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ARTICLE

Anti-N-methyl-D-aspartate Receptor Encephalitis Associated with Peripheral Nerve Injury: A Case Report

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ABSTRACT

A patient with Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis presented with quadriplegia and multiple peripheral neuropathy with axonal lesion, confirmed by electrophysiological examination. The muscle strength in the limbs of the patient gradually recovered almost completely, accompanied by the reversal of neuroelectrophysiological symptoms, and the improvement of clinical manifestations, including consciousness, respiration and cognitive function. It was revealed that the neuropathy in NMDAR encephalitis involved motor or sensorimotor nerves more than pure sensory nerves. No autoantibodies were detectable, in contrast to other anti-NMDAR overlapping syndromes. Although the underlying mechanism remains unclear, it may be associated with autoimmune generalization. In conclusion, when patients with NMDAR encephalitis present with severe limb paralysis, the possibility of peripheral nerve damage should be considered.

1. Introduction

Anti-N-methyl-D-aspartate receptor encephalitis is an autoimmune disease caused by the production of anti-NMDAR antibodies in the central nervous system. With the increasing awareness of the disease, anti-NMDAR overlapping syndrome has begun to attract more attention. However, cases with anti-NMDAR encephalitis rarely present with peripheral neuropathy complications. Anti-NMDAR encephalitis is a common autoimmune limbic encephalitis[1]. However, anti-NMDAR encephalitis with peripheral nerve damage is rarely reported. Patients with anti-NMDAR encephalitis may exhibit symptoms including memory loss, epilepsy, dyskinesia, involuntary movement, disturbance of consciousness and dysfunction of the autonomic nervous system [2]. The main cause of this disease is the production of antibodies against NMDAR, which is the main excitatory synapse protein in the central nervous system. NMDAR is a glutamate receptor found in cells of the peripheral nervous system [3]. Excessive activation of this protein can cause acute neuronal death and chronic neuronal degeneration, whereas insufficient levels of activation are associated with mental health disorders [4]. In the present case report,

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Abbreviations: NMDAR,N-methyl-D-aspartate receptor.

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a patient with anti-NMDAR encephalitis presented with prominent quadriplegia. Electrophysiological examination confirmed peripheral nerve damage in the limbs. Following the treatment of the condition by immunotherapy, the symptoms of peripheral nerve damage also subsided. In addition, relevant literature was reviewed and summarized.

2. Case Report

Patient information. The patient, a 21-year old female, complained of intermittent fever for >5 months and was admitted due to consciousness disorder in May 2018. The patient exhibited no apparent predisposition to headache or fever on February 17, 2018, and improved following the administration of oral medication at a local health facility. On the evening of February 27, 2018, the patient suffered from sudden loss of consciousness, double-fold inversion and twitching of the limbs. She was treated with anti-inflammatory treatment (unknown treatment) at a local psychiatric hospital, with no improvement of the symptoms. On March 1, 2018, the patient was transferred to a hospital in Ningxia, diagnosed with encephalitis and given antiviral and sedative treatment, leading to an adverse effect. On March 8, 2018, a sample of cerebrospinal fluid (CSF) was obtained and sent to the Peking Union Medical College Hospital to be tested for NMDAR antibodies. The results were positive (antibody titer 1:100) and the patient was diagnosed anti-NMDAR encephalitis. Two rounds of γ globulin pulse therapy (0.4 mg/kg/day; March 8-12 and 22-26) were administered. The daily methylprednisolone intravenous dose was gradually reduced from 500 to 40 mg, propofol was administered to control epilepsy, and other treatments were given. A tracheotomy was performed on March 15, 2018 due to dyspnea and the patient was put on assisted ventilation. On March 20, 2018, the patient displayed no autonomous movement in the lower limbs, and subsequently in the upper limbs. Further treatment was administered in a hospital in Beijing on April 10, 2018. Two rounds of γ globulin pulse therapy were administered again (0.4 mg/kg/day; April 12-15 and May 5-11). On April 13 and 20, 2018, a lumbar puncture was performed and an intrathecal injection of methotrexate (10 mg) and dexamethasone (10 mg) was administered. Further treatment included 0.75 g mycophenolate mofetil and 1 g levetiracetam twice daily, 2 mg clonazepam Q8h, 25 ml sodium valproate oral liquid to treat epilepsy and involuntary movements, an indomethacin suppository, oral Betaloc to control autonomic nervous disturbance, enteral nutrition, nerve nutrition, airway management. The patient was transferred to the Yuquan Hospital of Tsinghua University on June 11, 2018, and continued to be treated with mycophenolate mofetil (dose increased to 1 g), methylprednisolone, indomethacin, levetiracetam, metoprolol.

2.1 Physical Examination for Admission

The patient was transferred to the Yuquan Hospital of Tsinghua University on June 11, 2018.The vital signs of the patient were stable. On medical examination, no particular abnormality was revealed. The neurological examination revealed somnolence, shallow coma, no response to questions or instructions, self-opening eyes, the ability to look around, involuntary movements of the mouth, the remaining cranial nerve examination was not successful because the patient was unable to cooperate. Muscle atrophy, lower limb muscle tension, limb muscle strength III grade, double upper limb tendon reflex significantly reduced and double lower limb tendon reflex could not be induced. The Babinski signs of the legs were negative, and there was no indication of meningeal inflammation.

2.2 Supplementary Examination

The CSF examination (March 2, 2018) gave the following results: Protein, 0.27 g/l; sugar, 2.5 mmol/l; chloride, 125 mmol/l; 80 cells; lymphocytes, 94%; monocytes, 3%; and plasma cells, 3%. A 24-h video-electroencephalography (March 4, 2018) revealed severe abnormalities, background persistent wave changes, bilateral persistent frontal-mesotemporal sharp slow wave bursts, and a high-amplitude β-wave rhythm. The results of the test for the NMDAR antibody (1:100) were positive on March 8 and April 11, 2018. A pelvic and abdominal computed tomography (CT) (March 22, 2018) revealed a small amount of fluid in the pelvis and multiple lymph nodes in the abdominal aorta. A head CT on the same day revealed a right occipital lobe punctate high-density shadow and bilateral maxillary, ethmoid and sphenoid sinusitis. On April 12, 2018, the immunoglobulin levels of the patient were 22.06 g/l. In an abdominal ultrasound (April 11, 2018), the liver, spleen, pancreas, kidney and uterus exhibited abnormalities. The first electromyography (EMG) (April 27, 2018; a hospital in Beijing) revealed that motor nerve conduction in the extremities was normal, and the amplitudes of multiple motor nerve waves were decreased. The result of the second EMG (June 25, 2018; Yuquan Hospital of Tsinghua University) was similar to the previous one. The results of the third EMG (August 14, 2018; Yuquan Hospital of Tsinghua University) were improved significantly (Table I). A transabdominal color Doppler ultrasound (June 28, 2018) revealed a cyst in the right ovary with a small

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amount of fluid around it. Head magnetic resonance imaging (June 30, 2018) revealed no obvious imaging changes and right mastoid inflammation. CSF biochemical and immunological tests gave the following results (July 5 and 9, 2018): Pane cell positive; no cells; protein, 14.19 mg/dl; sugar, 3.14 mmol/l; chloride, 118.42 mmol/l; IgG (CSF), IgG (S), OB (S) negative, OB (CSF), SOB (CSF) positive. The NMDAR antibody (1:100) was detectable (July 9, 2018). Further immunological tests of the CSF (July 9, 2018) revealed that CASPR2-Ab, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)1-R-A, AMPA2-R-A, LGI1-Ab, GABAB-R-A, GAD65-Ab, GM1-IgG, GD1b-IgG, GQ1b-IgG, GM1-IgM, GD1b-IgM and GQ1b-IgM were negative. MBP levels were high (0.84 nmol/l), and CV2/CRMP5, PNMA2, Ri, Yo, Hu, Amphiphys were negative.

2.3 Diagnosis

Firstly, the patient exhibited conscious disturbance, abnormal mental behavior, epileptic seizures, involuntary movement, hypopnea and dysfunction of the autonomic nervous system. Furthermore, the result of the anti-NMDAR antibody test was positive. Therefore, the diagnosis of anti-NMDA encephalitis was confirmed, based on the diagnostic criteria reported by Graus *et al* [5]. Secondly, following the muscle weakness in the limbs of the patient, lower motor nerve palsy was observed in a physical examination. Multiple motor nerve axonal lesions were confirmed by neuroelectrophysiology, and the condition was diagnosed as multiple peripheral neuropathy (motor nerve axonal damage).

2.4 Limb Weakness and Symptom Improvements

At a period of 1 month after the onset of the disease, the patient first discovered the inability to move the lower limbs independently, and this soon also involved the upper limbs. Test results revealed that the tendon reflex of the upper limbs could not be induced, the symmetry of the lower limbs was decreased, muscle atrophy was observed in the limbs, and the muscle strength was measured at the lowest level (level 0). At 2 months the upper limbs resumed their autonomous functions, and at 3 months the limbs could move independently and the patient was able to walk. At 4 months, free movement was observed in the upper extremities. The patient was conscious, could understand questions and give brief answers, and was discharged from hospital. No autonomous movement in the mouth and face, no definite abnormality of limb sensation was detected. The limb muscle was atrophied, limb muscle strength is completely normal, limb tendon reflex was positive and pathological reflex was negative. The electromyogram revealed that the amplitude of motor nerve in extremities was decreased, the F wave and H reflex of the tibial nerve were present, no conduction block was observed, there was prolonged latency, and no abnormal sensory conduction was revealed (Table 1).

3. Discussion

Anti-NMDAR encephalitis is an autoimmune disease mediated by anti-NMDAR antibodies, involving the hippocampus and other parts of the limbic system, and the cerebral cortex. Anti-NMDAR antibodies detected in the serum or CSF are specific indicators of anti-NMDAR encephalitis. Since Dalmaul *et al* [1] reported the first case of anti-NMDAR encephalitis in 2007, the knowledge around anti-NMDAR encephalitis has advanced, and the number of clinically confirmed cases has increased.

In the present case report, a patient presented with fever onset, progressive abnormal mental and behavioral symptoms, epilepsy, language disorders, disturbances of consciousness, hypopnea, autonomic nervous system issues and other manifestations. The anti-NMDAR antibody was detected in the CSF, and, based on the diagnostic criteria by Graus *et al* [5], anti-NMDAR encephalitis was considered as a diagnosis. In the present case, obvious paralysis of the limbs was noted, and an EMG confirmed multiple axonal injuries. Following immunotherapy, the condition of the patient gradually improved, with the muscle strength first being restored in the upper limbs, followed by the lower limbs. Consistently, the motor axonal lesions found during the follow-up neuroelectrophysiological examinations also recovered (Table 1). The peripheral nerve damage could be explained by the classic clinical manifestation of anti-NMDAR encephalitis.

The peripheral nerve damage of the patient was also not due to drug poisoning, toxin poisoning or diabetes. As the CSF proteins were not elevated at different stages of the disease, serum ganglion creatinine lipid antibodies were negative, and the EMG revealed no evidence of root lesions, the peripheral nerve lesions in this patient could not be diagnosed as Guillain-Barre syndrome, despite there being a study reporting Guillain-Barre syndrome in patients with anti-NMDAR encephalitis [6]. The paraneoplastic antibody status in the serum of the patient was negative and no evidence of a tumor was observed in the tumor screening; therefore, paraneoplastic syndrome was ruled out.

The reversible peripheral nerve damage in the patient of the present case report was associated with an-

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ti-NMDAR encephalitis. NMDAR is a glutamate receptor expressed in the peripheral nervous system. It is therefore understandable that when antibodies against glutamate receptors occur in the central nervous system, abnormal immune responses against these glutamate receptors can also occur. This phenomenon is termed autoimmune panchemistry, first proposed by Xu Xianhao. The theory originated from the discovery of pyramidal tract disease in patients with myasthenia gravis. The explanation was that although myasthenia gravis was mediated by peripheral anti-acetylcholine receptor antibodies, this abnormal immune response could trigger attacks on central nervous system tissue, resulting in pyramidal tract damage. Associated conditions include thyroid disease and rheumatoid disease. Different autoimmune diseases coexisting in the same patient is also known as autoimmune disease superposition syndrome [7], where other autoantibodies can be detected in the bodily fluids of a patient with an autoimmune disease without presenting the corresponding clinical manifestations.

Many cases of anti-NMDAR encephalitis complicated with other autoimmune diseases or antibodies have been reported. Qin *et al* [2] reported that anti-NMDAR encephalitis existed in an atypical form and could coexist with optic neuromyelitis or neurosyphilis. Hatano *et al* [8] revealed that atypical Miller Fisher syndrome is associated with a glutamate receptor antibody. Titulaer *et al* [9] reported on patients with anti-NMDAR encephalitis who were also diagnosed with neuromyelitis optica. Hacohen *et al* [10] demonstrated that brainstem encephalitis, leukoencephalopathy following herpes simplex encephalitis, and acquired demyelination syndrome can occur with anti-NMDAR encephalitis. Baheerathan *et al* [11] discovered 2 patients who were diagnosed with multiple sclerosis following anti-NMDAR encephalitis.

Including the present case, 11 cases of autoimmune encephalitis with peripheral neuropathy have been reported to date. Among these cases, 8 were anti-NMDAR encephalitis and 3 anti-AMPA receptor encephalitis. Of the 9 patients with recorded nerve conduction velocity injuries, 1 exhibited pure sensory involvement, 3 displayed sensorimotor involvement, and 5 exhibited motor or mainly motor involvement. Among the 11 patients reported by Wei *et al* [2], 3 were anti-Hu antibody positive, of whom 2 were ultimately diagnosed with paraneoplastic syndrome.

Anti-NMDAR encephalitis can be associated with peripheral neuropathy, mainly in the motor or sensorimotor nerves, exhibiting symptoms including limb atrophy and paralysis. Notably, the weakness symptoms may be obscured by clinical manifestations, including a coma. The clinical management of this condition requires a suitable differential diagnosis, particularly in order to exclude Guillain-Barre syndrome, paraneoplastic syndrome and other common causes of peripheral neuropathy. It is presumed that autoimmune generalization is the possible pathogenesis. In clinical management, it is important to consider the possibility of anti-NMDAR encephalitis complicated with other autoimmune diseases or lesions, and to expand the range of autoantibodies tested (not only ones targeted to the nervous system, but also for conditions affecting other tissues, including the connective tissue and thyroid), which is of great significance for the evaluation of the condition and the prognosis of the patient. It is recommended that future work on anti-NMDAR encephalitis with peripheral neuropathy focuses on finding novel antibodies.

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Availability of Data and Materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' Contributions

FH and LH are responsible for statistics and writing articles and coordinate the work of personnel. SZ, MZ, JW, JH and HG are responsible for collecting data and providing advice. LQ and YZ are responsible for reviewing and revising articles. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

The study was approved by the ethics committee of Yuquan Hospital of Tsinghua University (Beijing, China). The patients who participated in this research, signed an informed consent and had complete clinical data.

Patient Consent for Publication

Not applicable.

Competing Interests

The authors declare that they have no competing interests.

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Table 1. Information regarding the EMGs performed at Yuquan Hospital of Tsinghua University.

Sensory nerve conduction

Stimulation site	First EMG		Second EMG	
	Conduction velocity, m/s	Amplitude, μV	Conduction velocity, m/s	Amplitude, μV
Right median nerve	62.5	28	57.9	16
Left median nerve	62.1	27	56.1	18
Left ulnar nerve	58.5	12	57.8	11
Right ulnar nerve	60.6	14	57.8	11
Right sural nerve	48.6	8.6	53.6	8.3
Left sural nerve	50	6.8	55.6	5.7

Motor nerve conduction

Stimulation site	First EMG		Second EMG	
	Amplitude, mV	Velocity, m/s	Amplitude, mV	Velocity, m/s
Left median nerve				
Wrist	10.5		10.2	
Elbow	9	54.3	8.7	62.9
Right median nerve				
Wrist	6.4 ↓ (71%)		7.7 ↓ (64%)	
Elbow	6.0 ↓ (66%)	55.9	6.6 ↓ (63%)	60.5
Left ulnar nerve				
Wrist	13		14	
Under the elbow	12.7	65.5	14.1	68.8
Upper elbow	12.1	68.8	13.1	71.4
Right ulnar nerve				
Wrist	13.9		13.4	
Under the elbow	13.4	64.5	13	67.7
Upper elbow	13.5	64.7	12.7	71.4
Left tibial nerve				
Medial malleolus	2.4 ↓ (87%)		4.8 ↓ (74%)	
Right tibial nerve				
Medial malleolus	3.3 ↓ (83%)		5.2 ↓ (73%)	
Popliteal fossa	2.8 ↓	43.6	5.1 ↓	44
Left common peroneal nerve				
Mesotarsal	N/A		1.1 ↓ (83%)	
Below the head of fibula	N/A		1.3 ↓	45.3
Above the head of fibula	N/A		1.3 ↓ (75%)	46.7
Right peroneal nerve				
Medial malleolus	0.4 ↓ (93%)		0.7 ↓ (89%)	
Above the head of fibula	0.6 ↓	46.7	1.2 ↓	46.4

EMG, electromyography.

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