Case Report

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Anti-Hu-related epilepsy diagnosed after surgical management

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Abstract

Autoimmune epilepsy (AE) refers to epilepsy mediated by autoantibodies or immune cells, and a large proportion of drug-resistant epilepsy cases are classified as AE. AE lacks standardized management guidelines. At present, little research has been conducted on the effectiveness of surgical treatment of AE. This paper reports a patient whose surgical treatment was ineffective before AE was diagnosed and who improved after immunotherapy. A literature review was conducted to examine the progress of surgical treatment of epilepsy, the relationship of temporal lobe epilepsy to neuronal antibodies, surgical and prognostic factors, research progress on the anti-Hu antibody, and treatment of autoimmune encephalitis to provide a clinical reference.

Keywords

Autoimmune epilepsy, neuronal antibodies, surgical treatment, anti-Hu antibody, immunotherapy, temporal lobe epilepsy

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Introduction

Epilepsy is a chronic disease caused by highly synchronous abnormal discharges of brain neurons. Autoimmune epilepsy (AE) refers to epilepsy mediated by autoantibodies or immune cells, and a large proportion of drug-resistant epilepsy cases are considered AE. AE lacks standardized management guidelines.[1] We report a patient with drug-resistant seizures.

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The patient was anti-Hu antibody-positive at 5 years after epileptic focus clearance, and his seizures were controlled after immunotherapy. This report provides clinical data and descriptions of the diagnosis process and treatment experience that might be useful for clinicians that are involved in the treatment of AE.

Case report

A 17-year-old male patient was admitted to the hospital for "recurrent episodes of right-side twitching for more than 6 years that was aggravated over 2 days". More than 6 years prior, right facial convulsions with no obvious cause were noted. The main manifestations were right-side twitching, salivation, and right-side face and right hand numbness. He was clearly conscious when twitching but could not perceive verbal information, and each instance lasted approximately 1 minute. After cranial magnetic resonance imaging (MRI) (Figure 1a/b), electroencephalography (EEG), and lumbar puncture in our hospital, the patient was diagnosed with "viral encephalitis" and discharged after treatment with antiviral and antiepileptic drugs. The patient used carbamazepine (100 mg twice/day orally) to control his epilepsy when he was discharged from the hospital, but his symptoms were poorly controlled. Five years prior, at Xinqiao Hospital affiliated with Chongqing Third Military Medical University, the patient underwent epilepsy focus resection. A postoperative pathological biopsy of the brain tissue indicated focal hemorrhage with softening and perivascular lymphocyte sheath formation (because of the length of time and since the operation was performed in another province, the biopsy image results could not be found). When the patient was discharged from the hospital, he continued to use oral sodium valproate (VPA, 500 mg twice/day), oxcarbazepine (450 mg twice/day), clonazepam (CZP, 1 mg twice/day), and levetiracetam (500 mg twice/day) to control his epilepsy. His convulsions were controlled for the first 3 months after discharge, but the effect was not satisfactory after 3 months.

Two days prior to his latest admission, because of a cold, the patient's convulsions appeared again. In our hospital, while in the intensive care unit, he had no seizures after intravenous infusion of midazolam and propofol. After consultation with a neurologist, immunoglobulin was added (12,500 mg/day for 5 days). At that time, detection of serum and cerebrospinal fluid (CSF)-related antibodies and other CSF-related tests were performed. The results showed that the patient was positive for serum anti-Hu antibodies. No abnormalities were detected in other related CSF examinations. Cranial MRI suggested abnormalities (Figure 1c/d). The EEG results showed background activity dominated by slow waves, paroxysmal delta waves in the left posterior area, and epileptiform discharges in the left central parietal-occipital area. Chest computed tomography (CT) and abdominal CT showed no abnormalities. After transfer to our department, the patient was treated with daily administration of methylprednisolone sodium succinate (1000 mg), which was slowly reduced after 5 days, followed by an intravenous drip of cyclophosphamide (1000 mg) and subsequent administration of immunoglobulin (17,500 mg/day for 5 days) and the oral antiepileptic drugs lamotrigine (75 mg twice/day), VPA (500 mg twice/day), CZP (2 mg every night), and topiramate (75 mg twice/day). After this treatment, the patient had no seizures.

A physical examination showed the following: temperature, 37.1°C; pulse, 130 beats/minute, respiration 20 breaths/minute, blood pressure, 135/86 mmHg, intermittent convulsions of the right upper limb and face, and thick double lung auscultation. Other parameters exhibited no

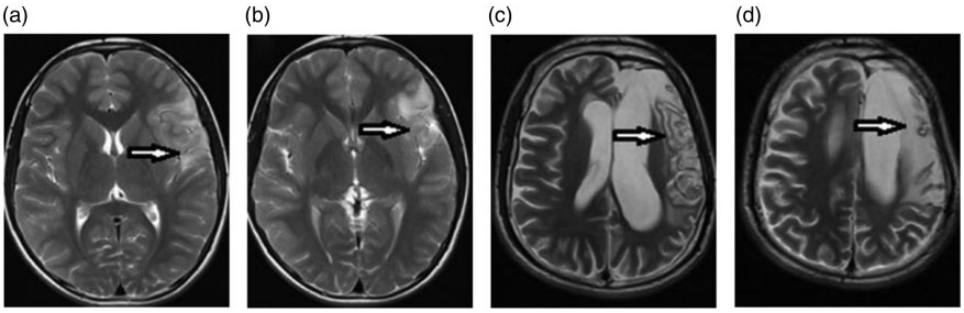

Figure 1. Cranial magnetic resonance imaging. a/b: The gyrus of the left frontotemporal lobe is reduced and exhibits a long T2 signal and widened sulcus. c/d: The position of the left anterior crest is altered, and left, frontal, apical, parietal, cerebral softening and cerebral perforation are accompanied by gliosis and brain atrophy.

abnormalities. A neurologic examination revealed the following: the patient was conscious, could not speak, and had right limb muscle strength of grade 4. Other neurological tests showed no abnormalities. The patient participating in the study and their next-of-kin provided verbal informed consent for the study.

Discussion

The incidence rate of immune-related epilepsy is increasing. In 2017, the International Association for the Prevention of Epilepsy included immunological factors in the classification of causes. There is no unified opinion regarding whether surgery is needed to treat the epilepsy focus in patients with AE. However, it is certain that immunotherapy is needed for AE patients.

Among temporal lobe epilepsy patients with unilateral hippocampal involvement that is not associated with neuronal antibodies, up to 70% have no seizures after surgery,[2] whereas only 16% of patients with similar MRI results but positive neuronal antibodies have no seizures.[3] There are several possible explanations for this result. First, we have found signs of inflammation not only in patients undergoing surgery during the "acute" stage of the disease but also in some patients with hippocampal sclerosis, reflecting that residual lesions and active inflammation may occur in the same patient at the same time.[3] Second, the ongoing inflammatory process is likely to extend beyond the surgical field (e.g., the insula), leading to postoperative epilepsy. Therefore, failure to identify "temporal plus" epilepsy (TPE) could be the cause of surgical failure in some cases.[4] Third, in patients with positive neuronal antibodies, it is not uncommon to observe bilateral temporal lobe involvement, including structural (magnetic resonance) and functional (e.g., memory impairment, bilateral interictal epileptiform discharges, and bilateral seizure onset on ictal EEG) involvement. Therefore, an unresected temporal lobe may become an epileptogenic focus, especially when a persistent inflammatory process is present in the brain.[5]

In total, 87% of TPE patients have recurrence of epilepsy within 2 years after surgery.[6] Although the occurrence of repeated episodes after surgery indicates that some epileptogenic tissue has not been removed, it is unclear whether this tissue is located in the temporal lobe (e.g., hippocampal remnant),[7] contralateral

temporal lobe,[6] or ipsilateral extratemporal regions.[8] The latter situation can be further subdivided into pseudotemporal epilepsy, in which a strictly extratemporal epileptogenic zone is misdiagnosed, thus encompassing a dual pathology combining an extratemporal epileptogenic lesion and hippocampal sclerosis,[9] and TPE, which is defined in cases where a primary temporal lobe epileptogenic zone extends into neighboring regions, such as the insula, suprasylvian operculum, orbito-frontal cortex, and temporo-parietooccipital junction.[10] In addition to TPE and hippocampal remnants, two other weak predictors of poor prognosis in epilepsy were discovered: a history of past trauma or infectious brain injury and secondary generalized tonic-clonic seizures.[11] This patient underwent epilepsy focus resection, but epilepsy was poorly controlled after surgery.

It is estimated that unknown causes account for one third of all cases of adult epilepsy.[12] Some of these patients may have immune-mediated neuronal dysfunction.[12,13] In recent years, many neuronal autoantibodies have been considered to be associated with autoimmune encephalitis or epilepsy.[14] Most of these antibodies target neural cell surface antigens, including synaptic neurotransmitter receptors, ion channels, or associated proteins, and some patients have specific antibodies against nuclear or cytoplasmic antigens.[15,16] Because of the poor epilepsy control and to continue to search for potential causes, the patient's neuron autoantibodies were tested after admission.

The patient's CSF anti-Hu antibody test was negative. No obvious abnormality was found in other relevant CSF examinations. The anti-Hu antibody, also known as the type I anti-neuronal nuclear antibody, can specifically bind to the antigen on the nucleus of neurons. The anti-Hu antibody is a polyclonal complement-activated IgG that significantly reacts with the nuclei of all neurons in the peripheral nervous system (PNS) but only reacts weakly with the cytoplasm; it does not react with glial cells and other non-nerve cells. An anti-Hu antibody-positive PNS is dominated by sensory neuropathy. Some studies have shown that sensory neuropathy occurs in approximately 55% of cases, and marginal lobular encephalitis occurs in approximately 10% of cases.[14,17] If anti-Hu antibodies are detected in the serum when a patient simply shows nervous system symptoms, it should be highly suspected that a tumor will develop or the tumor may already be in a latent state. This patient has no apparent tumor at present and requires regular follow-up.

AE refers to epilepsy mediated by autoantibodies or immune cells. The clinical incidence of AE is unknown. According to current data, 10% to 20% of epilepsy patients have AE.[18] Although precise immunotherapy regimens vary among patients with different types of AE, a short and versatile immunotherapy regimen currently exists.[19] In this patient, in addition to being treated with antiepileptic drugs, a first-line treatment regimen (methylprednisolone and immunoglobulin) and a second-line treatment regimen (cyclophosphamide) were applied. Finally, his seizures were controlled. Surgical treatment of epilepsy has become an important treatment modality, but the results are also affected by many factors. There are few reports on the effectiveness of surgical procedures for AE. Once an early diagnosis of AE is considered, timely and sufficient immunotherapy should be completed before surgery.

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Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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