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CASE SERIES

Clinical Characteristics and Mechanism Discussion of Peripheral Nerve Injury in 2 Cases of Severe Viral Meningoencephalitis

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Purpose: Peripheral neuropathy(PN) secondary to central nervous system(CNS) infections is rare in clinical practice. This study analyze the prognosis, clinical characteristics, and outcomes of patients with PN secondary to CNS infections to aid early diagnosis and improve prognosis.

Methods: Clinical data from two patients admitted to our Neurology Department with PN secondary to severe viral meningoencephalitis were collected, summarized, and analyzed. Using diagnostic tools like body fluid tests, imaging, EEG, and EMG, and based on the criteria of the International Encephalitis Consortium, encephalitis was diagnosed in Case 1 and Case 2. The European Academy of Neurology/Peripheral Nerve Society recommendations were applied to confirm patients' PN diagnosis.

Results: Patient 1 was diagnosed with encephalitis, presenting with elevated serum IL-6 levels, and received IVIG treatment upon admission. One week later, the infection remitted and IL-6 levels decreased. Physical and EMG examinations revealed peripheral nerve demyelination damage. After treatment, the nerve damage improved, and the patient had a good prognosis post-discharge. Upon admission, Patient 2 exhibited viral meningoencephalitis symptoms, with elevated serum IL-8 and normal IL-6 levels; limb muscle strength and tone were normal. Five days later, the infection deteriorated, accompanied by reduced lower limb strength, and elevated IL-6 and IL-8 in serum and CSF, with a striking peak of CSF IL-6. EMG confirmed peripheral nerve demyelination and axonal damage. Following 5-day IVIG treatment, IL-6 and IL-8 levels in serum and CSF declined. Peripheral nerve injury recovery was modest despite treatment, and the patient's prognosis remained moderate.

Conclusion: This study reported two rare cases of PN following CNS infection. Comparative analysis of symptoms, cytokine in body fluids, treatments, disease courses, and prognosis indicates that elevated peripheral and/or central cytokines, particularly IL-6 and IL-8, correlate with the severity and prognosis of this complication. IVIG modulates inflammation, and its administration timing likely determines differential outcomes.

Keywords: viral meningoencephalitis, peripheral nerve injury, electromyography

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Introduction

Central nervous system (CNS) infections are common neurological disorders characterized by brain inflammation caused by invading pathogens, resulting in symptoms such as fever, headache, and signs of meningeal irritation. The aetiology of the infection is diverse and includes viral, tuberculosis, bacterial (excluding tuberculosis), fungal, parasitic, syphilitic, and rickettsial agents, with viral infections being the most common.[1,2] These infections can be classified based on the different areas of involvement, such as encephalitis, meningitis, or meningoencephalitis. Furthermore, common complications of CNS infections include seizures, cognitive impairment, brain herniation, hydrocephalus, subdural empyema, and cranial neuropathy.[3] Although there are limited reports of peripheral nerve involvement secondary to CNS infection, we treated two patients with severe cases of virus-induced meningoencephalitis with subsequent peripheral nerve damage in our hospital. In this report, we provide the detailed diagnosis, treatment, and electrophysiological features of these patients to summarize the clinical characteristics of this type of disease and explore its potential immune mechanisms. Our aim is to offer insights and assistance to clinicians in the diagnosis and treatment of such conditions.

Method

Clinical information from two patients admitted to our Neurology Department with peripheral neuropathy secondary to severe viral meningoencephalitis were collected. The clinical symptoms of the two patients, including clinical manifestations, auxiliary examinations, therapeutic schedule, and disease outcomes, were evaluated by an attending physician in the Department of Neurology. The data were retrospectively analyzed and all the studies were part of a routine clinical examination. All identifiable patient information, such as names, addresses, and medical record numbers, was thoroughly anonymized to safeguard patients' privacy.

Results

Case 1

A 38-year-old man presented to the emergency department on November 17, 2022 with a chief complaint of fever and generalized fatigue for 5 days, accompanied by altered consciousness and seizures for 8 hours. After experiencing a "common cold" five days prior, the patient developed a fever. Despite taking "cold medication" for two days, he did not experience any improvement and subsequently sought medical attention at a local hospital. Upon examination, his body temperature reached 39 °C. After receiving symptomatic antipyretic treatment, his temperature decreased to 36 °C, but unfortunately, he experienced a recurrence of fever after 7~8 hours. Eight hours prior to admission, he suddenly experienced altered consciousness and seizure episodes characterized by unresponsiveness, upwards eye deviation, foaming at the mouth, urinary incontinence, limb flexion, and tonic–clonic movements but no tongue biting. Treatment at the local hospital was initiated to stop the seizures but failed, leading to the patient arriving at our emergency department. Urgent computed tomography (CT) of the head was normal (namely, no significant abnormalities), while a chest CT scan showed patchy shadows in the left lower lobe, suggestive of aspiration pneumonia. The patient was in status epilepticus, and his condition was critical, thus necessitating admission to the neurointensive care unit. The patient had no significant past medical history or personal history. On examination, he was noted to have a temperature of 40.3 °C (104.54℉), a blood pressure (BP) of 151/79 mm Hg, a pulse of 121 beats per minute, and a respiratory rate (RESP, RR) of 50 breaths per minute. Coarse breath sounds were heard bilaterally in the lungs, and moist rales were audible in the left lower lung. No other significant abnormalities were found on internal medicine examination. Neurological examination revealed a state of shallow coma. The pupils were bilaterally dilated and round with a diameter of approximately 2.5 mm. Pupillary light reflex was present. The patients' jaws were tightly closed, and the bilateral nasolabial folds were symmetrical. The patient was uncooperative for the rest of the cranial nerve examination. Muscle strength assessment of the limbs was difficult due to poor cooperation. Both upper limbs were flexed and adducted, and there were muscular spasms in the lower limbs. Muscle tone was increased in all limbs. The tendon reflex was slightly active in both upper limbs but did not elicit a response in either lower limb. The Babinski sign was absent. Neck resistance and Kernig's sign were positive. Initial laboratory analysis results showed leukocyte count 13.4×10^9/L (reference range $3.5\sim9.5\times10^9$/L), neutrophil 89.8% (40~75%), lymphocyte 4.8% (20~50%), neutrophil count

12×10^9/L (1.8~6.3×10^9/L), lymphocyte count 0.64×10^9/L (1.1~3.2×10^9/L), serum IL-6 (2022–11-17) 156.8 ng/L (0~7 ng/L), and procalcitonin (2022–11-17) 0.12 ng/mL (0~0.05 ng/mL). Lumbar puncture was performed, and cerebrospinal fluid (CSF) analysis revealed pressure 180 mmH_2O, no erythrocytes, normal total cell count (0~8×10^6/L), high protein level 1156.8 mg/L (150~450 mg/L), and low chloride 114.3 mmol/L (120~132 mmol/L); Xpert MTB/RIF, acid-fast stain, polymerase chain reaction (PCR) panel for *Toxoplasma gondii*, rubella virus (RV), herpes simplex virus (HSV), and cytomegalovirus of the CSF sample were all negative. Autoimmune encephalitis and paraneoplastic syndrome associated antibodies were also negative in both CSF and blood. Next-generation sequencing (NGS) of the pathogenic microorganisms was negative. A multiplex PCR panel of blood samples was also negative for influenza A/B virus, *Toxoplasma gondii*, RV, HSV, cytomegalovirus, Epstein–Barr virus (EBV), and coronavirus disease 2019 (COVID-19). Pneumoslide IgM/G and bacterial and fungal cultures of sputum were negative. An X-ray of the chest revealed patchy shadows in the middle and lower fields of the left lung. Video electroencephalogram (VEEG) data showed a large number of medium-amplitude slow waves (5~7 hz) continuously firing in the full channel. The diagnosis at admission was as follows: 1. Status epilepticus; 2. High probability of CNS infection; and 3. Pulmonary infection. Antiepileptic treatment with midazolam, sodium valproate, and levetiracetam injection; antiviral treatment with foscarnet sodium and sodium chloride; ganciclovir; anti-infective treatment with piperacillin sodium and tazobactam sodium combined with vancomycin; and intravenous human immunoglobulin (IVIG; 400 mg·kg-1·d-1; once a day for 5 days) combined with methylprednisolone sodium succinate (80 mg once a day for 7 days) as immunotherapy were administered. Mannitol dehydration was used to reduce intracranial pressure, and other symptomatic treatments, including aerosol inhalation and antipyretic treatment, were administered. Eight days after admission, the pulmonary infection improved, and vancomycin was discontinued. Neurologic examination revealed improved consciousness, and the patient was arousable and able to follow simple commands intermittently. His pupils were 2.5 mm in diameter and equally reactive to light. The bilateral nasolabial folds were symmetrical. The muscle strength of both upper limbs was grade 3 with normal muscle tone, and the muscle strength of both lower limbs was uncooperative with low muscle tone. The patient exhibited normal tendon reflexes in both upper limbs, absent tendon reflexes in both lower limbs and had a Babinski sign. The neck was softer than the prior, and the Kernig sign was negative. Repeat lumbar puncture revealed a CSF pressure of 90 cmH_2O and a protein concentration of 563.6 mg/L (150~450 mg/L). The results of nucleic acid tests and next-generation sequencing of the pathogenic bacteria were negative. The modified diagnosis was as follows: 1. Status epilepticus; 2. Viral meningoencephalitis; and 3. Pulmonary infection. However, the patient still had poor muscle strength and low muscle tone in both lower limbs, and no tendon reflexes were elicited. Neuroelectrophysiological examination was performed to determine the cause, which revealed that the conduction velocity and amplitude of the motor branch of the bilateral common peroneal nerve were decreased, while those of the other examined nerves were normal (Table 1). The F wave of the bilateral median nerve and H-reflex of the bilateral tibial nerve were abnormal. The patient could not actively contract the left tibialis anterior or peroneus longus muscles. Electromyography revealed a mixed phase during heavy exertion, and the sensory evoked potentials in both lower limbs were normal. The patient received the additional diagnosis of Guillain–Barré syndrome. Intravenous injection of mecobalamin and intramuscular injection of vitamin B1 were given, and electronic biofeedback therapy was administered to both lower limbs at the same time.

Table 1 Patient 1: NCS Findings

Nerve Conduction	Latent Period (ms)	Amplitude (mv)	Speed (m/s)
Motor conduction			
Left Tibial nerve			
Ankle-AH	3.38	14.8	
Popliteal fossa-ankle	11	13	47.9

(*Continued*)

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Table 1 (Continued).

Nerve Conduction	Latent Period (ms)	Amplitude (mv)	Speed (m/s)
Right Tibial nerve			
Ankle-AH	3.2	15.2	
Popliteal fossa-ankle	10.9	11	47.4
Left Common peroneal nerve			
Ankle-EDB	4.22	0.46	
Knee-ankle	11	0.48	44.2↓
Right Common peroneal nerve			
Ankle-EDB	4.46	2.3	
Knee-ankle	10.2	1.93	52.3↓
Sensory conduction			
Left Superficial peroneal nerve			
Ankle-instep of foot	1.93	13.8	41.5
Right Superficial peroneal nerve			
Ankle-instep of foot	1.41	15.2	49.6
Left Sural nerve			
Mid-calf-lateral malleolus	1.86	15	43
Right Sural nerve			
Mid-calf-lateral malleolus	2.02	14.4	44.6

Note: ("↓" represents a value lower than the normal value).

After 8 days of treatment, the patient was alert and could open his eyes voluntarily and follow commands. The bilateral pupils were 2.5 mm in diameter, a light reflex was present, bilateral nasolabial folds were symmetrical, tongue extension was in the centre, muscle strength was grade 5- in both upper limbs, muscle strength was grade 3+ in both lower limbs, muscle tension was normal, the tendon reflex was normal in both upper limbs, the tendon reflex was not elicited in either lower limb, the Babinski sign was not elicited, the neck was soft, and the Kernig sign was negative. The patient's lower limb muscle strength and muscle tension recovered, his condition stabilized, and he was subsequently transferred to the general ward for rehabilitation treatment. A plain and enhanced brain MRI scan showed no obvious abnormalities.

Thirty-four days after admission, neurological examination of the patient showed that his mind was clear, and cranial nerve examination revealed no obvious abnormalities, there may be transient or functional changes, which may not be detectable on imaging studies. The muscle strength of both upper limbs was grade 5, the muscle strength of the lower limbs was grade 4+, the muscle tension of the limbs was normal, the tendon reflex of both upper limbs was normal, the tendon reflex of both lower limbs was slightly weak, pathological signs were not found, the neck was soft, and Kernig's sign was negative. His condition improved significantly; thus, he was discharged. One month after discharge, the patient's overall recovery was rather limited. He was still dependent on assistance for walking and, upon an attempt at independent ambulation, suffered a sudden fall. In contrast, four months after discharge, EMG/NCS was reexamined at another hospital, and the results showed improvement since the last examination. During this follow-up, the patient reported no symptoms in the upper limbs, and the lower limbs could not be used to walk quickly; however, daily life and work were not affected, and there were no other sequelae. Suggesting a satisfactory recovery state at this stage.

Case 2

A 21-year-old man presented to the neurology department on February 12, 2023, with a chief complaint of headache and fever for 2 days. Two days prior, he developed headache without obvious inducement, accompanied by nausea and vomiting. The vomit consisted of gastric contents and was not ejected, and it was accompanied by fever, with a body temperature of 39.0 °C (102.2℉). The oral administration of nimesulide for fever was recommended, but the body temperature still fluctuated above 38.8 °C (101.84℉). He was treated at a local hospital, and there were no obvious abnormalities in routine blood test results, liver or kidney function, coagulation function, or head CT. After symptomatic treatment, he still had a high fever and intermittent nonsensical speech. For further diagnosis and treatment, the emergency CTA and CTV showed no obvious abnormalities, and the patient was admitted to the Neurology Department with "encephalitis". The patient had no significant past medical history or personal history. On examination, he was noted to have a temperature of 39.3 °C (102.74℉), a BP of 123/71 mm Hg, a pulse of 100 beats per minute, and a RESP of 20 breaths per minute. No other significant abnormalities were found on internal medicine examination. Neurological examination revealed that the patient had a clear mind, fluent language, advanced intelligence, and equal and round pupils (approximately 3 mm in diameter) with a sensitive pupillary light reflex. Both eyes' movements in all directions were free and without nystagmus. The bilateral nasolabial folds were symmetrical. The patient's limb muscle strength was grade 5, and the muscle tone was normal. Bilateral tendon reflexes were symmetrically present, no abnormalities were found during ataxia or sensory examination, and the Babinski sign was negative. Neck resistance. Initial laboratory analysis results showed neutrophil 89.7% (40~75%), lymphocyte 7.5% (20~50%), serum IL-8 80.15 pg/mL (0~20.6 pg/mL), serum IL-17A 26.58 pg/mL (0~20.6 pg/mL), procalcitonin 0.08 ng/mL (0~0.05 ng/mL)), and high-sensitivity C-reactive protein 4.82 mg/L (0~3 mg/L). Lumbar puncture was performed, and CSF analysis revealed pressure >300 mmH_2O, no erythrocytes, total cell count 25×10^6/L (0~8×10^6/L), leukocyte count 18×10^6/L(0~8×10^6/L), high protein level 1825.2 mg/L (150~450 mg/L), low glucose 2.07 mmol/L (2.5~4.5 mmol/L), low chloride 114.8 mmol/L (120~132 mmol/L). CSF cytology was abnormal and revealed mainly lymphocyte reactions. Gram, ink and acid-fast stains were all negative. Next-generation sequencing (NGS) of the pathogenic microorganisms was negative. All the serological tests for *Toxoplasma gondii*, RV, HSV, and cytomegalovirus were negative, the tuberculosis γ-interferon assay yielded a negative result, and the sputum culture did not reveal any pathogenic bacteria. Furthermore, tests for anti-nuclear antibodies, ANCAs, ENAs, thyroid function (7 items), and rheumatoid factors (4 items) all demonstrated normal results. Electroencephalogram (EEG) data showed that θ activity was notably increased, and the amplitude was 5~7 hz for sinusoidal slow wave arrays. Brain MRI+DWI+MRA revealed reversible splenial syndrome (see Figure 1). Therefore, the patient was diagnosed with viral meningoencephalitis with reversible splenial corpus callosum syndrome. Antiviral treatment with foscarnet sodium and sodium chloride and acyclovir; anti-infective treatment with cefoperazone sodium and sulbactam sodium; mannitol combined with glycerin fructose dehydration to reduce intracranial pressure; and antipyretic treatment were given.

Six days after admission, the patient's body temperature was 37.2 °C (98.96℉), and physical examination revealed a shallow coma, left pupil 3 mm, right pupil 2.5 mm, bilateral slow light reflex, bilateral chemosis, left eyeball and scleral local congestion, bilateral nasolabial fold symmetry, and inability to stretch the tongue. Pain stimulation revealed slight movement of the left upper limb and hypotonia. Ataxia and sensory examination were not cooperative, tendon reflexes in both lower limbs were not evoked, the bilateral Babinski sign was negative, neck resistance was found, and bilateral Kernig's sign was negative. A chest X-ray showed patchy high-density shadows in the middle and lower fields of the right lung and the middle field of the left lung. The patient's condition worsened, and he developed type II respiratory failure. Thus, he was transferred to the neurological intensive care unit and intubated with mechanical ventilation. Reexamination of CSF showed that the white blood cell counting increased (320×10^6/L) with decreasing chloride and glucose concentrations, while the protein concentration did not decrease significantly. CSF cytology revealed mainly lymphocytic reactions, and Xpert, acid-fast staining, and multiplex PCR of pathogens in the CSF were all negative. CSF and blood antibody results related to autoimmune encephalitis, paraneoplastic syndrome and pathogenic microorganisms were negative according to next-generation sequencing. Autoimmune encephalitis and paraneoplastic syndrome-associated antibodies were also negative in both CSF and blood. Moreover, the results of NGS for pathogenic microorganisms were negative. The patient was diagnosed with severe viral meningoencephalitis and treated with

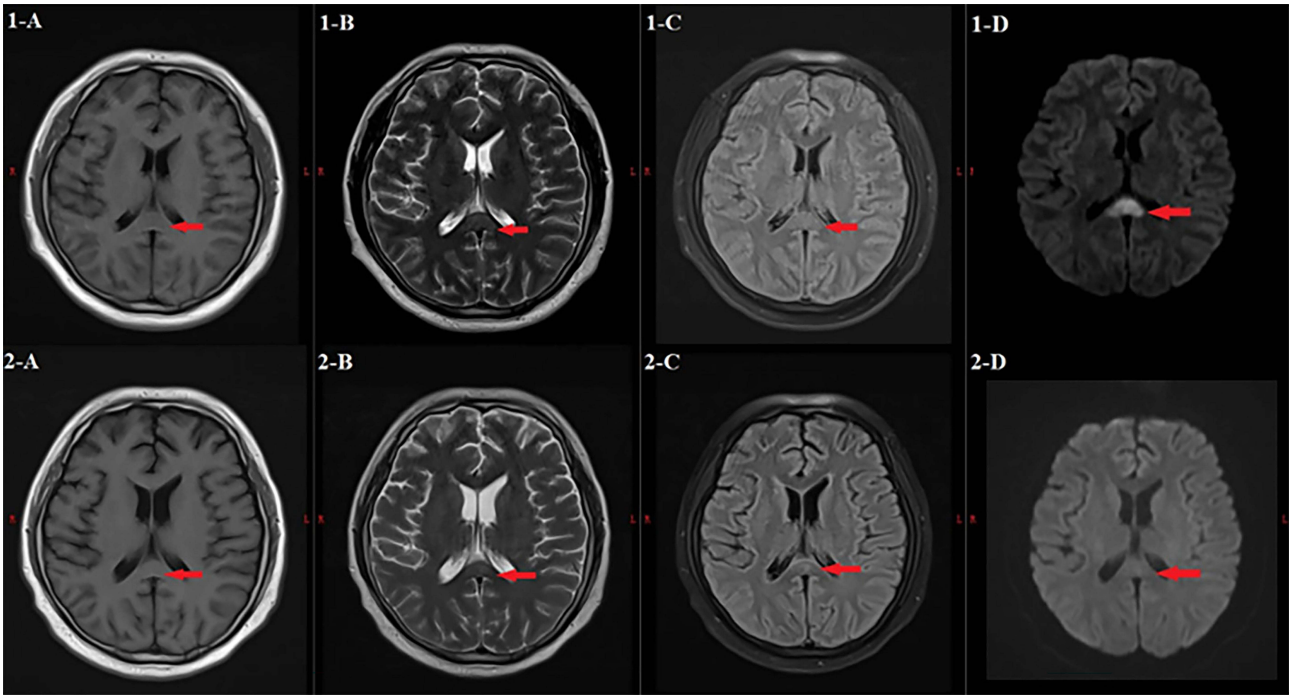

Figure 1 Patient 2: 1- MRI of the patient's head on February 16, 2023. 1-A, patchy slightly longer signals were observed in the splenium of the corpus callosum at T1; 1-B, a slightly longer T2 was observed; 1-C, FLAIR, showed hyperintensity; 1-D, high signal on the DWI sequence. 2- Repeat MRI on March 22, 2023. 2-A, T1; 2-B, T2; 2-C, FLAIR; 2-D, DWI; the abnormal signal range in the splenium of the corpus callosum was reduced. (The red arrow in the pictures denotes the abnormal signals of the splenium of the corpus callosum.).

IVIG (400 mg·kg-1·d-1, once daily for 5 days) combined with methylprednisolone sodium succinate (80 mg once daily for 14 days). Considering that the patient's pulmonary infection was drug resistant, the combination of meropenem and norvancomycin was escalated, and antiviral therapy was continued.

Nine days after admission, the patient could open his eyes, and the eyes were positioned basically in the centre. The coordination of eye movement was poor, and there was no obvious nystagmus. The diameter of both pupils was 3.0 mm, with a delayed response to light. The patient was uncooperative with respect to tongue extension and tooth clenching. Muscle strength in both upper limbs was at level 2, while no voluntary movement was observed in either lower limb. Muscle tone in all limbs was low. The tendon reflex in both upper limbs was symmetrically present, while no tendon reflex was elicited in either lower limb. Coordination and sensory examination were uncooperative, and the Babinski sign was absent. The neck resistance was lower than before, and both sides of the Chaddock's sign test were negative. The range of infection in the chest X-ray was less than before. The VEEG was abnormal, and a large number of medium-amplitude slow waves (2.5–6 hz) were continuously emitted in the full channel. A repeat lumbar puncture was performed, and the CSF pressure decreased to 160 mmH_2O. Eleven days after treatment, the patient's lower limbs could be slightly flexed, and the rest of the physical examination results were as above. Neuroelectrophysiological examination revealed neurogenic damage in the right tibialis anterior, gastrocnemius, and peroneus longus muscles and the left tibialis anterior muscle. The nerve conduction velocities are shown in Table 2, and bilateral median nerve F waves and bilateral tibial nerve H reflexes were normal. Sensory evoked potentials in both lower limbs were normal. Combined with the patient's onset form and clinical manifestations, the additional diagnosis was multiple peripheral neuropathy, and nutritional nerve treatment was given. The patient was diagnosed with viral meningoencephalitis upon admission and received antiviral treatment and broad-spectrum antibiotic treatment. Six days later, the symptoms worsened. Chest X-ray revealed signs of pulmonary infection, and the reexamination of CSF also showed the aggravation of the infection. At this time, the patient gradually presented manifestations of peripheral nerve injury, and IVIG was further administered to the patient to control the infection. Three days after the maintenance treatment, the patient's consciousness became clear, and the infection was alleviated. During the physical examination, muscle strength of the

Table 2 Patient 2: NCS Findings

Nerve Conduction	Latent Period (ms)	Amplitude (mv)	Speed (m/s)
Motor conduction			
Left Median nerve			
Wrists-APB	4.03↑	0.36↓	
Elbow-Wrists	8.31	1.89	54.9
Left Tibial nerve			
Ankle-AH	6.57↑	6.0↓	
Popliteal fossa-ankle	10.02	2.6	23.3↓
Right Tibial nerve			
Ankle-AH	4.42	21.4	
Popliteal fossa-ankle	15.9	1.95↓	32.2↓
Left Common peroneal nerve			
Ankle-EDB	5.51↑	0.14↓	
Knee-ankle	21.3	0.39	20.3↓
Right Common peroneal nerve			
Ankle-EDB	7.31↑	0.046↓	
Knee-ankle	13.5	0.38	51.7↓
Sensory conduction			
Left Ulnar nerve			
Finger IV-Elbow	1.31	351	32.0↓
Right Radial nerve			
EPL tendon-Elbow	2.56	9.9	31.3↓

Notes: ("↓" represents a value lower than the normal value; "↑" represents a value higher than the normal value).

four limbs, disturbance of muscle tone, and tendon reflexes were not elicited. EMG/NCS was performed to confirm the diagnosis of multiple peripheral neuropathy. The patient's condition was stable, and he was transferred to the general ward for further treatment.

Neurological examination before discharge revealed clear consciousness, fluent speech, a basically centred eye position, slight limitation of abduction in both eyes, no obvious nystagmus, a bilateral pupil diameter of 3.0 mm, a sensitive light reflex, a symmetrical bilateral nasolabial fold, and centred tongue extension. The muscle strength of both upper limbs was grade 5, and the muscle tension was normal. The muscle strength of the left lower limbs was Grade 2~2-, the muscle strength of the right lower limbs was Grade 1+ ~2, and the muscle tension was low. The tendon reflex of the left lower limbs was weak, the remaining tendon reflex was not elicited, the Babinski sign was not elicited, the neck was soft without resistance, and Kernig's sign was negative. The patient improved and was discharged. Two months later, the EMG was better than before. At the 12-month follow-up, the patient had full abduction of both eyes, and the patient reported that he still needed aids to walk. Numbness in his feet and legs occurred when he walked or stood for a long time and was relieved spontaneously after a few minutes.

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Discussion

Encephalitis is one of the most common CNS infections, and viral encephalitis has an annual worldwide incidence of approximately 10.5/100,000.[4] It is worth noting that a considerable proportion of patients with encephalitis cases have an unknown aetiology, with 48.2% of those with a clear aetiology, the most common of which are herpes virus, *Toxoplasma gondii* and West Nile virus.[2,5] To definitively diagnose CNS, a comprehensive approach involving a thorough medical history, physical examination, and first-line auxiliary examinations such as CSF analysis, serology, and neuroimaging is crucial. Despite the variety of pathogenic microbial agents implicated in encephalitis, there is no clear specificity in clinical manifestations. Most of the related literature reports that viral infection accounts for the highest proportion of infections.[3,5,6] From the perspective of localization diagnosis, encephalitis, meningitis and meningoencephalitis have certain differences in clinical manifestations and neuroimaging features, among which the mortality and disability rate of encephalitis are high. The clinical manifestations of the two patients discussed in this paper met the diagnostic criteria for encephalitis as outlined by the International Encephalitis Consortium.[6] Additionally, the CSF examination results suggested a viral infection, and the patients' symptoms improved after experimental antiviral treatment. Furthermore, bacterial culture of the CSF and staining tests effectively ruled out the possibility of infection by other common pathogens, such as bacteria and tuberculosis. Consequently, viral encephalitis was confirmed as the diagnosis for both patients.

Treatment and management of encephalitis include various measures, such as aetiology treatment, reduction of intracranial pressure, seizure control, circulation and respiration support, maintenance of water and electrolyte balance, and nutritional support. Targeted treatments are directly administered when the cause of encephalitis is known. IVIG has been employed as a treatment for immune encephalitis and an adjunct treatment for other encephalitides.[7] Despite some reports citing the neuroprotective effects of high-dose hormone therapy,[8] a randomized clinical trial[9] demonstrated its limited impact on mortality and neurological recovery in Japanese encephalitis patients. Consequently, most guidelines do not advocate for hormone therapy as a first-line treatment. Nevertheless, the clinical use of high-dose hormone therapy has been associated with inhibiting inflammation, reducing cerebral oedema, and improving patient symptoms. Empirical antibiotics combined with antiviral therapy and cranial pressure reduction were administered to two patients upon admission in this report. Following the serological and aetiological test results, the diagnosis of viral infection was gradually confirmed, leading to the continuation of antiviral treatment. Additionally, Patient 1 received IVIG therapy combined with hormone therapy upon admission, while Patient 2 initiated this treatment on the 5th day following admission. Subsequent to the treatment, blood and CSF infection indices decreased, cranial pressure decreased, consciousness was cleared, and the disease stabilized. Notably, Patient 1 did not experience any further seizures.

Notably, in contrast to the typical secondary manifestations of CNS infection, such as seizures, cognitive disorders, and brain hernias,[3] this paper documents the occurrence of peripheral nerve injury in 2 patients following encephalitis (see Figure 2), an exceedingly rare complication of CNS infection. Peripheral neuropathy (PN) is a structural and functional disorder of the peripheral motor, sensory, and autonomic nerves. The varied clinical manifestations of PN can be attributed to differences in the affected nerves and types of damage, and clinical diagnosis and classification rely primarily on nerve conduction experiments and electromyography.[10] Seven days after admission, the encephalitis symptoms in Patient 1 improved, but concurrent deterioration in lower extremity muscle strength, muscle tone, and tendon reflexes was observed. Comprehensive electrophysiological examination revealed characteristic peripheral nerve demyelination changes, while CSF analysis revealed a distinct protein–cell separation phenomenon consistent with Guillain–Barré syndrome, which is a type of immune-mediated acute inflammatory PN with acute onset and symptoms peaking at approximately 2 weeks.[11,12] In the second patient, neurological examination demonstrated symmetrical movement disorders in the extremities and the weakening and disappearance of tendon reflexes. Electrophysiological examination revealed damage to multiple nerves, mainly characterized by demyelination with reduced conduction velocity and decreased amplitude, indicating axonal injury, which is in line with the features of multiple peripheral neuropathy.

When analysing the aetiology of PN secondary to CNS infection in the presented cases, the possibility of immune-mediated neuropathy was considered for the following reasons. First, common causes of PN include metabolism, nutritional disorders, immunity, infection, drug poisoning, trauma impingement, etc.[10] After reviewing the medical history of the two patients, it was noted that their thyroid function and blood glucose levels were within normal limits, their diet was normal, and tests for various antibodies (ANCA, ENA, antinuclear) were negative. Furthermore, tests for

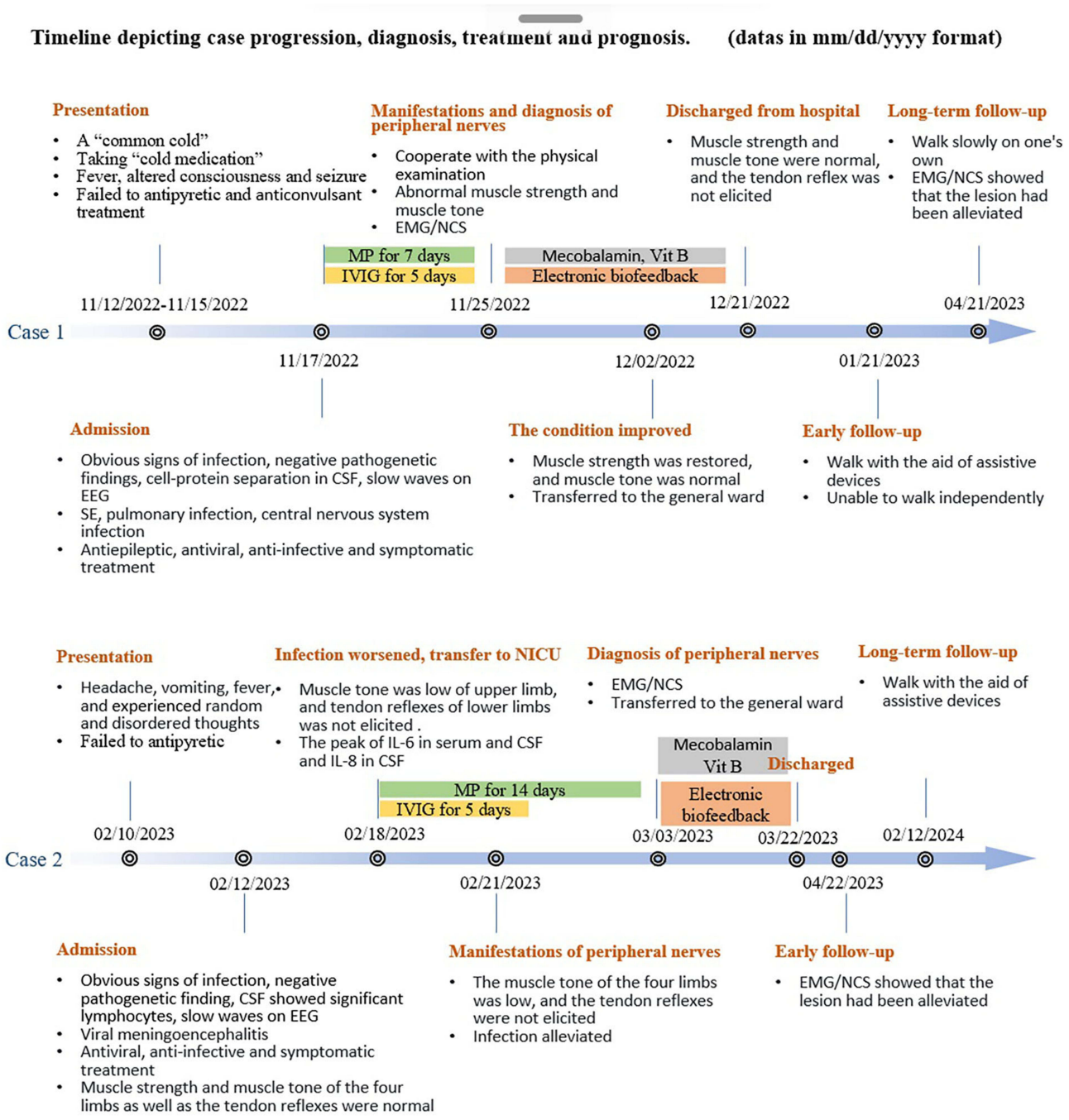

Figure 2 Timeline depicting case progression, diagnosis, treatment and prognosis. ("MP" denotes " Methylprednisolone"; other abbreviations follow their meanings in the text.).

acid-fast staining, tuberculosis bacteria, and CSF staining did not yield abnormal results. Tumour markers were not elevated, and there was no history of exposure to specific toxins or drugs or any traumatic events. This comprehensive assessment effectively ruled out drug poisoning, systemic immune diseases, specific infections, paraneoplastic syndromes, and metabolic-related PN. Second, the treatment perspective revealed that following IVIG treatment combined with neurotrophic drugs and electronic biofeedback, the limb movement disorders of the two patients gradually improved. Specifically, Patient 1 received IVIG immediately after admission; this patient exhibited mild demyelinating changes in secondary peripheral nerve damage and experienced significant recovery in motor function and overall functionality. There were no sequelae affecting daily life or work. Conversely, in Patient 2, the condition was controlled

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by IVIG 5 days after admission, and the patient exhibited axonal damage alongside demyelination, resulting in residual lower limb mobility dysfunction after discharge. In contrast, a patient suspected of having tuberculosis central nervous system infection with secondary manifestations of PN admitted to our hospital was not included in the report because relevant electrophysiological examination could not be performed to confirm the diagnosis and type of PN. This patient's main treatment was antituberculosis therapy, with no IVIG therapy performed. CSF examination of this patient revealed a decrease in various infection indicators, and clinical symptoms were substantially improved, but peripheral nervous system injury did not noticeably improve. In addition, by comparing the various inflammatory indices of the two cases, it can be found that the inflammatory level of Case 2 is much higher than that of Case 1. A higher inflammatory level may imply more significant peripheral nerve damage and slower functional recovery.

We propose the following hypotheses regarding the mechanism of immune-mediated secondary PN after CNS infection in two patients. First, the cytokine inflammatory storm triggered by infection increases the permeability of the blood–brain barrier (BBB),[13] facilitating the passage of immune components involved in combating infection into the CNS. For example, B cells can cross the BBB and activate complement to generate an anti-ganglioside reaction. These antibodies can bind both antigens produced by pathogenic microorganisms and gangliosides derived from nerves.[14] Qiuling Zang et al[15] reported the case of a 43-year-old female who was diagnosed with GBS 17 days after admission. Seven days after admission, cytokine examination of the CSF revealed an increase in IL-6, IL-8 and IFN-γ levels, which was interpreted as an indication of the initiation of a cytokine inflammatory storm. These findings were consistent with the CSF reexamination results after peripheral nervous system injury in the two patients in this study. Tables 3 and 4 provides the details of laboratory analysis results of two cases. Both patients exhibited elevated levels of IL-6 and IL-8 in their CSF examination results, and when comparing the pre- and post-CSF examination results of the two patients, it was observed that the IL-6 and IL-8 levels peaked during the course of the disease. Additionally, Patient 2 had substantially greater peak levels of IL-6 and IL-8 in the CSF than did Patient 1. Notably, the maximum level of IL-6 in the CSF of Patient 2 reached 1186.26 pg/mL (reference range 0~7 ng/L) 6 days after admission (2023-2-18), while the maximum value of IL-8 reached 927 pg/mL (reference range 0~20.6 pg/mL), persisting above normal levels for 25 days. In contrast, 7 days after admission (2022–11-24), the maximum level of IL-6 in the CSF of Patient 1 was 20 pg/mL (0~7 ng/L), and the maximum level of IL-8 was 63.37 pg/mL (0~20.6 pg/mL), which was substantially lower than that in Patient 2. Figures 3 and 4 shows the changes in cytokines related to Case 2. These differences in cytokine levels between the two patients further support the potential association of CSF cytokine levels with the process of acute inflammatory demyelination. By comparing the differences in cytokines of the two patients in this study, it is suggested that the higher the level of cytokines, the slower and worse the recovery of peripheral nerve function may be. Second, viral infection

Table 3 Summary of CSF Test Results

Patient	Date	Pressure (mmH_2O)	Total cell Number (10^6/L)	WBC (10^6/L)	Cl (mmol/L)	Glu (mmol/L)	Pro (mmol/L)
1	2022/11/17	180	3	0	114.3	2.73	1156.8
	2022/11/24	90	3	0	133.0	3.96	563.6
2	2023/2/13	300+	25	18	114.8	2.07	1825.2
	2023/2/17	244	450	320	118.6	1.77	1721.6
	2023/2/20	160	400	220	131.6	4.04	1491.8
	2023/3/13	200	80	11	122.5	3.81	311
The remaining tests:		Multiple times a. gram, ink, acid-fast stain b. pathogen nucleic acid detection c. autoimmune encephalitis, paraneoplastic syndrome associated antibodies and NGS all negative					

Table 4 Summary of the Cytokines in the Two Patients

Patient	Date	IL-6 (pg/mL)		IL-8 (pg/mL)		IFN-α (pg/mL)	
		Serum	CSF	Serum	CSF	Serum	CSF
1	11.17	690.93	0.61	151.15	0.32	0.12	0.12
	11.25	9.07	20	10.93	63.37	2.7	2.58
2	2.12	3.44	/	80.15	/	3.13	/
	2.17	32.14	1186.26	45.84	927	0.27	6.56
	2.20	/	37.42	/	306.38	/	3.78
	2.23	/	18.14	/	86.8	/	2.69
	2.25	5.87	/	24.73	/	3.1	/
	2.28	/	32.57	/	63.32	/	2.94
	3.2	10.72	/	10.83	/	1.94	/
	3.6	/	5.26	/	52.59	/	1.3
	3.8	2.44	/	14.63	/	2.58	/
	3.13	/	8.96	/	39.1	/	2.84

Note: ("/" means the item has not been tested).

triggers the activation of the type I IFN pathway, which results in aberrant expression and functional regulation of adenosine deaminase acting on RNA, leading to alterations in RNA editing in neurons and subsequently causing various manifestations, such as neuronal development and dysfunction.[16,17] Interferons (IFNs) are a category of cytokines present in both the central and peripheral nervous systems that encompass three families—namely, type I IFN, type II IFN, and type III IFN. Type I IFNs include IFN-α and IFN-β, which are suggested to inhibit nociception in the spinal cord within

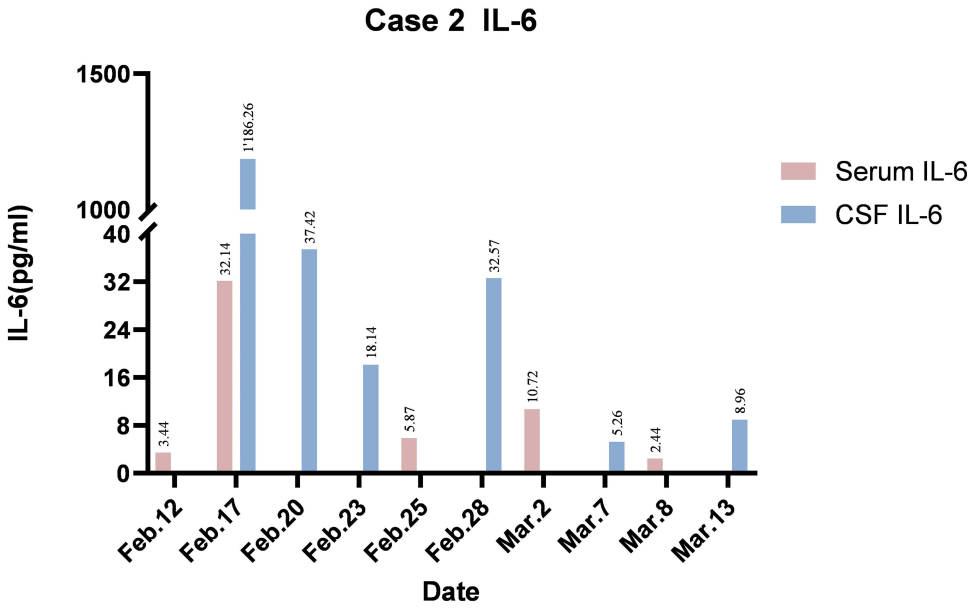

Figure 3 IL-6 of Case 2 in serum and CSF.

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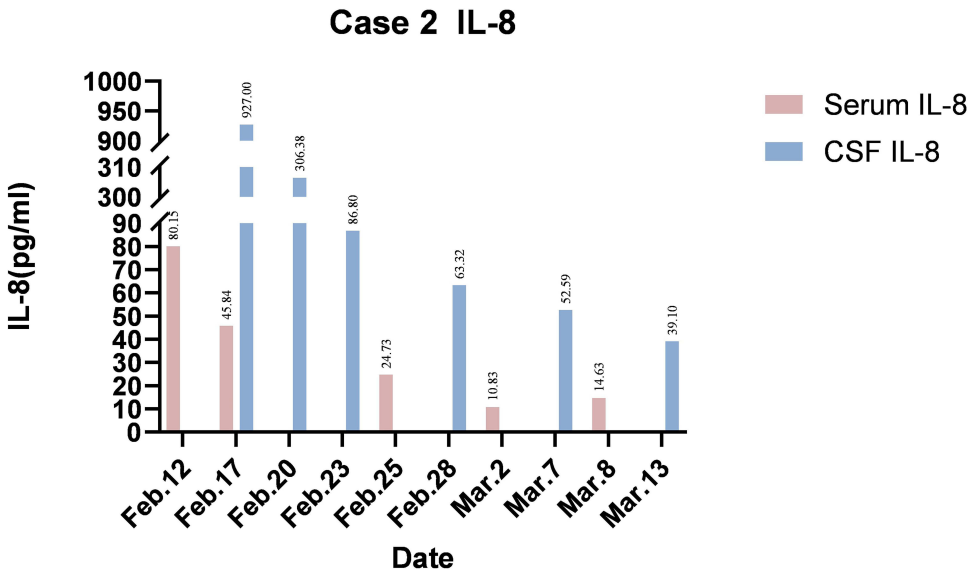

Figure 4 IL-8 of Case 2 in serum and CSF.

the peripheral nervous system.[18] Examination of IFN-α levels in both CSF and serum revealed transient increases during the course of the disease, indicating activation of the type I IFN pathway.

IVIG has been widely used as a treatment for a variety of immune-mediated diseases.[19] Judith N. Wagner et al systematically reviewed the literature on IVIG treatment for viral encephalitis and reported that early IVIG treatment tends to facilitate improved patient recovery.[20] The timing of IVIG therapy plays a crucial role, as demonstrated by the comparison of two cases. Patient 1, who achieved a better and faster recovery from peripheral nerve injury, was promptly administered IVIG upon admission. Conversely, in Patient 2, whose recovery was slower, IVIG treatment was initiated 5 days after admission when the patient's condition had deteriorated. This difference in recovery outcomes is attributed not only to the distinct types of peripheral nervous system damage in the two patients but also to the timing of IVIG therapy.

Furthermore, IVIG is not only applied in clinical practice as a therapeutic method but also as a means of preventing immune-mediated diseases.[19] In this paper, both patients received full and sufficient IVIG treatment for encephalitis before peripheral nerve injury diagnosed. According to the guidelines,[6,11] the dose of IVIG used for GBS treatment and the dose of IVIG used as an adjuvant treatment for encephalitis[7] were both 400 mg·kg-1·d-1 administered once daily for 5 consecutive days. The treatment was still within the validity period,[21] and no additional IVIG treatment was administered. Although the use of IVIG promoted patient recovery. This could be attributed to the following two reasons: first, despite the decreasing trend in cytokine levels in the CSF during the disease course, the IL-8 levels continued to increase, indicating that the progression of acute inflammatory demyelination persisted;[22] second, IVIG neutralizes the pathogenic antibody but cannot clear it, leading to secondary peripheral nerve injury due to the presence of immune complexes.[15]

The pathogenic microorganisms of infection could not be identified in either of the two patients in this study, making it impossible to investigate the relationship between the pathogen types and secondary PN as well as the underlying mechanism further. Continued inclusion of cases is required for more thorough research to reach more conclusive results.

Conclusion

Unlike common secondary manifestations secondary to CNS infection, such as seizures, cognitive impairments, and brain herniation, this study reports two rare cases of PN secondary to CNS infection.

Patient 1 presented with encephalitis symptoms (fever, fatigue, altered consciousness, seizures) accompanied by elevated serum IL-6 levels at initial diagnosis and received IVIG upon admission. A week later, the patient's infection showed signs of remission, and the IL-6 level decreased. Physical examination indicated peripheral nerve impairment,

and EMG/NCS showed demyelinating lesions. Following appropriate treatment, the peripheral nerve damage was alleviated, and the patient had a good prognosis after discharge. Patient 2 presented with headache, fever, nausea, and vomiting. Imaging supported an encephalitis diagnosis. After infection exacerbation, and peripheral nerve impairment emerged with high levels of IL-6 and IL-8 in both serum and CSF, IVIG was given. EMG/NCS revealed demyelination and axonal injury. As the patient's inflammation was controlled and the cytokines decreased, the peripheral nerve injury gradually recovered. When comparing the prognoses of the peripheral nerve injuries of the two patients, the recovery speed and degree of Patient 2 were slightly inferior to those of Patient 1.

By comparing the symptoms and signs, the levels of inflammatory indices such as interleukin and interferon in body fluids, imaging examinations, treatment measures, disease progression, and prognosis between Case 1 and Case 2, the findings of this study suggest that the elevation of cytokines in the peripheral and/or central nervous system is associated with the severity and bad prognosis of PN secondary to CNS infection, especially IL-6 and IL-8. IVIG affects the level of inflammation, and the timing of its administration may be a key factor contributing to different prognoses. Clinicians should closely monitor the cytokines levels and peripheral nerve function of such patients. Initiating immunotherapy in a timely manner when needed may improve the prognosis of patients.

Abbreviations

IVIG, intravenous human immunoglobulin; CNS, central nervous system; CT, computed tomography; BP, blood pressure; RESP, RR, respiratory rate; CSF, cerebrospinal fluid; PCR, polymerase chain reaction; RV, rubella virus; HSV, herpes simplex virus; NGS, next-generation sequencing; EBV, Epstein–Barr virus; COVID-19, coronavirus disease 2019; VEEG, video electroencephalogram; EMG, electromyography; NCS, neuroelectrophysiological; MRI, magnetic resonance imaging; CTA, computed tomography angiography; ANCAs, anti-neutrophil cytoplasmic antibodies; ENAs, extractable nuclear antigens; EEG, Electroencephalogram; DWI, diffusion weighted imaging; MRA, magnetic resonance angiography; FLAIR, fluid attenuated inversion recovery; PN, peripheral neuropathy; BBB, blood–brain barrier; IL, interleukin; IFN, interferon; GBS, Guillain–Barré syndrome; RNA, ribonucleic acid.

Consent of Publication

Informed consent to publish was obtained from the study participants and the First Hospital of Hebei Medical University.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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