

Case Report

## Staged Treatment for Anti-NMDA Receptor Encephalitis Based on Combined Western and Traditional Chinese Medicine

Jing Zhang<sup>1</sup>, Xinglu Dong<sup>2</sup>, Cuiyu Xu<sup>1</sup>, Gao Li<sup>1</sup>, and Juexian Song<sup>1</sup>

<sup>1</sup> Department of Neurology, Xuanwu Hospital, Capital Medical University, Beijing 100053, and

<sup>2</sup> Dongzhimen Hospital Affiliated to Beijing University of Chinese Medicine, Beijing 100029, PRC.

Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis is a type of autoimmune brain inflammation. By combining clinical practice and an examination of the disease characteristics, Professor Li Gao has proposed that “phlegm heat” is the core pathogenesis of anti-NMDA receptor encephalitis, and has suggested a staged treatment strategy based on heat clearing, phlegm dissolving, and detoxification. In the early stages of the disease, pathogens are removed to prevent further changes; in the middle stages, purgation and tonification are implemented simultaneously; in the late stages, efforts are made to replenish the deficiencies and support healthy energy. This approach has been used in a combined treatment strategy developed based on clinical cases who were treated using both Western and traditional Chinese medicine for anti-NMDA receptor encephalitis.

**Key words:** anti-NMDA receptor encephalitis, combined Western and traditional Chinese medicine, staged treatment, expert experience

### Introduction

Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis is a disease characterized by seizures, mental disorders, disorders of consciousness, amnesia, and compromised cognitive abilities (2). Initially, this condition was thought to be a rare type of paraneoplastic syndrome (13). However, as understanding of the neuron cytomembrane and synapsins advanced, it was identified as a type of independent autoimmune brain inflammation (3). For the treatment of anti-NMDA receptor encephalitis, Western medicine focuses on tumor removal and immunosuppressive therapy, which has the drawbacks of a prolonged treatment period, a high cost, and a poor improvement in quality of life (9). Studies on treatment of this condition with traditional Chinese

medicine are scarce, and there is no systematic diagnostic and treatment routine for this disease. There are also as yet no reports of a combined treatment approach based on both Western and traditional Chinese medicine. Under the direction of Professor Li Gao, we have been treating challenging neurological diseases using traditional Chinese medications in clinical practice, and have developed a unique understanding of the treatment of anti-NMDA receptor encephalitis with a combination of Western and traditional Chinese medicine. Our treatment has a strong curative effect and patients have shown good treatment adherence.

### Case Report

Patient Quan, male, aged 36 years, was hospitalized between 2010 and 2019 because he had suffered from confusion and incoherence during the 23 days prior to admission. These symptoms had appeared after a common cold and did not improve following infusion therapy at a local hospital. Half a month before his hospitalization, he had started to show intermittent convulsions and dental trismus, which were diagnosed as epileptic seizures. The symptoms then worsened, and he came to suffer gradually deteriorating disorders of consciousness accompanied by incoherence, intermittent limb stiffness, and convulsions. When he was admitted to hospital, the patient had a high-grade fever with both eyes closed, and he was restless and shouting loudly. He had not passed any stools in the previous six days and his tongue was red with a greasy yellow coating, accompanied by a slippery and forceful pulse.

The physical examination results recorded a body temperature of 38.6°C and a state of confusion. The patient was not cooperative during the

Corresponding authors: Juexian Song, Department of Neurology, Xuanwu Hospital, Capital Medical University, Beijing 100053, PRC. Email: songjuexian@vip.163.com.

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examination and could not speak. His neck was not stiff; his pupils were symmetrical in shape and size, with a diameter of 2 mm, and responded slowly to light. The patient was not cooperative during the eye-tracking examination. He had symmetrical nasolabial folds. There was a lack of coordination in the limb muscles during the physical examination, and his muscle strength was rated at grade V. The muscular tension in his limbs was normal, and although the upper extremities showed weakened reflexes, the lower extremities had normal reflexes. No pathological signs were exhibited. Cranial MRI showed subcutaneous spot-like ischemic lesions in both frontal lobes. A lumbar puncture found that the cerebrospinal fluid pressure was 250 mmHg and the total protein and chloride content were 20 mg/dl and 117 mmol/l, respectively; all remaining indices were normal. The patient's serum and cerebrospinal fluid tested positive for NMDA receptor antibodies.

Under the direction of Professor Li Gao, we diagnosed the patient's condition as anti-NMDA receptor encephalitis with a high degree of confidence. On the basis of Western medicine, we treated him with gamma globulins and pulsed methylprednisolone therapy. His condition then manifested as unconsciousness and epilepsy. From a traditional Chinese medicine perspective, we diagnosed his condition as Yangming fu-viscera excess, blocked orifices due to phlegm heat, and an internally disturbed mind. For treatment with traditional Chinese medicine, it was suggested that we apply the approach of heat clearing and detoxification, purging the fu-viscera to eliminate heat, and unblocking orifices to clear the mind. The prescription composition was as follows: 30 g chlorite schist, 6 g Chinese rhubarb, 15 g *Cyrtomium fortunei*, 30 g indigowoad root, 10 g *Bombyx batryticatus*, 10 g whole scorpion, 30 g nacre, 10 g *Coptis chinensis*, 9 g *Fructus aurantii immaturus*, 10 g *Magnolia officinalis*, 10 g Herba lycopi, and 15 g *Gastrodia elata*.

After taking three doses of this script, the patient twice passed foul-smelling, black, semiliquid stools and showed improved consciousness and reduced epilepsy episodes. He manifested a gradual clearance of pathogenic heat, but had a weakened pulse and a greasy white tongue coating. This suggested a retardation caused by phlegmatic hygrois. We reduced the heat-clearing and fu-viscera-purging ingredients (indigowoad root, *Cyrtomium fortunei*, *Fructus aurantii immaturus*, and *Magnolia officinalis*) in the original prescription and added Erchen decoction to boost the effect of eliminating dampness and dissolving phlegm.

After he had taken five does of the new script, the patient returned to normal consciousness and the number of epilepsy episodes decreased further. His

tongue was dark red and had a white and mostly dry coating. He had a weak, wiry pulse and feeling his pulse deeply produced a weak response in the fingers. His stool and urine were both normal. This suggested that the pathogen had been expelled, although the positive qi remained weak and there was blood stasis and an overconsumption of yin.

We then added *Astragalus membranaceus*, fleeceflower root, *Radix paeoniae rubra*, and *Rhizoma chuanxiong* to the basic prescription to boost the effects of benefiting qi and nourishing yin while promoting blood circulation to remove the blood stasis. After taking five doses of this prescription, the patient did not have any more epilepsy episodes and had an improved mood, was able to communicate normally with his family, and was discharged from the hospital once his condition had improved.

## Discussion

The ancient literature on traditional Chinese medicine contains no specific record of any disease corresponding to anti-NMDA receptor encephalitis. Modern studies mostly assign it to the category of epilepsy, insanity, or unconsciousness, due to its symptomatic manifestations of episodes of epilepsy, mental disorders, and disorders of consciousness (7, 15). However, the clinical manifestations of anti-NMDA receptor encephalitis are relatively diverse, and are generally divided into five phases (6): in the prodromal stage, symptoms mostly resemble those of the common cold or a viral infection; in the psychotic phase, symptoms are positive signs of mental disorders (e.g., obsessive ideas, illusions, hallucinations, and mania), epileptic episodes, and short-term memory loss; in the nonreactive phase, patients are detached and nonreactive; in the excessive movement phase they show abnormal movements and dysautonomia; finally, in the recovery phase, the condition improves. These symptoms may appear simultaneously or sequentially. No single term in traditional Chinese medicine is sufficient for defining this condition, so we combined the disease and symptoms and used a dynamic, comprehensive approach to analyze its internal pathogenesis and development characteristics.

Xu of the Ming Dynasty proposed in Yu Ji Wei Yi that 'Yang epilepsy without vomiting results from the phlegm heat around the chest. It usually happens when the patient is frightened or the heat accumulated in the patients. Drugs of cold nature should be used to treat the Yang epilepsy. Yi epilepsy results from phlegm heat, originally. Patients are treated with too much drugs of cold nature. Their spleen and stomach are harmed. Therefore, the symptom turns to Yi epilepsy'. He thus identified

phlegm heat as the ultimate cause of the onset of epilepsy. In *Dian Kuang Tiao Bian*, Guo of the Qing Dynasty proposed the view that “epilepsy is mainly caused by phlegm” and “attacks of phlegm heat lead to mania”, as well as the following theory regarding transmission between the organs and the meridians: “heat causes phlegm to be expelled” (11). In *Wenre Lun*, Ye of the Qing Dynasty proposed a pathogenesis development from high heat to unconsciousness as follows: “if a person usually suffers from a heart deficiency and has phlegm problems, his internal meridians will be blocked when external heat penetrates”. Based on our patient’s disease characteristics and pathogenesis development, Professor Li Gao proposed “phlegm heat” as the core pathogenesis of anti-NMDA receptor encephalitis, a disease that manifests as epileptic episodes, insanity, and unconsciousness.

The pathogenic development of phlegm heat runs through the entire disease course of anti-NMDA receptor encephalitis. This provides an example of the characteristics described in the traditional Chinese medicine theories regarding the “symptoms and root of the disease” and “deficiency and excess” in different phases of the disease course, even though different symptoms appear and disappear during the course. In the early stages of anti-NMDA receptor encephalitis (the prodromal and psychotic phases), when the healthy energy is not deficient but the pathogen is excessive, the disease manifests as a common cold invasion and a competition between the pathogen and healthy energy. The symptoms include fever and headache or positive signs of mental disorders, such as obsessive ideas, illusions, hallucinations, and mania, or epileptic seizures with stiffness and convulsions. In the middle stages (the nonreactive and excessive movement phases), as the course extends, the healthy energy gradually becomes deficient, while the pathogen persists. The patient, on one hand, shows symptoms such as weakened or abnormal responses or disorders of consciousness and sleep, or, more seriously, manifests central hypoventilation syndrome as the positive signs of mental disorders diminish (1). On the other hand, dysfunctions of the motor and autonomic nervous system, such as uncontrolled movements of the mouth, face, and tongue, are all evidence of a mixed deficiency and excess. In the final stage (the recovery phase) of the disease, the pathogen recedes, although the healthy energy is still deficient. Some patients retain residual symptoms, and the course of the disease can extend for months if not treated properly (4).

Under the guidance of Professor Li Gao, we have thus established that the core pathogenesis of anti-NMDA receptor encephalitis is phlegm heat,

and this is the key to treating it with traditional Chinese medicine. For our treatment approach, we choose medicinal ingredients that can clear heat, resolve phlegm, and detoxify; after that, we conduct further diagnoses based on the patient’s physical condition and the current stage of the disease, and add or subtract ingredients accordingly.

By analyzing the prescription we use to treat anti-NMDA receptor encephalitis, we found that there are six core ingredients that are used most frequently: *Coptis chinensis*, *Scutellaria baicalensis*, raw Chinese rhubarb, chlorite schist, glabrous greenbrier rhizome, and *Scutellaria barbata*. This prescription is formed by adding ingredients to the Xiexin decoction, which is made from Chinese rhubarb, *Scutellaria baicalensis*, and *Coptis chinensis*. The Xiexin decoction is taken from Jin Kui Yao Lue and treats symptoms such as intense internal pathogenic fire and internal accumulation of stagnant heat. It is a classic prescription for detoxification and clearing fire (10). The addition of chlorite schist adds the effect of dissolving phlegm, and the glabrous greenbrier rhizome and *Scutellaria barbata* add the effect of detoxification and clearing turbidity. These six ingredients used together may exert the effect of clearing heat, dissolving phlegm, detoxification, and clearing turbidity, as well as resuscitation and restoring consciousness.

Modern pharmacology studies have revealed that *Coptis chinensis* and *Scutellaria baicalensis* can significantly suppress lipopolysaccharide-induced inflammation reactions, and their extracts and flavone components exhibit a relatively strong antiviral effect (12). In traditional Chinese medicine, *Coptis chinensis* has the effect of “dissolving blood stasis, disintegrating the accumulation of abdominal mass, treating indigestion, purifying the digestive system, boosting metabolism, helping with food digestion, and stabilizing the five internal organs”. The active substance in *Coptis chinensis* can suppress the generation and release of inflammatory cytokines and has antibacterial and anti-inflammatory effects. It thus relieves cerebral edema, reduces intracranial pressure, and acts like a dehydrating agent (5). Glabrous greenbrier rhizome extract may selectively suppress the inflammatory process following the release of lymphokines by sensitized lymphocytes, which means it can selectively suppress the cellular immune response but not the humoral immune response. This feature of Glabrous greenbrier rhizome extract has significant implications for the clinical treatment of diseases that are mediated by cellular immune responses (14). The flavones in *Scutellaria barbata* flavone have anti-inflammatory, antioxidative, and neuroprotection effects, and also reduce memory impairment (16). Chlorite schist may re-

duce the levels of excitatory amino acid neurotransmitters in the hippocampus of epileptic rats and suppress abnormal neuron discharges, thus exerting an anti-epileptic effect (8).

In the early stages of the disease (excessive pathogen and healthy energy not yet deficient), treatment should reinforce the pathogen-attacking power of the basic prescription according to the patient's physical condition and symptom manifestations. If the common cold symptoms persist, the disease is still in its prodromal phase and treatment should focus on relieving the exterior symptoms and expelling the pathogen. Depending on where the pathogen attacks, Yinqiao powder can be added to assist with the function of upper jiao and lung defense, or the Baihu decoction can be added to clear and unclog the qifen in the Yangming meridians, so as to expel the pathogen. If the patient suffers from fever, has a full and hard abdomen, shows constipation or heat retention with a watery discharge, or, more seriously, becomes unconscious due to heat disturbances, this indicates that there is excessive heat in the Yangming meridians and excessive phlegm heat in the fu-viscera. In this case, the Chengqi decoction can be added to purge the fu-viscera and clear heat, as well as to resuscitate and restore consciousness. If the phlegm heat disturbs the interior, triggering the liver wind and disturbing the mind, *Gastrodia elata*, *Uncaria rhynchophylla*, whole scorpion, and nacre should be added, to settle the liver wind and calm the nerves.

The middle stages of treatment should focus on not only expelling the pathogen, but also combining tonification and purgation, according to the level of impairment of the patient's healthy energy. Disorders of consciousness or even central hypoventilation syndrome are manifestations of the nonre-active phase, and patients are often found to have increased phlegm and saliva, shortness of breath and gasping, and a pale, inflated tongue with a greasy white coating. These are signs of spleen deficiency and phlegm turbidity, and treatment should focus on eliminating dampness and dissolving phlegm while tonifying the spleen and benefiting the qi. This can be achieved by adding prescriptions like the Erchen decoction or the Liujuanzi decoction to the basic prescription. If the patient shows uncontrolled movements of the mouth, face, and tongue, the disease is in the excessive movement phase. This is similar to the so-called "muscular twitching and cramping" in Shanhan Lun and is caused by overconsumption of the fluid and blood, lack of nourishment of the muscles, deficiency and stasis in the blood, and the generation of wind due to movements. Therefore, treatment should include medicinal ingredients such as fleece flower root, *Cistanche deserticola*, Radix

paeoniae rubra, and oyster, to replenish the vital essence and nourish the blood while promoting blood circulation and settling the wind.

The final stage of treatment, during the recovery phase of the disease, focuses on resolving the residual symptoms from the early and middle stages, as well as treating the body, which has been suffering from a long-term illness and is still deficient in healthy energy. The injuries caused by the long-term illness should be identified, for example impaired qi, blood, yin, and yang, and deficiencies should be restored while the healthy energy is consolidated. The Shanghan Lun statement "observe the pulse pattern and identify the disease while treating it in the light of the symptoms" should thus be followed. Therefore, in addition to tonifying medications, medicinal ingredients such as lotus petiole, bamboo leaves, *Eupatorium fortunei*, Radix paeoniae rubra, and pseudo-ginseng should be selected, based on the patient's residual symptoms, to achieve the aims of clearing heat while avoiding impairing the qi and dissolving blood stasis while avoiding disturbing the blood circulation.

Under the guidance of Professor Li Gao, we choose heat clearing, phlegm dissolving, and detoxification as our treatment approach. In the next step, we conduct further diagnosis according to the patient's physical condition and the characteristics of the current disease stage. We then add or subtract medicinal ingredients so that the phlegm heat can be cleared, pathogenic qi can be expelled, healthy energy can be restored, and consciousness can be protected. Eventually, we achieve the effect of expelling the pathogen and strengthening the healthy energy.

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## Conflict of Interest

The authors declare no conflict of interest.

## References

1. Cao, Li., Ji, X. and Wang, Y. Clinical analysis of seven anti-NMDA receptor encephalitis cases. *Chinese J. Practical Nerv. Dis.* 20: 42-45, 2017.
2. Dalmau, J., Gleichman, A.J., Hughes, E.G., Rossi, J.E., Peng, X., Lai, M., Dessain, S.K., Rosenfeld, M.R., Balice-Gordon, R. and Lynch, D.R. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. *Lancet Neurol.* 7: 1091-1098, 2008.
3. Dalmau, J., Tüzün, E., Wu, H.Y., Masjuan, J., Rossi, J.E., Voloschin, A., Baehring, J.M., Shimazaki, H., Koide, R., King, D.,



- Mason, W., Sansing, L.H., Dichter, M.A., Rosenfeld, M.R. and Lynch, D.R. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. *Ann. Neurol.* 61: 25-36, 2007.
4. Florance, N.R., Davis, R.L., Lam, C., Szperka, C., Zhou, L., Ahmad, S., Campen, C.J., Moss, H., Peter, N., Gleichman, A.J., Glaser, C.A., Lynch, D.R., Rosenfeld, M.R. and Dalmau, J. Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. *Ann. Neurol.* 66: 11-18, 2009.
  5. He, J., Song, Z. and Huang, B. Observation and analysis of the effect of Chinese rhubarb in treating cerebrovascular diseases. *Clin. J. Chinese Med.* 22: 18-19, 2015.
  6. Hughes, E.G., Peng, X. and Gleichman, A.J. Cellular and synaptic mechanisms of anti-NMDA receptor encephalitis. *J. Neurosci.* 30: 5866-5875, 2010.
  7. Li, C. and Dong, Z. Treating a case of anti-NMDA receptor encephalitis through combined Western medicine and traditional Chinese medicine. *J. Beijing Soc. Tradit. Chinese Med. Drugs* 32: 387-388, 2013.
  8. Liu, S., Wu, L. and Wu, D. The influence of the mineral medicine Lapis Chloriti on levels of amino acid neurotransmitters in the brain tissue of PTZ-kindled epileptic rats. *J. Chinese Mass Spectrom. Soc.* 37: 533-541, 2016.
  9. Lynch, D.R., Rattelle, A., Dong, Y.N., Roslin, K., Gleichman, A.J. and Panzer, J.A. Anti-NMDA receptor encephalitis: clinical features and basic mechanisms. *Adv. Pharmacol.* 82: 235-260, 2018.
  10. Miao, T. Advances in Sanhuang Xiexin decoction research. *Hunan J. Tradit. Chinese Med.* 32: 190-192, 2016.
  11. Sun, W., Zheng, Q. and Tian, Q. Academic thoughts regarding the treatment of mania through phlegm theories in Dian Kuang Tiao Bian. *World Chinese Med.* 12: 1004-1006, 2017.
  12. Tang, N.P., Li, H., Qiu, Y.L., Zhou, G.M. and Ma, J. Tea consumption and risk of endometrial cancer: a meta-analysis. *Am. J. Obstet. Gynecol.* 201: 605.e1-8, 2009.
  13. Vitaliani, R., Mason, W., Ances, B., Zwerdling, T., Jiang, Z. and Dalmau, J. Paraneoplastic encephalitis, psychiatric symptoms, and hypoventilation in ovarian teratoma. *Ann. Neurol.* 58: 594-604, 2005.
  14. Wang, J., Zhang, H. and Fu, X. Advances in research concerning the chemical composition and pharmacological actions of glabrous greenbrier rhizome. *Strait Pharmaceut. J.* 25: 42-44, 2013.
  15. Xu, Y. Treating a case of anti-NMDA receptor encephalitis by combining Qingying detoxification, a mind-clearing and resuscitation method, and immunotherapy. *Chinese J. Integrat. Med. Cardio-Cerebrovascular Dis.* 14: 2207-2208, 2016.
  16. Yin, X., Zhang, S. and Xi, Y. Expression of apoptosis proteins in the brains of ovariectomized rats and the interference effect of *Scutellaria barbata* flavone. *Chinese J. New Drugs* 19: 1255-1259, 2010.

