiology. EEG was performed in all patients according to international recommendations (16).

Statistics

Continuous data are summarized as median and interquartile range (IQR). Categorical data are presented as counts and percentages. Data were analyzed using SPSS version 25.0.

RESULTS

During the inclusion window, seven out of 28 patients recruited (25%) filled inclusion criteria (**Figure 1**). Characteristics of the study population are described in **Table 1**. Six of the seven subjects (85.7%) were female, and the median age (IQR) was 44 (39–47) years. Five (71.4%) had comorbidities, two each with hypertension or diabetes and one with asthma. Five were diagnosed with mild COVID-19, and two had a moderate disease based primarily on the presence or absence of symptoms of mild pneumonia. Neurologic symptoms developed at a median of 16 (15–33) days after initial COVID-19 manifestations. All patients had headache and altered behavior (reported as mild irritability

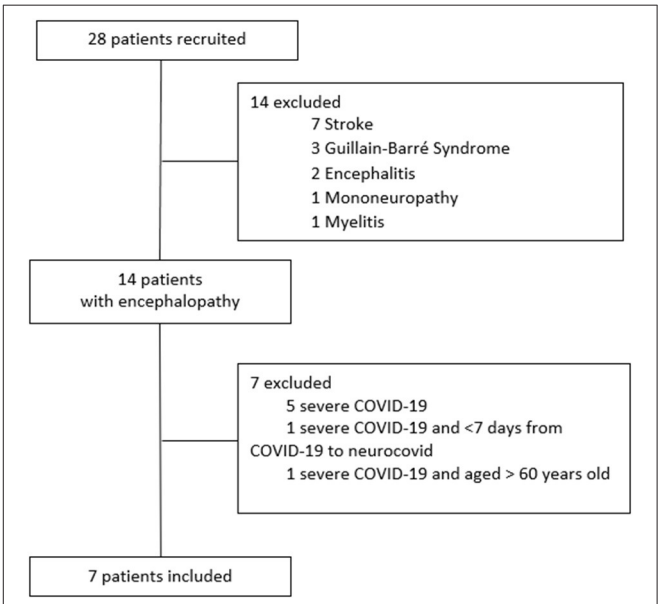

FIGURE 1 | Patients flow-chart. neurocovid, neurological manifestations of COVID-19. Encephalopathy was defined according to the Ellul et al.

TABLE 1 | Clinical and laboratory characteristics of patients with neurological symptoms associated with COVID-19.

Patient	Age	Sex	Comorbidities	COVID-19 severity	Days from COVID-19 to neurologic symptoms	Neurologic symptoms	MMSE	MoCA	CDT	CSF PCR/ IgA/IgG	Serum PCR/ IgA/IgG	OCB pattern	IgG Index
1*	30	F	Asthma	mild	15	Headache, altered behavior, sleep disturbance, T/S confusion, seizure	23/30	–	4/10	/ – /– / – /	/ – /– / + /	1	0.43
2*	47	F	HT	mild	16	Headache, altered behavior, sleep disturbance, T/S confusion	30/30	24/30	9/10	/ + /– / – /	/ – /– / + /	NA ‡	0.44
3*	44	F	–	mild	33	Headache, altered behavior, sleep disturbance, T/S confusion	–	–	4/10	/ – /– / – /	/ – /+ / + /	NA ‡	NA‡
4*	39	F	–	mild	52	Headache, altered behavior, sleep disturbance	–	28/30	9/10	/ – /– / – /	/ – /– / + /	1	0.5
5*	45	F	DM	mild	9	Headache, altered behavior, sleep disturbance, T/S confusion, altered level of conscience	29/30	–	4/10	/ – /– / – /	/ – /+ / + /	1	0.46
6*	53	F	HAS	moderate	15	Headache, altered behavior, sleep disturbance	23/30	–	4/10	/ – /– / – /	/ – /+ / + /	1	0.52
7†	40	M	DM	moderate	26	Headache, altered behavior, T/S confusion, altered level of conscience	17/30	9/30	1/10	/ – /– / – /	/ – /– / + /	1	0.44

*MMSE, mini-mental state examination; MoCA, montreal cognitive assessment; CDT, clock drawing test; OCB, oligoclonal bands; HT, hypertension; DM, diabetes mellitus; T/S, time and space; NA, not applied. * >8 scholar years; † <4 scholar years; ‡not enough sample to proper perform the test; OCB patterns: 1 no OCBs seen, 2 OCBs in CSF only, 3 identical OCBs in CSF and serum with extra in CSF, 4 identical OCBs in both, 5 ladder OCBs.*
IgG index cut off < 0.7.
CDT points range from 1 to 10.
COVID-19 severity is defined according to WHO.

or aggressiveness). Five also reported periods of time/space confusion lasting <24 h, and six had difficulties in going to sleep or remaining asleep.

Table 1 lists the laboratory test results. Cognitive dysfunction was observed in all patients, mainly in phonemic verbal fluency (MoCA) with a median of six words/min (IQR 5.25–10.75) and visuospatial construction with a median of four points (IQR 4–9) in the CDT. Patients 1 to 5 had normal brain MRI scans, and patients 6 and 7 had normal brain CT scans. In addition, routine blood and CSF analyses were all within normal limits.

Only one patient (number 2) was positive for SARS-CoV-2 by PCR, and all seven were negative for IgG and IgA anti-SARS antibodies. In the serum, all were PCR-negative, including the patient who was positive for SARS-CoV-2 in her CSF. Three patients were positive for IgA antibodies, and all seven had IgG anti-SARS-antibodies. The one patient positive for SARS by PCR in her CSF had a score of 30/30 on her MMSE and 9/10 on her CDT test. The results of the CDT test on all patients are shown in **Figure 2**. Of the four patients who had a score of 4/10 on their CDT test, three were IgA anti-SARS antibody-positive in their serum. There were no apparent associations between the PCR and antibody findings, the three neurology test results, and the occurrence of specific symptoms. None of the patients had an OCB pattern indicative of autoantibodies, and all had an IgG index in the normal range.

DISCUSSION

We describe seven patients with subacute SARS-CoV-2 encephalopathy and cognitive impairment associated with mild to moderate COVID-19. Their cognitive dysfunction was predominantly a dysregulation of executive activities that are associated with frontal lobe damage. Dysexecutive syndrome typically encompasses emotional, motivational, and behavioral symptoms, as well as cognitive deficits (17–19). There were no signs of intrathecal antibody production or blood–brain-barrier disruption, and MRI, EEG, and CSF findings were unremarkable. These observations are consistent with the existence of a syndrome related to SARS-CoV-2-induced damage to cortico-subcortical associative pathways.

SARS-CoV-2 is an RNA virus, and as a general rule RNA viruses remain in the circulation for only a limited time period. By the time we designed NeuroCovBR, we employed techniques for direct and indirect viral screening to maximize our chances to identify evidence of virus within the CNS. However, SARS-CoV-2 RNA was detected in only one of our patients, and no atypical OCB patterns or an abnormal IgG index was seen. Nevertheless, cognitive dysfunction in each of the seven cases was evident.

Other examples of virus-induced neurological impairment, such as HIV-Associated Neurocognitive Disorder (HAND) and Hepatitis C neurocognitive impairment (20, 21), exhibit similarities with SARS-CoV-2 encephalopathy. In those other infections, cognitive disturbances were not attributable only to direct virus-induced neurological damage. Instead, they were a consequence of a persistent subclinical inflammatory state resulting from the host's attempts at viral clearance as well as to viral-induced dysfunctions in neurotransmitter receptors that were detectable by SPECT but untraceable in routine MRI, CSF, or EEG (20, 22). HIV, for example, is not neurotropic but resides within lymphocytes that, acting as Trojan horses, can cross the blood–brain barrier and induce pro-inflammatory cytokines in the brain parenchyma causing secondary and progressive damage. The infected lymphocyte Trojan horse mechanism can also disrupt neuronal communication by inducing an environment rich in reactive oxygen species that results in both neuronal dysfunction and cell death (6). This mechanism is also feasible for SARS-CoV-2 infection, since the virus successfully infects lymphocytes (23). Another possibility for invasion is by infection of epithelial cells that express the angiotensin-converting enzyme 2 (ACE 2) receptor. SARS-CoV-2 binding to the ACE2 receptor is the major mechanism for viral entry into cells (7).

Hypoxia and pro-inflammatory cytokines are possible contributory mechanisms in SARS-CoV-2 encephalopathy (24). The analysis of pro-inflammatory cytokines along with neuronal biomarkers in patients with severe COVID-19 resembles alterations of the immune effector cell-associated neurotoxicity syndrome (ICANS), a neuropsychiatry syndrome related to chimeric antigen receptor (CAR) T cell therapy (25, 26). ICANS is associated with a cytokine release syndrome (CRS) (27) secondary to CAR-T cell therapy, and a plausible SARS-CoV-2 encephalopathy mechanism could be a COVID-19-induced CRS (28, 29). However, considering that our patients had mild/moderate COVID-19, the hypothesis of an immune-mediated neurotoxicity ICANS-like is not as strong as in patients with severe COVID-19; nevertheless, a mild persistent immune-mediated inflammatory state (considering that neurological manifestations occurred in median 16 days) might lead to SARS-CoV-2 delayed cognitive disturbances as in HAND or Hepatitis C neurocognitive impairment. This time lapse between the first COVID-19 symptoms and the first neurological symptoms also resembles the pathophysiological mechanisms of autoimmune induction present for instance in viral post-infectious polyradiculoneuritis (7).

It can be argued that neuropathology studies were not able to identify modifications caused by SARS-CoV-2 invasion beyond nonspecific signs of inflammation and hypoxia (24, 30). However, a prior MRI-based study observed microstructural damage in the cerebral cortex with possible neurogenesis in frontal-subcortical pathways independent of COVID-19 severity (31). Thus, our findings most likely were not solely due to inflammation or hypoxia, since those manifestations were not major attributes in our patients. We must also consider the possibility of a specific SARS-CoV-2-induced mechanism resulting in CNS damage not identified by gross pathological analysis and that can be independent of COVID-19 severity.

Dysexecutive function is characteristic of disruptions in frontal-subcortical circuits, large neuronal circuits that originate in the frontal cortex but spread to many different cerebral areas such as the striatum and thalami (32).

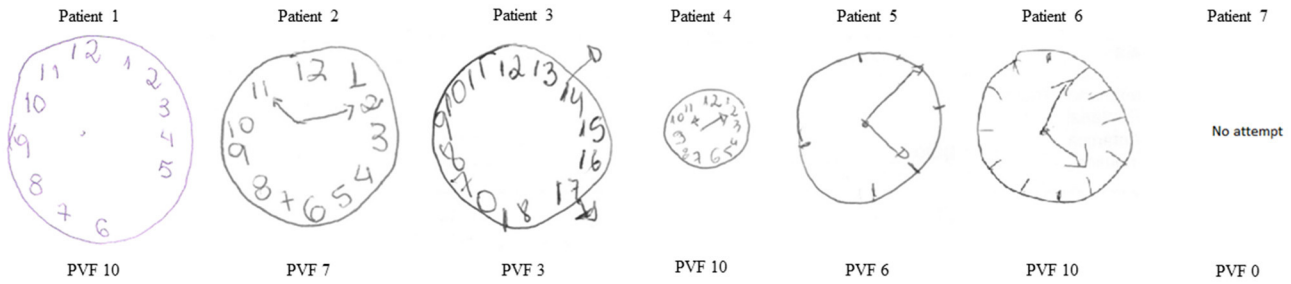

FIGURE 2 | Clock drowing test and phnemic verval fluency from patients with neurological symptoms associated with COVID-19. PVF, phonemic verbal fluney. PVF cut off ≥11 words in a minute.

Considering our patients' impairments in verbal fluency, poor constructional strategies, and behavior alterations, the dorsolateral prefrontal circuit, the anterior cingulate cortex, and the lateral orbitofrontal circuit are likely the most affected regions in SARS-CoV-2 encephalopathy. These circuits have been associated with different types of subcortical infectious dementia and hypothesized as affected in COVID-19 (32, 33).

Our study has limitations. We lack data on the time course of patients' recovery from COVID-19 and on long-term follow-up of cognitive alterations. Although none of our patients were oxygen-dependent and D-dimer was unremarkable as CSF lactate, we cannot definitively rule out an underlying mechanism of brain microcapillary dysfunction associated with brain tissue hypoxia and neuroglycopenia in sepsis. The observation that six of our seven subjects were female suggests a possible gender bias in SARS-CoV-2-related adverse neurological sequelae. However, this finding may be due solely to our small sample size and additional studies are needed to evaluate this further.

In conclusion, our results are compatible with subacute cognitive dysfunctions associated with mild/moderate COVID-19 that develops in patients independent of identifiable comorbidities. The dysfunctions cannot be explained solely by inflammation or hypoxia, although these effects might contribute to the observed alterations. Our findings point to the existence of a SARS-CoV-2-induced damage of cortico-subcortical associative pathways whose natural history remains unknown.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Universidade de São Paulo ethics committee (CAAE: 31378820.1.1001.0068). The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individuals for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

AM, CM, and AO were responsible for the study concept and design, data acquisition, analysis and interpretation of data, and critical revision of the manuscript. FD, JM, RM, AG, FC, GF, AF, JS, and JV were responsible for data acquisition, analysis and interpretation of data, and critical revision of the manuscript. JC, AE, TS, and SW were responsible for the critical revision of the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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CASE REPORT
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Progressive Stroke Caused by Neurosyphilis With Concentric Enhancement in the Internal Cerebral Artery on High-Resolution Magnetic Resonance Imaging: A Case Report

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Background: Neurosyphilis can initially present as a stroke. However, the general management strategy for stroke may not be effective for this condition. Intracranial vessel wall imaging indicating arteritis can help differentiate neurosyphilis from other causes of stroke.

Case presentation: A 59-year-old Chinese woman presented with an acute infarct in the left basal ganglia and multiple stenoses in the bilateral middle cerebral arteries, anterior cerebral artery, and basilar artery, which aggravated twice, despite antiplatelet treatment. High-resolution magnetic resonance imaging (HR-MRI) suggested concentric enhancement in the left middle cerebral artery. *Treponema pallidum* test results were positive, suggesting neurosyphilis.

Conclusions: HR-MRI provides valuable information regarding arteritis, which is helpful in differentiating neurosyphilis from other causes of stroke. Antiplatelet medication should be used judiciously for neurosyphilis-related stroke.

Keywords: stroke, high resolution magnetic resonance imaging, neurosyphilis, meningovascualr syphilis, neurosyphilic arteritis

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INTRODUCTION

Syphilis, a sexually transmitted disease, is caused by *Treponema pallidum*. Neurosyphilis occurs when *T. pallidum* invades the central nervous system, which may initially present as a stroke (1, 2). For these patients, the general management strategies for stroke, including the use of antiplatelet and anticoagulant agents, may be less effective. Therefore, the identification of neurosyphilis during the early stages of the disease is essential. Apart from serum or cerebrospinal fluid (CSF) findings of *T. pallidum*, high-resolution magnetic resonance imaging (HR-MRI) indicating arteritis can help differentiate neurosyphilis from strokes caused by other factors (3, 4). Here, we present a unique case of progressive stroke caused by neurosyphilis and radiological characteristics of the intracranial vessel wall imaging.

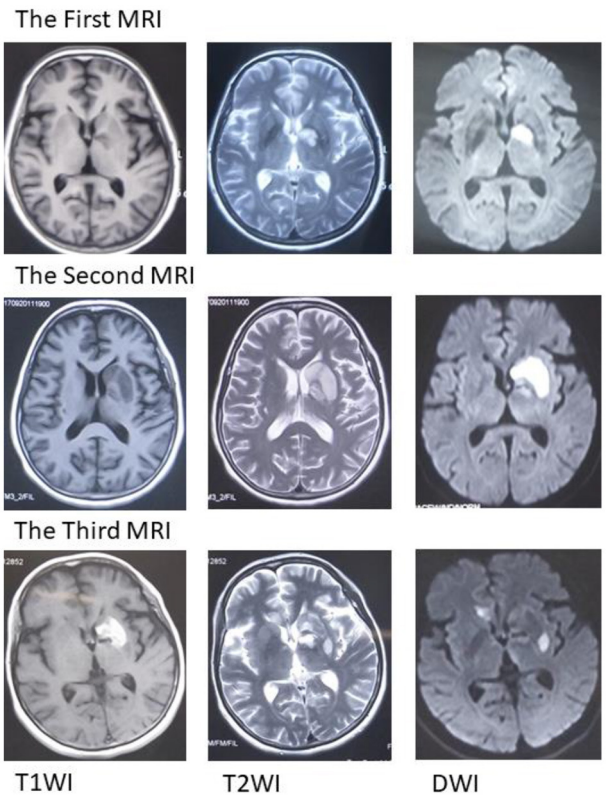

FIGURE 1 | Magnetic resonance imaging (MRI). The first MRI suggests an acute infarct in the left basal ganglia. The second MRI scan suggests an expanded infarct in the left basal ganglia. The third MRI suggests acute infarction in the left basal ganglia and right callosum genu and bleeding in the left basal ganglia. MRI, magnetic resonance imaging; T1WI, T1-weighted imaging; T2WI, T2-weighted imaging; DWI, diffusion-weighted imaging.

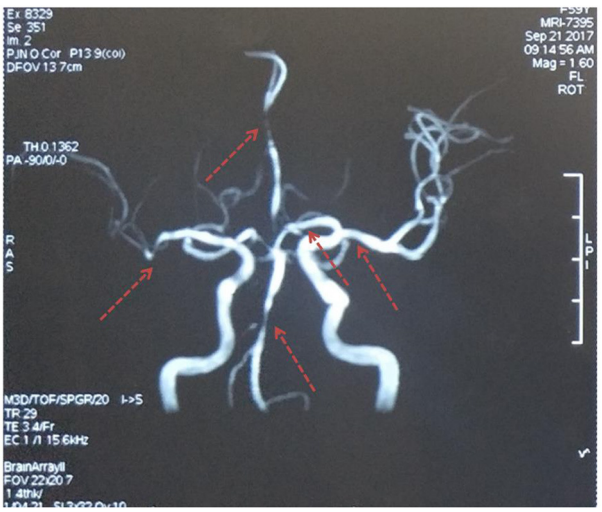

FIGURE 2 | Magnetic resonance angiography. Multiple stenoses in the bilateral middle cerebral arteries, anterior cerebral artery, and basilar artery. The red arrows indicate stenosis.

CASE PRESENTATION

A 59-year-old Chinese woman was hospitalized due to bradyglossia and weakness of the right lower limb. She denied smoking, drinking, hypertension, diabetes mellitus, coronary heart disease, and previous stroke. MRI suggested an acute infarct in the left basal ganglia (**Figure 1**) and the right posterior horn of the lateral ventricle. Aspirin, clopidogrel, atorvastatin, and butylphthalide were initiated based on a diagnosis of ischemic stroke.

Unfortunately, her clinical symptoms deteriorated 16 days after disease onset. She could not walk independently and leaned to the right side. Drooping of the right angulus oris was also noted. The patient was then admitted to our stroke center. Neurological examinations identified hemiglossoplegia, prosopoplegia, paraparesis of the right limb (5–/5), bradyglossia, and positive Babinski and Chaddock signs. Muscle tone, deep tendon reflexes, cerebellar signs, sensory abnormalities, and cranial nerves were unremarkable. The National Institutes of Health Stroke Scale score was assessed as 2. A repeat brain MRI suggested expanded infarct lesions in the left basal ganglia (**Figure 1**). New lacunar infarct lesions in the right corona radiata and stenosis in the bilateral middle cerebral arteries (MCA), anterior cerebral artery (ACA), and basilar artery (BA) were noted (**Figure 2**). The standard therapy for stroke management, including aspirin, clopidogrel, atorvastatin, butylphthalide, and edaravone, was administered continuously.

Routine serology and hematological tests suggested elevated blood glucose levels with a fasting blood glucose of 6.37 mmol/L, 2 h post-prandial blood glucose of 8.62 mmol/L, and glycosylated hemoglobin level of 6.10%. Blood pressure, serum homocysteine levels, and electrocardiography and echocardiography results were normal. Other risk factors for cerebral vascular disease were not remarkable.

Serum *T. pallidum* particle agglutination (TPPA) was positive, and the rapid plasma reagin assay (RPR) value was 1:16. A lumbar puncture was performed, and the results showed that the CSF was clear with a pressure of 110 mm H_2O. CSF protein (0.67 g/L, 0.15–0.44) and leukocyte (148×10^6/L, normal 0–8) levels were elevated with a positive Pandy test. CSF TPPA test results were positive, while RPR results were negative. No chancres or any other signs of syphilis were identified. The patient denied promiscuity. Her husband died 5 years ago. However, the patient used to get pedicures.

Intracranial vessel wall imaging with HR-MRI and cognitive scales was performed. Concentric contrast enhancement of the vessel walls was observed in the left MCA and ACA (**Figure 3**). The enhancement was observed in the entire M1 segment of the left MCA and A1 segment of the ACA, which was uniform, continuous, and similar in intensity. In the contralateral MCA, ACA, and BA, the enhancement was not remarkable. Syphilitic arteritis was thus considered in the left ACA and MCA, and the infarct in the left basal ganglia could be explained accordingly. The Mini-Mental State Examination score was 23/30, and the Montreal Cognitive

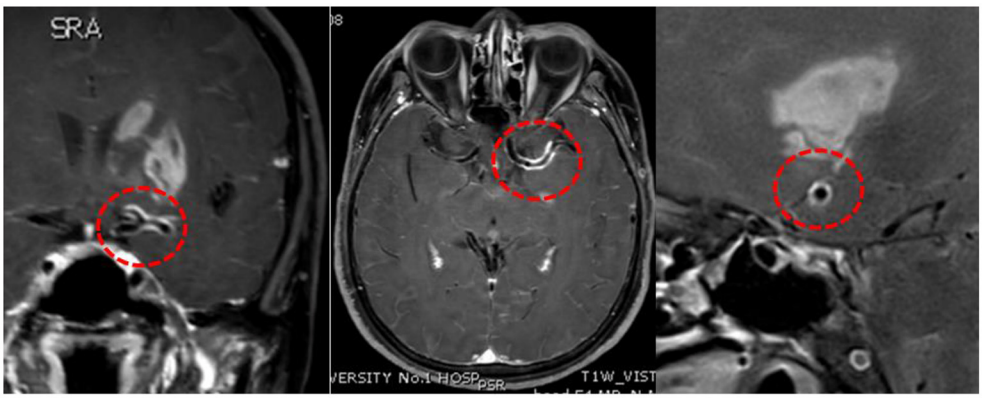

FIGURE 3 | High-resolution magnetic resonance imaging. Concentric enhancement in the left middle cerebral artery and anterior cerebral artery. Red circles suggest vessel wall enhancement.

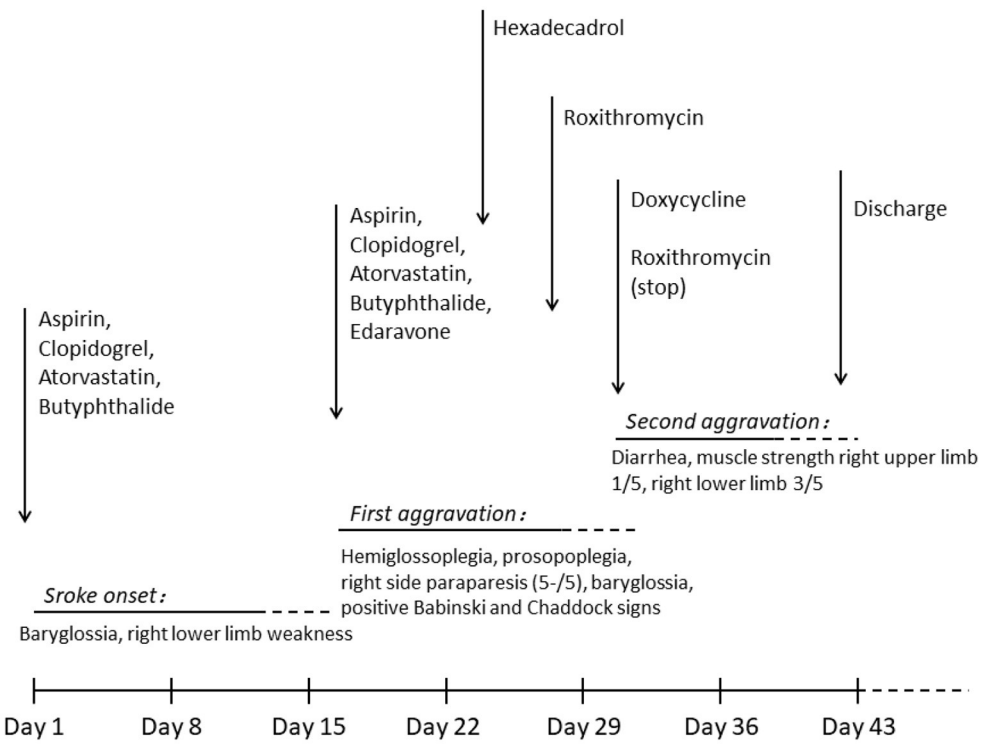

FIGURE 4 | Timeline of stroke aggravation and intervention. Stroke occurred on day 1 and was aggravated twice (days 16 and 30). Hexadecadrol was initiated on day 23, roxithromycin was initiated on day 27, and roxithromycin was replaced with doxycycline on day 30. The patient was discharged on day 41.

Assessment score was 17/30. Cognitive impairment, neurological impairment, damage to intracranial arteries, positive CSF TPPA test results, and elevated CSF protein levels and leukocyte counts were identified. Neurosyphilis, as generalized paresis of the insane and meningovascular syphilis, was considered. Antibiotic treatment was initiated. Roxithromycin (500 mg, four times orally per day) was administered as the patient was allergic to penicillin and ceftriaxone. Hexadecadrol was initiated 3 days prior to roxithromycin administration, to prevent the herxheimer reaction.

On the third day following antibiotic initiation, the neurological function of the patient deteriorated again, which was accompanied by severe diarrhea. Muscle strength of the right side declined with upper limbs measuring one-fifth and lower limbs measuring three-fifths. Her brain MRI suggested acute infarction in the left basal ganglia and right callosum genu and bleeding in the left basal ganglia (**Figure 1**). Considering that diarrhea may be a side effect of roxithromycin, roxithromycin was replaced by doxycycline (0.1 g) intravenously twice a day. The

timeline of stroke aggravation and intervention is shown in **Figure 4**.

Fourteen days after antibiotic treatment, the clinical symptoms of the patient did not improve remarkably, with a serum RPR of 1:16. The patient was discharged and visited a venereal disease hospital for further treatment.

DISCUSSION

Syphilis, caused by *T. pallidum*, is a sexually transmitted disease. Syphilis can invade many organs, including the central nervous system. Neurosyphilis, including meningovascular syphilis, parenchymatous syphilis, syphilitic meningomyelitis, tabes dorsalis, general paresis, and gummas, can occur during any disease stages (1).

The invasion of *T. pallidum* in the central nervous system may cause immune cell aggregation and subsequent immune responses. Following invasion by spirochetes, lymphocytes, plasma cells, and other immune cells are infiltrated into the meninges and meningeal vessels. Subsequently, the cerebral arteries and brain parenchyma can be affected, causing parenchymatous syphilis and meningovascular syphilis. Heubner arteritis, mainly affecting the medium or large arteries, is characterized by intimal fibroblastic proliferation, medial thinning, adventitial inflammation, and fibrosis (5). Nissl-Alzheimer arteritis mainly involves the small vessels and is characterized by adventitial and intimal thickening (5, 6). Arterial stenosis or occlusion caused by syphilitic arteritis may lead to ischemic stroke (7).

Accurate diagnosis of neurosyphilis is difficult due to the wide range of potential clinical symptoms. It has been reported that stroke, as the first symptom, is found in 14.09% of individuals with neurosyphilis, while meningovascular syphilis accounted for most neurosyphilis cases (8). It is also difficult to differentiate neurosyphilis from an ischemic stroke during the early disease period. In this case, the patient first presented with stroke and multiple stenoses in the cerebral arteries. The common risk factors for stroke were absent, except for impaired glucose tolerance. We believe that the elevated blood glucose levels alone were not sufficient to explain such severe arterial stenosis. HR-MRI was performed to determine other possible causes. On HR-MRI, arteritis normally presents with concentric enhancement, which is segmental, uniform, and circular, and encloses the border of the artery with homogeneous signal intensity. In contrast, atherosclerotic stenosis tends to present with eccentric enhancement with irregular and heterogeneous wall thickening. In contrast, reversible vasoconstriction syndrome presents as diffuse, uniform, continuous wall thickening and enhancement with less signal intensity (9, 10).

In our case, concentric vessel wall enhancement in the left MCA was observed. The entire M1 segment of the left MCA and the A1 segment of the left ACA were involved, suggesting a high possibility of arteritis. Previous studies have reported similar concentric enhancement in the BA due to syphilitic arteritis (3, 4). Concentric enhancement on HR-MRI may help identify syphilitic arteritis. Infarction of the left basal ganglia was observed in our case, which was nourished by the lenticulostriate arteries. The lenticulostriate arteries were perforating arteries originating from the MCA and ACA. We propose that the abnormality of the vessels caused by arteritis in the left MCA and ACA destroyed the orifice of the lenticulostriate arteries, leading to ischemic lesions in the left basal ganglia. Arteritis in the lenticulostriate arteries might have also existed in the present case, although it was difficult to observe on radiological images. Both large and small arteries can be affected. Heubner arteritis and Nissl-Alzheimer arteritis can also occur concomitantly. Pathological examination may provide valuable information regarding the affected arteries. Multiple stenoses, including the right ACA, MCA, and BA, were observed in this case, while the enhancement of the affected vessel wall was not obvious. Similar stenosis has also been reported in other studies, and the reasons may be the inactive phases of arteritis or concomitant atherosclerosis (11, 12). Considering that the infarct area of the left basal ganglion could be explained by the blockage of the left lenticulostriate arteries, whereas no severe infarct was identified in the right hemisphere, syphilitic arteritis-induced blood flow arrest may account for the necrosis of certain brain areas. The characteristics of syphilitic arteritis on HR-MRI are rarely reported in the literature. Therefore, our case provides valuable information regarding the radiological features of syphilitic arteritis.

No international diagnostic criteria for neurosyphilis have been proposed to date. A Chinese clinical guideline indicated that CSF protein level $\geq$0.5 g/L, leukocyte count $>10 \times 10^6$/L, and positive non-treponemal or treponemal may be indicative of a diagnosis of neurosyphilis (13). In the present case, CSF TPPA test results were positive, together with elevated CSF protein levels and leukocytes. However, the CSF RPR test results were negative, while both RPR and TPPA test results were positive in the serum. One potential explanation is that the non-treponemal test has a high specificity but low sensitivity. In contrast, the treponemal test has a high sensitivity but low specificity (2, 14). It is not reliable to use a single test to identify neurosyphilis. Both non-treponemal and treponemal tests of the serum and CSF should be performed.

The neurological symptoms of the patient deteriorated twice. In the local hospital, the syphilitic etiology was not identified, and only ordinary stroke therapy was administered. The second aggravation occurred during antisyphilis therapy. The patient was allergic to both penicillin and ceftriaxone; therefore, roxithromycin was administered instead. Erythromycin was orally administered. However, it was less effective and did not readily infuse the brain (1, 14). Diarrhea is a potential side effect of erythromycin use, which may cause dehydration and hypoperfusion. Roxithromycin was then replaced with doxycycline. Another possible reason for the second aggravation may be hemorrhagic transformation. Antiplatelet therapy was administered initially. Most cases of meningovascular syphilis present with stroke (8) and many specialists use antiplatelet regimens (3, 7). However, there are no recommendations (7, 14–17). Intracerebral hemorrhage in neurosyphilis is rarely reported (18, 19). Antiplatelet therapy and reperfusion may increase the risk of hemorrhagic transformation. Some previous studies have reported that meningovascular syphilis causes not only arterial stenosis but also aneurysmal dilation or dissection, which may rupture leading to hemorrhage (19). The

administration of antiplatelet therapy in neurosyphilis should be judiciously considered.

This case has several implications for the future management of neurosyphilis presenting with stroke. (1) HR-MRI findings of neurosyphilis have rarely been reported. This case provides the enhancement patterns of neurosyphilis arteritis on HR-MRI. (2) Antiplatelet medication should be judiciously administered since there is a potential risk of hemorrhagic transformation. Our study had some limitations. (1) Pathological examination was not performed because the patient declined examination. (2) Follow-up HR-MRI is needed to better understand the dynamic changes in the enhancement patterns of neurosyphilis arteritis.

CONCLUSION

This case report described a patient with neurosyphilis who initially presented with aggravated stroke. HR-MRI showed concentric enhancement in the internal cerebral artery, suggesting arteritis, which is helpful in differentiating neurosyphilis from other cause-induced strokes. Antiplatelet medication should be used judiciously for neurosyphilis-related stroke.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Human and Research Ethics committees of the First Hospital of Jilin University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

KZ: organization and drafting and review of the manuscript. FC: review and critique of the manuscript. CW: review of the manuscript and improvement of English expressions. MS and YY: conception, organization, execution of the manuscript, and review and critique of the manuscript. All authors contributed to the article and approved the submitted version.

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CASE REPORT
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Acute Psychosis Due to Anti-N-Methyl D-Aspartate Receptor Encephalitis Following COVID-19 Vaccination: A Case Report

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Anti-N-methyl D-aspartate (NMDA) receptor (anti-NMDAR) encephalitis has been reported after SARS-CoV-2 infection, but not after SARS-CoV-2 vaccination. We report the first known case of anti-NMDAR encephalitis after SARS-CoV-2 immunization in a young female presenting with acute psychosis, highlighting a rare potential immunological complication of vaccination against SARS-CoV-2 that is currently being distributed worldwide. The patient presented initially with anxiety and hypochondriacal delusions which progressed to psychosis and catatonia but returned to baseline with aggressive immunomodulatory therapy consisting of intravenous immunoglobulin, high-dose glucocorticoids, and rituximab. This study highlights that the workup of acute psychosis should include establishing a history of recent vaccination followed by a thorough neurological assessment, including for anti-NMDAR antibodies in blood and cerebrospinal fluid.

Keywords: COVID-19, vaccine, NMDA-receptor, encephalitis, psychosis

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INTRODUCTION

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is an autoimmune mediated condition characterized by complex neuropsychiatric syndromes and the presence of antibodies against the GluN1 receptors in the CSF (1). This disease was first described in 2007 as a paraneoplastic syndrome in women presenting with ovarian teratomas but has since been designated as the second most common immune mediated encephalopathy (2, 3). Anti-NMDAR encephalitis has been associated with viral illnesses such as Japanese encephalitis, HSV-1, Epstein-Barr virus, and most recently COVID-19 infection (**Table 1**) (5, 9–11). Additionally, anti-NMDAR encephalitis has been associated with vaccinations against H1N1, yellow fever, TdaP-IPV booster, and the Japanese Encephalitis (3, 12–14). In this case report, we present the first instance of anti-NMDAR encephalitis after receiving the Pfizer-BioNTech COVID-19 vaccine.

CASE NARRATIVE

A female in her 20's presented to the Emergency Department (ED) with a chief complaint of urinary frequency 1 week after receiving her first dose of the Pfizer-BioNTech COVID-19 vaccine (**Figure 1**). The patient's family stated she had increasingly frequent bouts of anxiety, decreased

TABLE 1 | Published cases reports of anti-NMDA encephalitis secondary to COVID-19 infection.

Patient	Gender	Age	Outcome	Anti-NMDA diagnosis from onset of primary disease	Time from positive COVID-19 test to anti-NMDA diagnosis	Neurological symptoms	Neurological findings
1 (4)	M	20's	Condition improving at time of print	3 weeks	3 weeks	**Initial presentation:** psychomotor agitation, disorganized speech, anxiety, persecutory delusions and auditory hallucinations, and global insomnia	**Initial presentation:** cerebral CT scan was negative for acute neuroanatomical abnormalities
2 (5)	F	<2	Return to baseline 1 month after onset of initial symptoms	2 weeks	1 week	**Initial presentation:** fever, fussiness, poor sleep, constipation, and decreased oral intake. **Week 1:** constant thrashing movements of extremities, non-communicative, and seizures. **Week 2:** worsening encephalopathy and persistent hyperkinetic movements of the arms, legs, and head.	**Week 1:** CSF analysis demonstrated a glucose of 56 mg/dL (serum 105 mg/dL), total protein 25 mg/dL, seven leukocytes/μL (89% lymphocytes and 11% monocytes), and two red blood cells/μL. **Week 2:** NMDAR-IgG positivity in the serum (1:640) and CSF (1:40).
3 (6)	M	<10	Released with mildly ataxic gait	12 days	5 days	**Initial presentation:** ataxia, wide-based gait, loss of DTR, somnolence, and seizures. **Week 2:** choreiform movements in the hands and feet, tongue protrusion, bruxism, lip smacking, agitation, catatonia, echolalia, and tachycardia. **Week 4**: focal seizure	**Initial presentation:** MRI and CSF analysis was normal awake and sleep EEGs were encephalopathic with widespread delta waves. **Week 4:** normal MRI
4 (7)	M	50's	Patient was discharged with no neurological deficits and in good condition after 4 months	8 days	−1 days	**Initial presentation:** Confabulations and delirious ideas. **Day 4:** focal motor seizures with impaired awareness and oro-facial dyskinesia/automatisms appeared. **Week 1:** refractory status epilepticus, oro-facial dyskinesias, loss of consciousness.	**Initial presentation:** 2 brain MRI's negative in the first week.
5 (8)	F	Teens	Full recovery after 2 months treatment	3.5 weeks	Same Day	**Initial presentation**: 3-week history of mood change as depression and anhedonia accompanied by lack of concentration and Generalized Tonic-Clonic seizures.	**Initial presentation: g**eneralized brain edema, minor meningismus, and neck stiffness. CSF analysis showed semi turbid, light pink fluid. WBC: 27, RBC: 1,997, lymphocytes: 93%, PMN: 7%, glucose: 55 mg/dL, and protein: 241 mg/dL

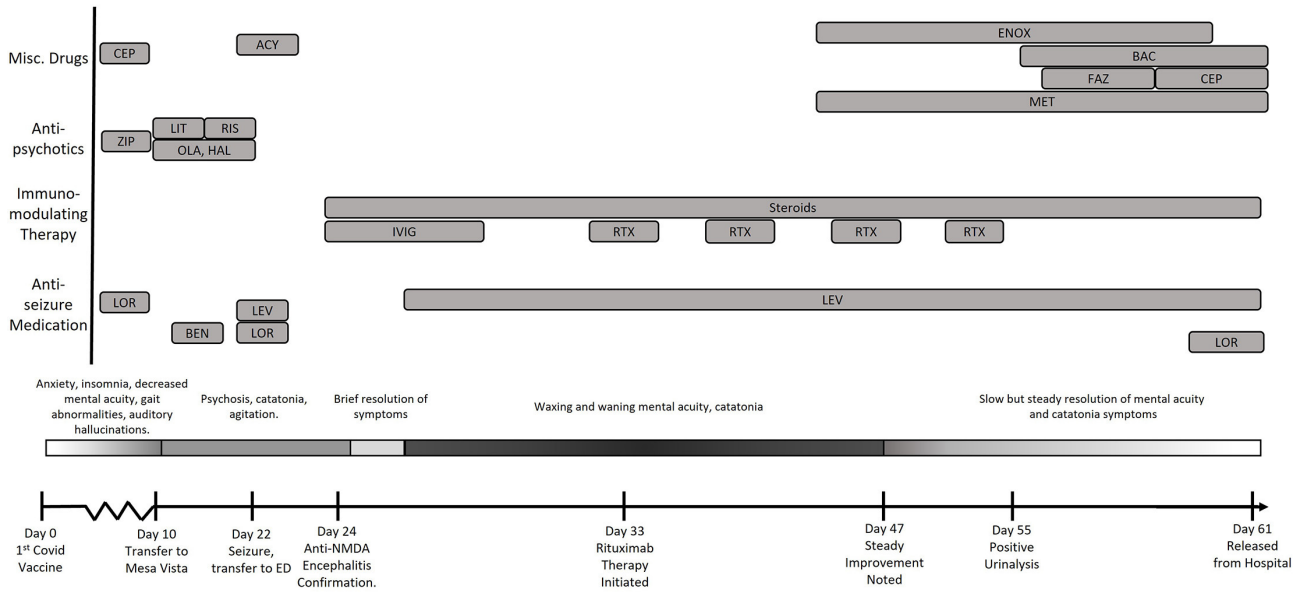

FIGURE 1 | Timeline of the evolution of the patient's condition in relation to treatments and findings. CEP, Cephalexin; LEV, Levetiracetam; LOR, Lorazepam; RIX, Rituximab; FAZ, Cefazolin; ENOX, Enoxaparin; MET, Metoprolol; BAC, Bactrim; ZIP, Ziprasidone; OLA, Olanzapine; HAL, Haldol; RIS, Risperadol; Ben, Benztropine.

mentally acuity, insomnia, and a fixation that she suffered from irritable bowels and kidney disease. She displayed waxing and waning hypochondriacal delusions that she had contracted COVID-19 and that "her body was shutting down." The patient was also noted to have some motor dysfunction and a transient bout of aphasia during this time. There were no complaints of antecedent infection, fever, or headache. Family history and past medical history were non-contributary. The physical examination showed tachycardia and hypertension but otherwise unremarkable. Hematology and metabolic labs and urinalysis were normal.

The patient was discharged from the ED with instructions to follow up with her primary care physician but returned the following day with complaints of increasing anxiety as well as continued somatization of bowel and kidney disease. The patient also endorsed accusatory auditory hallucinations but denied suicidal or homicidal ideation. Repeat blood tests demonstrated mild leukocytosis and slightly increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST). The physical exam was again normal except for elevated blood pressure and tachycardia. SARS-CoV-2 nasopharyngeal polymerase chain reaction (PCR) was negative. Due to the persistent tachycardia and hypertension, she was kept overnight for observation. No cerebrospinal fluid (CSF) analysis was performed during these initial two ED visits.

The following morning the patient removed her clothing and had a bowel movement on the floor. With no discovery of metabolic or toxic causes based on bloodwork and imaging for her acute psychosis, she was transferred to an inpatient psychiatric unit for voluntary admission. Treatment was begun with olanzapine and haloperidol (5 mg, Q4H). Despite these therapies, patient became increasingly psychotic, which was initially managed with lithium, but this was discontinued due to symptoms of catatonia. Risperidone therapy was then trialed (0.5 mg, Q4H), however the patient experienced a grand mal seizure which prompted transfer back to the ED and subsequent admission to the intensive care unit. Detailed question of family members revealed no evidence of upper respiratory, gastrointestinal, or other antecedent illness in the preceding few weeks.

At that time, the patient's memory was intact, and she was responsive to questions but lethargic. She also exhibited symptoms of ongoing catatonia, answered questions in short sentences in a monotonous tone with low phonation. She could ambulate, but slowly and with a one-person assist mainly to aid with initiation of movement. Computerized tomography (CT) and magnetic resonance imaging (MRI) of the brain were normal, as were and hematologic and metabolic laboratory evaluations. Eventually, a lumbar puncture was performed, and patient's CSF analysis showed a mild lymphocyte pleocytosis with 12–14 nucleated cells/mm^3. CSF polymerase chain reaction studies for enterovirus, herpes simplex, varicella zoster, and Epstein-Barr virus were negative. Blood serologies for Mycoplasma pneumoniae, and HIV were negative. Studies for Cryptococcus neoformans and Coccidioides immitis were negative.

The constellation of symptoms (spontaneous defecation, catatonia, sudden encephalopathy without metabolic or infectious findings) coupled with the preliminary CSF results and the history of deterioration after SARS-CoV-2 vaccination led to a strong clinical suspicion of an autoimmune-mediated encephalitis driven by the vaccine. While awaiting for the appropriate diagnostic test results, a 5-day course of IVIG (25 g

given at 0.5 mg/kg/min initially and increased to 8 mg/kg/min as tolerated) and steroid treatment (methylprednisolone, 40 mg Q8H) were begun, with clinical improvement demonstrated within 24 h. The patient become fully alert and oriented, with increased dexterity and decreased catatonia, although her affect remained flat. Additionally, metoprolol was prescribed to manage the patient's tachycardia and hypertension.

Eventually, CSF anti-NMDA titers of 1:20 returned. Due the high correlation between anti-NMDAR encephalitis and paraneoplastic teratomas, a transvaginal ultrasound, chest x-ray and CT, and MRI of the chest, pelvis, and abdomen were performed, all of which were unremarkable. EEG revealed no abnormalities. When the 5-day IVIG course was completed, her neurological status deteriorated. The patient continued to present with a flat affect and increasingly poor volitional initiation of movement and speech.

Weekly rituximab therapy was initiated (375 mg/m^2 initial infusion of 50 mg/h increased to a maximum of 400 mg/h), and methylprednisolone dose was increased. The patient's mental acuity and catatonia continued to wax and wane in severity until the administration of her third dose of Rituximab. Repeat evaluation of CSF revealed resolution of her lymphocytic pleocytosis (4 WBC/mm^3, normal $\leq$) Anti-NMDAR CSF titers had decreased to 1:10. Slow but consistent improvements in her neurological status were observed following her third rituximab dose. Eventually, 45 days in the hospital and 61 days after receiving the SARS-CoV-2 vaccine, she was discharged from the hospital with minor neurological deficits. She remains well 3 months after hospital discharge on anticonvulsant therapy, with no signs of relapse and has returned to work.

DISCUSSION

SARS-CoV-2 vaccines have been critical in reducing COVID-19 morbidity and mortality and facilitated the societal return to normalcy during the COVID-19 pandemic. While numerous psychiatric conditions, including anti-NMDAR encephalitis, have been shown to complicate COVID-19 infections (**Table 1**), this case report is the first reported incident of anti-NMDAR encephalitis temporally linked to SARS-CoV-2 vaccination (4, 5, 7, 8, 15). Extensive workup showed no evidence that patient's symptoms were due to a paraneoplastic condition, which is more common for this specific neurologic condition. Instead, based on precedent cases of anti-NMDAR encephalitis caused by vaccines against influenza, yellow fever, Japanese encephalitis, and tetanus/diphtheria vaccines, clinicians in this case quickly considered the recent receipt of SARS-CoV-2 vaccine as a possible trigger of anti-NMDAR encephalitis (3, 12–14).

The diagnosis of an auto-immune encephalitis was not considered during the initial presentation to the emergency room because the anxiety, hallucinations, insomnia, psychosis, and were initially considered symptoms of primary psychiatric diseases, further supported by absence of fever or other objective signs of systemic infection or inflammation. Therefore, one of the major teaching points of this case is the need for serious consideration of organic nervous system causes of psychosis, despite the absence of recent or current signs of infection. This requires careful imaging of the brain, performance of a lumbar puncture, and the search for anti-NMDAR in both CSF and peripheral blood. There have been two recent studies on the psychiatric manifestations of anti-NMDAR encephalitis which report that severe agitation, speech disturbance, and catatonia amongst other psychiatric features, may signal the presence of organic pathology, particularly when dealing with a young female presenting at an atypical age for primary psychosis (16). The concomitant presence of seven features-agitation, aggression, hallucinations, delusions, mutism, irritability or mood instability, and depressed mood would not be typical of any single psychiatric diagnosis and point to organic brain pathology (17).

Despite initial delay in establishing the diagnosis, the presentation of seizure, psychiatric symptoms, and history of recent of SARS-CoV-2 vaccination resulted in prompt treatment with IVIG and glucocorticoids even before the diagnosis was established *via* anti-NMDAR antibody detection. This provided temporary improvement of symptoms, perhaps due to the blockade of harmful anti-NMDAR antibodies driving the disease. However, it was not until rituximab-mediated B-lymphocyte depletion blocking formation of new anti-NMDAR antibodies that the patient's symptoms finally started to show signs of improvement (6). However, given the long 3-week half-life of IgG, the process of clinical improvement was very slow, dependent on gradual clearance of previously formed anti-NMDAR antibodies induced by the vaccine while rituximab prevented formation of new antibodies. We hypothesize that concomitant plasmapheresis alongside rituximab may have hastened the neurological recovery by more rapid removal of harmful anti-NMDAR antibodies.

In summary, we present the first case of anti-NMDAR encephalitis complicating SARS-CoV2 vaccination in a previously healthy young woman. This case provides an important reminder that (i) psychiatric clinical presentations warrant a thorough medical workup, including brain imaging, CSF analysis, anti-NMDAR antibody testing, and a vaccine history; (ii) combined therapies of blocking (IVIG), reducing production of (rituximab), and even removing (plasmapheresis) harmful anti-NMDAR may be the optimal strategy to reverse the neurological and psychiatric symptoms driven by anti-NMDAR antibody production. Fortunately, prompt therapy targeting anti-NMDAR antibodies resulted in achieving and sustaining an excellent clinical outcome. In addition to providing clinicians the opportunity to identify potential vaccine-associated anti-NMDAR encephalitis, particular attention may be needed to patients receiving COVID-19 vaccine who have previously have had anti-NMDAR encephalitis.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

PF wrote the first draft of the paper and compiled background information. IY, MK, and GS were treating physicians and edited manuscript draft. All authors contributed to the article and approved the submitted version.

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frontiers in Neurology

CASE REPORT
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Relapsing Neurological Complications in a Child With ATP1A3 Gene Mutation and Influenza Infection: A Case Report

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Mutations in the ATP1A3 gene encoding the α3 subunit of Na+/K+-ATPase are associated with different neurological manifestations that may be elicited by febrile episodes. A recently described phenotype, linked to the p.Arg756Cys mutation, is clinically characterized by Relapsing Encephalopathy with Cerebellar Ataxia (RECA). In our case, a diagnosis of RECA has been established, and despite an alternative, reasonable cause had been already identified.

We describe the case of a child with two recurrent episodes, 2 years apart, of hypotonia and ataxia. In both episodes, a laboratory-confirmed influenza virus infection suggested the diagnosis of influenza-associated encephalopathy. After the second episode, a search for genetic mutations was performed, and ATP1A3 mutation associated to RECA was found. After both episodes, the child was discharged after partial improvement of neurological conditions.

The diagnosis of encephalopathy in children is often challenging. A genetic predisposition to neurological decompensation should be suspected in case of recurrent episodes, even if an alternative diagnosis has been established. Indeed, febrile infections may only represent the trigger of neurological involvement. In these patients, the knowledge of a genetic predisposing factors may help in the prevention of neurological episodes by the prompt use of anti-pyrectics and preventive measures as appropriate vaccination.

Keywords: ATP1A3 gene mutations, influenza, encephalopathy, differential diagnosis, case report

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INTRODUCTION

In recent years, the role of mutations in the ATP1A3 gene, encoding the α3 subunit of Na^+/K^+-ATPase, have been discussed and increasingly described in literature (1, 2). Three main syndromes have been associated to these mutations: Alternating Hemiplegia of Childhood (AHC), Rapid-onset Dystonia Parkinsonism (RDP), and CAPOS syndrome (cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss). From 2004 to 2012 both autosomal dominant and *de novo* mutations in ATP1A3 have been detected in patients affected by these three conditions (3–6).

Other clinical presentations of ATP1A3 mutations that do not fall within one of these major syndromes have also been reported and new phenotypes have been described (7). A new phenotype linked to the p.Arg756Cys mutation, characterized by relapsing encephalopathy with cerebellar ataxia, named RECA has been recently identified (8). Clinical manifestations of these mutations may be elicited by infective triggers or febrile episodes.

Also, influenza virus is a cause of encephalitis or encephalopathy. Although rare, neurological involvement may occur especially in children and is characterized by a broad spectrum of manifestations, including movement disorders and ataxia (9, 10). These manifestations are similar to those observed among children with ATP1A3 mutations.

We describe a case report of a child who experienced two recurrent episodes of encephalopathy, 1 year apart, apparently associated to influenza infection. After the second episode, despite the positivity of nasal swab for influenza, a genetic analysis was performed, and a diagnosis of ATP1A3 mutation was made.

CASE DESCRIPTION

An 18-month-old male child, with no underlying medical conditions, presented in January 2018 with a history of 4 days of fever reaching 39°C and cough, followed on day 2 by irritability and decreased muscle tone.

The child was fully vaccinated according to the Italian vaccination schedule (11), and met all developmental milestones until the onset of the symptoms. The child was not vaccinated for seasonal influenza. His parents and his older sister were healthy.

On admission, he was whiny and showed hypotonia of the four limbs with poor head control and inability to maintain a sitting position. No signs of meningeal irritation were present and cranial nerve examination was normal. A few days later, the child developed ataxic gait.

Blood testing revealed white blood count 4,600/mm3 with neutrophil at 42.6%, lymphocytes at 42.6%, monocytes at 14.8%, hemoglobin: 12.1 g/dl, platelet counts: 257.000/mm3, and C-reactive protein:0.2 (normal value 0–0.3) mg/dl. Biochemical investigations, including serum liver and kidney function tests and electrolytes were normal. Multiple Polymerase chain reaction (PCR) (Seeplex®RV15 one step and Seeplex® Pneumobacter Ace detection) performed on nasal swab for common bacterial and viral respiratory infections resulted positive for Influenza A-H1N1 pdm09, *Streptococcus pneumoniae*, and *Haemophilus influenzae*.

A chest radiograph evidenced a parenchymal consolidation, and computed tomography (CT) scan of the brain revealed no pathologic lesions.

Cerebrospinal fluid (CSF) was clear and colorless, and its examination showed 4 cells, protein of 29 mg/dl, and glucose of 65 mg/dl (glycemia 105 mg/dl). CSF cultures were bacteriologically sterile. Multiple PCR (Biofire® Film Array Meningitis Encephalitis (FAME) was negative for the most frequent viruses, bacteria causing meningo-encephalitis, and further microbiologic workup of CSF for other viruses and bacteria (influenza, parainfluenza 1–2–3–4, adenovirus, metapneumovirus, Epstein Barr virus, mycoplasma pneumoniae, Chlamydophila pneumoniae) and acid-fast bacilli bacteria were negative.

The electroencephalogram (EEG) showed a picture of severe cortico-subcortical suffering.

Contrast enhanced magnetic resonance imaging (MRI) demonstrated slight vermian cistern enlargement. The patient was diagnosed with influenza-associated encephalopathy (IAE) based on the clinical findings. He was treated with oral oseltamivir, intravenous ceftriaxone, pulse dexamethasone, and levetiracetam.

After 18 days of hospitalization, the child was discharged in improved clinical conditions, i.e., resolution of trunk and head hypotonia, while persisting cerebellar ataxia without impairment of cognitive functioning.

In January 2020, the same child returned to our observation because of influenza-like symptoms (fever and cough) associated with difficulty in maintaining upright position and ataxic gait.

On admission, physical examination showed absence of meningeal signs, irritability, mild positive red dermographism, and absence of osteotendinous reflexes.

Blood exams, including blood count, C- reactive protein, liver, and kidney functions, were all in the normal range.

Multiple PCR (Seeplex®RV15 one step and Seeplex® Pneumobacter Ace detection) performed on nasal swab resulted positive for influenza AH3N2.

Cerebrospinal Fluid (CSF) analysis showed: 2 cells, protein 25 mg/dl and glucose 70 mg/dl (glycemia 180 mg/dl). Multiple PCR (Biofire® Film Array Meningitis Encephalitis (FAME) was negative along with PCR for influenza virus and the search for other infectious causes of encephalitis (parainfluenzae viruses, adenovirus, parvovirus B19, Epstein Barr virus, acid fast bacilli bacteria). CSF culture was also negative.

The search of autoimmune and paraneoplastic markers of encephalitis (anti-NMDA, anti-Hu, anti-Yo, Anti-Ri, Anti-CV2, Anti-Ma2, anti-amphiphisin) were investigated and were all negative. Brain MRI was normal, and the EEG showed sleep-related brain physiological activity.

Treatment with oseltamivir and pulse dexamethasone was started. Furthermore, in the hypothesis of an immune mediated mechanism as a pathogenetic component of IAE, intravenous immunoglobulin was added. Clinical conditions progressively improved with reduction of tremors and trunk oscillations and more coordinated walking.

However, despite improvement, this second episode raised suspicion of a genetic predisposition to neurological manifestation triggered by specific events, so a single nucleotide polymorphism (SNP) array was performed, revealing the heterozygous *de novo* mutation c.2266C > T (p.Arg756Cys) of ATP1A3 gene.

The child was discharged on day 16 with slight ataxic gait.

DISCUSSION

Influenza is a common diagnosis during the winter season. Despite how it is mostly a self-limiting mild disease, primarily

affecting upper respiratory tract, neurological complications may occur, especially among children. These complications include encephalopathy/encephalitis, seizures, transverse myelitis, acute disseminated encephalomyelitis, and Guillain-Barré syndrome. Cerebellar involvement has also been described with generalized hypotonia and ataxia, as occurred in our patient (1, 2). For this reason, a diagnosis of Influenza associated encephalopathy (IAE) has been made after the first episode, with no further research for alternative or concomitant causes.

A diagnosis of IAE is also possible in the absence of Influenza virus isolation in cerebrospinal fluid (CSF). Indeed, in agreement with literature data, influenza virus is rarely neurotropic and rarely found in CSF. The pathogenesis of these manifestation seems to be driven by immunologic and/or metabolic processes damaging vascular endothelium and causing inflammation and apoptosis of vascular endothelium and brain tissue ("cytokine storm") (12). For these reasons, the term encephalopathy is often preferred (13, 14).

The clinical characteristics of the recurrent episode, despite the hypothesis of influenza encephalopathy was made again, stimulated us to explore alternative diagnosis or the presence of predisposing factors of neurological decompensation, including genetic mutations.

Genetic analysis revealed the presence of the heterozygous ATP1A3 gene mutation, specifically the p.Arg756Cys variant.

Mutations in ATP1A3 gene lead to different phenotypes having in common acute neurological decompensation episodes triggered by different factors, including febrile episodes. In our case, the Influenza could only have acted as a trigger, probably as a febrile illness, and not itself the cause of the encephalopathy.

Alongside the well-characterized clinical phenotypes AHC, RDP, and CAPOS, a new phenotype clinically characterized by relapsing encephalopathy with cerebellar ataxia (RECA) has been firstly diagnosed in an adult in 2015 and associated with p.Arg756Cys variant (15). Since then, several cases have been described in children.

The main characteristic is hypotonia associated to areflexia and ataxia. However, the severity of symptoms can be variable along with the long-term sequelae. In fact, each episode is followed by slow and partial recovery. Also, for our case, persisting weakness, tremor in the limbs, and ataxia were present at discharge and required, after both episodes, motor rehabilitation.

Our description aims to enrich the literature of clinical cases related to ATP1A3 gene mutations in consideration of recent discovery of this phenotype. Furthermore, it underlines that even if a primary diagnosis has been established, in the presence of recurrent episodes, a genetic evaluation is always advisable and should be considered. Indeed, the knowledge of a genetic predisposing factor may help in the prevention of neurological episodes, e.g., by the prompt use of anti-pyretic drugs. Specifically, in our case, the seasonal influenza vaccination would represent an effective protective measure.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

RP conceived and drafted the paper and performed literature search. NC and GP performed literature search and contributed for important intellectual contents. CT and CR revised the paper and contributed for important intellectual contents. All authors participated in clinical and diagnostic management of the patient, and approved the final version of the paper.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.774054/full#supplementary-material

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CASE REPORT
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Case Report: Neurodegenerative Diseases After Severe Acute Respiratory Syndrome Coronavirus 2 Infection, a Report of Three Cases: Creutzfeldt–Jakob Disease, Rapidly Progressive Alzheimer's Disease, and Frontotemporal Dementia

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The relationship between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and neurodegenerative diseases is yet to be fully clarified. Rapid worsening and even new-onset cases of those disorders have been reported in association with coronavirus disease 2019 (COVID-19). We describe three cases of neurodegenerative diseases in patients with SARS-CoV-2: a case of Creutzfeldt–Jakob disease during the COVID-19 acute phase, to our knowledge, is the second one described in the literature; a rapidly progressive Alzheimer's Disease; and a patient with frontotemporal dementia, and a quick decline of both cognitive and behavioral domains. This report suggests an association between SARS-CoV-2 infection and a higher probability of developing or accelerating neurodegenerative chronic neurologic conditions. We reinforce the need for a close cognitive follow-up in the aftermath of Sars-Cov2 infection.

Keywords: SARS-CoV-2, COVID-19, neurodegenerative disease, case report, Creutzfeldt96Jakob disease, Alzheimer's disease, frontotemporal dementia

INTRODUCTION

Patients with coronavirus disease 2019 (COVID-19) present neurological manifestations such as dizziness, headache, and impaired consciousness (1). The impact on cognitive symptoms is still under debate.

Even mild forms of COVID-19 can present sustained neurocognitive deficits (2, 3). Furthermore, patients previously diagnosed with dementia may be at risk of rapid cognitive deterioration during and after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (4).

Mild forms of frontotemporal dementia (FTD) may have significant worsening in behavior and social cognition after COVID-19 (5). Recently, Creutzfeldt–Jakob disease (CJD) was reported in a previously healthy man during the acute phase of COVID-19 (6).

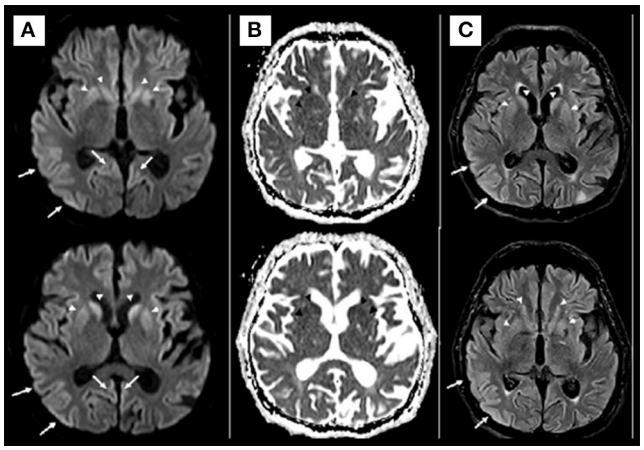

FIGURE 1 | Axial diffusion [diffusion weighted imaging (DWI)] **(A)** and apparent diffusion coefficient (ADC) map **(B)** MRI at admission. Diffusion restriction involving the cerebral cortex and basal ganglia (arrows in **A**). No convincing white matter involvement. The hypotheses for MRI findings were pos-ictal state, hypoxic-ischemic encephalopathy, and spongiform encephalopathy. Axial Diffusion and FLAIR **(C)** MRI after 2 weeks demonstrated similar imaging findings, making the hypothesis of spongiform encephalopathy more likely.

We report three cases of neurodegenerative cognitive diseases in patients with COVID-19, and discuss the relationship between CJD, Alzheimer's Disease (AD), FTD, and SARS-CoV-2 infection.

CASE PRESENTATION 1

A 75-year-old man presented with a 15-day history of confusion, agitation, suicidal ideation, and inability to walk. He did not have any history of previous behavioral or cognitive symptoms. A brain magnetic resonance imaging (MRI) and lumbar puncture were performed. No abnormalities were identified at that time.

On the following days, he developed fever, and an RT-PCR for SARS-CoV-2 tested positive. At that time, chest CT revealed ground-glass opacities of more than 50% of lung territory. A further deterioration of respiratory function led to orotracheal intubation. He was treated with methylprednisolone, sulfamethoxazole-trimethoprim, meropenem, and linezolid for associated bacterial pneumonia. Acute renal failure was managed with hemodialysis.

He was transferred to our service for further investigations and treatment. Neurologic examination revealed impaired consciousness, bilateral spastic hemiparesis, and myoclonic jerks. No other abnormalities were detected.

Brain MRI showed restricted diffusion with corresponding FLAIR hyperintensity diffusely in the cortex and striate nucleus, sparing pre-central gyrus and hippocampus (**Figure 1**). Cerebrospinal fluid (CSF) had a normal cell count, and a mildly elevated protein level. Glucose, bacterial culture, molecular testing for herpes virus, and SARS-CoV-2 PCR performed in the CSF were negative. Electroencephalogram (EEG) revealed 1-2 Hz generalized periodic discharges (GPDs) and a diffuse theta-delta slowing (**Figure 2**).

The patient was treated with intravenous immune globulin (IVIG) until CSF, and the serum autoimmune encephalitis panels resulted negative. After 3 weeks, positive 14-3-3, T-TAU (> 20,000 pg/ml), and CSF RT-QuIC tests reinforced the hypothesis of probable sporadic CJD (7, 8). Unfortunately, he died of sepsis, secondary to bacterial pneumonia 4 months after the symptoms onset.

There was no family history of CJD or any other dementia. No risk factors for iatrogenic CJD such as previous neurosurgery and blood transfusions were reported.

CASE PRESENTATION 2

A 69-year-old female, with neither cognitive nor psychiatric antecedents, started having symptoms of panic disorder and complaints of forgetfulness (name of family members and friends, appointments, addresses) 1 month after a mild COVID-19 infection. There was no family history of neurological conditions.

Her past medical history was remarkable only for hypercholesterolemia and hypothyroidism. The patient had no history of smoking, abusive alcohol intake, or illicit drug use. A rapidly progressive dementia diagnostic workup excluded infectious, metabolic, and inflammatory causes.

Neurocognitive assessment at the first clinic visit revealed a Montreal Cognitive Assessment test of 7/30. Her speech was non-fluent with word-finding difficulties. Semantic and phonemic verbal fluency was 6 and 5 words per minute, respectively. Additionally, the patient had trouble in both naming objects and repeating sentences. Memory was also impaired on bedside testing, the Figure Memory Test (9). The rest of the neurological examination was unremarkable.

Brain MRI did not show any structural abnormality that could explain the cognitive decline. The FDG-PET showed diffuse cerebral hypometabolism in the posterior parietal regions with extension to the posterior cingulate gyrus and bilateral pre-cuneus, temporal, and frontal lobes, suggesting Alzheimer's disease (**Figure 3**). Amyloid biomarkers such as Pittsburgh compound-B positron emission tomography scan (PiB-PET) and CSF Aβ42 levels were not available at our service; therefore, they could not be performed. However, according to the National Institute on Aging and the Alzheimer's Association (NIA-AA), the patient still fulfilled the criteria for possible AD dementia (10).

She was started on acetylcholinesterase inhibitors and remained stable at 1-year follow-up.

CASE PRESENTATION 3

A 55-year-old man was hospitalized due to a clinical syndrome suggestive of COVID-19 (cough, anosmia, and fever). After discharge, he developed progressive difficulty in paying bills, carrying out domestic activities, and organizing activities at work in the last 5 months.

Family members informed that the patient had been showing behavioral changes, episodes of apathy, excessive money

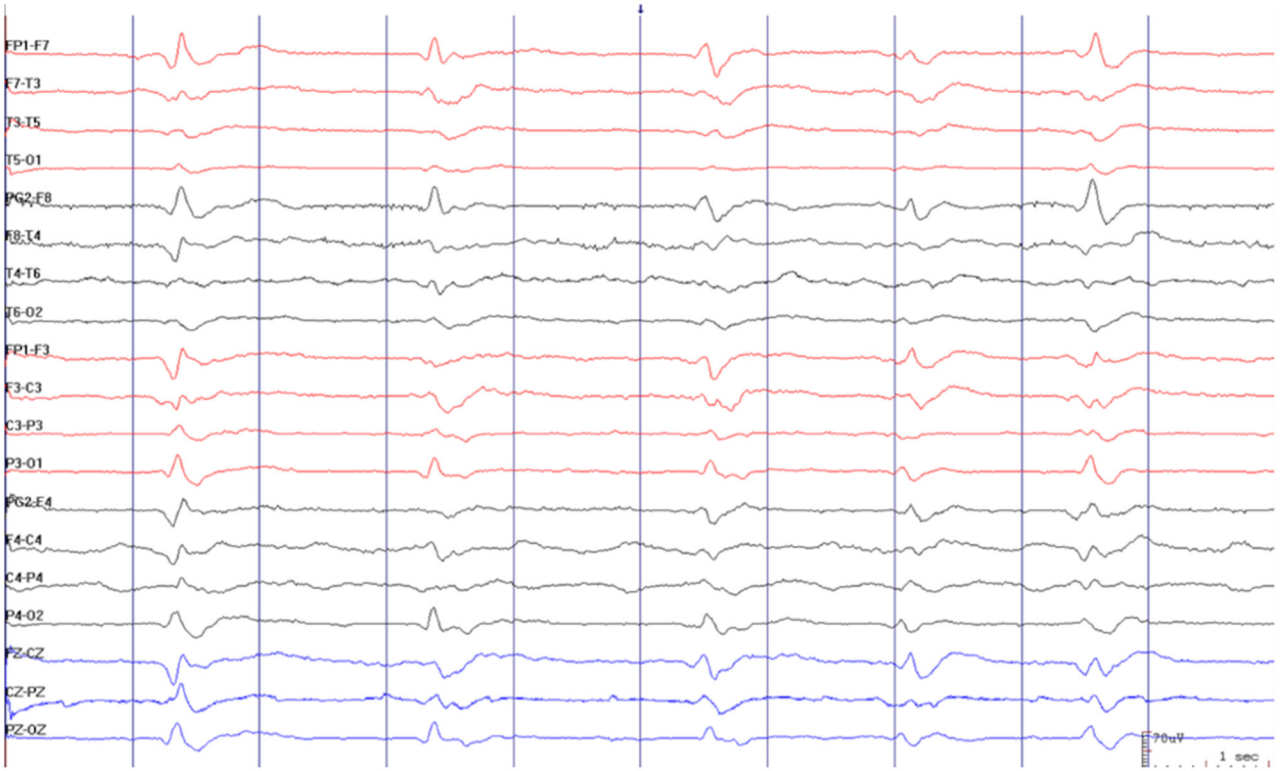

FIGURE 2 | Electroencephalogram revealed 1–2 Hz generalized periodic discharges (GPDs) and diffuse theta-delta slowing.

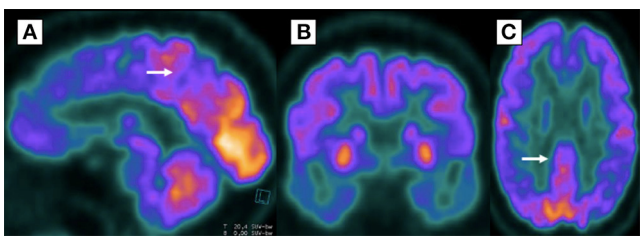

FIGURE 3 | Diffuse glycolytic hypometabolism in posterior parietal regions, extending bilaterally to precuneus **(A)**, temporal **(B)**, posterior cingulate gyrus **(C)**, and frontal lobes in 18-fluorodeoxyglucose positron emission tomography.

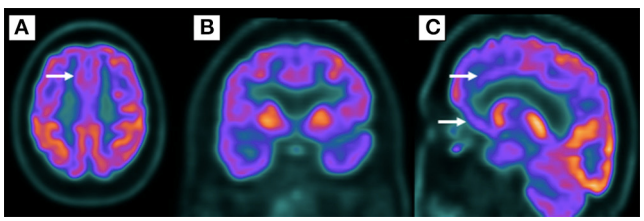

FIGURE 4 | Bilateral frontal hypometabolism **(A,B)**, more evident in the medial and mid-basal frontal lobe **(C)** in 18-fluorodeoxyglucose positron emission tomography.

spending, and social inadequacy for the past 2 years, which led to the end of a romantic relationship. These behavioral changes were treated as depressive symptoms with sertraline 50 mg/day. Subsequently, clonazepam 1 mg/day was started for an associated anxiety disorder, with no significant response. There was no other remarkable personal or family medical history.

Upon cognitive examination, the patient scored 17/30 on the Mini-Mental State Examination, which revealed impairment in executive function and language. In the clock drawing test, the patient wrote numbers from 1 to 24. The rest of the neurological examination was unremarkable.

The patient underwent a brain MRI, which was unremarkable. Then, a cerebral PET-FDG was performed, which revealed a moderate bilateral frontal hypometabolism, more evident in medial and mid-basal appearance, including anterior cingulate gyrus, and, to a lesser extent, temporal lobes, supporting the hypothesis of FTD (**Figure 4**).

The patient fulfilled the criteria for a probable behavioral variant of FTD: executive dysfunction, apathy, impulsivity (impulsive purchases), loss of empathy (social inadequacy with the end of a loving relationship), and a suggestive PET-FDG. Unfortunately, after hospital discharge, the patient was lost to follow-up.

DISCUSSION

The SARS-CoV-2 is detected in the central nervous system (CNS) in patients with COVID-19 (11). Coronavirus accesses the CNS *via* the olfactory bulb and cerebral vasculature through the angiotensin-converting enzyme 2 (ACE-2) receptor (12).

The CNS damage is probably attributable to systemic inflammation, peripheral organ dysfunction, and cerebrovascular changes. Hyperinflammation with elevated interleukin-1β, interferon-γ (INF-γ), C-reactive protein (CRP), granulocyte colony-stimulating factor (G-CSF), CXCL10, monocyte protein 1-α, and tumor necrosis factor-α (TNF-α) was described during COVID-19 infection (13, 14).

Recently, a case-control study has found that elevated CRP levels were associated with cognitive dysfunction in patients with COVID-19, specifically sustained attention. Authors cited previous works that suggested CRP might have an early effect on frontal lobe functioning and highlighted the association of other viral infections with cognitive impairment (15).

Studies on sepsis have associated systemic inflammation with cognitive decline and neurodegenerative disease (16–19). A condition related to severe systemic inflammation, COVID-19, may similarly increase the risk to develop or accelerate the subclinical neurodegenerative conditions.

Both SARS-CoV-2 and AD present a similar inflammatory markers profile: IL-6, IL-1, GAL-9 (galectin-9), and CKAP4 (cytoskeleton-associated protein 4). ACE-2 receptor, and SARS-CoV-2-binding protein for cell entry, was found to have a ten-time higher expression in AD brains than controls (20). The presence of APOE-ϵ4 mutation, the strongest genetic risk factor for AD, was associated with an increased risk of infection and mortality due to COVID-19 (21).

The FTD also presents a pro-inflammatory cytokine signature with increased IL-6 and IL-1 (22), similar to COVID-19. The progranulin levels, a protein mutated in familial forms of FTD, were associated with the severity of COVID-19 (23).

The SARS-CoV-2 contributes to chronic neurological damage through hypoxia and cerebral hypoperfusion secondary to: (a) cardiorespiratory disease, (b) coagulopathy resulting in thrombotic occlusion of cerebral blood vessels, (c) and cerebral microvascular damage due to endothelial dysfunction. Cerebral hypoperfusion accelerates amyloid-β (Aβ) accumulation and is linked to tau and TDP-43 pathology (12).

This paper has several limitations. None of the cases had anatomopathological confirmation, amyloid biomarkers were unavailable for Patient 2, and Patient 3 was lost to follow-up. However, we believe that sufficient data on clinical history and complementary exams could be gathered to exclude differentials and fulfill either possible or probable diagnosis based on published criteria (7, 8, 10, 24).

Although far from establishing a causal relationship, our report may be added to the previous and future ones in the hope of building more robust evidence of association between SARS-CoV-2 and a higher probability of developing or accelerating the neurodegenerative chronic neurologic conditions. We believe this association may be explained by inflammatory and vascular mechanisms. Furthermore, it reinforces the need for cognitive follow-up after the infection is resolved, especially in older patients at risk of developing dementia.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

MS revised the case report for intellectual content. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.731369/full#supplementary-material

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CASE REPORT
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Case Report: Moving Tumor-Like Foci Behind Refractory Epilepsy-Cerebral Sparganosis Successfully Treated by Surgery After Failure of Praziquantel Treatment

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Cerebral sparganosis is clinically non-specific and easily misdiagnosed, exposing patients to the risk of severe brain damage and neurological dysfunction caused by actively migrating larvae. Diagnostic biomarkers from typical cases can help to establish an early diagnosis and proper treatment. We present a 25-year-old woman who suffered from 9 years of refractory epilepsy and was misdiagnosed with glioma and subjected to surgery. The postoperative pathology confirmed granuloma, and the tumor-like foci reappeared 3 months later. Along with the "tunnel sign" on MRI, cerebral sparganosis was suspected and confirmed by positive serum and cerebrospinal fluid antibodies against *Spirometra mansoni*. The patient visited us after a failure of four cycles of praziquantel treatment, recurrent seizures and hemiplegia with basal ganglia foci. Craniotomy was not carried out until the larva moved to the superficial lobe on follow-up MRIs, and pathology revealed sparganosis granuloma. The patient became seizure-free and recovered myodynamia but had long-lasting cognitive dysfunction due to severe brain damage. This case indicated the importance of tunnel signs and moving tumor-like foci on MRI as diagnostic clues of cerebral sparganosis. An early diagnosis is vitally important to avoid severe neural dysfunction by the long-living and moving larvae. Surgical removal of the larva is a critical remedy for cases failed by praziquantel treatment.

Keywords: cerebral sparganosis, craniotomy, refractory epilepsy, *Spirometra mansoni*, tunnel sign

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INTRODUCTION

Cerebral sparganosis is a cerebral parasitic infection caused by the sparganum, the metacestode larva of *Spirometra mansoni*, which has a strong contraction ability, moves into the brain tissue and lives in necrotic tunnels, causing formation of a parasite granuloma, typically with eosinophil infiltration. The ovum of *S. mansoni* develops into the coracidium in the contaminated water after excreted by the definitive host (often dogs and cats) and is then absorbeds by the cyclops, its first intermediate host, in which the coracidium develops into the procercoid. The procercoid infects its second intermediate host, tadpoles, which catches the infected cyclops and develops into the sparganum in the muscle as tadpoles grow into frogs. Contact to either infected first or second

intermediate hosts can cause cerebral sparganosis. The clinical manifestation is usually non-specific and depends on the lesion location, including headache, epileptic seizure, mild hemiparalysis and blurred vision. Blood and cerebral spinal fluid (CSF) antibodies against *Spirometra mansoni* have high sensitivity and specificity for diagnosis. Neuroimaging can provide diagnostic clues, such as moving lesions and typical tunnel signs, which mainly located at the border between the white and gray matter of the frontal and parietal lobes and the centrum semiovale but rarely appears in the cerebellum and the basal ganglia (1, 2). However, cerebral sparganosis is easily misdiagnosed as dysembryoplastic neuroepithelial tumor (DNET), glioma or a cerebral abscess (3) because the lesion commonly features space-occupying foci with enhancement, edema and mass effects on computed tomography (CT) or magnetic resonance imaging (MRI), and the diagnosis is challenging, especially during the early disease stage. Many cases are only diagnosed from pathological examination after surgical resection based on a presurgical diagnosis of various types of brain tumors (4). The delayed diagnosis leaves the patient suffering from severe neurological dysfunction and uncontrolled seizures, treated with polytherapy with various anti-epileptic drugs (AEDs), as in the patient we reported.

The treatment strategy includes drug therapy with praziquantel and surgical removal of the granuloma and the scolex (craniotomy as well as stereotactic aspiration) (5, 6). In Hong et al.'s study, 26 patients with sparganosis from mainland China received different therapies. Sixteen of them underwent craniotomy, seven underwent stereotactic aspiration and three were treated with praziquantel only, which had a similar effect of seizure control (7). Surgery could be an effective remedy, but it is still difficult to optimize the operation time considering the secondary damage from the surgery and the possibility of a failure to remove the granuloma (8).

Here we presented a case of cerebral sparganosis with tortuous diagnosis and treatment process because of misdiagnosis as brain tumor and subjected to surgery. Four circles of praziquantel treatment was unsuccessful though diagnosis was corrected, and the larva moved to basal ganglia with surgical contraindication. Finally, the larva was finally removed by craniotomy when it moved to the superficial part of the lobe by repeated follow-up MRI scanning. Related literature was also reviewed in this paper.

CASE DESCRIPTION

Our patient was a 25-year-old woman without a past medical history who complained of recurrent convulsive seizures for 9 years and a massive cerebral lesion observed 5 years prior. Her first unprovoked episode was considered an epileptic seizure at a local primary care clinic with a reported "abnormal EEG", but no neuroimaging evaluation was performed due to her father's refusal (details unavailable), and no medication was given considering it was just one isolated episode when she was 16. A second similar episode recurred 2 years later, and she was discharged with oral valproic acid, without any other examinations due to her poor economic condition. The patient experienced tonic clonic seizures without specific aura every 3–4 months thereafter.

At the age of 21, she presented the same symptoms of poorly controlled seizures and was admitted to the local hospital, where routine magnetic resonance imaging (MRI) revealed an intracranial space-occupying lesion suspected to be a glioma. She was discharged with carbamazepine (CBZ) after her father's refusal to allow surgery. One month later, she withdrew from the CBZ due to a skin rash and was seizure free for 1 year.

When she was 22, she presented to the hospital again because of recurrent seizures and had a routine and enhanced MRI scan that revealed space-occupying foci with hypointensity on T1 and hyperintensity on T2 and fluid attenuated inversion recovery (FLAIR) sequences in the right frontal and temporal lobes with striped and patchy enhancement along with malacia foci without enhancement in the right frontal and parietal lobes (**Figure 1A**). Based on the probable diagnosis of a brain tumor, she underwent craniotomy at the sixth year after onset. However, pathology confirmed the lesion was a granuloma. The patient was discharged without AEDs and no seizure attacks after the surgery.

Three months after the operation, her follow-up MRI revealed postoperative foci with hypointensity on T1 and hyperintensity on T2 and FLAIR sequences in the right frontal lobe and encephalomalacia foci in the parietal and temporal lobes with additional tunnel-like enhancement in the left frontal lobe (**Figure 1B**). A detailed overview of the MRIs before and after surgery also indicated dural enhancement in the bilateral frontal lobe and anterior cingulate. It was clear that the enhanced foci had shifted to the other side and combined with her irregular parenchyma and dural enhancement and the coexistence of newer and older foci, parasitic infection was then suspected. Her history was further inquired, and her mother confirmed that she fell into a pond in their village where frogs lived at 4 years of age and underwent antibiotic treatment because of pneumonia caused by inhaling the dirty water.

Therefore, antibody tests against various parasites in her blood and CSF samples were performed, and positive results confirmed the diagnosis of cerebral sparganosis. She was prescribed anthelmintic drugs (praziquantel, details about the dosage schedule unavailable) for four cycles and levetiracetam (LEV) for seizure control. The treatment effect seemed to be satisfactory. Repeated MRI after anthelmintic treatment suggested improvement (**Figure 1C**), and her seizures were reduced to two to three episodes per year even after the dose of LEV was reduced to 0.5 g per day by herself.

Three years after the operation, she was 25 and suddenly developed weakness in her left extremities with a delayed response and extended sleep time. She was transferred to our epilepsy center. All physical examinations showed negative results except that the motor exam showed left-sided strength of level IV^+ and left-sided increased tendon reflexes. Further examination confirmed decreased blood hemoglobin (106 g/L, normal range 110–150 g/L) and slightly increased cerebrospinal fluid (CSF) total protein of 45.2 mg/dL (normal range 10–45 mg/dL). Her routine blood tests, serum electrolytes and glucose levels, liver and kidney function, and nuclear cell count and electrolytes and glucose levels in CSF were all normal. Whether

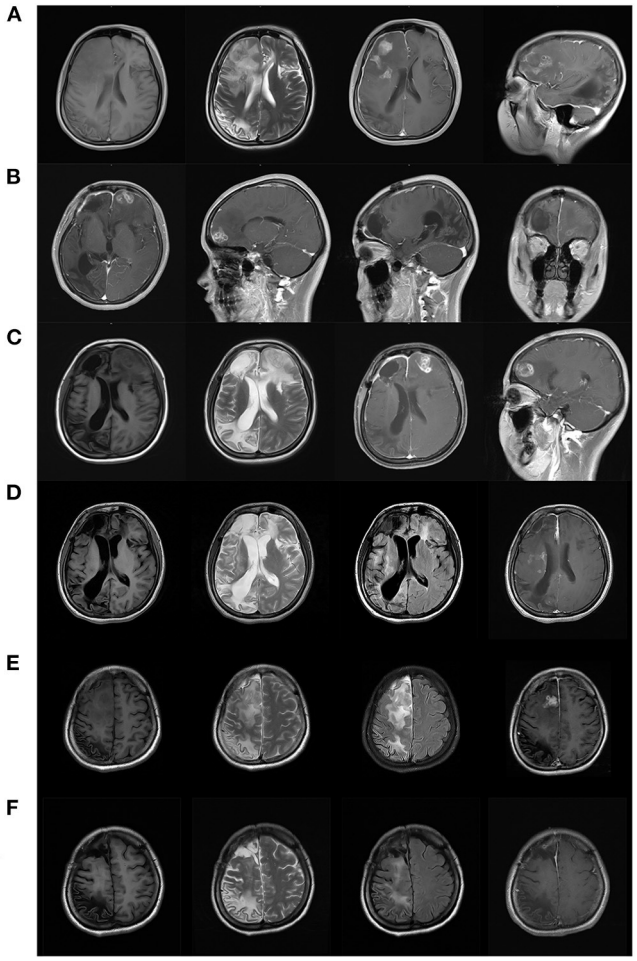

FIGURE 1 | Neuroimaging results of cerebral sparganosis in the case. **(A)** Six years after the onset (aged 22), tumor-like occupation foci at the right frontal lobe with edema and irregular enhancement causing midline shift on MRI before the first operation. Note that regular ring-shaped enhancement appeared on the sagittal view (the rightmost figure) (Left to right: T1, T2, axial T1 post gad, sagittal T1 post gad). **(B)** Three months after the operation, the enhanced foci shifted to the left frontal lobe, and postoperative encephalomalacia occurred at the original right frontal lobe on her follow-up MRI images (Left to right: axial T1 post gad, sagittal T1 post gad (left side), sagittal T1 post gad (right side), coronal T1 post gad). **(C)** Five months after the operation, a typical tunnel sign at the left frontal lobe was found on both axial and sagital view of her repeated MRI with enhancement (Left to right: T1, T2, axial T1 post gad, sagittal T1 post gad). **(D)** Three years after the operation (aged 25), the patient came to our center with left side paralysis. Restricted enhancement foci in the right centrum semiovale and basal ganglia with punched-out and tunnel-like presentation were found at the right basal ganglia (Left to right: axial T1, T2, T2 FLAIR, T1 post gad). **(E)** Four years after the operation (aged 26), the larva moved to the superficial area of the right frontal lobe where surgical removal became possible (Left to right: axial T1, T2, T2 FLAIR, T1 post gad). **(F)** 16 months after the removal operation (aged 28), MRI revealed softened foci, gliosis and shrinkage of the parenchyma at the right frontal and parietal lobe. No focal or meningeal enhancement was found (Left to right: axial T1, T2, T2 FLAIR, T1 post gad).

eosinophils presented in CSF or not were not performed because total white blood cell count in CSF was zero at that time and cell category was disabled in our instrument as the total number of nuclear cell was $<50 \times 10^6$/L. Her third MRI since the onset was performed and it revealed restricted enhancement focus in the right centrum semiovale, corona radiate, insula and basal ganglia with punched-out and tunnel-like presentation, and a resective operation was contraindicated due to the high risk of hemiparalysis (**Figure 1D**). Symptomatic treatment with LEV was prescribed with dexamethasone 10 mg iv drip daily. Standard praziquantel treatment was advised but refused by her father because of the failure of four cycles of previous treatment. The strength of her left limbs recovered 5 days later, and she was discharged with LEV.

Unfortunately, she developed another seizure episode with upward eye gaze, convulsion, frothing at the mouth and loss of consciousness for 3–4 min, and transient weakness that lasted for several hours on her left side in the following month. Her convulsive seizures stopped but the intermittent clonic seizures of her left upper limbs continued for ∼1 month even though combination of three AEDs at full dosage was given. A month later, another seizure episode recurred, and follow-up MRI noted no progression with multiple enhanced foci in the right basal ganglia, insula, centrum semiovale and corona radiata, similar to the third MRI after onset. Awake electroencephalogram (EEG) displayed intermittent generalized 4–5 Hz theta waves and 2–3 Hz delta waves in the bilateral hemispheres. Sleep EEG displayed high-extremely high amplitude 11–12.5 Hz scattered sharp wave discharges and asynchronization in bilateral hemispheres. Her father refused praziquantel treatment again, and her AEDs were further adjusted to four AEDs combination at full dosage but with poor seizure control (secondary tonic-clonic seizures once per 1–2 months and clonic seizures in her left upper limb 2–3 times per month).

She was admitted again to search for a better treatment strategy for her refractory epilepsy and active cerebral sparganosis. At the age of 26, her follow-up MRI revealed a new enhanced focus in her right frontal lobes, indicating that the larva had moved to the surface (**Figure 1E**). Her repeated blood and CSF sparganosis antibody testing still showed positive results. Considering that the effect of praziquantel therapy was limited and the larva had moved to an unimportant functional area on the surface of the frontal lobe, she was then transferred to the Department of Neurosurgery for her second operation. A parasite granuloma adhering to the surrounding cerebral tissue was found in the right frontal lobe, the same location as the enhanced areas on MRI, and was removed (**Figure 2**). Pathology confirmed an irregular striped necrotic object in the center of the resected tissue with inflammatory infiltration mainly by lymphocytes and plasma cells. Multinucleated giant cells and foreign body granulomas were found around the necrotic object. Blood vessels were surrounded by lymphocytes in a sleeve-like manner (**Figure 2**). The pathological result indicated that after four circles of anthelmintic therapy by praziquantel, the larva was dead at the end of the course and formed the parasite granuloma with inflammatory reaction and AEDs was therefore ineffective.

Her postoperative recovery was uneventful without neurological dysfunction except an increased tendon reflex of the left limbs at discharge and she was prescribed two

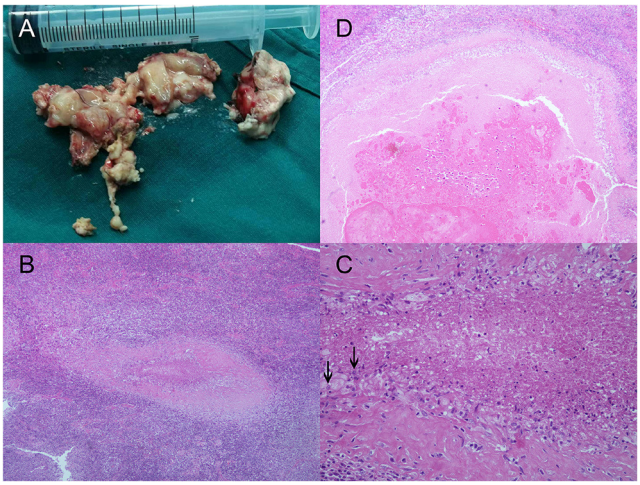

FIGURE 2 | Larval samples and the pathologic results of cerebral sparganosis in the case. **(A)** Larva samples acquired during the operation in our hospital. Necrotic objects split into band shaped sections from the larva were wrapped in surrounding brain tissue. The larva adhered to the surrounding brain tissue because of severe inflammatory reactions and therefore was not fully presented. **(B,C)** Images of microscopy inspection of the sample under low power (HE, ×100) and high power (HE, ×400) are also presented, which are characterized by irregular striped necrotic objects with inflammatory infiltration of multinucleated giant cells and the formation of foreign body granulomas. Calcareous corpuscles, which were characterized by basophilic vacuolated structures in the larva body, were indicated with black arrows. **(D)** Coronal section of the necrotic object (HE, ×100).

AEDs at middle dosage. She achieved a seizure-free status in postoperative follow-up for 16 months. However, during the follow-up, the patient had impaired short-term memory and executive function, depression and daytime sleepiness and was unable to work. Her Mini-Mental State Examination (MMSE) score was 27 (losing three scores for orientation to space and time), and her Montreal Cognitive Assessment (MoCA) score was 24 (losing one score for visuospatial cognition, one score for naming, one score for attention and three scores for delayed memory). Her follow-up MRI scanning indicated only slight dural enhancement in the bilateral frontal lobe and anterior cingulate (**Figure 1F**), and EEG indicated intermittent middle amplitude 5–7 Hz slow waves on bilateral frontal electrodes with right side predominant. She was given escitalopram 10 mg per day along with OXC monotherapy and was still not able to return to work but was more active in daily life with an improved mood at the 18-month telephone follow-up.

Our patient was eventually diagnosed with cerebral sparganosis at the sixth year after her first seizure onset and even underwent craniotomy based on a misdiagnosis of glioma. Unfortunately, her cerebral structure and function were irreversible due to the damage caused by migration of the worm and repeated cerebral surgery. Our case demonstrates how easily cerebral sparganosis can be misdiagnosed and how important an early diagnosis and treatment is to avoid permanent and severe brain damage and to achieve a good prognosis.

DISCUSSION

Cerebral sparganosis is a relatively rare parasitic disease with a high misdiagnosis rate before biopsy or operation, which is up to 57.7% at the first admission according to a Chinese cohort including 52 patients (9). Cerebral sparganosis is commonly misdiagnosed as a brain tumor, brain abscess or encephalitis granuloma, mainly because of the space-occupying mass with edema and enhancement on the neuroimage (7). Cerebral sparganosis can also be misdiagnosed as transfer tumors that typically present with irregular enhancement with ring-shaped edema at a fixed position on MRI and as cerebral cysticercosis, since the patients often have a contact history of eggs of *Taenia solium* and typical cyst images in the brain (10). The current case was misdiagnosed as glioma and even underwent surgery until a shift of enhancement on MRI 3 months after surgery, indicating parasitic infection, and the antibody test confirmed *Spirometra mansoni* infection.

For diagnosis, the image presentation, immunologic tests and contact history can provide some clues. CT presents a fresh lesion and the Sparganum granuloma as a low-density edema region and nodular or stripe high-density shadow, respectively, with marked enhancement. The lesion on MRI presented as an iso- or hypointense region on T1-weighted imaging (T1WI) and an irregular hyperintense region on T2-weighted imaging (T2WI). Typical tunnel signs can be revealed as tubular or distorted bead-like structures with T1WI hypointensity, T2WI hyperintensity and evident enhancement (11). The positive result of CSF IgG antibodies against *Spirometra mansoni* is critical to the diagnosis, with high sensitivity but relatively low specificity. It is reported that among 18 patients with positive results acquired by ELISA targeting sparganosis IgG in CSF, only two was confirmed to be pathologically definite sparganosis after surgery (12). ELISA assays targeting the parasitic antigen Spirometra erinaceieuropaei cysteine protease were therefore developed to promot the specificity of serodiagnosis (13, 14). A contact history with second intermediate hosts, such as undercooked meat, frogs, snakes and birds in the carrier state or their living environment, is a predisposing factor for sparganosis. This is an important reason why sparganosis is more common in Asian countries, where eating raw snake blood or galls is popular in some areas, along with applying snake or frog blood or skin to treat wounds (15). In the current case, further inquiry when the patient came to our center reminded her of the experience of falling into a pond with copepods (first intermediate host) in her childhood. Absorption of copepods and skin/mucosa contact with copepods could cause infection, which became an important diagnostic clue.

Treatment modalities of cerebral sparganosis include the anthelmintic praziquantel and surgery removal. Although praziquantel is regarded as the standard medical treatment for human infection with trematodes and cestodes (16), conventional doses (25 mg/kg for 3 days) are frequently reported to fail in the treatment of cerebral sparganosis (17). This may attribute to the fact that the level of praziquantel in CSF is about 1/7 to 1/5 of the plasma concentration (18). It is noted that administration with a high dose but a short duration causes non-lethal injury to the parasite and could induce parasite recovery

and escape. Therefore, enough treatment course should also be emphasized (19). High-dose and longer duration of treatment (75 mg/kg for 7 days) is then considered for the cerebral infection and can achieve improved effects including decreased levels of CSF antibodies, elimination of radiographical lesions, and discontinued seizures with reduced doses of AEDs (6, 8, 20). However, there still exist cases in which multiple cycles of high-dose praziquantel treatment (75 mg/kg administered in three divided doses for 10 days) failed to reduce the seizure frequency or relieve neurological deficits in more than 14% of patients after follow-up with a duration over 13 months (6). Steroids are also used to control the immune response in cerebral sparganosis and the incidence of Herxheimer reaction of praziquantel. Additionally, Although steroids were indicated to raise the permeability of blood-brain barrier and increase the concentration of praziquantel in CSF, previous studies have shown that the plasma level of praziquantel was decreased when simultaneously treatment with steroids, which may attribute to the nature of steroids as a cytochrome P450 inducer and accelerated metabolization (21, 22). Evidence for enhancing the anti-parasite efficacy of praziquantel by prescribing steroids was absent. In turn, the efficacy of praziquantel can be enhanced by co-administration with cytochrome P450 inhibitors such as cimetidine (23). Over all, we should noted that all these data were from small studies and no randomized trials existed.

Surgery for cerebral sparganosis is considered the optimal and radical treatment (24, 25), which is also confirmed in our case by the fact that the effect of previous drug treatments, including high-dose praziquantel and AEDs, was limited to symptom control (7). To guarantee the success of the operation, the scolex of the larva must be removed either by traditional craniotomy or stereotactic aspiration to avoid recurrence. Stereotactic aspiration has developed into a mature operation in the treatment of cerebral sparganosis, which causes limited wounds and prevents larval breakage, so this should be the first choice of surgery (5). With image-guided localization and aspiration from multiple directions, removal of the larva and the granuloma can be achieved. Once repeated aspiration fails, craniotomy should be considered, which could remove the larva entirely, especially for superficial and adhesive lesions caused by severe inflammatory reactions of the surrounding brain tissue. The surgery of our patient indicated that the larva was less likely to be removed by stereotactic aspiration because it was adhesive to the surroundings. This might be caused by four cycles of praziquantel treatment harming the larva, along with the long life of larvae in the brain, resulting in the focal inflammatory reaction. However, surgery is commonly contraindicated if the larva is located in functional areas, as in our case. In this case, preoperative praziquantel treatment is sometimes applied to compel the movement of larvae from functional areas, and repeated MRI will help judge the opportunity for surgery when the larva moves to be superficial. Therefore, the opportunity should be carefully considered based on the position of the larva.

CONCLUSION

This report presents a case of cerebral sparganosis with long-lasting refractory epilepsy, which was first misdiagnosed as glioma and underwent craniotomy. The larva failed to be removed by four circles of praziquantel treatment but was finally removed by opportune surgery. The current case indicated the typical diagnostic biomarkers of cerebral sparganosis and confirmed that early diagnosis and complete surgical removal of sparganosis granuloma is critical to the successful treatment, control of refractory epilepsy and the avoidance of severe tissue damage by the larva.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee on Human Research of Tongji Hospital. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

YC wrote the draft of the manuscript. XC collected all the clinical data. HK gave the main idea and edited the whole manuscript. All authors contributed to the article and approved the submitted version.

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CASE REPORT
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Case Report: Yellow Fever Vaccine-Associated Neurotropic Disease and Associated MRI, EEG, and CSF Findings

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Yellow fever vaccine-associated neurotropic disease (YEL-AND) is a rare and serious complication following vaccination with the 17D live attenuated yellow fever vaccine. Cases of YEL-AND have presented as acute inflammatory demyelinating polyneuropathy, acute disseminated encephalomyelitis, and meningoencephalitis. To date, intracranial imaging of the progression and resolution of this disease has been minimally depicted in the literature. We present the case of a 67-year-old woman who developed YEL-AND following vaccination. Her diagnosis was complicated by imaging findings consistent with variant Creutzfeldt Jakob Disease. Her clinical history and the progression of her intracranial imaging is discussed in this case report.

Keywords: yellow fever associated neurotropic disease, yellow fever vaccine, yellow fever virus, Creutzfeldt-Jakob Disease, vaccine adverse event, autoimmune encephalitis, post-infectious parkinsonism

CASE PRESENTATION

A 67-year-old woman with a history of atrial fibrillation and hyperlipidemia was transferred to our hospital for management of status epilepticus. She had no prior history of seizure, dementia or neuro-psychiatric disorder. Two months prior to presentation, she received CDC recommended vaccinations in anticipation of traveling to Guyana, South America, which included the 17D yellow fever virus (YFV) and Hepatitis B vaccines (1). Two weeks after vaccination she developed dizziness, double vision, sore throat and low-grade fever which she reported to her primary care provider (PCP). Five weeks later she presented to an outside hospital for evaluation of ongoing disequilibrium, vertical diplopia and numbness of her hands and lips. She was evaluated with a non-contrast computed tomography (CT) of the head which revealed age-related parenchymal atrophy without evidence of acute intracranial abnormality. The following morning, a magnetic resonance imaging (MRI) study of the head with and without gadolinium-based intravenous (IV) contrast, magnetic resonance angiography of the head and

TABLE 1 | Patient CSF findings.

Laboratory test	LP 1 (1 day prior to admission)	LP 2 (hospital day 2)
White blood cells (cells/μL)	<1	7
Lymphocytes (%)	n/a	97
Protein (mg/dL)	54	43
Glucose (mg/dL)	51	66
Meningitis/encephalitis panel	Negative	Negative
Gram stain	Negative	Negative
Cryptococcal antigen	Not done	Negative
Cytology/Cytometry	Negative	Negative
14-3-3	Not done	Positive
T-tau protein	Not done	Positive
RT- QuIC	Not done	Negative
Paraneoplastic Autoantibodies	Not done	Negative
Encephalopathy Autoantibodies	Not done	Negative
Cultures		
Bacterial	Negative	Negative
Fungal	Not done	Negative
Tick-Borne disease panel	Not done	Negative
Yellow Fever IgM	Not done	Not done
Serum IgG titers		1:640
CSF IgG titers		1:256

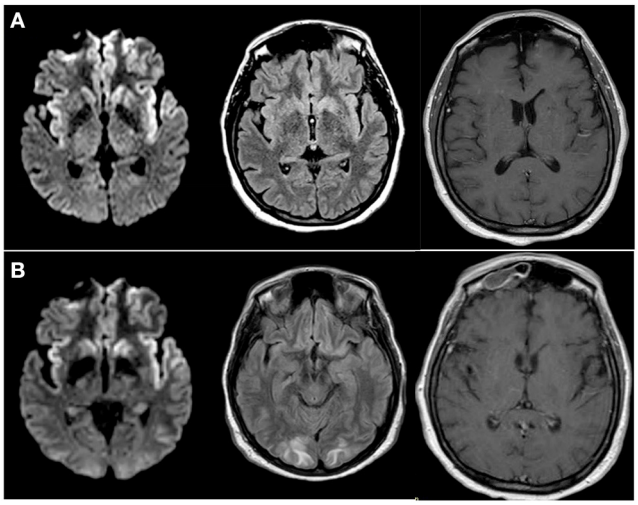

FIGURE 1 | Progression of MRI Findings **(A)** MRI brain with and without intravenous contrast; Axial diffusion-weighted imaging (DWI) (left), FLAIR (middle) and T1 post-contrast (right) images obtained at the time of initial presentation to our institution demonstrated cortically-based increased signal within the paramedical frontal lobes and insular cortices bilaterally. Additional diffusion restriction is present within bilateral caudate heads and the left putamen. **(B)** Follow up MRI brain without contrast; axial DWI) (left), FLAIR (middle) and T1 post-contrast (right) images obtained 4 days later demonstrate unchanged cortically-based and basal ganglia diffusion restriction. FLAIR images also reveal new patchy subcortical white matter hyperintensity with involvement of the subcortical U-fibers. Contrast enhancement of pachymeninges seen diffusely.

neck with and without contrast, and electroencephalography (EEG) demonstrated a few non-specific white matter changes, but were otherwise unremarkable. Comprehensive metabolic panel, complete blood count, erythrocyte sedimentation rate, C-reactive protein and random cortisol were all within normal limits. A lumbar puncture (LP) was performed and showed mildly elevated protein but no nucleated cells (**Table 1**); vitamin B12 levels were low in the 200 pg/mL range and repletion was begun. The patient was discharged home the next day. Three days later, her husband found her aphasic at home and she was taken back to the outside hospital. A repeat non-contrast CT of the head was again unremarkable without evidence of acute intracranial abnormality. Her labs were again normal, her aphasia improved and she was discharged home with concern for a functional neurologic disorder. She returned to the outside hospital within 48 h after the husband found her persistently aphasic and minimally interactive with right lower extremity shaking. She was admitted to the intensive care unit (ICU) with hypoxia and increased oral secretions requiring intubation for oxygenation and airway protection. This clinical picture, along with repeat EEG showing diffuse background slowing and "persistent left periodic lateralized epileptiform discharges suggestive of focal cortical excitability and an increased risk of seizures arising from that region," prompted aggressive treatment with administration of levetiracetam and propofol infusion for tube tolerance as well as seizure control. At that time she was transferred to Oregon Health & Science University for continuous EEG monitoring as well as further workup and management.

On admission to the Neurosciences ICU (NSICU), the patient was comatose. Her exam was notable for intact cranial nerve reflexes, witnessed rhythmic movement of the right lower extremity, triple flexion to noxious stimulus in both lower extremities, no movement of right upper extremity to noxious stimulus, hyper-reflexia throughout with bilaterally up-going toes and clonus at the right ankle. MRI with and without contrast (**Figure 1A**) demonstrated new diffusion restriction and mild T2/fluid-attenuated inversion recovery (FLAIR) hyperintensity along the left greater than right paramedian frontal lobes and insular cortices bilaterally as well as within the caudate heads and left lentiform nucleus. There was no associated enhancement or significant mass effect. While the predominantly gray matter signal abnormalities were suspicious for prion disease such as variant Creutzfeldt-Jakob Disease (vCJD), especially within the context of her EEG findings, given no preceding cognitive dysfunction, the imaging findings were favored to represent sequelae of recent epileptic activity. She received additional levetiracetam and placed on continuous EEG which showed rare epileptiform discharges in the left temporal region as well as bilateral lateralized periodic discharges (L > R) (**Figure 2**). Repeat LP was performed which appeared non-infectious with lymphocytic pleocytosis, with negative oligoclonal bands, cytology and cytometry. An infectious disease consult was obtained given recent YFV vaccination prior to presentation along with neurology consultation for seizure management and neuro-immunology given concern for potential inflammatory encephalitis. Additional cerebral spinal fluid (CSF) was sent to the Centers for Disease Control and Prevention (CDC) to

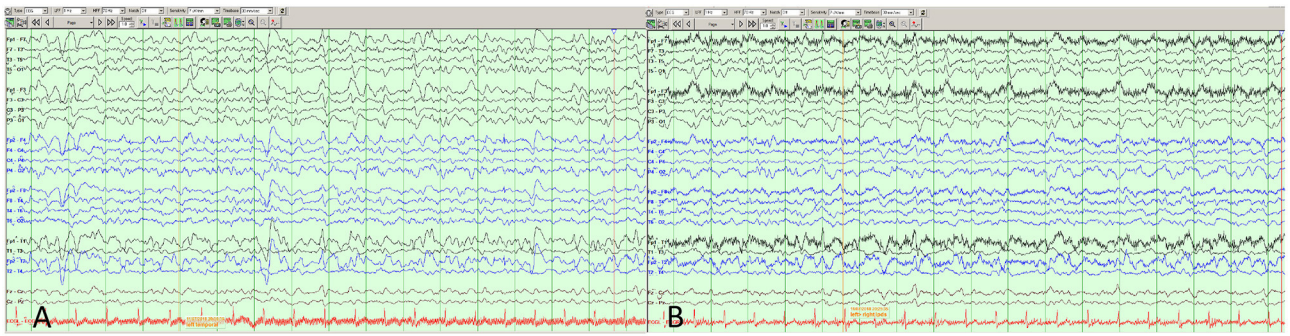

FIGURE 2 | EEG in anterior to posterior bipolar montage showing **(A)** left temporal discharges with maximal electronegativity at T3 as well as **(A,B)** left greater than right ∼1 hertz sharply-contoured lateralized discharges, frontally predominant, mostly biphasic with occasional triphasic morphology consistent with Laterialized Periodic discharges (LPDs, formerly called PLEDs) though at times they have more of a bihemispheric representation.

evaluate for YFV antibodies as well as Mayo Clinic Laboratories to evaluate for autoimmune and paraneoplastic autoantibodies. The patient was started on empiric IV immunoglobulin (IVIG) at 0.4 mg/kg for 5 days while the remainder of workup was in process given the potential for YEL-AND (2).

A repeat MRI on day two of IVIG treatment (**Figure 1B**) revealed unchanged diffusion restriction and FLAIR signal abnormalities within the paramedian frontal lobes, insular cortices, and basal ganglia. At that time, however, a new patchy T2 and FLAIR hyperintense signal was seen in a symmetric distribution within the subcortical white matter of bilateral occipital lobes and precunei with involvement of the subcortical U-fibers without enhancement or mass effect. Diffuse pachymeningeal enhancement was also seen at that time, which was attributed to the patient's recent LP. Given the stability of the gray matter signal abnormalities, vCJD and sequelae of status epilepticus remained within the differential diagnosis. Additionally, the distribution of white matter involvement were considered potentially consistent with posterior reversible encephalopathy syndrome and progressive multifocal leukoencephalopathy. At this point, the decision was made to stop IVIG after three treatments given efficacy equivalence as well as increased risk with extra doses (possible posterior reversible encephalopathy syndrome-like picture on MRI, and transaminitis). A CT scan of her chest/abdomen/pelvis revealed no malignancy and paraneoplastic panels were negative.

The patient's neurological and respiratory exam slowly improved and she was extubated to high-flow nasal cannula for several days before safe to transition out of the NSICU to the acute care ward. Repeat MRI brain at time of floor transfer (hospital day 16) revealed near-complete interval resolution of the T2 and FLAIR signal abnormalities within the parietal and occipital lobe white matter, decreased diffusion restriction within the basal ganglia, but persistent diffusion restriction within the paramedian frontal and insular cortices. Pachymeningeal enhancement had also resolved, further supporting the prior LP as the etiology for those transient findings. Spot EEG at this time did not show any seizures though it continued to have moderate diffuse slowing as well as subtle focal slowing over the left hemisphere. Her NSICU course was otherwise complicated by *Escherichia coli* urinary tract infection which was treated with cefepime for 48 h and then narrowed to cephalexin to complete a 7-day course and *Streptococcus anginosus* bacteremia thought to be from a sinus infection based on CT sinus findings (10 day ampicillin/sulbactam course). Her seizures were well-controlled with levetiracetam 1,000 mg twice daily.

The remainder of her labs returned negative or within normal limits, including real-time quaking induced conversion, with the notable exception of: CSF protein 14-3-3 positive and elevated tau protein (>4,000); serum and CSF YFV IgM positive; YFV CSF 90% plaque reduction neutralization test ($PRNT_{90}$) titer 1:256, and a serum $PRNT_{90}$ titer of 1:640. CSF YFV polymerase chain reaction was not performed by the CDC given time elapsed post-vaccination. Given these results, it was felt that the positive 14-3-3 and tau were due to neuronal damage. The negative RT-QuIC ruled out vCJD. CSF YFV IgM positivity with titer levels close to those in serum confirmed a diagnosis of YEL-AND (3).

Neuro-immunology consultants recommended intravenous methylprednisolone at 1,000 mg per day for 5 days with a follow-up brain MRI after completion, which demonstrated continued improvement of the previously noted signal abnormalities with only mild persistent diffusion restriction and FLAIR hyperintensity within the frontal and insular cortices.

Her hospital recovery was complicated by swallowing apraxia and dysphagia requiring eventual percutaneous endoscopic gastrostomy tube placement, urinary retention requiring indwelling urinary catheterization, excess oral secretions treated with glycopyrrolate, and suspected frontal lobe apathy which improved mildly with low dose methylphenidate. At time of discharge to an inpatient rehabilitation facility, she was awake and oriented with choices, smiled appropriately to jokes but did not attempt spontaneous speech or movement and had dramatic bradyphrenia. She displayed a restricted affect and had positive palmo-mental reflex and grasp reflex in her right hand. She had a mild right lower facial droop, increased tone right-side greater than left with drift in the right upper extremity and reduced strength in all muscle groups on the right. Her reflexes were brisk but symmetric and she had now down-going toes bilaterally. She

TABLE 2 | Comparison of patient factors with known YEL-AND encephalitis average and ranges according to McMahon et al. report of 15 cases (10).

Factor	Patient	YEL-AND Encephalitis Averages (10)
Age (years)	67	54 (16–78)
Onset (days)	13	14 (5–2)
Temperature on admission (F)	99.0	101.9 (98.3–105)
WBC peak (cells/μL)	11.22	11.95 (6.3–15)
Creatinine peak (μmol/L)	0.77	1.4 (0.9–1.6)
WBC in CSF peak (cells/μL)	18	41.5 (0–406)
Lymphocytes in CSF peak (%)	97	27 (0–73)
Summary of CSF IgM (#positive/#tested)	1/1	5/6

was able to walk with walker with stooped posture and significant bradykinesia. At discharge, the patient had a Montreal Cognitive Assessment (MoCA) score of 7/30.

The patient completed 4 weeks of intensive inpatient rehabilitation therapy and subsequently went to an adult foster home. She had moderately improved speech fluency and was able to ambulate with walker without support though she had continued significant psychomotor slowing. She was tolerating oral intake but was unable to meet caloric needs due to significant apraxia vs. apathy. At neurology clinic follow up visit 3 months after hospital discharge, MRI showed complete resolution of intracranial abnormalities previously seen. Due to the symptom constellation of bradyphrenia, bradykinesia, restricted affect and prior diffusion restriction in basal ganglia, diagnosis of post-infectious/post-inflammatory parkinsonism was made and she was started on levodopa-carbidopa. This was well-tolerated and increased as indicated over several months with improvement in all above symptoms. The patient has subsequently moved back home and is able to maintain caloric needs without tube feeding. Anti-epileptic therapy was successfully weaned without further seizure activity, frontal release signs (primitive reflexes) were absent on exam and repeat MoCA score were >20 on repeat clinic visits.

DISCUSSION

LP is rarely performed for symptomatic wild-type YFV disease as it is not classically associated with neurotropic illness (4). YEL-AND and other neurotropic manifestations following vaccination is most likely related to the manner in which 17D was attenuated to make the vaccine: serial passages through mouse and chick brains, leading to neuroadaptive but otherwise attenuating mutations (5, 6). YEL-AND remains a rare complication of 17D YFV vaccination with incidence estimated at eight individuals per one million vaccines administered (7, 8). Though a variety of encephalitic presentations for YEL-AND have been described including post-vaccinal encephalitis, aseptic meningitis, Guillain-Barre syndrome, meningoencephalitis, and acute disseminated encephalomyelitis, this is the first case where imaging, EEG and subacute rapidly progressive encephalopathy raised concern for prion disease, even though the time course was equivocal and no definitive exposure was established with comprehensive history. Additionally, reports of MRI imaging findings in YEL-AND have been limited to date. Similarly, our patient's EEG findings are notable when compared to other published cases which have either been unremarkable ($n = 2$), demonstrate disorganized background ($n = 8$), or revealed generalized low-amplitude slowing (4, 9). Recovery in most cases is complete in relatively quick fashion without significant sequelae (4) although deaths have been described in patients with YEL-AND (3), definitive attribution to the vaccine is difficult to establish (9). Our patient had a relatively prolonged course and while her imaging findings, seizures, and EEG did improve significantly relatively early in her hospital course, sequelae of intraparenchymal damage, specifically to the basal ganglia, complicated recovery with the development of Parkinsonism requiring dopaminergic therapy. Her clinical exam and functional status substantially lagged behind improvement in her imaging.

Comparison of this case to other case reports of YEL-AND (**Table 2**) (10) show patient factor similarities to the average and/or range in a variety of domains including time from vaccination to onset, serum WBCs, age, CSF WBC peak, and temperature, apart from a CSF lymphocytic count that was among the highest reported. We also suspect that her seizures and associated neuronal damage were more than a purely encephalitic process, possibly due to seizures and degree of neuronal damage. Additionally, while it is possible that her Parkinsonian symptoms were not due to her YEL-AND but instead presented as a true-but-unrelated syndrome, we think this is unlikely given resolution of her basal ganglia/putamen abnormalities at the time that she had clinical features of Parkinson's disease.

CONCLUSION

YEL-AND can present in a variety of ways and mimic a variety of other neurologic conditions, including prion disease. YEL-AND should be suspected in individuals with temporal relationship of symptom onset to vaccination, especially (but not exclusively) if patients are over the age of 65, with workup to include YFV IgM, sometimes IgG, and comparative serum to CSF titers to confirm the diagnosis. Clinical symptoms can persist beyond resolution of abnormalities in laboratory and clinical data including imaging.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The study was reviewed by the OHSU Institutional Review Board and was granted a waiver of authorization

(IRB# 00022903). Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

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CASE REPORT
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Misdiagnosis of HIV With Toxoplasmosis Encephalopathy With Progressive Memory Loss as the Initial Symptom: A Case Report

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Toxoplasmosis encephalopathy (TE) is a kind of encephalopathy parasitic disease caused by *Toxoplasma gondii*. It is the most common opportunistic for central system infection in patients with acquired immunodeficiency syndrome (AIDS) or human immunodeficiency virus. Without early diagnosis and proper treatment, this opportunistic infection can be life-threatening. The common clinical manifestations of the disease include altered mental state, epilepsy, cranial nerve damage, paresthesia, cerebellar signs, meningitis, motor disorders, and neuropsychiatry. The most common presentation in about 75% of cases is a subacute episode of focal neurological abnormalities such as hemiplegia, personality changes, or aphasia. Imaging needs to be differentiated from multiple sclerosis, lymphoma, and metastases. We report a case of acquired immune deficiency syndrome complicated with toxoplasma encephalopathy with rapid progressive memory loss as the initial symptom and misdiagnosed as multiple sclerosis. Through the comprehensive analysis of the clinical symptoms and imaging examination of this disease, we hope to enhance the confidence of clinicians in the diagnosis of this disease.

Keywords: toxoplasmosis, toxoplasma encephalopathy, AIDS, memory loss, misdiagnosis

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INTRODUCTION

Toxoplasma gondii is a parasite that spreads widely around the world, affecting more than a third of the world's population (1). In healthy, immuno-functioning hosts, acute infection progresses to asymptomatic latent infection, in which the parasite encysts in the heart, skeletal muscle, brain parenchyma, and retina with no or mild symptoms. However, when there is a problem with immune function, such as after an immune deficiency or organ transplant or chemotherapy in cancer patients, latent infection can be reactivated and latent bradyzoites transformed into rapidly replicating tachyzoites. If no intervention is taken at this time, the consequences can be severe and life-threatening, with mortality rates up to 100% (1, 2).

AIDS remains an important public health problem in China despite the tremendous efforts made by the Chinese government over the past 30 years (3, 4). Since HIV was first reported and noticed in China, the prevalence of HIV has changed. In the past 10 years, the incidence of AIDS has increased significantly, but it has been well controlled in the provinces with high incidence and among young and middle-aged people. However, the incidence of the disease has increased in some provinces and among people over the age of 55, which deserves our attention (5). Opportunistic

infection caused by parasitic infection is one of the most common causes of morbidity and mortality of AIDS patients, among which *T. gondii* infection is a very important parasitic infection (6). About 40% of studies reported so far in South America and the Asian continent have found toxoplasma latent infection rates as high as 41.9-72% in HIV-infected people (7).

About 30-40% of HIV-infected individuals with *T. gondii* will develop Toxoplasmosis encephalopathy (TE) (8). Nissapaton et al. (9) reported a serum survey of 505 AIDS patients and found that 226 (44.8%) were infected with Toxoplasma, of which 27 had toxoplasma encephalitis. Patients with TE presented with focal neurological dysfunction and signs. Usually, 58.89% of patients presented with subacute onset. Between 15 and 25% of patients present with acute aggression, presenting as sudden seizures or bleeding. Mild hemiplegia and/or language abnormalities are the most common initial symptoms. Headaches, mental changes, lethargy, and brain stem and cerebellar disorders have also been reported (10, 11).

However, reports of TE with progressive memory loss as the initial symptom are rare. It is also difficult to diagnose TE. Due to insufficient understanding of HIV, people often hide their medical history, and it is difficult to diagnose TE by imaging alone. The imaging manifestations of TE are very similar to other encephalopathies, such as brain abscess, metastatic tumor, and central nervous system lymphoma (10). Primary hospitals have limited means of examination, and the serum and cerebrospinal fluid tests for parasites need to be completed by delivery companies. The results will be delayed, so it is easy to misdiagnose and miss diagnosis. Therefore, it is very important to broaden clinical thinking. This paper mainly discusses how to detect and diagnose HIV infection complicated with TE as early as possible and how to treat it early.

CASE REPORT

On September 25, 2017, a 33-year-old rural woman was admitted to the Department of Neurology of The First People's Hospital of Zunyi city due to "progressive memory decline for half a year and left upper limb weakness for 2 weeks."

Since March 2017, the patient has developed progressive memory decline without obvious causes, which is manifested as scatterbrain (often unable to find things), decreased calculation ability (wrong calculation when shopping), and gradually aggravated. Later, the patient could not find his home, accompanied by slow reaction and slow walking, and did not pay attention to it. On May 20, 2017, there was no obvious cause of headache, blurred vision and decreased vision, which was slightly better after traditional Chinese medicine (TCM) acupuncture treatment in another hospital (the specific diagnosis and treatment process is unknown). On or about September 10, 2017, the patient developed weakness and numbness in the distal fingers of the left upper limb, and the unstable holding of the left upper limb, without convulsions, disturbance of consciousness and fever, no vomiting, difficulty swallowing, dysphagia and diplopia. Past medical history: The patient had suffered a head trauma 10 years earlier; 2 years ago, she was treated for viral herpes in another hospital and got better. Later, she developed local itching after sun exposure. The patient denied any history of drug use, unclean sexual behavior, or blood product use.

Auxiliary Examination Prior to Admission

Follow the MRI scan of the Affiliated Hospital of Zunyi Medical University for cranial MRI + MRA: Multiple lesions of the brain, cerebellum, brainstem and corpus callosum were found in both sides (2017-9-21, **Figure 1A**) are likely to be acute disseminated encephalomyelitis. However, infectious lesions and metastatic tumors still need to be considered, and an enhanced scan is recommended. Partial cavitation sella bilateral maxillary sinus and ethmoid mucosa thickening; MRA shows the right anterior cerebral artery is smaller and slimmer. Enhanced cranial magnetic resonance (2017-9-21): Multiple bilateral lesions of the brain, cerebellum, and brainstem were considered (**Figure 1A**), and small spinal cord enhancement lesions were considered (**Figure 1B**). Multiple sclerosis was diagnosed based on history and general examination. Hormonal treatment was ineffective, and then the patient was referred to our hospital.

Physical Examination at Admission

T 36.1°C, P 70 bpm, R 18 bpm, Bp 114/82 mmHg, clouding of consciousness, smooth language, slow response, memory impairment, normal judgment and timing orientation, poor eye movement, grade 5 muscle strength in the right upper limb, 4 muscle strength in the left upper limb, grade 3 muscle strength in the lower limbs, normal muscle tension, tendon reflexes (++), pathological signs were not elicited, meningeal irritation was negative.

Auxiliary Examination After Admission

pulmonary CT: grinding glass in the left lower lobe, considering inflammation; ESR: 69.7 mm/h, abnormal detection of cerebrospinal fluid (**Table 1**), abnormal blood electrolyte (**Table 2**), blood lipid: TG 6.06 mmol/L, high density lipoprotein 0.55 mmol/L, low density lipoprotein 2.01 mmol/L, apolipoprotein A 0.76 g/L. Fasting blood glucose, myocardial enzymes, liver function, renal function, blood routine, AFP, tuberculosis antibody IgG, rheumatoid factor, thyroid function, HCG, lung cancer tumor markers, parathyroid hormone, urine routine, coagulation function, troponin I, all the above inspection items was not abnormal; in total abdominal CT, cardiac ultrasound, electrocardiogram, and abdominal ultrasound were no abnormalities at all. A diagnosis of multiple sclerosis was made based on history and general examination, but hormone treatment in other hospitals was ineffective.

Our hospital usually takes HIV test as one of the routine examinations, and the patient was found to be HIV positive several days after admission. Although the patient had denied any history of drug abuse, unclean sex or blood product use when admitted, we still cannot exclude whether the patient and his family members have hidden medical history. At this point, we need to consider a central nervous system infection. Combined with the results of cerebrospinal fluid examination, there is insufficient evidence for viral infection (high cerebral pressure), tuberculosis infection (no history of tuberculosis

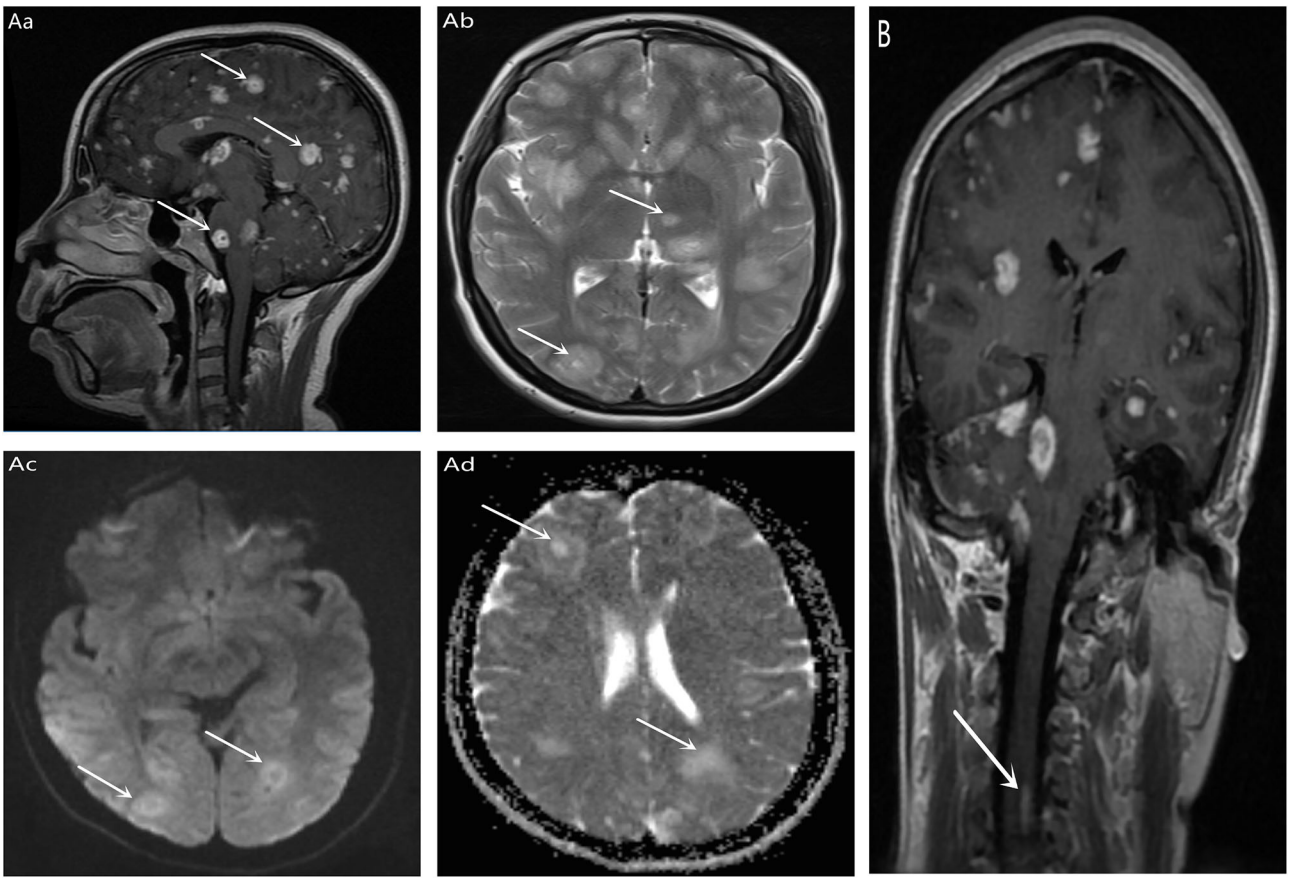

FIGURE 1 | T1 **(Aa)** and T2 **(Ab)** signal of multiple Clumps long T1 in bilateral brain, cerebellum, brainstem, and corpus callosum. DWI **(Ac)** and ADC **(Ad)** showed high signal (indicated by white arrows in the figure); Enhanced scan showed bilateral nodules, cerebellum and brainstem multiple nodular, annular enhancement, the largest diameter of about 18 mm (indicated by the white arrow in the figure). **(B)** No separate MRI of the spinal cord was performed, and there was also an unexpected high signal in the spinal cord during cranial enhancement (indicated by the white arrow in the figure).

infection and obvious wasting symptoms, negative acid-fast staining) and cryptococcus infection (negative ink staining). We then sent the patient's blood to Zunyi CDC(The Centers for Disease Contro, CDC) for a retest of HIV antibody test, and sent cerebrospinal fluid and blood to Jinyu Center for parasite test.

On September 28, 2017, Zunyi CDC and Prevention HIV antibody test positive Jinyu testing center for cerebrospinal fluid and blood parasite test results showed that Toxoplasma IgG antibody positive diagnosis consideration:1 AIDS; 2 TE; We treated with dehydration of mannitol and glycerin fructose to reduce intracranial pressure, and sulfamethoxazole trimethoprazole (smz-tmp) 1.44 g/time orally, 3 times/day, combined with clindamycin 600 mg/time intravenously, every 6h1 times according to the expert consensus ("Expert consensus on clinical diagnosis and treatment of AIDS complicated with Toxoplasma encephalitis"). Radiographs were to be reassessed after 6 weeks of regular treatment, but the patient and his family refused further treatment and discharged from the hospital after several days of treatment.

DISCUSSION

In this case, a young female patient presented with rapid progressive memory loss as the first symptom, but the patient and her family did not notice it. The main symptoms are headache, blurred vision and weakness. Brain MRI showed a "starry sky" appearance, and enhanced MRI showed multiple nodular enhancement lesions in brain, cerebellum, brainstem and corpus callosum (**Figure 1A**), and small focal enhancement lesions in cervical spinal cord (**Figure 1B**). Overall, initial diagnosis of multiple sclerosis is reasonable for the following reasons: (1) Gender, age, and clinical symptoms support, Multiple sclerosis is the most common inflammatory nervous system disease in young people, it is a potentially serious cause of neurological dysfunction throughout the adult population (12). (2) In the course of the disease, there is a suspicious remission process after TCM treatment, most patients may present with recurrent remission of recurrent neurological symptoms (12). (3) MRI showed obvious symptoms of cervical spinal cord (consistent with spatial multiple), on conventional MRI imaging, 90% of multiple sclerosis patients will have spinal cord injury once

TABLE 1 | Results of cerebrospinal fluid test.

Cerebrospinal fluid testing item	2017-9-26	2017-9-28	Reference value
Turbidity	clear and transparent	clear and transparent	clear and transparent
Color	Colorless	Colorless	Colorless
Clot	without clot	without clot	without clot
CSF pressure	330 mmH_2O	Untested	70-180 mmH_2O
Total cell number	20*10^6/L	44*10^6/L	-
WBC	18*10^6/L	32*10^6/L	0-8
Monocytes number	16*10^6/L	28*10^6/L	<10*10^6/L
Number of multinucleated cells	2*10^6/L	4*10^6/L	-
Chlorine	126.1 mmol/L	127.1 mmol/L	120-130mmol/L
Glucose	2.4 mmol/L	2.1 mmol/L	2.5-4.4 mmol/L
ADA	2.4 U/L	4.0 U/L	0-3 U/L
Protein	2.03 g/L	2.04 g/L	0-0.45 g/L
Lactate dehydrogenase	38.6 U/L	59.6 U/L	10-25 U/L
Acid-fast dyeing	No acid-fast bacillus found	No acid-fast bacillus found	No acid-fast bacillus found
Ink dyeing	Not found Cryptococcus neoformans	Not found Cryptococcus neoformans	Not found Cryptococcus neoformans
Exfoliated cells	Untested	see a small number of lymphocytes	- -
Cerebrospinal fluid culture	72 h of sterile growth	72 h of sterile growth	-

*The *symbol indicates multiply.*

TABLE 2 | Results of blood ion tests.

Blood plasma examination item	2017-09-25	2017-09-28	2017-09-29	Reference interval
Potassium	3.5 mmol/L	3.8 mmol/L	3.4 mmol/L	3.5-5.5 mmol/L
Sodium	132.1 mmol/L	132.8 mmol/L	133.2 mmol/L	135-145 mmol/L
Chlorine	104.1 mmol/L	104.6 mmol/L	102.4 mmol/L	98-111 mmol/L
Calcium	2.27 mmol/L	2.16 mmol/L	2.10 mmol/L	2.25-2.58 mmol/L
Osmotic pressure	284.2 mmol/L	285.6 mmol/L	286.4 mmol/L	0.97-1.16 mmol/L
CO2	20.6 mol/L	19.4 mol/L	17.9 mol/L	22-32 mol/L

onset (13), and 30-40% of patients will have spinal cord injury before onset or symptoms (14). Spinal cord lesions are part of the diagnostic criteria for spatial spread in the International Panel guidelines (15). But ultimately, we don't consider Multiple sclerosis and here's the reasons: (1) The overall course of disease continues to be one-way progression, Although the patient showed cognitive impairment with rapid memory loss, there were no obvious neurological manifestations common to multiple sclerosis, such as optic neuritis, diplopia, sensory loss, limb weakness, gait ataxia, and loss of bladder control (12). (2) Magnetic resonance imaging is inconsistent with classical MS results. (3) Cerebrospinal fluid pressure has obvious changes. However, there is no specificity in the changes of cerebro spinal fluid (CSF) of TE. Chinese studies have shown that about 42.6% of AIDS/TE patients can have increased CSF pressure, and 66.0% of PATIENTS can have increased CSF protein content (16). (4) Symptoms of multiple sclerosis did not improve after treatment. TE is eventually diagnosed by a combination of HIV antibody positivity, CSF and plasma IgG antibody positivity. New epidemiological evidence based on a meta-analysis of 74 studies of toxoplasma and HIV coinfection in 34 countries shows a combined serum prevalence of 35.8% worldwide. The prevalence in Asia and the Pacific was 25.1% and, as expected, populations in developing countries showed higher comorbidities (54.7%) compared with middle-income countries (34.2%) and high-income countries (26.3%). As developing countries, we should pay more attention to the diagnosis and treatment of the disease. Next, we will discuss the problems that should be paid attention to in the diagnosis of this case.

Relationship Between HIV-Infected Toxoplasma Encephalopathy and Memory Loss

Toxoplasma titer is generally associated with poorer cognitive performance (17). A 2010 study by Fekadu (18) showed that such cognitive decline caused by toxoplasma seropositivity is particularly obvious in low-income people (19) and people with low education level (20). However, while many studies have shown that tracking toxoplasma seropositivity is associated with poorer cognitive function, other studies have shown that

positive seropositivity is not entirely harmful. In a 2017 study by Wyman et al., Toxoplasma antibody titers in toxoplasma infection sero-positive participants were negatively correlated with memory (21). This is contrary to our understanding that the higher the antibody titer is, the more serious the cognitive impairment is.

Studies have shown that almost half of people living with HIV have mild to moderate neurocognitive impairment (22, 23). Since both HIV and Toxoplasma infection affect cognitive function, could the combination of the two diseases make cognitive impairment worse? It is well known that there are many reasons affecting cognitive impairment in HIV patients, such as age, drug abuse, chronic hepatitis C, etc. (24). However, the effect of latent *T. gondii* (LT) on NC has not attracted enough attention. In a 2016 study (25) of nearly 250 adults with HIV+ and HIV–, found that underlying toxoplasmosis was associated with poorer overall cognitive performance. Neurocognitive impairment (NCI) was very common among HIV+ patients (36.5 vs. 11.7%; $p < 0.001$). Most HIV+ patients had mild NCI (29.21.6%) and the rest had moderate NCI. In HIV-infected patients, lower levels of Toxoplasma IgG were associated with poorer cognitive performance, contrary to what we expected. Perhaps because toxoplasma levels decline over time, it is possible that toxoplasma negatively affects cognition due to the slow and cumulative effects of infection rather than the acute effects (which are associated with higher levels) (26, 27). This is consistent with the results of the 2017 study by Wyman et al. (21), which is worth thinking about and points to the direction of further research.

The patient was a young patient with rapid progressive memory loss. It is not clear whether HIV or Toxoplasma is the cause, but the combination of the two diseases is not likely, and some confounding factors, such as smoking, alcohol consumption, education level, family environment and psychological factors, should also be considered. At the same time, it also suggests that HIV with toxoplasma infection should be considered as one of the differential diagnoses in young patients with rapid progressive memory loss in addition to some common diseases.

A Brief Discussion on the Differential Diagnosis of TE on Imaging

In this case, MRI showed multiple ring enhancement lesions. Can multiple sclerosis be considered in the initial diagnosis of this case? The presence of annular lesions in clinical isolation syndrome and early multiple sclerosis disease may have implications for future studies of disease activity and progression, Blindenbacher et al. (28) reported in the 2020 study. However, the ring signs mentioned above mainly appear on SWI of MRI, this is different from the annular appearance in this case.

So, what should be considered in the differential diagnosis of annular lesions? The differential diagnosis of ring enhancement is very extensive. In non-immunocompromised patients, the most common diseases were metastatic disease and septic emboli, and in immunocompromised patients lymphoma was the most common (29). Metastatic disease usually has a definite history of tumor and is of equal size, usually at or near the gray-white matter junction. Emboli usually result in acute infarction of the associated vascular distribution, which is not seen in toxoplasmosis or metastatic disease. Lymphoma is usually larger than TE, more invasive in shape, heterogeneous in enhancement, and may spread to a limited extent (30, 31).

The case was definitively diagnosed as TE, the most classic and common MRI manifestation of toxoplasmosis is the enhanced T1W "eccentric target sign," which consists of three alternating regions: the innermost eccentric enhanced core, the moderate-low signal region, and the peripheral high-signal enhanced edge. This appearance produces a ring of enhancement, and the presence of a central nodule is usually eccentric, hence the term "eccentric target." Can TE be excluded if there is no eccentric target sign? Although such presentations are highly suggestive of toxoplasmosis, such presentations are found in only 30% of cases (32). Therefore, TE cannot be excluded even if there is no characteristic manifestation, and the patient's medical history, physical examination and serological results should be combined to assist the diagnosis.

Analysis of Causes of Misdiagnosis

In this case, the patient presented with progressive memory loss as the first symptom and received little attention. This is a wake-up call for us to see such clinical manifestations in young patients without any vital events, and we should think about the presence of organic disease. The patient in this case may have hidden his medical history, so we should strengthen health education in the economically underdeveloped and relatively backward areas. At the same time, whether the examination of some infectious diseases should be included in the routine examination is worth our vigilance and consideration. If HIV infection is known, we need to be aware of the possibility of TE. A meta-analysis involving global studies found that the serum antibody (IgG) positive rate of *T. gondii* was significantly higher in AIDS patients than in healthy people (46.1 vs. 36.6%) (33). A recent systematic review of 111 studies from 37 countries reported a pooled incidence of 44.22% of Toxoplasma infection in AIDS patients, higher than that obtained based on IgM analysis (3.24%) and molecular methods (26.22%), highlighting the high incidence of Toxoplasma infection in AIDS patients (34). Belanger et al. (35) analyzed 116 AIDS patients with toxoplasmosis, including 103 cases (88.8%) of TE, 7 cases (6%) of Toxoplasmosis lung disease, 4 cases (3.5%) of toxoplasmosis, and 2 cases (1.7%) of disseminated toxoplasmosis. At the same time, we send check out by considering the patients' economic reasons only checked IgG antibody in serum and cerebrospinal fluid, did not check the IgM and the degree of antibody, check diagnose diseases for us both for the recent infection or reactivation of *T. gondii* and prognosis is meaningful, if conditions allow should try to improve the inspection. Of course, if the CD4+T lymphocyte count can be tested, and regular review after anti-toxoplasma treatment, it will be more conducive to our diagnosis. Due to the financial constraints of patients, we did not send out the examination of oligoclonal zone. The specific change of MS in CSF is marked by the detection of oligoclonal band (OCB). The absence of OCB has a high negative predictive value, indicating the presence of a danger signal on diagnostic tests, and other diagnoses should be considered in such patients (36), this is also important for our differential diagnosis.

Meanwhile, we considered the spatial multiple of MS when we saw lesions in cervical spinal cord on MRI, but ignored the involvement of spinal cord in TE. The most common clinical manifestation of toxoplasmosis in HIV infection is encephalitis, which usually occurs when the CD4+ cell count is below 200 cells/μl and generally follows the reactivation of latent infection (37). Spinal cord involvement can occur and manifest as motor or sensory impairment of the limbs, bladder or bowel dysfunction or both, and local pain, Therefore, numbness and weakness of the left upper limb in this patient should be related to spinal cord injury.

Clinical Guiding Significance

TE can be diagnosed for AIDS patients by meeting the following three points: (1) Patient's cerebrospinal fluid or serum anti-Toxoplasma IgG and/or IgM antibody are positive; (2) Head magnetic resonance imaging (MRI) showed multiple nodular or round-shaped lesions, T1W1 Low signal, T2W2 hyperintensity, with edema zone around, T1W1 showed "target sign" enhancement; (3) Brain lesions absorbed by brain MRI lesion 2 weeks after diagnostic treatment (7). It should be noted that toxoplasma exists only intermittently in the spinal fluid. In this case, a single positive CSF result is lucky, but if no positive CSF result is found, the diagnosis should be confirmed by repeated tests. It has been proved that repeated samples can improve the sensitivity of the test.

Studies have shown that HIV/AIDS patients in Asia and Africa are more likely to be infected with Toxoplasma than those in the Americas and Europe (38), and that timely and sustained highly active antiretroviral therapy (HAART) and preventive therapy are important for HIV-positive patients, reducing TE risk by 50% on antiretroviral therapy and 53% on preventive therapy (39). Therefore, we recommend routine serological screening for Toxoplasma infection in HIV patients in endemic areas. Positive patients are at risk of infection reactivation, and negative patients should also be informed to prevent primary infection.

At the same time, we should also actively carry out health education, AIDS is usually high among young people, but some studies show that the coverage of AIDS health education reaches 80% in rural areas of western China, and attention should be paid to the elderly, poor people and minority communities (40). The aim is to establish routine serological monitoring, counseling, nursing and preventive treatment programs to prevent HIV infected with severe toxoplasma encephalopathy and, if infected, identify and treat them as soon as possible.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

JW completed literature search and article writing. XL and YuL assisted in the collection of materials and related data and pictures. NH assisted in the collation of pictures and the modification of the article. YoL designed the ideas of the article and the modification of the article. All authors read and approved the final manuscript.

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CASE REPORT
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Rhino-Orbital Cerebral Mucormycosis in a Patient With Diabetic Ketoacidosis: A Case Report and Literature Review

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Background: Rhino-orbital cerebral mucormycosis (ROCM) is a rare, invasive, and fatal fungal disease. Due to the lack of specific clinical manifestations and adequate auxiliary examinations, patients are easily misdiagnosed in the early stage. Early diagnosis and timely therapy are essential for successful treatment.

Case Report: We report a 68-year-old man with diabetic ketoacidosis, presented with orbital apex syndrome (OAS), fever, and pansinusitis, which progressively worsened to death only 4 days after admission. It was finally confirmed as a fungal *Rhizopus arrhizus* infection by metagenomics cell-free DNA next-generation sequencing (mNGS) testing.

Conclusion: Orbital apex syndrome could be the initial presentation for mucormycosis. Thus, it is necessary to evaluate the presence of mucormycosis in patients with OAS, especially in diabetic or immunosuppressed hosts, and mNGS testing and timely antifungal therapy should be strongly recommended in highly suspected cases.

Keywords: rhino-orbital cerebral mucormycosis, diabetes, metagenomics cell-free DNA next-generation sequencing, orbital apex syndrome, ketoacidosis

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INTRODUCTION

Mucormycosis is a lethal, angioinvasive fungal disease, which primarily occurs in individuals with an immunocompromised state including uncontrolled diabetes, ketoacidosis, trauma, iron overload, hematological malignancies, and allogeneic stem cell transplantation (1–4). The prevalence of mucormycosis among patients without predisposing medical conditions has also been reported (5). Rhino-orbital cerebral mucormycosis (ROCM) is the most common form of mucormycosis. The incidence of ROCM has been rising worldwide, particularly in India and the Middle East (4, 6, 7). It has recently become a matter of immediate concern in the setting of COVID-19 in India (6). The order Mucorales comprises 261 species in 55 genera, of which 38 are associated with human infection (4). As reported in a global review, the most common responsible agents of mucormycosis are *Rhizopus* spp., *Lichtheimia* spp., and *Mucor* spp., with the most frequent being *Rhizopus* spp. (8). Furthermore, its distribution varies depending on the geographical zones. *Lichtheimia* spp. are the second most frequently isolated agents in Europe and Africa, while in India, the second most commonly isolated agents are *Apophysomyces* spp. (4, 9).

Rhino-orbital cerebral mucormycosis is a rapidly progressive disease, and even a slight delayed diagnosis may lead to devastating consequences. It has been reported that even if intensive antifungal and surgical interventions were achieved, ROCM-related mortality is persistently very high, ranging from 50 to 100% (10). Owing to the lack of specific clinical presentations, the misdiagnosis rate is very high in the early stage. Santosh G Honavar exhibited some warning symptoms and signs in the setting of COVID-19, including nasal stuffiness, foul smell, eyelid, periocular or facial edema, regional pain-orbit, paranasal sinus or dental pain, worsening headache, proptosis, sudden loss of vision, sudden ptosis, facial palsy, and fever (11). We believe that the "red flags" of ROCM mentioned above also apply to other ROCM patients. Thus, any of the over-mentioned symptoms appearing in an immunocompromised patient requires a very high index of suspicion for ROCM. However, in the real world, it has been reported that up to 90% of cases are undiagnosed and untreated (12, 13).

In this case study, we report a 68-year-old man with diabetic ketoacidosis, who had a five-day history of right ptosis, swelling, and pain, and a four-day history of fever, which progressed to consciousness disorder and worsened to death only 4 days after presentation. Metagenomics cell-free DNA next-generation sequencing (mNGS) has confirmed the diagnosis of ROCM in blood and cerebrospinal fluid. Here, we review the literature on the epidemiology, clinical presentation, and advancement in diagnostic and therapeutic approaches of ROCM.

CASE PRESENTATION

In November 2020, a 68-year-old man presented at the emergency department in the First Affiliated Hospital of Soochow University with a five-day history of right ptosis, swelling, and pain, accompanied by a four-day history of fever. He was treated with ceftriaxone, dexamethasone, and low molecular weight heparin (LMWH) at the local hospital for 2 days. However, his condition progressively worsened. He denied headache or convulsion, and his medical history was poorly controlled diabetes.

On neurological examination, the patient presented a complete ophthalmoplegia in the right eye, ptosis, swelling, a fixed dilated pupil unresponsive to light, no light perception, and loss of sensation in the right forehead and eyelids. No purulent nasal discharge, fetor, or anosmia was observed. Meningeal signs were negative, and motor exam revealed normal muscle bulk and tone, power 5/5, and more than two reflexes with normal plantar responses. The sensory exam found that the patient was intact to pinprick and vibration on trunk and limbs. There were no positive signs in the cerebellum.

On laboratory testing, the capillary glucose was 230 mg per deciliter, and the hemoglobin A1c was 14.6%. Basic hematology showed a white blood cell count of 22,410 per deciliter, 80% of neutrophils, and urinalysis was notable for glucosuria and ketonuria. Cerebrospinal fluid examination revealed elevated white cells of 463 per deciliter (48.2% monocyte), a protein level of 850 mg per deciliter, and glucose of 122 mg per deciliter. Magnetic resonance imaging of the brain revealed pansinusitis and multiple lesions scattered in the right cerebral hemisphere and right pons (**Figure 1**).

The patient presented complete ophthalmoplegia (combination of unilateral impairment of cranial nerves III, IV, and VI), loss of vision (II), and loss of sensation in the right forehead (ophthalmic branch of V). Based on the positive signs above and the imaging results, we located the lesions on the right orbital apex and right brainstem. The etiologies considered included infectious, vascular, inflammatory, neoplastic, and traumatic. In the absence of a definitive diagnosis, the patient was administered ceftriaxone, linezolid, metronidazole, acyclovir, dexamethasone, and LMWH after admission. Due to the rapid development of the patient's condition, the samples of blood and cerebrospinal fluid were immediately sent to Genoxor Medical Science and Technology Inc. for mNGS testing. On the following day, the report indicated that *Rhizopus arrhizus*, which is the most prevalent causative agent of mucormycosis, was detected in both the patient's cerebrospinal fluid and peripheral blood. The reads were 78 in cerebrospinal fluid and 131 in the blood (the sequencing coverage and sequencing depth in **Figure 2**). The result was verified by quantitative polymerase chain reaction (qPCR) later with the same cerebrospinal fluid sample for mNGS. The qPCR was performed to amplify the specific part of *Rhizopus arrhizus*, with *Rhizopus arrhizus* -specific primers *Rhizopus arrhizus*-F (TTCAAAGAGTCAGGTTGTTTGG) and *Rhizopus arrhizus*-R (CAGTCTGGCTCCAAACGGTTC). Combined with the patient's clinical manifestations, it was finally confirmed to be a fungal *Rhizopus arrhizus* infection. Liposomal amphotericin was timely treated. However, the patient began to experience disturbance of consciousness and unfortunately died within 4 days after presentation.

DISCUSSION

Champion was the first to propose that a fungal infection involving the cerebellar and orbital sinuses be defined as ROCM, early in 1969 (14). ROCM is a rare yet lethal fungal infection, which is wreaking havoc at an alarming rate in India and other countries (15). In the past few years, the incidence rate of this rare disease has been rising with advances in experimental and imaging systems. However, as ROCM continues to be associated with high mortality, early diagnosis and aggressive treatment are essential for survival. The infrequent presentation of ROCM poses both diagnostic and therapeutic challenges for doctors who are not familiar with the disease. Here, we have presented a case with a fatal ending and discussed the challenging obstacles that lead to high mortality of ROCM from the perspectives of advances in diagnosis and treatment difficulties.

Epidemiology

It is difficult to measure the incidence of ROCM precisely, since the majority of studies regarding its prevalence originate

Abbreviations: ROCM, rhino-orbital cerebral mucormycosis; OAS, orbital apex syndrome; mNGS, metagenomics cell-free DNA next-generation sequencing; HBO, hyperbaric oxygen; FLAIR, fluid-attenuated inversion recovery.

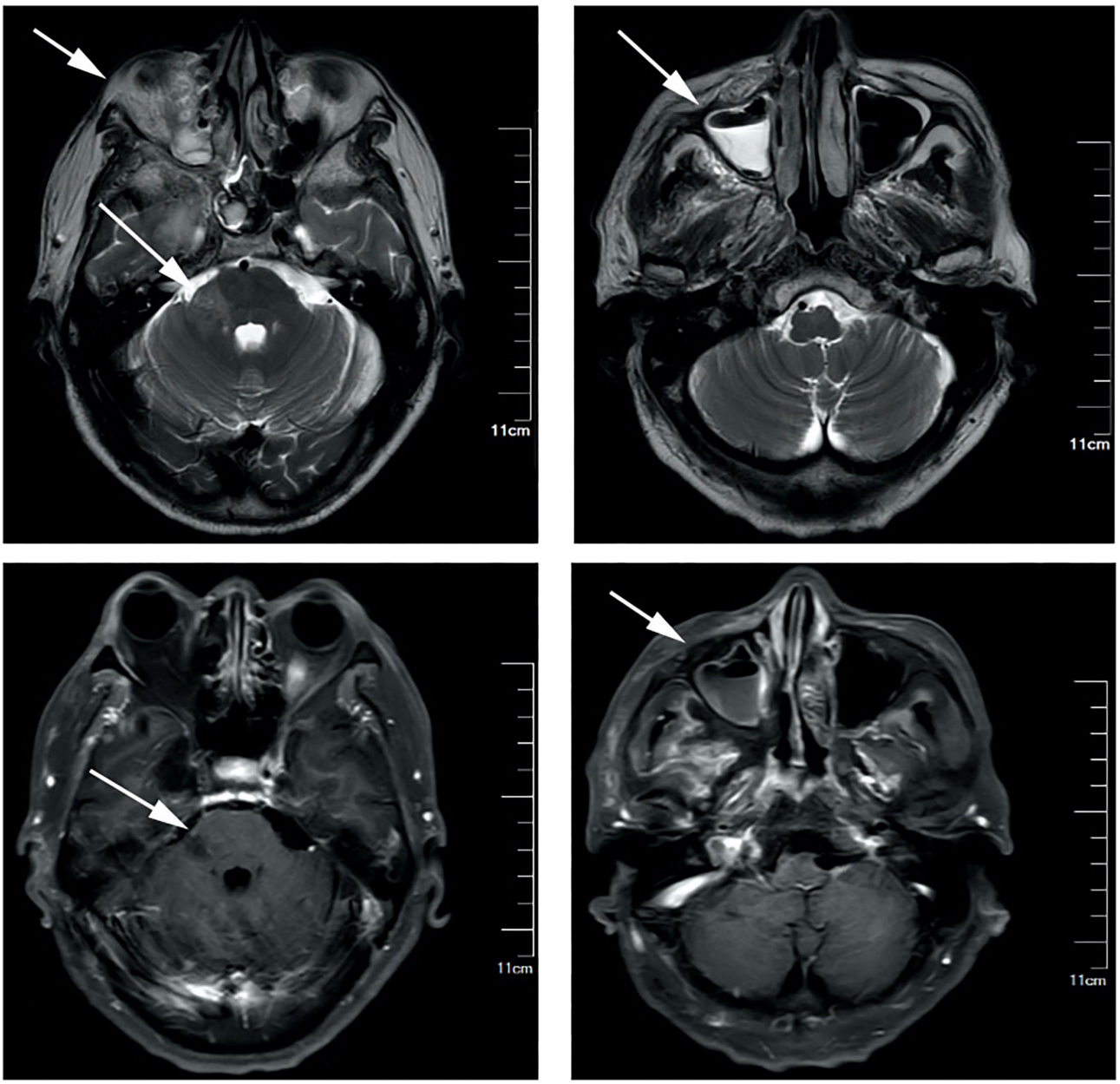

FIGURE 1 | Gadolinium-enhanced brain magnetic resonance imaging (MRI) revealed bilateral pansinusitis and multiple lesions scattered in the right cerebral hemisphere and right pons, showing hypointensity on T1-weighted images, and hyperintensity on T2-weighted and fluid attenuated inversion recovery (FLAIR) images, without contrast enhancement.

from case reports, case series, or non-population-based cohort studies rather than population-level studies. Furthermore, the added difficulty in collecting samples and the low sensitivity of etiology tests may underestimate its actual prevalence. In 2017, the authoritative Leading International Fungal Education (LIFE) reprorted that the prevalence of mucormycosis was approximately 910,000 cases annually, almost 98.9% of those were found in India, and the estimated mean mortality was about 38.2% per year (16, 17). Mucormycosis may infect any organ at any age and is classified based on its clinical presentation into the following six clinical forms: rhinocerebral, pulmonary, cutaneous, gastrointestinal, disseminated, and other rare forms (18). A multicenter prospective study, which included 465 subjects with mucormycosis in India, presented that ROCM was the most common (67.7%) presentation, followed by pulmonary (13.3%), cutaneous (10.5%), and other types. The analysis of predisposing factors indicated that diabetes (73.5%) was the dominant factor in all forms of mucormycosis (8). A meta-analysis by W. Jeong identified that ROCM is the most common form in patients with diabetes. In contrast, pulmonary

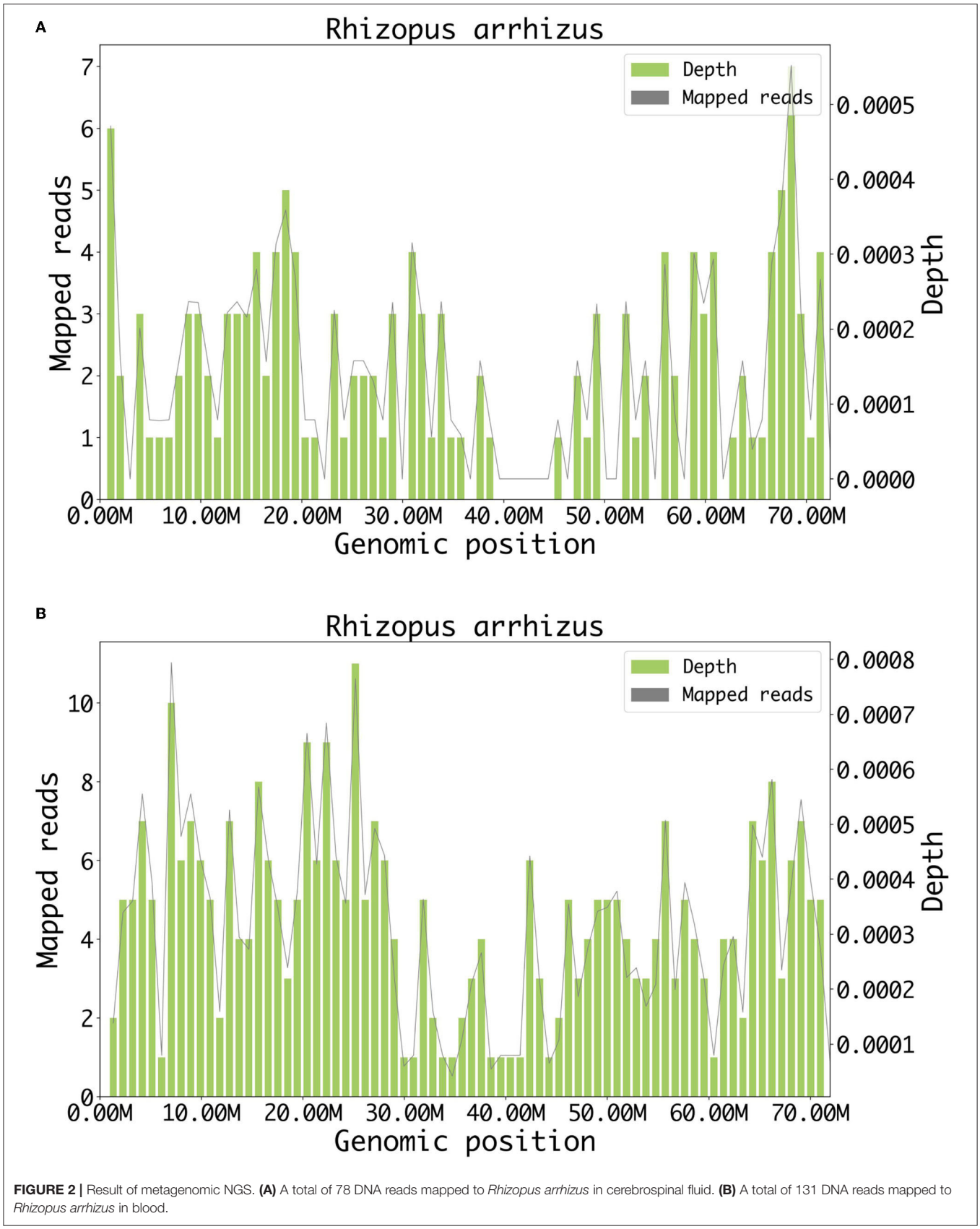

FIGURE 2 | Result of metagenomic NGS. **(A)** A total of 78 DNA reads mapped to *Rhizopus arrhizus* in cerebrospinal fluid. **(B)** A total of 131 DNA reads mapped to *Rhizopus arrhizus* in blood.

and disseminated forms were more common in those with malignancies and transplantation recipients (19).

Non-Specific Features of Clinical Presentation

The clinical manifestations of ROCM are related to the location of fungal invasion, which provides clues to lesion location. Among them, bone destruction of the paranasal sinus in the early stage, OAS in the progressive phase, and venous sinus syndrome in the advanced stage are highly suggestive of a potential fungal infection. ROCM is presumed to begin with paranasal sinuses, presenting initially as nasal congestion, headache, fever, or sinus pain, which is indistinguishable from those of more common causes of sinusitis. All sinuses may be involved, and the infection may progressively spread to adjacent structures such as the palate, orbit, and brain tissues within only a few days. Also, there were cases that followed a relatively indolent course progressing over a few weeks (20).

Because of the lack of specific features in the early stage of ROCM, patients often visit ophthalmology, otorhinolaryngology, respiratory, neurology, or other departments. Progressive manifestations are mainly retrobulbar soft tissue inflammation and invade multiple cranial tissues including vessels, optic nerve, the oculomotor nerve, and trochlear nerve, resulting in periorbital pain, eye distension, conjunctival congestion, decreased vision, exophthalmos, and painful ophthalmoplegia like OAS. The appearance of OAS is highly suggestive of a fungal infection. Ursula et al. suggested that when OAS accompanying any sinusitis is observed in a diabetic or immunocompromised patient, a fungal etiology should be suspected (21). Intracranial manifestations often signify a late-stage infection, and intracranial lesions often present on the side of sinusitis. In the pathway of intra-vascular invasion, fungi firstly invade the nasal sinus and intra-orbital vein with abundant blood supply, and further spread by entering the internal carotid artery, surrounded by the venous sinus, forming a fungal embolus, which may embolize in the ipsilateral middle cerebral artery after falling off, resulting in hemiplegia, sensory disturbance, epilepsy, and disturbance of consciousness (22). At the same time, fungi in the venous sinus often invade its surrounding cranial nerves III, IV, V, and VI, presenting ophthalmoplegia and facial pain. In the pathway of a direct invasion through bone lamella, the fungi invade by breaking through the paranasal sinus and orbital apical bone lamella into the brain, resulting in a neurological deficit in the corresponding damaged areas. As the two pathways do not exist independently, the symptoms are complex and variable. However, the trans-vascular approach is relatively common, so venous sinus syndrome indicates that fungal infection has invaded the brain (23).

Due to the close anatomical proximity, it is necessary to distinguish OAS from superior orbital fissure syndrome (SOFS) and cavernous sinus syndrome (CSS). OAS is characterized by the involvement of cranial nerves II, III, IV, VI, and V1 (24). The involvement of the optic nerve differentiates OAS from the other two. In addition, the involvement of sympathetic fibers and the maxillary branch of the trigeminal nerve differentiates CSS from the others (25).

Advancement in Diagnostic Tests

At present, there are no available circulating clinical biomarkers of ROCM. Definitive diagnosis still depends on conventional diagnostic biopsy, which is invasive and lacks sensitivity and species-level identification (26, 27). Prompt diagnosis of ROCM infection with aggressive antifungal therapy is crucial to increase survival and reduce mortality (28).

In the present case, we used a novel technology to get a rapid and accurate etiological result within 24 h. mNGS has emerged as an effective, non-invasive, and quick laboratory technology. Compared with traditional diagnostic methods, such as histopathological and culture diagnosis, mNGS testing showed better sensitivity to pathogen detection, for its ability to identify a wider range of organism and microbial profiles including uncommon agents, and is less affected by prior antibiotic exposure (29). Armstrong et al. detected 40 plasma samples from at-risk patients for fungal infection, who had pediatric hematology, oncology, or stem cell transplantation. mNGS was used to detect fungal pathogens and was compared to conventional clinical testing. It turned out that mNGS identified fungal pathogens in 7 of 40 patients, among which 66.7% were further proved by biopsy (30).

Metagenomics cell-free DNA next-generation sequencing is a novel promising methodology for invasive fungal infections, supporting rapid and specific detection in various sites of infection. The results of mNGS can become available within 24 h, thereby providing a quick reference for timely diagnosis and antifungal therapy for clinicians (31, 32). Furthermore, in the age of "omics", mNGS-based approaches can provide more insights into our understanding of various aspects of mucormycosis, including genome structure, biology, determinants of virulence, growth, and metabolism, pathogenicity, drug resistance, and fungus-host interactions, all of which may promote significant progress in the clinical and scientific research of ROCM (33–35). Previous studies indicated that mNGS has a similar sensitivity to specific PCR assays, which is higher than conventional methods (36). However, reduced specificity due to background microbial contamination and inability to distinguish valuable infection or colonization remains challenging for clinicians, emphasizing the significance of cautious interpretation in the context of clinical practice (29).

Advancement in Therapy

Successful treatment of ROCM requires timely diagnosis, prompt antifungal therapy, and correction of the underlying predisposing factors. Yet, high mortality rates from ROCM infection persist even if all of the above are achieved. There are few prospective randomized controlled clinical trials to evaluate the efficacy of antifungal treatment of ROCM. Global guidelines for diagnosing and managing of mucormycosis in 2019 suggested that intravenous administration of amphotericin B should be considered as the first choice for initial treatment (37). It also stresses that in immunocompromised patients with suspected infection, immediate treatment initiation

is strongly recommended. Among the commonly used antifungal drugs, liposomal amphotericin B (L-AMB) is recommended as the first-line antifungal monotherapy for its better brain penetration and less nephrotoxicity (38). Azoles like isavuconazole and posaconazole oral suspensions are also used in first-line treatment, while terbinafine and echinocandins are not effective against mucormycosis (4). Ibrahim et al. demonstrated the superiority of L-AMB/isavuconazonium sulfate combination over either drug alone in treating murine mucormycosis, however, whether this finding could be transformed into humans warrants further investigation (39).

A recent research demonstrates that delayed antifungal therapy significantly increases mortality in patients with mucormycosis when compared with early treatment (40). Except for systemic intravenous medication, topical medication has also been considered valuable. The 2019 guidelines strongly recommend a combination with early complete surgical treatment whenever possible, which should be repeated if necessary (37). Doub et al. reported a unique case of *Rhizopus arrhizus* brain abscess treated with intracavitary amphotericin in the presence of a blood-brain barrier breach of amphotericin B. Unfortunately, the efficacy of this therapy was not ultimately able to be evaluated (41). Safi et al. reported a case of ROCM with focal anterior cerebritis, treated favorably with a retrobulbar injection of deoxycholate amphotericin B and systemic antifungal therapy (42).

Surgical debridement is essential for the successful treatment of ROCM. A study from 13 European countries involving 230 cases of mucormycosis (27% of ROCM) indicated that combination therapy with amphotericin B and debridement achieved a lower mortality rate (24%) than either medication (58%) or surgery alone (44%) (12). Moreover, orbital exenteration is occasionally necessary. Hargrove et al. reported that exenterated patients with fever have a higher survival rate than nonexenterated patients with fever ($p = 0.0468$) (43). Kshitij et al. devised a scoring system to predict the stage when the exenteration is needed, then the scoring system, if validated with 15 cases and turned out to be efficient (44).

Hyperbaric oxygen (HBO) has a fungistatic effect *in vitro* (45), suggesting that it may serve as an adjunctive therapeutic modality for ROCM. Early in 1988, Couch et al. treated two patients with ROCM with adjunctive HBO therapy based on amphotericin B and surgical debridement. A literature review that included 21 patients with ROCM receiving HBO treatment found a high survival rate of 86%, and even higher (94%) when examining outcomes among the diabetic patients (46).

Immunomodulatory therapy including granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), and macrophage colony-stimulating factor (M-CSF) are other medical options to enhance the immune system and aid antifungal activities. Although studies have shown that immunotherapy can improve the prognosis of invasive fungal infection, large-scale randomized controlled trials are needed (47, 48). Recently, Ibrahim et al. discovered a monoclonal anti-ricin B chain antibody named 'mucoricin,' which may be a promising therapeutic target for mucormycosis (49).

In conclusion, ROCM is a rare, lethal, infectious disease that requires early diagnosis and timely treatment for successful therapy. Clinicians should maintain heightened suspicion for cases with OAS in diabetic or immunocompromised conditions, and pre-emptive antifungal treatment should be recommended in such highly suspicious patients.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Soochow University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ND drafted the initial manuscript. ND and AJ contributed equally to this article. All authors were involved in the care of the patient, revised the manuscript and approved the final version.

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