ADVANCES IN STEROID-RESPONSIVE ENCEPHALOPATHY

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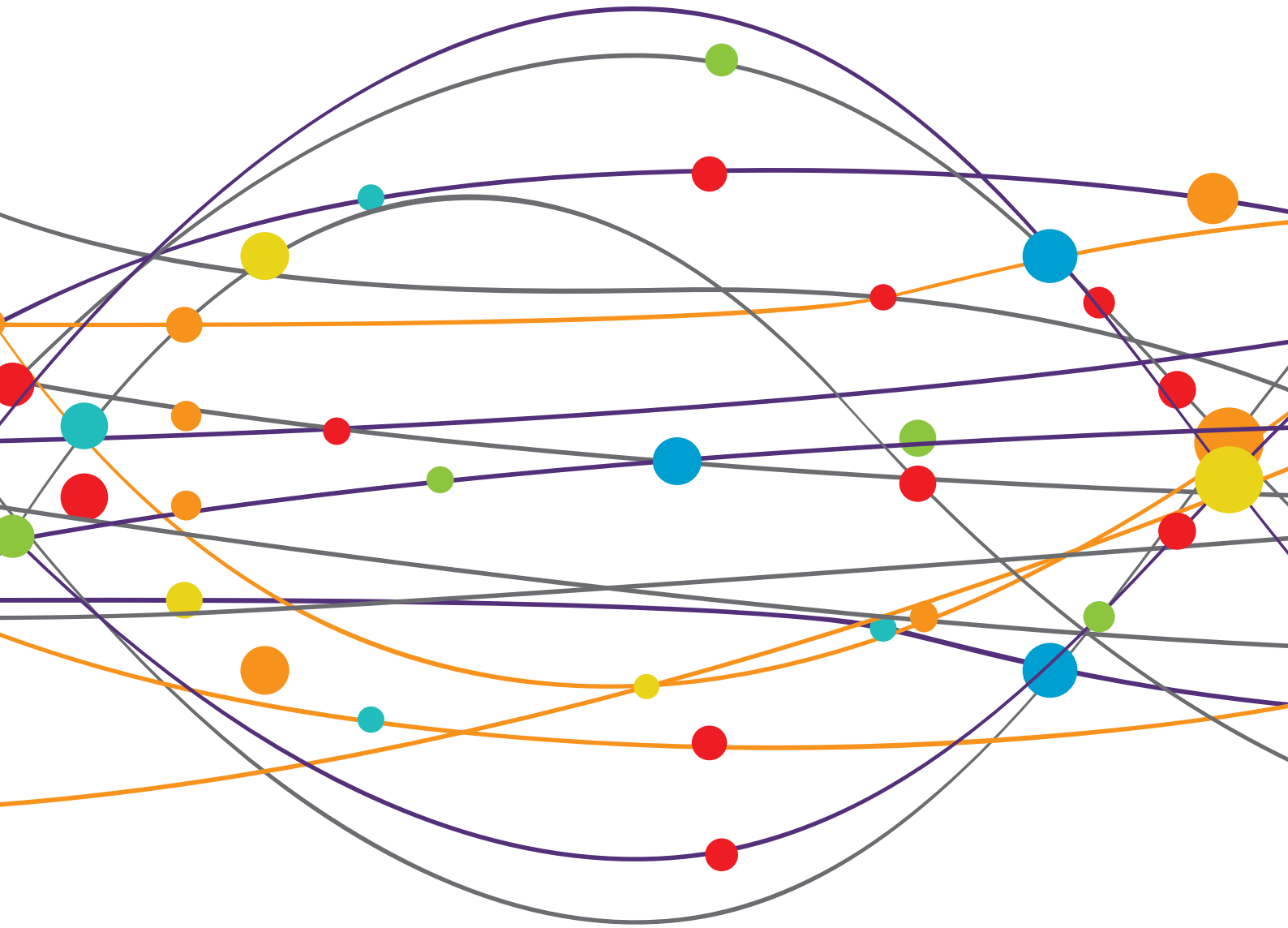

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ADVANCES IN STEROID-RESPONSIVE ENCEPHALOPATHY

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EDITORIAL
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Editorial: Advances in Steroid-Responsive Encephalopathy

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Editorial on the Research Topic

Advances in Steroid-Responsive Encephalopathy

In neurology, "steroid-responsive encephalopathy" is a general term for diseases characterized by diffuse brain injury and responsiveness to steroids. These diseases include autoimmune encephalitis (AE), Hashimoto's encephalopathy (HE), limbic encephalitis, and anti-neutrophil cytoplasmic antibody (ANCA)-associated vacuities encephalopathy, among others. These diseases are common and complicated in clinical management. Further understanding of their epidemiology, pathophysiological mechanism, diagnosis, treatment and prognosis from various perspectives can help improve the insights of clinicians and researchers. To provide a platform for sharing the latest research findings in steroid-responsive encephalopathy, we organized this special issue, in which 11 manuscripts have been accepted for publication, including 6 original research articles, four reviews, and one mini review. To a certain extent, these manuscripts have expanded the current understanding of such diseases.

To date, there have been few large-scale epidemiological investigations of AE in adults or children, and its epidemiological characteristics remain unclear. Gu et al. provided a detailed description of the epidemiological characteristics of 189 patients with antibody-positive AE at six large general hospitals, and they also analyzed the differences in composition ratios, ICU occupancy, ventilator use, tumor and surgery, and prognosis among different age groups, gender groups, antibody groups, and disease characteristics. Separately, Qiu et al. retrospectively analyzed clinical features, laboratory and imaging results, and predictors of poor prognosis in 50 patients with an initial diagnosis of AE at their hospital. The authors found that the neutrophil-to-lymphocyte ratio might have predictive value for poor outcomes in AE and that early initiation of immunotherapy was associated with a good prognosis.

In a study focusing on pediatric AE, Zhang et al. retrospectively analyzed the clinical characteristics of 103 children with AE in two Chinese tertiary pediatric neurology centers, including 89 patients with anti-NMDA receptor (NMDAR) encephalitis, two with anti-LGI1 encephalitis, one with anti-CASPR2 encephalitis, and 11 autoantibody-negative patients with probable AE. Anti-NMDAR encephalitis is the most common form of AE in pediatric patients. Another study by Zhang et al. analyzed the demographic characteristics, clinical features, treatment, and outcomes of 34 children with anti-NMDAR encephalitis treated at Children's Hospital of Fudan University. The authors found that most of the included children were sensitive to first-line immunotherapy

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and achieved good outcomes, and higher Modified Rankin Scale scores before immunotherapy predicted poor outcomes. In addition, the authors also concluded that long-term use of antiepileptic drugs (AEDs) may not be necessary for pediatric patients with anti-NMDAR encephalitis.

Many patients with encephalitis have seizures during the development of the disease. Huang et al. followed up 75 outpatients with AE and reported in detail on the characteristics of those patients' seizures and their long-term use of AEDs. That study compared outcomes between patients with early and late AED withdrawal and determined the probable risk factors for seizure relapse and refractory epilepsy. As in Zhang et al. findings on pediatric anti-NMDAR encephalitis, these AE patients had a high rate of seizure remission after proper immunotherapy, and long-term use of AEDs may not be necessary to control their seizures. Compared with adults, young patients are more likely to become seizure free without AEDs. In addition, Huang et al. also reported that patients with anti-$GABA_B$ receptor ($GABA_BR$) antibodies, status epilepticus (SE), and cortical abnormalities had an increased risk of developing refractory epilepsy or seizure relapse.

A study by Lin et al. focused on the different clinical signs of infectious and autoimmune SE. These two entities may present with similar symptoms initially but require different treatment strategies. Since the prognosis of SE largely depended on etiology, faster-targeted treatment is required at the initial encounter. On this basis, Lin et al. conducted a retrospective study that included 501 patients with SE within a period of 10.5-years. Their study suggested that autoimmune SE had a relatively early age of onset; that it occurred predominantly in females; and that it often presented as psychosis, non-convulsive SE, and super-refractory SE. A lymphocytic predominance in cerebrospinal fluid was more commonly observed in patients with autoimmune SE than in those with infectious SE. These patient characteristics and signs may help clinicians select initial investigations and ensuing therapies that may improve overall outcomes.

HE has become increasingly recognized as an important and treatable cause of AE. Seizure disorders were observed in ∼60–70% of patients with HE, and often as the first manifestation of the disease. HE is easily misdiagnosed because of the low incidence and the atypical symptoms. The manuscript by Li et al. discusses HE, the characteristic of its accompanying seizure disorders and the appropriate diagnostic approach.

Many neurologists may have limited experience in treating primary systemic vasculitis (PSV), mainly because most of these patients are diagnosed and managed by rheumatologists. However, PSV can affect every structure in both the central and the peripheral nervous systems, causing various neurological manifestations of dysfunction. Therefore, PSV patients may sometimes be referred to a neurologist first. The clinical manifestations of PSV are often non-specific, and differential diagnosis may be difficult. With these considerations in mind, Zhang et al. provide a comprehensive review of the clinical manifestations of PSV in the nervous system.

ANCA-associated vasculitis (AAV) is a multisystem inflammatory disease that can involve the central nervous system (CNS). Treatment with steroids, sometimes combined with immunosuppressants, can dramatically improve the outcome. However, for neurologists, the wide clinical spectrum of CNS involvement often complicates the diagnosis and thus delays treatment. Thus, Zheng et al. reviewed the manifestations of CNS involvement in AAV and emphasized ANCA testing, a crucial AAV diagnostic that requires appropriate result interpretation; the authors hoped to increase awareness and expand understanding of AAV-related CNS diseases among neurologists.

Immunoglobulin formulations have been used in an increasing number of diseases. In most cases, such formulations are safe and well-tolerated, but an increasing number of studies have reported potentially adverse effects of immunoglobulin treatment, some of which are severe and even fatal. In Guo et al. 's manuscript, the authors reviewed the incidence, risk factors and clinical characteristics of these adverse immunoglobulin-induced effects and addressed methods to minimize and prevent them.

Plasma exchange is widely used in the treatment of neurological diseases in which autoimmune mechanisms play a leading role. A growing body of research suggests that in the clinical treatment of steroid-responsive encephalopathies such as HE, limbic encephalitis, systemic lupus erythematosus encephalopathy, and ANCA-associated vacuities encephalopathy, plasma exchange is a safe and effective option when steroids or other immunosuppressive therapies are ineffective in the short term or when contraindications are present. A study by Jiang et al. provides a detailed review of the indications, onset time, course, curative effects, and side effects of plasmapheresis as applied clinically to steroid-responsive encephalopathy.

AUTHOR CONTRIBUTIONS

XT, XW, and PK organized this special issue and wrote the editorial. All authors have approved the final version of the editorial.

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REVIEW
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Adverse Effects of Immunoglobulin Therapy

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Immunoglobulin has been widely used in a variety of diseases, including primary and secondary immunodeficiency diseases, neuromuscular diseases, and Kawasaki disease. Although a large number of clinical trials have demonstrated that immunoglobulin is effective and well tolerated, various adverse effects have been reported. The majority of these events, such as flushing, headache, malaise, fever, chills, fatigue and lethargy, are transient and mild. However, some rare side effects, including renal impairment, thrombosis, arrhythmia, aseptic meningitis, hemolytic anemia, and transfusion-related acute lung injury (TRALI), are serious. These adverse effects are associated with specific immunoglobulin preparations and individual differences. Performing an early assessment of risk factors, infusing at a slow rate, premedicating, and switching from intravenous immunoglobulin (IVIG) to subcutaneous immunoglobulin (SCIG) can minimize these adverse effects. Adverse effects are rarely disabling or fatal, treatment mainly involves supportive measures, and the majority of affected patients have a good prognosis.

Keywords: immunoglobulin, adverse effects, risk factors, preventive measures, premedication

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INTRODUCTION

Immunoglobulin, also known as gamma globulin, is a therapeutic preparation comprising pooled blood donated from large numbers of healthy people. IgG is the main component of immunoglobulin, but it also contains small amounts of IgA and varying trace amounts of auxiliary materials (maltose, sucrose, etc.) (1). Applications involving immunoglobulin have expanded to include treatment for immunodeficiency diseases, idiopathic thrombocytopenic purpura (ITP), Kawasaki disease, and neurologic disorders (including Guillain–Barre syndrome, chronic inflammatory demyelinating polyneuropathy, myasthenia gravis, multiple myositis, multiple sclerosis, and autoimmune encephalitis) (2–8). Although immunoglobulin is well tolerated, adverse effects do occur. The majority of these adverse effects are mild and alleviated after infusion withdrawal, but some rare side effects are serious, including aseptic meningitis, renal impairment, thrombosis, and hemolytic anemia (9). In this paper, we reviewed the incidence, risk factors, clinical manifestations of and preventive measures for adverse effects related to immunoglobulin. The processes employed to minimize adverse reactions are briefly addressed in **Figure 1**.

HISTORICAL PERSPECTIVE

In 1890, the German scholar Behring won the 1901 Nobel Prize in medicine for developing a serum therapy for diphtheria, representing a new chapter in the search for immunotherapies (10). In 1941, Cohn et al. (11) successfully developed a process for the large-scale production of human immunoglobulin. Next, immunoglobulin was widely used during World War II. In 1952, Bruton

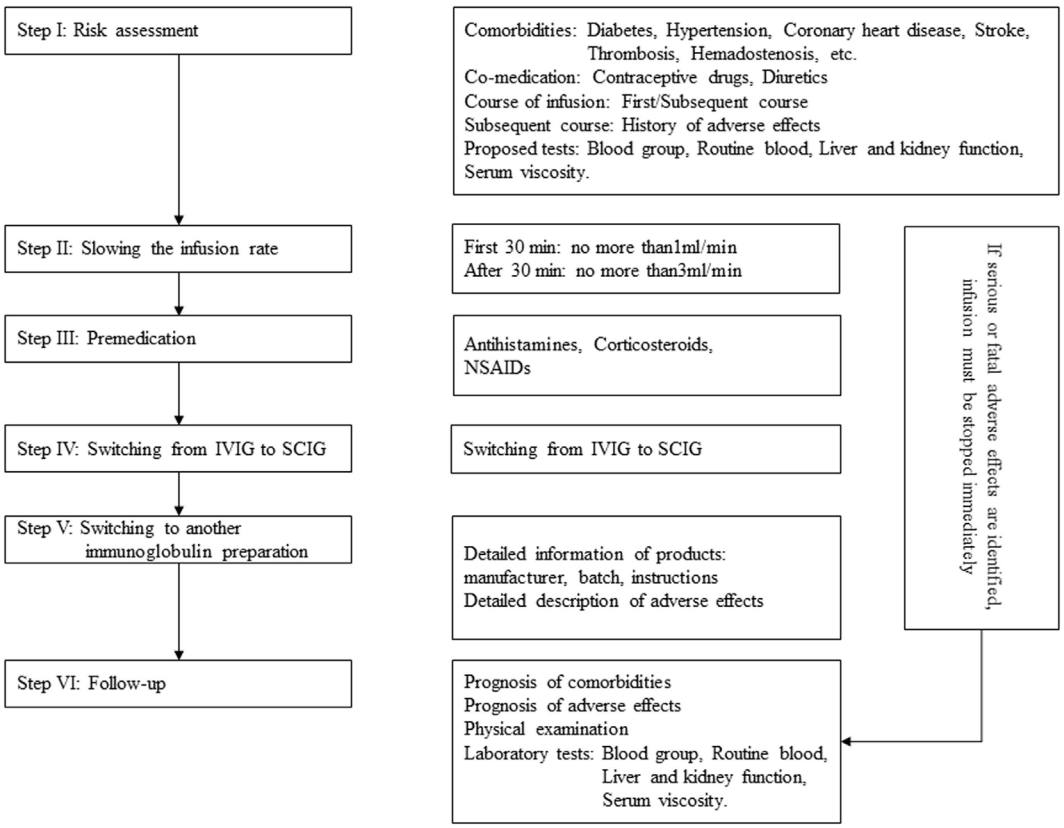

FIGURE 1 | Process that minimizes or prevents immunoglobulin-associated adverse reactions.

(12) was the first to use immunoglobulin to treat a patient identified as immunodeficient, and it later became a standard therapy for immunodeficiency diseases. Intramuscular immunoglobulin preparations were not widely applied because of their poor tolerance. Hence, many scholars began to explore intravenous immunoglobulin (IVIG) preparations. Until 1979, IVIG was approved to treat immunodeficiency disease by the American Food and Drug Administration (13). Imbach et al. (14) then introduced IVIG as a treatment for ITP, with desirable effects. Since then, IVIG has been widely used for an increasing number of diseases.

INCIDENCE OF ADVERSE EFFECTS

Patients who receive immunoglobulin therapy are often treated with immunoglobulin in repeated infusions over a long period of time, and the incidence of adverse effects related to immunoglobulin varies across a wide range. For example, in the study by Matsumoto et al. (15), 14 of 567 (2.5%) patients experienced adverse effects during infusion with IVIG. However, another study reported that 87.5% (14/16) of patients had adverse effects during treatment with repeated infusions of IVIG (16). The majority of studies have focused on the rate of adverse effects in patients receiving multiple infusions over time; however, information regarding the rate of a single infusion is scarce. For subcutaneous immunoglobulin (SCIG) preparations, many studies suggested that the adverse effects of SCIG were much lower than those of IVIG, and the incidence varied across a wide range. However, these studies cannot reveal the occurrence of adverse effects due to multiple interfering factors, such as differences in immunoglobulin preparations, individual differences, or study design variations.

Variations in immunoglobulin brands used may be the main cause for this lack of information regarding the occurrence of adverse effects, considering that different immunoglobulin formulations can have different adverse event profiles. Many clinical trials aimed to evaluate the safety of investigational immunoglobulin products that were not standardized with respect to data collection and provide a definition for adverse effect. Different studies focused on various segments of the population, and these patients had many diseases and fluctuating risk factors. Furthermore, patients who tolerated the infusions may have been shifted from the hospital to home-based infusion therapy, thereby explaining the broad range of adverse effects.

Study design variations also affected the rate of adverse effects. Most trials have involved a limited sample size, and few trials that were performed to support licensed marketed products included a control group. The lack of a control group increases the difficulty involved in unambiguously ascribing causality, and some studies did not report the frequency. In the study design, we advised investigators to predefine the time frame over which adverse effects are considered temporally associated with the

infusion of the product (i.e., within 24, 48, or 72 h of the end of the infusion) in the protocol. Based on prior experience with the same products and to include all the adverse effects, *a priori* algorithm for assigning causality was developed to observe adverse effects and preidentify a list of these adverse events, which are presumed to be related to the administration of the test products.

Analyzing the epidemiology of adverse effects in clinical research is important. For patients receiving long-term IVIG replacement, the rate of adverse effects should be calculated according to the infusion times (per infusion, not per patient). Furthermore, a nationwide database for immunoglobulin-related adverse effects should be created, but the following factors that affected the passive reporting of post-marketing surveillance data in this database should be taken into consideration: (1) Some adverse effects occurring during the IVIG infusion may not be associated with IVIG; (2) some adverse events can be duplicated and result in double counting, especially adverse events that last over an extended period of time; and (3) substantial underreporting is likely to occur as it is a voluntary system.

GENERAL RISK FACTORS

Immunoglobulin Preparation-Related Risk Factors

A high concentration of IgA and anti-Rh blood group, D antigen (RhD) increases the occurrence of immunoglobulin-related adverse effects. Manlhiot et al. (17) found that adverse effects were reported more often in patients treated with immunoglobulin products that contained a concentration of IgA higher than 15 μg/ml (15 VS 8%). Similarly, a high titer of anti-RhD also increased the occurrence of adverse effects; therefore, the level of anti-RhD should be maintained as low as possible (18, 19). However, preparations produced by different manufacturers have different excipients that may increase the rates of specific adverse reactions (20) (**Table 1**).

Patient-Related Risk Factors

Patients who developed adverse effects during a previous course and those receiving a first infusion are at an increased risk of adverse effects. Sherer et al. (21) found that 9 of 10 (90%) patients who experienced an adverse effect during the first treatment course also had adverse effects during subsequent courses. A survey conducted in Iran verified that the risk was higher in patients receiving a first course than in those receiving subsequent treatment courses (16.2 VS 6.9%, respectively) (22).

Some studies have suggested that IgA-deficient patients may be at a higher risk of adverse effects. Iranian researchers found that the incidence of immunoglobulin-induced adverse effects was higher in patients with primary antibody defects, especially those with low levels of IgA (22, 23). In contrast, Rachid and colleagues found that the role of IgA-deficiency in anaphylaxis in patients during immunoglobulin therapy remains controversial (24, 25). Therefore, immunoglobulin infusion should never be withheld from IgA-deficient patients.

TABLE 1 | Components of immunoglobulin products associated with adverse effects.

Component	Patients with increased risk
Sucrose	Patients with renal failure
Glucose	Patients with diabetes
Maltose	Patients with glucose fluctuation
Sorbitol	Patients with hereditary fructose intolerance
High IgA	Patients with risk of anaphylaxis

CLASSIFICATION OF ADVERSE EFFECTS

Adverse effects are classified as immediate or delayed depending on the time of occurrence. Immediate adverse effects mainly include flu-like syndrome, dermatologic side effects, arrhythmia, hypotension, and transfusion-related acute lung injury (TRALI). Immediate side effects are categorized as mild, moderate, and severe. Mild adverse effects include light headache, fever, chills, and fatigue; they are alleviated when the infusion is slowed down or when antihistamines and nonsteroidal anti-inflammatory drugs (NSAIDs) are administered. Moderate adverse effects include chest pain, anhelation, vomiting, arthralgia, and severe headache; these effects require the infusion to be discontinued or antihistamines and NSAIDs to be administered. Severe adverse effects include hypertension, anaphylaxis, bronchospasm, and altered consciousness; these adverse effects require the infusion to be stopped immediately and for corresponding medical attention to be provided (22).

Immediate Adverse Effects

Flu-Like Symptoms

Flu-like symptoms are the most frequent adverse effects. These include flushing, nausea, fatigue, fever, chills, malaise, and lethargy. One retrospective study showed that 14 of 16 (87.5%) patients developed flu-like symptoms during immunoglobulin administration (16). Bichuetti-Silva et al. (26) found that flu-like symptoms account for more than 80% of immunoglobulin-induced adverse effects. These symptoms always occur within the first hour of infusion, and some adverse effects (such as fever or fatigue) may also arise within 24 h. The mechanism underlying these symptoms remains unclear, but it may be associated with the presence of cytokines, such as IL-6, TNF-α, prekallikrein activator, and kallikrein, in immunoglobulin products. The solution media and complement activation of an immunoglobulin preparation may also represent causes of these effects (27, 28). The majority of these symptoms are associated with rapid infusion and develop during the initial period of infusion. Hence, it is recommended that infusion should start at a slow rate for the first 30 min (29).

Dermatological Adverse Effects

The incidence of immunoglobulin-related dermatological adverse effects is nearly 6% (30, 31). The manifestations of dermatological adverse effects vary among individuals and can include urticaria, spot papules, eczema, pompholyx, lichenoid dermatitis, and desquamation. Epidermolysis is observed in some severe cases, and all of these skin lesions can occur in all parts of the body, although the hands and feet are the most common sites. Gerstenblith et al. (32) found that 62.5% of patients had pompholyx alone or

a combination including pompholyx on the hands or feet. The mechanism underlying these dermatological adverse effects is unclear. Most of these reactions develop within 2 weeks of immunoglobulin administration. Interestingly, a significant number of patients with skin lesions had neurological disorders, and the repeated administration of a high-dose immunoglobulin infusion within a short period of time may be the cause of this high preponderance (32, 33). Dermatological adverse effects can be successfully treated with corticosteroids. Some severe cases require hospitalization for further management, but there are no reports of deaths resulting from severe adverse reactions of the skin in immunoglobulin-treated patients. Switching to another batch of immunoglobulin product may also reduce adverse effects to some extent (33).

Arrhythmia and Hypotension

Arrhythmia occurring during or after immunoglobulin infusion has been reported in several studies and can include supraventricular tachycardia and bradycardia, while most of the cases had a history of heart disease. In 1997, Savasan et al. (34) showed that arrhythmia developed during IVIG in two children with thrombocytopenia who both had a history of arrhythmia, and the condition was resolved in both cases with antiarrhythmic therapy. In 2015, Tufekci et al. (35) reported that supraventricular tachycardia occurred during IVIG administration in two newborn infants with immune hemolysis. Raheja et al. (36) described a case of asymptomatic bradycardia that occurred after IVIG administration in a female with ITP who reached a lowest heart rate of 30 bpm before returning to baseline levels without any therapy. Although it is not fully understood whether arrhythmia is directly related to immunoglobulin infusion, cardiac monitoring during IVIG infusion is recommended in patients with a history of cardiac disorders.

Hypotension is a rare symptom related to immunoglobulin. Some patients with hypotension also experience anaphylactic shock. Dashti-Khavidaki et al. (22) reported 216 patients who developed adverse effects, and only one of these patients developed hypotension combined with allergy and bronchospasm. Charhon et al. (37) later described a case with hypotension (a decrease in systolic blood pressure from 130–60 mmHg) and an altered mental state during immunoglobulin therapy.

Transfusion-Related Acute Lung Injury

Transfusion-related acute lung injury, a serious blood transfusion-related adverse effect with high mortality, manifests with acute respiratory distress and noncardiac pulmonary edema within 6 h of transfusion and is the main cause of blood transfusion-related death. Immunoglobulins are blood products and may also be associated with TRALI. In 2001, Risk (38) first reported a 23-year-old male with multifocal motor neuropathy who developed TRALI following IVIG therapy; the patient's condition resolved in 5 days with only nasal oxygen and bed rest. In 2008, Ahituv et al. (39) presented an adolescent patient with ITP who developed TRALI during immunoglobulin infusion. In several cases, patients with Sjögren's syndrome, Guillain–Barre syndrome, lung transplantation, immunodeficiency, or myasthenia gravis have reportedly developed TRALI after immunoglobulin infusion (40–44). Akin to blood-infusion TRALI, immune-mediated processes and the neutrophil-priming hypothesis have been proposed as possible mechanisms (45). TRALI following IVIG is a serious complication that requires urgent treatment. Diagnosing TRALI depends mainly on clinical symptoms that present after blood products are infused in the absence of other evident causes of respiratory insufficiency; a chest radiogram showing diffuse bilateral pulmonary edema is also needed (46). Patients with TRALI often require adjuvant ventilatory therapy and will recover with proper ventilation.

Delayed Adverse Effects

Delayed adverse effects can be severe or even lethal and affect less than 1% of patients. These events include thrombotic events, neurological disorders, renal impairment, hematologic disorders, electrolyte disturbance, and transfusion-related infection.

Thrombotic Events

Thrombotic events are serious adverse effects of immunoglobulin treatment with an estimated incidence of 1–16.9% (47). Daniel et al. (48) reviewed thrombotic adverse events recorded in a large administrative database from 2008 to 2010 and found that 1% (122/11785) of the patients developed immunoglobulin-induced thrombotic events. Ramírez et al. (49) found that thrombotic events affected up to 16.9% of 303 patients who received immunoglobulin infusion. The manifestations of thrombosis, which can occur in arteries, veins, and intracranial vein sinuses, are varied, and arterial thrombotic events (such as stroke, myocardial infarction, and pulmonary embolism) are the most common. A recent review identified 100 cases of thrombotic events related to the administration of immunoglobulin that occurred from 2006 to 2011; among this cohort, 80% of the thrombotic events were stroke and myocardial infarction that occurred within 24 h of completing immunoglobulin administration (50). Risk factors for thrombosis include a first infusion consisting of a large dose, oral contraceptive use, advanced age, prior/current thrombosis, preexisting atherosclerotic disease, elevated serum viscosity, a hereditary hypercoagulable state or ITP. Rajabally et al. (51) found that patients with coronary disease and prior thrombosis who were administered a daily dose ≥35 g of IVIG had a higher risk of thrombotic events. Daniel et al. (48) also found that advanced age (>45years old), prior thrombotic events, and a hypercoagulable state were risk factors for the development of thrombotic events. Moreover, an increasing number of studies have confirmed that patients with ITP are more likely to develop thrombosis when receiving IVIG (52–55). The presence of four or more risk factors seems to be significantly associated with the onset of immunoglobulin-related thrombotic events (51, 56).

Mechanisms that could potentially trigger thrombotic events include an increase in plasma viscosity, the activation of procoagulant factors, vasospasm, autoimmune vasculitis, and an increased platelet count. Increased plasma viscosity contributes most to the occurrence of thrombotic events. Bentley et al. (57) showed that IVIG can cause plasma viscosity to acutely and cumulatively rise across the complete treatment course. Similarly, Baba et al. (58) also found that increased plasma viscosity was associated with IgG concentrations during or after immunoglobulin infusion.

In addition, the average IgG half-life among individuals varied from 23 to 30 days and could be even longer in some cases (59, 60). Thrombotic complications can be prevented or minimized by early assessment in patients suspected of being at high risk, and anti-thrombus treatment is needed in patients with thrombotic complications.

Neurological Disorders

Neurological disorders associated with immunoglobulin treatment include headache, aseptic meningitis, posterior reversible encephalopathy syndrome (PRES), seizure, and abducens nerve palsy.

Headache post IVIG is a common adverse effect. More than half of patients develop headaches after immunoglobulin administration. Many studies have reported headache as an immunoglobulin-related adverse effect, while no studies have described the characteristics of immunoglobulin-related headache in detail. Headache also has a delayed onset of 6–12 h after an infusion and can last between 24 and 72 h. High-dose immunoglobulin infusion is the main risk factor for headache. Some studies have found that patients with a history of migraine are prone to developing headaches after IVIG infusion (61, 62). Among these studies, the overall incidence of IVIG-related headache in patients with a history of migraine was small, which may be due to the small sample size and patient selection bias. Prophylactic treatment used in several studies included acetaminophen, aspirin, opioids, NSAIDs, propranolol, sumatriptan, and corticosteroids alone or in combination, and all the protocols seemed to be fairly effective in the recruited individuals; however, the best drug for the treatment of immunoglobulin-related headache remains unknown (63). Alternatively, non-pharmacotherapy-related approaches, including a reduction in the infusion rate and switching to an alternative brand of IVIG or SCIG, can also reduce headache to some extent. When a headache lasts for a long time or is resistant to drug therapy, the possibility of aseptic meningitis should not be ignored.

Aseptic meningitis has been identified as an adverse effect of IVIG and affects 0.6–1% of patients. Kemmotsu et al. (64) retrospectively examined 384 patients with Kawasaki disease who received immunoglobulin infusion during 2000–2009 and identified four patients who developed aseptic meningitis, suggesting an overall incidence of 1%. In another retrospectively study, Bharath et al. (65) found that 0.6% (8/1324) of patients developed immunoglobulin-related aseptic meningitis. Several studies have reported that aseptic meningitis appears within 48 h of the initiation of IVIG therapy (64, 66, 67). The most common presenting symptoms of this condition are persistent headache, nausea, vomiting, photophobia, fever, chills, and positive Kernig's and Brudzinski's signs. In addition, in affected patients, lumbar puncture typically produces clear cerebral spinal fluid with an increased level of nucleated cells, high protein content and negative culture results (64, 66). Contributing factors include a large cumulative IVIG dose and a history of migraines. Previous studies have suggested that most patients who develop aseptic meningitis receive 1–2 g/kg immunoglobulin therapy (64, 65). Sekul et al. (66) found that patients with a history of migraines are particularly susceptible to developing aseptic meningitis.

Posterior reversible encephalopathy syndrome is another neurological disorder that can develop following immunoglobulin therapy. In 2005, Nakajia (68) reported a patient with Miller–Fisher syndrome who developed PRES following IVIG therapy. Stetefeld et al. (69) and Ribeiro et al. (70) later reported additional patients with Miller–Fisher syndrome who developed PRES during immunoglobulin infusion. The clinical manifestations in these patients include an acute onset characterized by headache, generalized seizure, visual impairment, and an altered mental state (69–71). In all of these cases, complete resolution was achieved after immunoglobulin administration ceased. While PRES is a rare complication of IVIG treatment, it should be considered in all cases with disease-typical MRI findings and clinical manifestations.

Few case reports have described patients with IVIG-associated seizures. In 2003, Kao et al. (72) reported a 37-year-old male with myelopathy who developed repetitive generalized tonic-clonic seizures following IVIG therapy. Later, aseptic meningitis was considered the cause of the seizures, and the patient's condition was controlled with valproate. In 2014, Bichuetti-Silva et al. (26) identified a separate case of seizure in a patient with common variable immunodeficiency disease following IVIG infusion, and a history of herpetic encephalitis was later recorded.

Immunoglobulin infusion may rarely be the underlying etiology of abducens nerve palsy. Wright et al. (73) reported a patient with renal transplantation who developed abducens nerve palsy during high-dose IVIG infusion. The patient recovered completely after 2 weeks, and aseptic meningitis was considered the underlying cause. Furthermore, two case reports described patients with Kawasaki disease who developed abducens nerve palsy after IVIG therapy (74, 75). However, whether abducens nerve palsy was directly related to immunoglobulin therapy in these cases is unclear.

Renal Impairment

Renal impairment following immunoglobulin treatment is a rare but dangerous adverse effect. The incidence of immunoglobulin-associated renal impairment has not been accurately determined. The FDA received information related to 114 cases of immunoglobulin-associated renal impairment or acute renal failure that occurred between 1981 and 1998 (76). Moreover, from 1999 to 2005, the French National Security Agency of Medicines and Health Products recorded 91 cases of renal impairment associated with immunoglobulin infusion (77). The precise mechanism underlying IVIG-related renal impairment remains unclear. Potential mechanisms include the precipitation of immune complexes in the glomeruli, osmotic nephritis, immunological hemolysis-associated acute tubular obstruction, and transient vascular ischemia due to a reduction in renal perfusion (78–80).

Patients with advanced age, diabetes, preexisting renal dysfunction, and dehydration have an increased risk of developing renal impairment following immunoglobulin administration. Renal impairment typically develops within 10 days after the start of immunoglobulin infusion. Oliguria, hematuria, a decreased glomerular filtration rate, and elevated serum creatinine levels are typical manifestations of renal impairment. Serum creatinine levels usually peak around day 5, and oliguric renal failure is more common than other types of renal dysfunction (9, 81, 82).

Renal function usually returns to normal after IVIG infusion is discontinued or short-term hemodialysis is performed, but a few patients with immunoglobulin-related renal impairment have developed chronic renal insufficiency or died (83, 84). Previous studies have shown that death occurs in 8–15% of these patients, but the majority of patients who die have severe underlying conditions, such as advanced age, uncontrolled diabetes, or prior renal dysfunction; therefore, the cause of this effect needs further study (83, 85, 86). In patients with renal insufficiency, renal function should be closely monitored both before and after treatment (including serum creatinine, blood urea nitrogen levels, and glomerular filtration rate). If renal function progressively declines, the rate of infusion should be reduced or treatment should be discontinued. Epstein et al. (76) verified that sucrose-containing preparations should be avoided because they are associated with a risk of osmotic nephritis. However, Kim et al. (87) found that sucrose-free IVIG could also result in renal impairment.

Hematologic Disorders: Hemolysis and Neutropenia

Hemolysis is an adverse effect related to IVIG administration that occurs in approximately 1.6% of patients but is usually neither recognized nor treated because it lacks clinical symptoms. Hemolysis can result in acute renal failure and thrombosis. In 2008, a case series conducted at Ottawa Hospital identified 16 cases of hemolysis among approximately 1,000 patients who received IVIG infusion (resulting in an incidence of 1.6%) (88). Most cases with hemolysis present no obvious clinical symptoms and are diagnosed with low hemoglobin levels on a blood examination. IVIG infusion-associated hemolysis was observed from 12 h to 10 days after the first infusion of IVIG, with the lowest hemoglobin level occurring between 1 day and 2 weeks after the last IVIG infusion. Hemolysis is a common complication of high-dose IVIG derived from non-group O blood. In a systematic review conducted by Desborough and colleagues, 62 cases of hemolysis were identified, and 97% of those patients had received a high dose of IVIG (at least 2 g/kg). Of those 62 cases, IVIG-induced hemolysis was most common in patients with type A (65%) or AB (26%) blood (89). Several more recent studies have also verified that administration of a high dose of IVIG is a contributing factor in hemolysis (90–92). This effect may be associated with the presence of A and B isoagglutinin (anti-A and anti-B antibodies) in the IVIG product. A recent cohort study found that the risk of hemolysis was lower when donors with high plasma titers of anti-A antibodies were excluded, especially in patients requiring ≥1.75 g IVIG/kg (93). Abnormal laboratory tests that may indicate hemolysis include decreased hemoglobin and haptoglobin levels, increased lactate dehydrogenase levels, and increased hemobilirubin and reticulocyte counts (94). The management plans generally proposed in affected patients aim to slow down the rate of infusion, switch to another IVIG product, or check the blood type for potential indications for hemolysis. Hemolysis is self-limiting in the majority of mild and moderate cases. However, proper blood transfusion is needed in severe cases when a Coombs test or a direct or indirect antiglobulin test is negative (89, 95, 96).

Immunoglobulin therapy can cause hemolysis, but it can also cause neutropenia (97). In 1998, Majer et al. (98) first described neutropenia as a complication of IVIG therapy in children with ITP. Veys et al. (99) also reported two cases of neutropenia following IVIG infusion for ITP. In addition, Matsuda et al. (100) and Bajaj et al. (101) reported that patients with neurological disorders could develop neutropenia with IVIG administration. Currently, immunoglobulin-induced neutrophils have been reported only in case reports. This condition usually occurs within 4 days after infusion and recovers spontaneously without infection in 2 weeks. However, premedication with corticosteroids may be an effective measure to prevent neutropenia (98–103).

Electrolyte Disturbance

Electrolyte disturbance is a rare adverse effect of immunoglobulin administration. In 1997, a study that examined variations in serum chemistry among 46 patients receiving IVIG infusion found that sodium and magnesium levels were significantly lower in infused patients (4 and 7% below baseline, respectively) (104). Daphnis et al. (105) retrospectively evaluated a cohort of 66 patients with ITP who received repeated IVIG infusions and found that serum sodium levels fell by 2.7 mmol/l in patients with normal renal dysfunction and 5.7 mmol/l in patients with acute renal failure. These electrolyte disturbances usually have no clinical symptoms, and affected patients generally recover without electrolyte supplementation. With regards to patients with severely compromised renal function, it is recommended that electrolyte levels can be monitored to identify hyponatremia and hyperkalemia.

Infection Risk

The long-term safety of immunoglobulin preparations is excellent. Until recently, the majority of physicians believed that IVIG infusion was associated with no risk of infection. Since immunoglobulins are blood products, there will always be a risk of underlying infection, which may be fatal. Until recently, the most commonly reported infection was the hepatitis C virus. In 1994, the FDA and Centers for Disease Control and Prevention received reports of over 100 cases of acute hepatitis virus infection in recipients of IVIG from several countries (Norway, United States, Europe, and Puerto Rico). The brand names Gammagard and Polygam accounted for the majority of the cases of hepatitis C in both the United States and Europe (106, 107). Razvi et al. (108) reported the outcomes of 58 cases with IVIG-transmitted hepatitis C, and the prognosis of these subjects was poor. Since then, no cases of immunoglobulin-induced hepatitis C have been reported.

Apart from immunoglobulin-transmitted hepatitis C, no cases of IVIG-related hepatitis B virus (HBV) have been reported. However, IVIG-related passive transfer of hepatitis B antibodies has also been reported. Several scholars have reported cases in which the patient developed positive HBV core antibodies and surface antibodies after IVIG infusion, and subsequent multiple tests revealed false-positive results due to immunoglobulin (109, 110). Ramsay and colleagues conducted a cross-sectional study that suggested that HBV antibodies (HBsAb and HBcAb) are common in patients receiving IVIG and who have confounding diagnostic results (111). Thus, the measurement of baseline HBV antibodies should be implemented when commencing immunoglobulin infusion. If the test results are negative, and there is an absence of hepatitis or risk factors, any future positive

results in the context of ongoing immunoglobulin therapy should be considered false positives, HBV-DNA levels should be measured, and antiviral treatment should be given cautiously.

Since the introduction of adequate management and advanced testing technologies, no cases of IVIG-related prion disease or HIV transmission have been reported. Radomski et al. (112) found that two dedicated and one supplemental step [solvent/detergent (S/D) treatment and nanofiltration (20 nm) in combination with ion-exchange chromatography] could prevent pathogen transmission. Although the infection risk is much lower in IVIG than in other blood products, the possibility of infection can never be neglected.

Other Adverse Effects

Other adverse effects of immunoglobulin therapy include uveitis, passively acquired thyroid autoantibodies and reversible splenial lesion syndrome. Kocak et al. (113) reported a case in which a 44-year-old female developed bilateral uveitis following the administration of IVIG for 2 days. The patient was treated with topical corticosteroids and had achieved complete resolution at 1-month follow-up. In 2017, Uchida et al. (114) reported two cases in which thyroid autoantibodies passively acquired following IVIG administration. Finally, Uygur et al. (115) described a case of reversible splenial lesion syndrome caused by IVIG therapy.

TABLE 2 | Predisposing factors for immunoglobulin-induced adverse effects.

Adverse effect	Predisposing factors
Flu-like symptoms	High dose, rapid infusion rate, accompanying infection, previous adverse effects
Dermatological adverse effects	High dose, rapid infusion rate, accompanying infection, male patients with chronic inflammatory demyelinating polyneuropathy
Arrhythmia and hypotension	History of heart disease
Transfusion-related acute lung injury	Rapid infusion rate
Thrombotic events	High dose, rapid infusion rate, advanced age, being bedridden, diabetes mellitus, hypertension, dyslipidemia, prior/current thrombosis, preexisting atherosclerotic disease, elevated serum viscosity, oral contraceptive use, hereditary hypercoagulable state, idiopathic thrombocytopenic purpura
Aseptic meningitis	High dose
Renal impairment	Rapid infusion rate, advanced age, renal insufficiency, nephrotic syndrome, diabetes mellitus, dehydration, sepsis paraproteinemia, nephrotoxic drugs, hemolysis, sucrose-containing preparations
Hemolysis	High dose, rapid infusion rate, non-O blood group, underlying inflammatory state

PREVENTIVE MEASURES

Risk Assessment and Adequate Monitoring

Immunoglobulins cause various adverse effects; some of these effects are severe and fatal. Hence, a detailed medical history should be obtained in every patient being considered for immunoglobulin treatment. This information should include age, the infusion course of immunoglobulin, concomitant diseases (diabetes, hypertension, coronary heart disease, stroke, thrombotic events, hemadostenosis, etc.), and co-medications (e.g., contraceptive drugs and diuretics). Laboratory tests are also needed, such as a blood group test, routine blood tests, and tests of liver and kidney function. A variety of risk factors must be considered when evaluating possible adverse effects, and special precautions should be considered in patients with a history of allergies or thrombotic events. In these patients who have a heightened risk of developing adverse effects, special monitoring should be employed within the first 24 h following immunoglobulin administration in a hospital. The proposed factors that predispose a patient to immunoglobulin-induced adverse effects are shown in **Table 2**.

Slowing Down the Infusion Rate

The adverse effects described here are closely related to the rate of immunoglobulin infusion. Hence, slowing down the rate of infusion can greatly reduce the rate of adverse reactions, especially flu-like symptoms, hemolysis, thrombosis, and renal impairment (22, 63, 116). Strictly controlling the infusion rate during the first administration is recommended. During the first infusion, an initial slower rate should be implemented for the first 30 min, and then the rate may be increased if no adverse effects occur (we recommend using the infusion rate according to the instructions provided by different brands). Slowing the rate should be considered if any adverse effects occur. The infusion should be discontinued if slowing the rate does not alleviate these adverse reactions.

Premedication and Prehydration

Premedication with antihistamines, corticosteroids, or NSAIDs can markedly reduce the severity and incidence of IVIG-induced adverse effects. In 1998, Roberton et al. (117) assessed the effect of premedication with methylprednisolone in a large crossover study that included 10 patients who had previously experienced frequent adverse reactions. Methylprednisolone was administered at a dose of 1 mg/kg 20 min prior to IVIG infusion, and the pretreated patients exhibited a marked decrease in the severity of IVIG-induced immediate adverse events ($P < 0.01$), with only one patient discontinuing IVIG infusion, whereas IVIG was interrupted in 8 of the 10 patients who were not pretreated with methylprednisolone. Souayah et al. (118) examined the safety profile of home infusion of IVIG in patients with neuroimmunologic disorders. In all, 276 patients were premedicated with antihistamines, corticosteroids, or NSAIDs, and the incidence of IVIG-induced adverse effects was significantly lower in the premedicated group than in the non-premedicated group (18.4 VS 27.1%, $P = 0.04$). However, the results of a separate study indicated that the rate of immunoglobulin-induced immediate adverse events was not altered by premedication (29). With regards to thrombotic events, Huang et al. (119) implemented a protocol in which treatment with antiplatelets and anticoagulation before IVIG infusion eliminated IVIG-related thrombotic events. However, because their sample size was small, further studies are needed to determine the safety and efficacy of this protocol.

Prehydration with normal saline is also used to prevent immunoglobulin-induced adverse effects. Many studies have proposed that prehydration can be helpful for headache, thrombolysis, renal impairment, and hemolysis (63, 120, 121); however, the implementation protocol, the dose of saline (250 or 500 ml, etc.), and the duration of saline infusion remain unclear. All of these studies utilized a protocol that combined hydration and other measures; therefore, the efficacy of prehydration should be further evaluated in a well-designed study.

Switching From IVIG to SCIG or Other Immunoglobulin Preparations

Switching from IVIG to SCIG seems to be an effective strategy that attenuates immunoglobulin-induced adverse effects, especially for patients who have previously experienced severe adverse effects or are at high risk of developing adverse effects. An increasing number of well-designed studies show that SCIG can be used as a treatment for immunodeficiency diseases, multifocal motor neuropathy, chronic inflammatory demyelinating polyneuropathy, and myasthenia gravis (6, 122–136) (**Table 3**). The results of two randomized, crossover studies indicate that the rate of systematic adverse effects was lower following SCIG than following IVIG, and no severe adverse effects were reported in patients treated with SCIG (123, 135). However, the sample sizes of these two studies were small (30 and 20). Racosta et al. (137) performed a meta-analysis of reports that explored the efficacy and safety of SCIG VS IVIG and identified a total of 8 studies comprising 138 patients with inflammatory demyelinating polyneuropathies. Their results showed that the relative risk of moderate and/or systemic adverse effects was 28% lower in the SCIG group [95% confidence interval, 0.11–0.76]. Due to the small sample size of these studies, the efficiency of SCIG

TABLE 3 | Subcutaneous immunoglobulin (SCIG) treatment in a variety of diseases.

Reference	Sample	Diagnosis	Study design	SCIG dose	Rate of side effects	Severity
Misbah et al. (130)	8	Multifocal motor neuropathy	Prospective, open-label, multicenter study	271.8 ± 139.13 mg/kg (range, 100–488 mg/kg)	50% had 18 AEs 0.098 per infusion	Mild to moderate No discontinuations
Kanegane et al. (133)	25	Primary immunodeficiency	Prospective, multicenter, open-label, single-arm study	Not mentioned	96.0% had 269 AEs 0.461 per infusion	Mild to moderate No discontinuations
Empson et al. (131)	35	Primary immunodeficiency	Phase III, single-arm, open-label, multicenter study	Median 6.70 g/week (range, 3–13.5 g/week)	40% of patients 0.059 per infusion	Mild to moderate No discontinuations
Hoffmann et al. (128)	82	Primary and secondary antibody deficiencies	Prospective, observational, multicenter study	91 ± 31 mg/kg/week	2/82 patients had 2AEs	Local tissue reactions 1 patient discontinued
Thépot et al. (129)	65	Primary hypogammaglobulinemia	Monocentric, longitudinal trial	108 mg/kg (range, 62–174 mg/kg)	3/65 patients	Mild to moderate 3 patients switched to intravenous immunoglobulin
Berger et al. (126)	51	Primary immunodeficiency	Not mentioned	100–200 mg/kg/week	86.3% of patients 0.15 per infusion	1 severe adverse effect 2 patients withdrew
Spadaro et al. (134)	14	Hypogammaglobulinemia	Not mentioned	100 ± 4.4 mg/kg/week	Not mentioned	Not mentioned
Harbo et al. (127)	6	Multifocal motor neuropathy	Prospective, observational study	13–51 g per week	6/6 patients had local tissue reactions	Local tissue reactions 1 patient withdrew
Ochs et al. (124)	65	Primary immunodeficiency	Prospective, open-label, multicenter study	158 mg/kg (range, 155–165 mg/kg)	60/65 patients 0.52 per infusion	Mild to moderate 14 patients withdrew
Markvardsen et al. (132)	20	Chronic inflammatory demyelinating polyneuropathy	Randomized, single-blind, crossover study	0.4 g/kg	Not mentioned	Not mentioned
van Schaik et al. (136)	172	Chronic inflammatory demyelinating polyneuropathy	Randomized, multicenter, double-blind, placebo-controlled, parallel-group, phase III study	0.2 or 0.4 g/kg	30% in the low-dose group 34% in the high-dose group	Six (3%) patients had 11 serious adverse events
Beecher et al. (6)	23	Myasthenia gravis	Prospective, open-label, phase 3 trial	2 g/kg	Headache and injection site reactions were common	Mild to moderate No discontinuations
Markvardsen et al. (135)	30	Chronic inflammatory demyelinating polyneuropathy	Randomized, double-blind, placebo-controlled trial	4.8–48 g/week	6/15 patients	Mild to moderate No discontinuations
Gardulf et al. (122)	165	Primary immunodeficiency	Not mentioned	Not mentioned	17% of patients 0.03 per infusion	Mild to moderate No discontinuations
Eftimov et al. (125)	10	Multifocal motor neuropathy	Prospective, open-label, noncontrolled study	0.46 g/kg/month (range, 0.27–0.62)	9 patients developed local adverse events	Mild to moderate No discontinuations
Chapel et al. (123)	30	Primary immunodeficiency	Randomized, multicenter, open-label, crossover trial	Not mentioned	0.1 per infusion	Mild to moderate No discontinuations

should be further explored, and more randomized controlled trials with larger samples of patients with various diseases are needed.

It remains unclear how the dose should be adjusted when switching from IVIG to SCIG. Berger and colleagues found that using 137 and 153% of the IVIG dose when switching to SCIG produced the same effect in patients being treated for primary immunodeficiencies (138). Another study concluded that sustained serum IgG levels can be achieved after switching to SCIG despite the use of a reduced immunoglobulin dose in patients with primary hypogammaglobulinemia (129). Individualizing the dosage based on the disease state and the clinical response is preferable to using mean pharmacokinetic parameters when switching from IVIG to SCIG. In addition, more studies focused on pharmacokinetics in immune-mediated diseases are needed.

Detailed information regarding the immunoglobulin preparation should always be recorded, including the manufacturer, batch, and drug instructions. It is clear that the content, composition, and characteristics of each immunoglobulin preparation can adversely affect patients in different manners. Hence, if patients frequently develop adverse effects following administration with an IVIG preparation, switching to another immunoglobulin preparation may lead to fewer adverse effects (62).

Other Measures

Many patients develop immunoglobulin-associated adverse effects, and the majority of these effects are mild to moderate and resolve with appropriate treatment. The observed effects include immediate adverse effects, aseptic meningitis, hemolysis, neutropenia, and electrolyte disturbances. Some of these severe adverse effects should be treated according to the principle underlying the corresponding diseases, such as an effective antithrombotic therapy in patients with thrombosis or short-term renal replacement therapy in patients with severely damaged renal function.

FUTURE PROSPECTS

Immunoglobulin preparations have been widely used in a variety of diseases, but controlled studies have not been performed for many diseases, such as myasthenia gravis, some forms of lupus erythematosus, septic syndrome, and polymyositis. The improper usage of immunoglobulin increases the risk of adverse effects to some extent; therefore, further studies are needed to demonstrate the proper indications for the use of immunoglobulin.

The majority of adverse effects are associated with high doses of immunoglobulin; thus, determining individualized dosages to guarantee the efficacy of therapy and minimize adverse effects is an urgent focus. Ameratunga (139) suggested that the initial IVIG dose should be based on adjusted body weight in obese patients with primary immunodeficiency disorders. As this study was a single observation and focused on only obese patients, additional special populations, such as the elderly, should be studied to determine the parameters of individualized dosing for immunoglobulin therapy.

Many measures have been used to prevent or minimize immunoglobulin-related adverse effects, as summarized above. Given that these studies were case controlled or small sample size studies, the efficacy of these measures should be verified by randomized controlled studies or head-to-head studies with larger sample sizes. Simultaneously, the use of only one preventive measure may not prevent adverse effects, and a series of measures serving as a standard protocol may be effective for preventing serious adverse effects, such as combining prehydration with anti-thrombosis to minimize thrombotic events.

Currently, immunoglobulin may be given intravenously or subcutaneously to treat a variety of disorders. However, IVIG and SCIG preparations also result in adverse effects. It is possible that other routes of immunoglobulin administration may reduce the rate of adverse effects. In 1982, Barnes et al. (140) found that oral administration of immunoglobulin could be used for the prevention and treatment of rotavirus diarrhea in low-birth weight babies. Later, several meta-analysis studies concluded that oral administration of immunoglobulin could not prevent rotavirus diarrhea and necrotizing enterocolitis (141, 142). Although these studies have several limitations (small sample size and few well-designed studies), oral administration may be a promising preparation to attenuate the occurrence of adverse effects.

Many factors affect the rate of immunoglobulin-related adverse effects. Several characteristics of newer generation immunoglobulin products should be improved, including specific functions, purity, and biological safety. Thus, advanced separation and purification technologies should be developed.

AUTHOR CONTRIBUTIONS

YG and XT conceived the article and wrote the manuscript. XW and ZX reviewed and edited the manuscript. All authors read and approved the manuscript.

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Characteristics of Seizure and Antiepileptic Drug Utilization in Outpatients With Autoimmune Encephalitis

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Autoimmune encephalitis (AE) is one kind of encephalitis that associates with specific neuronal antigens. Most patients with AE likely suffer from seizures, but data on the characteristics of seizure and antiepileptic drugs (AEDs) utilization in this patient group remains limited. This study aimed to report the clinical status of seizure and AEDs treatment of patients with AE, and to evaluate the relationship between AEDs discontinuation and seizure outcomes. Patients with acute neurological disorders and anti-N-methyl-D-aspartate receptor (NMDAR), γ-aminobutyric acid B receptor ($GABA_BR$), leucine-rich glioma inactivated 1, or contactin-associated protein-like 2 (CASPR2) antibodies were included. As patients withdrew from AEDs, they were divided into the early withdrawal (EW, AEDs used ≤3 months) and late withdrawal (LW, AEDs used >3 months) groups. Seizure remission was defined as having no seizures for at least 1 year after the last time when AEDs were administered. Seizure outcomes were assessed on the basis of remission rate. The factors affecting the outcomes were assessed through Spearman analysis. In total, we enrolled 75 patients (39 patients aged <16 years, male/female = 39/36) for follow-up, which included 67 patients with anti-NMDAR encephalitis, 4 patients with anti-$GABA_BR$ encephalitis, 2 patients with anti-voltage-gated potassium channel encephalitis, and 2 patients with coexisting antibodies. Among the 34 enrolled patients with anti-NMDAR encephalitis who were withdrawn from AEDs, only 5.8% relapse was reported during the 1-year follow-up, with no significant difference in the percentage of relapse between the EW and LW groups ($P = 0.313$). Fifteen patients (an average age of 6.8, 14 patients with anti-NMDAR encephalitis and 1 patient with anti-CASPR2 encephalitis) presented seizure remission without any AEDs. Seventy five percent of patients with anti-$GABA_BR$ antibodies developed refractory seizure. Other risk factors which contributed to refractory seizure and seizure relapse included status epilepticus ($P = 0.004$) and cortical abnormalities ($P = 0.028$). Given this retrospective data, patients with AE have a high rate of seizure remission, and the long-term use of AEDs may not be necessary to control the seizure. Moreover, seizures in young patients with anti-NMDAR encephalitis presents self-limited. Patients with anti-$GABA_BR$ antibody, status epilepticus, and cortical abnormalities are more likely to develop refractory seizure or seizure relapse.

Keywords: autoimmune encephalitis, outpatients, seizure remission, antiepileptic drug withdrawal, refractory seizure

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INTRODUCTION

Autoimmune encephalitis (AE) is kind of encephalitis which associates with humoral or cellular responses against specific neuronal antigens (1, 2). The clinical characteristics of these patients include seizure, abnormal behavior, speech dysfunction, movement disorders, and autonomic dysfunction (3). With the development of biochemical assays, several antibodies, such as the anti-*N*-methyl-D-aspartate receptor (NMDAR), anti-γ-aminobutyric acid B receptor ($GABA_BR$), anti-leucine-rich glioma inactivated 1 (LGI1), and anti-contactin-associated protein-like 2 (CASPR2) antibodies, have emerged as the leading causes of AE. Therapeutic regimens included first-line immunotherapy (steroids, intravenous immunoglobulin, plasmapheresis), and second-line immunotherapy (rituximab, cyclophosphamide). Despite the severity of the disease in acute phase, most patients recover after proper immunotherapy and intensive support (4).

In acute phase, seizure is a highly prevalent symptom, and parts of patients develop status epilepticus (SE) (5–7). Hence, multiple anti-epileptic drugs (AEDs) are often necessary to control the attacks. However, based on the previous studies and data from our center, most patients likely recover completely after adequate immunotherapy, and seizure is rarely reported in the chronic phase (5, 8, 9). Considering the adverse events of AEDs, some patients stop taking AEDs at the early stage. However, an instructional database describing the long-term use of AEDs with AE is lacking.

This retrospective study aimed to report the seizure characteristics and long-term use of AEDs in outpatients with AE. Our secondary goals included assessing the outcomes between patients with early and late AEDs withdrawal, and determining the probable risk factors for seizure relapse and refractory seizures.

MATERIALS AND METHODS

Study Population

This study was conducted in compliance with the ethical standards of Guangxi Medical University. Written consents were obtained from the patients.

The antibodies, including NMDAR, $GABA_BR$, LGI1, and CASPR2, were detected in patients' cerebrospinal fluid and serum samples. The anti-NMDAR antibody was detected by specific staining against NMDAR isolated from rat' hippocampus and cerebellum, and positive cell-based assay with HEK293 cells transfected with NR1. Other antibodies were detected using transfected HEK293 cells with the respective target proteins.

Patients with acute neurological disorders of either sex or any age were considered eligible for this study if they presented any positive antibodies from January 2012 to May 2017. The exclusion criteria included (1) patients diagnosed with epilepsy, cerebral infarction, cerebral trauma, cerebral tumor, and other nervous system disease prior to the onset of encephalitis, (2) patients with evidence of infectious encephalitis, for example, viral, bacteria, mycobacterium tuberculosis, or fungal, (3) patients in the acute phase of autoimmune encephalitis and still required hospitalization. Immunotherapies were used in the acute phase (**Figure 3A**). The decisions about the type and duration of immunotherapy were based on the clinical symptoms, curative, and side effects. The available onset medical data (seizure characteristics, AEDs utilization, and electroencephalogram/neuroimaging findings) were recorded. The electroencephalogram and neuroimaging findings were recorded in the acute phase of the disease.

Definitions

The chronic stage of AE was defined by 3 months after the onset of AE symptoms. SE was defined as continuous seizure activity lasting >5 min or recurrent seizures without regaining consciousness between seizures for >5 min (10). Refractory seizure was defined as an uncontrolled seizure after treatment by more than three standard therapeutic schedules (11). Seizure remission was defined as having no seizure for at least 1 year after the last time when AEDs were used (12). Seizure with focal characteristics was defined as a partial seizure or a patient with seizure and hemiplegia or hemianesthesia.

Outcome Assessment and Grouping

AEDs utilization and seizure outcomes were assessed through outpatient services and/or telephone interview. AEDs utilization in the chronic stage (time of continuation/withdrawal) and outcomes (refractory, relapse, or remission) data were collected on patients. Before evaluating the outcomes, the patients who discontinued AEDs were observed for at least 1 year after the last AEDs use.

Patients who withdraw AEDs were divided into two groups based on the duration of AEDs use. The early withdrawal (EW) group had AEDs withdrawn within 3 months, and the late withdrawal (LW) group had AEDs withdrawn after 3 months. Outcomes were assessed based on seizure remission rate and the modified Rankin Scale (mRS) (13).

Statistical Analysis

Data analysis was performed using IBM SPSS Statistics 22. The skewness and kurtosis coefficients were used to evaluate whether the quantitative data fit a normal distribution. Data were regarded as a normal distribution if the skewness and kurtosis coefficients <1. For the data that did not fit this criterion, we used the Mann–Whitney test to evaluate significance. Other data was compared using a *t*-test or a Fisher's exact test. The factors affecting the outcomes were assessed through Spearman analysis.

RESULTS

We identified 83 patients with AE. **Figures 1**, **2** show a summary of these patients. In the charts reviewed, 5 patients were lost and 3 patients died of severe pneumonia. As a result, 75 patients were enrolled to follow-up. Among the 75 patients, 12 continued taking AEDs, 15 were not given any AEDs, and 37 patients who withdrew from AEDs were followed up for at least 1 year (**Figure 1**). The group with AEDs withdrawal

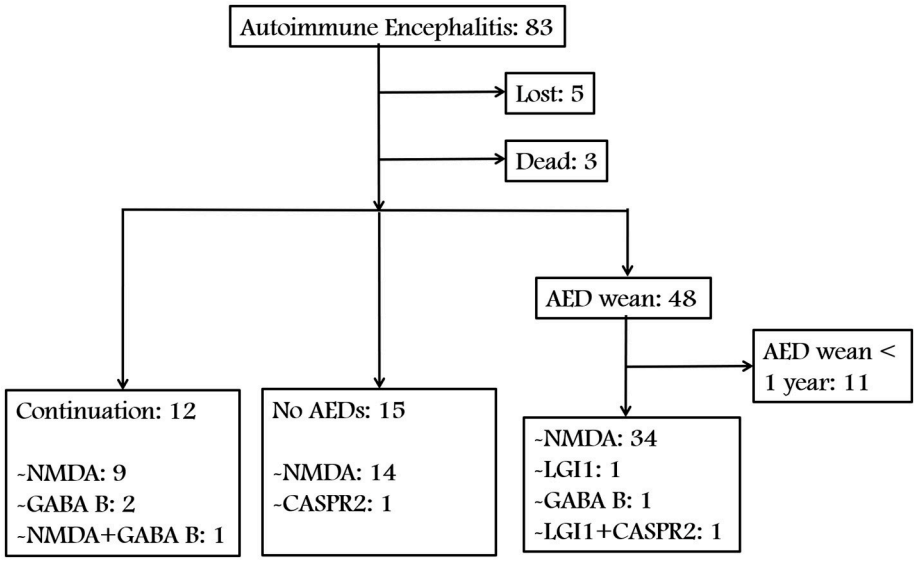

FIGURE 1 | Flow diagram of patient inclusion and grouping.

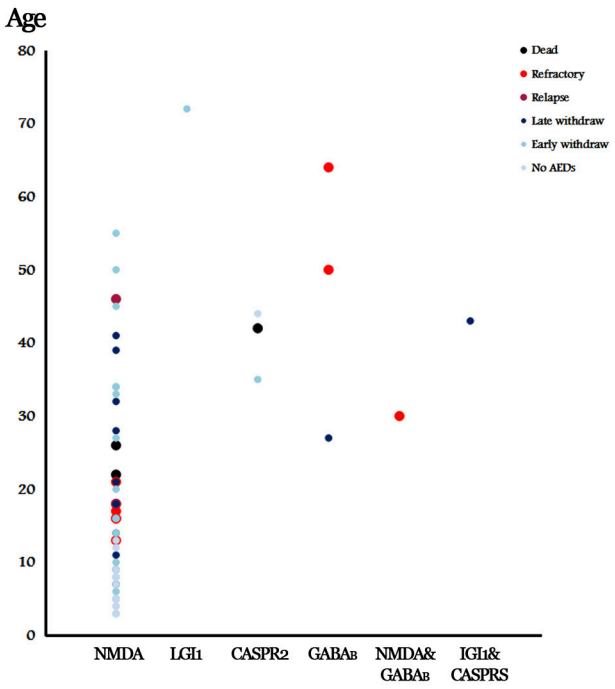

FIGURE 2 | Summary of the presenting patients and outcomes in accordance with the involved antibodies. No AEDs, No AED was given and no relapse was reported. Early withdrawal (EW), AEDs weaned within 3 months and no relapse was reported. Late withdrawal (LW), AEDs weaned after 3 months and no relapse was reported.

included 34 patients with anti-NMDAR encephalitis, 1 with anti-LGI1 encephalitis, 1 with anti-$GABA_BR$ encephalitis, and 1 patient presented coexisting antibodies of anti-LGI1 and CASPR2 (**Figure 1**).

Anti-NMDAR Encephalitis

Among the patients with anti-NMDAR encephalitis, 14 were not given any AEDs, in which 7 suffered from one-time seizure attack at the onset of the encephalitis. Compared to the patients with AEDs, the majority of this group was considerably young (6.8 ± 3.26, $P = 0.004$, **Table 1**) and less likely to have repetitive seizures ($P = 0.038$, **Table 1**). The median duration of follow up was 20 months (range: 14–36 months), and no relapse was reported. Furthermore, 12 patients (85.7%) had good outcomes with a 0 mRS score; the remaining 2 patients presented with cognitive dysfunction.

Among the 34 patients (20 men and 14 women, 23 in EW and 11 in LW) who were discontinued from AEDs, 7 patients (20.6%) did not report seizure, and 5 patients (14.7%) reported a one-time seizure at the onset. Two patients in the EW group reported hemianesthesia before presenting seizures. The occurrence of SE was 32.4% in total. Eighteen patients had an magnetic resonance imaging (MRI) scan and abnormalities were found in 33.3% of the patients, including 4 patients with white matter changes and 2 patients with cortical mass (**Table 1**). The patterns of AEDs selection and discontinuation were variable (**Figure 3B**). Monotherapy was the most common selection, with 69.5% in the EW group and 63.9% in the LW group. At the early stage, carbamazepine ($n = 11$) and oxcarbazepine ($n = 16$) were the most chosen AEDs. Valproic acid was among the most commonly continued therapies over the course of follow-up (**Figure 3B**). Seven patients without seizure were treated with AEDs upon onset. Five of these discontinued AEDs within 1 month, and the remaining 2 patients underwent LW because of frequent subclinical discharge.

The patients' data were compared between the EW and LW groups (**Table 1**). No statistically significant difference was observed between the two groups in terms of age ($P = 0.935$), sex ($P = 0.458$), seizure characteristics ($P = 0.359$), antibody

TABLE 1 | Clinical characteristics and outcomes of patients with anti-NMDA encephalitis.

	No AEDs (14 patients)	Early withdraw (23 patients)	Late withdraw (11 patients)	P1	P2
Sex (male/female)	7/7	15/8	5/6	0.474	0.458
Age (Ave ± SD)	6.8 ± 3.26	21.0 ± 16.19	21.4 ± 11.89	0.004	0.935
Seizure frequency				0.038	0.359
None	4	5	2		
Once	7	2	3		
Repeated	3	16	6		
Seizure with focal characters	0	2	0	0.322	0.313
Status epilepticus(Yes/No)	0/14	6/17	5/6	0.024	0.259
Antibody titer				0.129	0.727
1:10	6	3	1		
1:32	7	19	10		
1:100	1	1	0		
MRI abnormalities				0.400	0.329
None	4	6	6		
White matter	3	3	1		
Cortex	3	2	0		
Anti-epileptic drugs				–	0.934
1 kind	–	16	7		
2 kinds	–	5	3		
3 or more kinds	–	2	1		
Followed up					
Median duration (months)	20 (14–36)	36 (15–50)	32 (17–62)		
Relapse	–	2/21	0/11	–	0.313
mRS score (≤1/>1)	12/2	22/1	9/2	0.398	0.239

AED, Antiepileptic drug. P1, P-value among No AED, Early withdraw, and late withdraw group. P2, P-value between Early withdraw, and late withdraw group.

titers ($P = 0.727$), SE ($P = 0.259$), MRI findings ($P = 0.329$), or AEDs selection ($P = 0.934$). The medium durations of follow up were 36 months (range: 15–50 months) and 32 months (range: 17–62 months) for the EW and LW groups, respectively. 2 patients in the EW group relapsed in the first month after drug discontinuation. No remarkable difference in the percentage of relapse was observed between the two groups.

Detail of patients with anti-NMDAR encephalitis was presented in **Supplementary File 1**.

Other AEs

A 44-year-old woman who was diagnosed with anti-CASPR2 encephalitis presented lethargy and headache without seizure at the onset. She did not take any AEDs. No relapse was reported during her 16-month follow up. A 72-year-old man with anti-LGI1 encephalitis and a 35-year-old woman with anti-$GABA_BR$ encephalitis presented frequent seizures at onset and underwent an AED withdrawal 3 and 6 months later, respectively. No relapse was reported during their 1-year follow up. The other two elder patients (50 and 64 years-old, respectively) with anti-$GABA_B$ encephalitis presented refractory seizures (**Figure 2**).

We also reviewed 2 coexisting AE. One is a 30-year-old female who presented with anti-NMDAR and $GABA_BR$ encephalitis. She had a seizure 10 years ago before she was diagnosed with AE through CSF detection. Her EEG presented δ brushes with generalized paroxysmal θ activities. The brain MRI was unremarkable. She developed refractory seizures after being treated by oxcarbazepine, carbamazepine, and clonazepam. The other patient was a 43-year-old woman with LGI1 and CASPR2 antibodies. She presented repeated generalized tonic-clonic seizure and paroxysmal speech dysfunction. Bilateral paracentral lesion was found in the MRI scan. She was given levetiracetam and valproic acid. The AEDs were withdrawn 2 years later, and no relapse was reported during her 1-year follow up (**Figure 2**).

Risk Factors

Among the 12 patients who remained on AEDs, 9 patients presented refractory seizure, including 6 patients with anti-NMDAR encephalitis, 2 patients with anti-$GABA_BR$ encephalitis, and 1 patient with anti-NMDAR and $GABA_BR$ encephalitis (**Figure 2**). Among patients with anti-NMDAR encephalitis, refractory seizures occurred more often in the patients younger than 30 years of age (**Figure 2**), and who presented repetitive seizures and SE, moreover, 4 patients (66%) showed cortical abnormalities on the MRI scan.

By combining the data of the 2 relapse cases, we evaluated the risk factors that contributed to the worse outcomes of anti-NMDAR encephalitis. The patients with relapse or refractory seizure were more likely to be accompanied with cortical lesions on MRI ($P = 0.028$) and SE ($P = 0.004$) than those who reached seizure remission (**Table 2**). Moreover, the seizures with

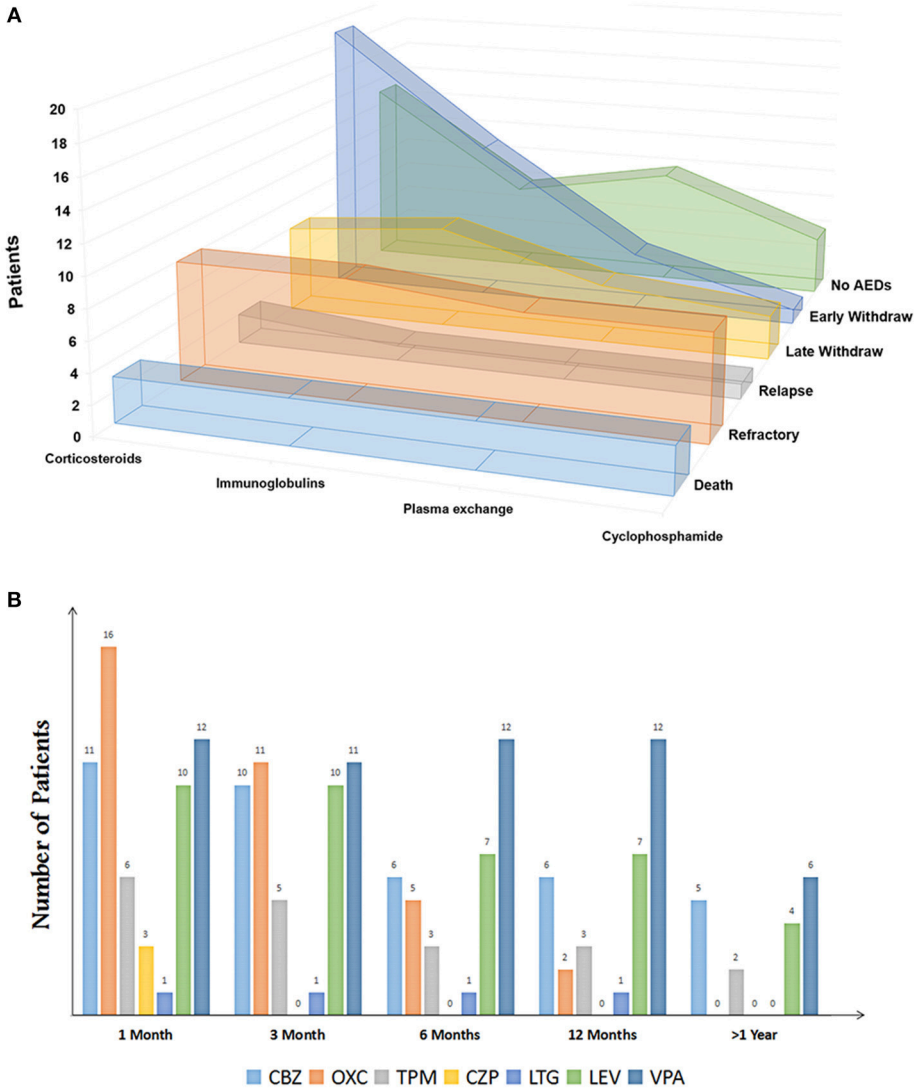

FIGURE 3 | (A) Immunotherapies of patients with autoimmune encephalitis (Sort by outcomes). **(B)** Clinical patterns of AED discontinuation of patients with anti-NMDA encephalitis. CBZ, carbamazepine; OXC, oxcarbazepine; TPM, topiramate; CZP, clonazepam; LTG, lamotrigine; LEV, levetiracetam; VPA, valproate.

TABLE 2 | Spearman analysis of factors associated with outcomes.

	Refractory Seizure/P	Relapse/P	Both/P
Sex	0.571	0.859	0.516
Age	0.528	0.116	0.259
Antibody titers	0.640	0.590	0.555
Seizure with focal characters	<0.001	0.769	0.099
Status epilepticus	<0.001	0.415	0.004
MRI abnormalities	0.010	0.961	0.028

focal characteristics ($P < 0.001$), SE ($P < 0.001$), and MRI abnormalities ($P = 0.010$) were significantly associated with refractory seizure (**Table 2**). For other kinds of AEs, we found 3 patients with anti-$GABA_BR$ encephalitis (75% in all, including 1 patient with concomitant disease) developed refractory seizure; this number is much higher than those of others.

DISCUSSIONS

Parts of AE have been linked to cell surface antigens, which included voltage-gated potassium channel (VGPC, e.g., LGI1 and CASPR2), NMDAR, and $GABA_BR$ (14). To evaluate the AEDs utilization associated with AE, we focused on seizure in a cohort of patients with anti-NMDAR, anti-$GABA_BR$, anti-LGI1, and CASPR2 encephalitis. This study demonstrated low recurrence rates in young patients with AE who experienced first unprovoked seizures and highlighted an overall remission rate of 94% after the patients discontinued AEDs therapy. No difference was noted between the EW (≤3

months) and LW (>3 months) of AEDs. Moreover, a higher number of patients with anti-$GABA_BR$ antibody, SE, cortical abnormalities, and focal neurological dysfunction experienced refractory seizure or seizure relapses compared to those who did not.

Seizure Remission in Anti-NMDAR Encephalitis

Since 2005, the characteristics and long-term outcomes of anti-NMDAR encephalitis have aroused public attention due to the high incidence in young patients with serious neurological dysfunctions (15). According to a previous study, we found that the probable predicted factors for poor outcomes in the acute phase included older age, altered consciousness, and SE, and the process of terminating SE was particularly important for anti-NMDAR encephalitis (5). By evaluating patients through the mRS score, the other multi-institutional study which included clinical data from 577 patients with anti-NMDAR antibodies observed that 81% of the patients responded to immunotherapy (8). Seizure occurs as a prominent feature in AE (16), whether long-term AEDs are necessary after patients achieving good outcomes has not been established (14, 16).

AEDs withdrawal after a successful seizure control may prevent adverse side effects and excessive cost. However, the studies which have evaluated the safety of AEDs weaning in patients with anti-NMDAR encephalitis are rare. One study demonstrated that no difference in seizure recurrence between 1 and 2 years of AEDs therapy in children with viral encephalitis (17), and the relative risk factors might have included EEG abnormalities or HIV infection (18). However, the duration of AEDs in anti-NMDAR encephalitis tended to be shorter (19). Among the 34 enrolled patients with AEDs withdrawal, only 5.8% suffered from relapse during the follow up. Moreover, no difference was found between the EW (≤3 months) and LW (>3 months) groups, which is consistent with that of a previous study (16).

Information regarding AEDs use in adolescents and adults with anti-NMDAR encephalitis has been reported previously, but data from younger children remain limited (16). In the present study, we enrolled 14 young patients with average age of 6.8 (range: 3–12 years). Compared with the older age group, the young group was more likely be seizure free during the long-term follow-up without AEDs, even if they suffered one-time seizure attacks at the onset. The key treatment decisions after the first unprovoked seizure are a controversial issue in children (20, 21). In some epilepsy syndromes, such as in benign childhood epilepsy with centrotemporal spikes or childhood absence epilepsy, remission is a regular feature of the natural history, whereas juvenile myoclonic epilepsy or other symptomatic epilepsies have long been considered to present in AEDs continuation (22). By using the statistical methods for survival analysis, one study indicated that the cumulative risk of repetitive seizure in children was 29% in the first year and elevated to 45% within the 10-year follow up (23). However, the factors associated with recurrences after the first seizure are complex. The probable risk factors may include age (24) and etiology (25). For anti-NMDA encephalitis, our data indicated that seizure in young patients tended to be self-limited. Moreover, some scholars indicate that a cognitive comorbidity likely accompany with the initial seizure if AEDs are not used (26). However, evaluation of mRS score revealed that the majority of children in this group presented normal daily activities.

Although our data supports that seizure remission is common and that long-term use of AEDs may not be necessary, the significance of immunotherapy cannot be ignored to control the seizure. Numerous studies demonstrated that it is the immunotherapies that control the symptoms in anti-NMDAR encephalitis (5, 8, 9). Moreover, one retrospective study which focused on the outcome of AEDs alone in controlling the seizure of patients with anti-VGPC-complex antibodies indicated that only 23.5% of patients became seizure free compared with 61.5% of patients with immunotherapy (14).

Seizure Remission in Anti-GABABR, LGI1, and CASPR2 Encephalitis

Anti-$GABA_BR$, LGI1, and CASPR2 antibodies have been recently detected in patients with limbic encephalitis (27). Seizures are frequently reported in limbic encephalitis, but autonomic and psychiatric symptoms are more highlighted. In these antibody-mediated seizures, remission rate is variable, and may be related to complications, immunotherapy, and ICU management (7).

Although rare, seizure with additional auto-antibodies may be a other probable risk factor. LGI1 and CASPR2 are the extracellular domains of VGPC. The coexistence of anti-LGI1 and anti-CASPR2 encephalitis may contribute to seizure, cognitive disturbance, movement disorders, and pain (7). Besides AEDs use, the empirical approach to seizure control is corticosteroid treatment (28, 29). A $GABA_BR$ antibody is rarely accompanied with other antibodies in a same patient, and a probable reason may involve different genetic predispositions (30, 31). In our study, the presented patients developed refractory seizure and severe cognitive dysfunction. One possible mechanism of AEDs resistance may be associated with different interaction sites, as anti-NMDAR antibodies have been suggested to decrease the synaptic levels of receptors, whereas the anti-$GABA_BR$ antibody would further alter the synaptic function (32).

Risk Factors for Refractory Seizure and Seizure Relapse

As AEDs are supposedly unnecessary to seizure outcomes in AE after appropriate immunotherapy, we evaluate the other probable independent risk factors that contribute to refractory seizure and seizure relapse. In addition to involving the anti-$GABA_BR$ antibody, our result shows that patients with SE, cortical abnormalities in MRI, and focal neurological dysfunction are more likely to develop worse outcomes than those who did not accompany these findings. SE has been proven to be an independent risk factor in major types of epilepsy (33, 34). The complications of SE, such as severe

pneumonia and ICU admission, have also contributed to poor outcomes (5). Cortical abnormalities seem positively correlate with refractory seizure. By using structural MRI scans, one study demonstrated a strong association between incomplete recovery and superficial white matter lesions (35). This observation indicates that the injured connection between adjacent cortices may play a crucial role in seizure control after AE.

LIMITATIONS

This study has some limitations. First, we tried to discuss the risk factors of seizure outcomes for AE after appropriate immunotherapy. However, as antibodies were not measured at later time points, the direct relationship between persistent antibody levels and seizure outcomes remained unclear. A previous study presented that the neurological recovery accompanied with reduced antibody titer (15), while the correlation between antibody titer and refractory seizure showed unremarkable in our study. One probability which caused the difference might involve the time when antibody was measured. Though the seizure outcomes were assessed based on the data of outpatients, the patients who developed refractory seizure might have persistent higher titer level than those who did not. Second, as the relapse rate was altered with the follow-up period (23), long follow-up times are necessary. However, 54–100% of seizures after AE occurred within the first year, and new-onset seizure after 1 year of follow up was rare (36–38). Third, the results were limited because of the relatively small cohort. Combined with the previous data (16), a probable correlation between seizure remission and AED utilization was noted, and further trials and meta-analysis are needed to confirm these results.

CONCLUSION

Patients with AE have a high rate of seizure remission after proper immunotherapies. The long-term use of AEDs appears not be necessary to control their seizures. Compared with adults, young patients are more likely to become seizure free without AEDs. The risk factors that contribute to refractory seizure or seizure relapse may include anti-$GABA_BR$ encephalitis, SE, and cortical abnormalities.

AUTHOR CONTRIBUTIONS

QH is the first author of this manuscript. YuaW is the corresponding author of this manuscript, they contributed to the study design, data collection and analysis, and draft writing of this work. MM, XW, and YL have revised and improved the manuscript. HQ and YueW contributed in the data collection and figures. All authors have seen and agreed on the finally submitted version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2018.01136/full#supplementary-material

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REVIEW
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Central Nervous System Involvement in ANCA-Associated Vasculitis: What Neurologists Need to Know

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Objective: To provide a comprehensive review of the central nervous system (CNS) involvement in anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), including the pathogenesis, clinical manifestations, ancillary investigations, differential diagnosis, and treatment. Particular emphasis is placed on the clinical spectrum and diagnostic testing of AAV.

Recent Findings: AAV is a pauci-immune small-vessel vasculitis characterized by neutrophil-mediated vasculitis and granulomatousis. Hypertrophic pachymeninges is the most frequent CNS presentation. Cerebrovascular events, hypophysitis, posterior reversible encephalopathy syndrome (PRES) or isolated mass lesions may occur as well. Spinal cord is rarely involved. In addition, ear, nose and throat (ENT), kidney and lung involvement often accompany or precede the CNS manifestations. Positive ANCA testing is highly suggestive of the diagnosis, with each ANCA serotype representing different groups of AAV patients. Pathological evidence is the gold standard but not necessary. Once diagnosed, prompt initiation of induction therapy, including steroid and other immunosuppressants, can greatly mitigate the disease progression.

Conclusions and Relevance: Early recognition of AAV as the underlying cause for various CNS disorders is important for neurologists. Ancillary investigations especially the ANCA testing can provide useful information for diagnosis. Future studies are needed to better delineate the clinical spectrum of CNS involvement in AAV and the utility of ANCA serotype to classify those patients.

Evidence Review: We searched Pubmed for relevant case reports, case series, original research and reviews in English published between Sep 1st, 2001 and Sep 1st, 2018. The following search terms were used alone or in various combinations: "ANCA," "proteinase 3/PR3-ANCA," "myeloperoxidase/MPO-ANCA," "ANCA-associated vasculitis," "Wegener's granulomatosis," "microscopic polyangiitis," "Central nervous system," "brain" and "spinal cord". All articles identified were full-text papers.

Keywords: anti-neutrophil cytoplasmic antibodies, vasculitis, granulomatosis with polyangiitis, microscopic polyangiitis, central nervous system

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INTRODUCTION

Central nervous system (CNS) vasculitis, with its myriad and evolving presentations, always poses a great diagnostic challenge for neurologists. It occurs either as part of a systemic vasculitis, or a primary disorder restricted to the CNS (1). Anti-neutrophil cytoplasmic antibody (ANCA) - associated vasculitis (AAV), a systemic small-vessel vasculitis, is characterized by pathogenic ANCA production (1). In the clinical practice, AAV mainly includes granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA) (1). Timely recognition and diagnosis of AAV is important, since the progressive disease can be dramatically mitigated by prompt use with steroid and other immunosuppressive agents.

Neurologic involvement is not uncommon in AAV throughout the disease course, ranging from 22 to 54% in patients with GPA (2–5) and 34 to 72% in those with MPA (2–4). CNS is affected in <15% of patients with AAV (5) but accounts for much of the morbidity in those patients (1–3, 7–10). However, the heterogeneous CNS symptoms in AAV may hinder early diagnosis among neurologists, causing treatment delays and disease progression, leading to relapses, or even death.

Therefore, this review aims to increase the awareness of AAV among neurologists. We mainly focus on GPA and MPA, which have distinctive features compared with EGPA (6–10). This review comprehensively illustrates the pathogenesis, CNS manifestations, ancillary investigations, and treatment algorithms warranted for AAV patients with CNS involvement. In particular, we put a special emphasis on its clinical spectrum and the utility of ACNA testing in diagnosing and subtyping those patients.

PATHOPHYSIOLOGY

A basic understanding of how pathogenic ANCAs are induced, take effect and invade the CNS helps to understand its manifestations and illuminate potential targets for treatment in AAV. Pathogenic ANCAs, targeting mainly at proteinase 3 (PR3) and myeloperoxidase (MPO) expressed by innate immune cells, are the major contributor to the pathogenesis of AAV, according to *in vitro* and *in vivo* experimental data (11). An overview of the pathophysiology is shown in **Figure 1**. Pathogenic ANCAs are induced by the interplay of multiple environmental, genetic, and immunological factors (8, 11, 15). An encounter with the antisense peptides of PR3 or MPO triggers the immunological self-amplication network (11). The antigen-recognition capability of each individual, however, is more likely genetically determined (8). In addition, the generation of pathogenic ANCAs is further facilitated by an impaired immunological regulation, as in the pathogenesis of the few treatable neurological disorders (16–19). The function of regulatory T (T_{REG}) cells and regulatory B cells with CD5 expression are suppressed, whereas the circulating effector memory T cells (T_{EM}) (20) and ANCA-producing B cells (15) are proliferated and activated.

Following the generation of pathogenic ANCAs, different pathways lead to the two major pathological changes in AAV, namely vasculitis, and granulomatosis. Neutrophils, activated by pathogenic ANCAs and fueled by the alternative complement pathway (13), play the central role. Activated neutrophils can transmigrate the vessel wall and undergo respiratory burst, degranulation, neutrophil extracellular traps (NETs), apoptosis and necrosis (14), causing disruptions of the endothelium and thus activation of the coagulation cascade, leading to fibroid necrosis at sites of vasculitic inflammation. This neutrophil-activation process is further augmented by the complement system, especially the alternative pathway, with C5a playing a key role in-between (13). By contrast, the pathogenesis of extravascular granulomatosis is less well-understood. Current thinking holds that the chronic inflammation is initiated by the acute neutrophil-mediated necrosis (21). Subsequently, defects in the cell death machinery and aberrant reaction of monocytes and macrophages contribute to the chronic inflammation and granulomatosis formation in AAV.

CNS can be affected in AAV through one of the following pathways (22, 23): (1) inflammation, obstruction or increased permeability of the small to medium-sized cerebral vessels due to systemic vasculitis; (2) infiltration or compression of granulomatous pathology from adjacent structures; (3) granulomatous lesions developing *de novo* within the CNS. Mechanisms vary according to the specific CNS structures involved. In general, extra-axial lesions involving the dura, or pituitary gland are mainly attributed to granulomatous inflammation, while parenchyma pathologies are mediated by vasculitis and breakdown of blood brain barrier (24). However, it remains unclear whether pathogenic ANCAs are produced intrathecally or from the systemic circulation and how the two ANCA serotypes contribute to different CNS manifestations.

THE MANY FACES OF AAV WITH CNS INVOLVEMENT

Epidemiology

AAV, especially GPA and MPA, is a multisystem disease. Up to 40–50% of patients have a remitting-relapsing course (7, 12). The onset of CNS flare is mostly acute or subacute, depending on the specific neurological syndrome. CNS symptoms usually present late in the disease course (5, 25). No gender predilection is observed and most patients tend to have their first CNS flare in the middle age (5, 25, 26).

Overview of Systemic AAV

It is of great help to know the accompanying systemic symptoms at the time of or prior to CNS flare. A long-term history of constitutional symptoms like fever, weight loss, fatigue and arthralgia are often suggestive of an autoimmune etiology. In addition, organs susceptible to AAV damage include ear, nose and throat (ENT), lung and kidney (6). ENT involvement for over 3 months, presenting as chronic sinusitis, otitis media, or mastoiditis, is diagnostic of AAV, (3, 7, 24). History of renal dysfunction (proteinuria, hematuria

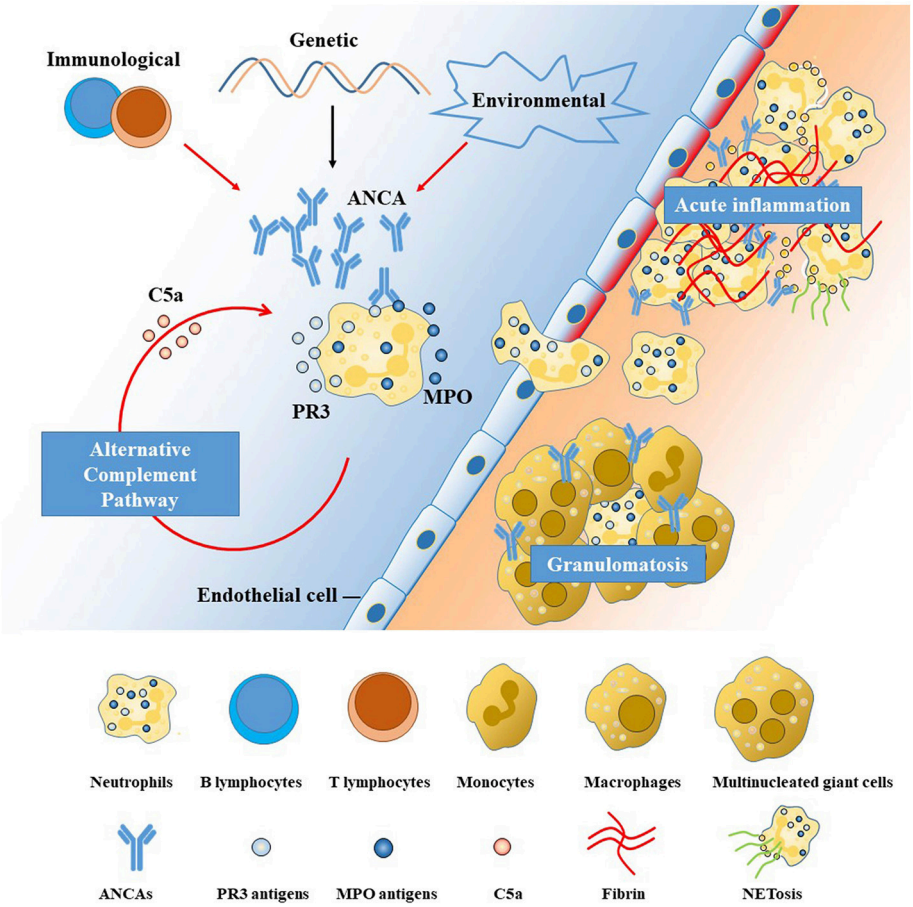

FIGURE 1 | Pathogenesis of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV). The left side of the diagram (with blue background) represents the blood stream and the right (with orange background) the interstitial tissue, separated by a line of endothelial cells. ANCAs are autoantibodies directed against proteins in the cytoplasmic granules of neutrophils. The two antigenic targets are proteinase 3 (PR3) and myeloperoxidase (MPO) normally expressed on the surface or inside the cytoplasm of resting neutrophils (11, 12). The interplay among genetic, environmental, and immunological factors contributes to the high membrane expression and release of PR3 and MPO, leading to the production and proliferation of pathogenic ANCAs. Primed neutrophils are activated by ANCAs and transmigrate the vessel wall, undergoing respiratory bursts, degranulation, and neutrophil extracellular traps (NETs) generation (11), which are further augmented by the alternative complement pathway (13). The neutrophil-mediated processes are the major contributor to the injury and inflammation of the endothelial cells lining the vascular wall in the early phase (14). Monocytes are subsequently recruited at sites of acute inflammation and necrosis, inducing the development of granulomatous inflammation mainly mediated by an exaggerated monocyte/macrophage reaction (11). Potential treatment targets are illustrated by red arrows in the figure, including the T-cell and B-cell dysregulation, environmental triggers (microbes, drugs), aberrant activation of alternative complement pathway and NETs. ANCA, anti-neutrophil cytoplasmic antibody; MPO, myeloperoxidase; PR3, proteinase 3; NET, neutrophil extracellular trap.

and acute kidney failure) and pulmonary problems (pulmonary nodules, infiltration, alveolar hemorrhage, chronic cough, asthma, or rarely respiratory failure) were also frequently reported. Therefore, for patients suspected with AAV, an investigation of systemic symptoms is warranted. Manifestations highly suggestive of AAV are listed in **Table 1**.

Clinical and Imaging Spectrum of CNS Involvement in AAV

CNS presentations in AAV patients vary, including headache, ischemic infarction, intracranial hemorrhage, encephalopathy (seizures, neuropsychiatric disorders, confusion, or altered consciousness), and rarely spinal cord symptoms. Those symptoms are caused by the involvement of corresponding CNS structures including the dura mater, brain parenchyma, pituitary gland, spinal cord, and leptomeninges with decreasing frequency.

Brain Parenchyma Involvement

(a) Cerebrovascular events

Ischemic infarctions and intracranial hemorrhages, though rare, can be the initial presentation of AAV and are always associated with significant morbidity (29–31). Timely recognition of AAV as the underlying cause is difficult at the first visit in the emergency room due to its rarity. Therefore, the distinguishing features of AAV-related strokes can aid in early diagnosis and improve

TABLE 1 | Systemic manifestations of AAV other than CNS[#].

Involved organ	Manifestations
Constitutional symptoms	Fever, weight loss, polyarthralgia, polymyalgia, malaise, polyarthritis
Ear nose and throat (ENT)	Chronic sinusitis*, chronic otitis media*, chronic mastoiditis*, bloody nasal discharge/crusts/ulcers/granuloma*, subglottic stenosis*
Trachea and lung	Hemoptysis (due to pulmonary hemorrhage* or tracheobronchial disease), lung nodules*, cough, dyspnea, pleuritic pain
Kidney	Glomerulonephritis (especially rapidly progressive glomerulonephritis)*
Skin	Leukocytoclastic angiitis* (typically palpable purpura involving the lower extremities with focal necrosis and ulceration)
Eye and orbit	Epislceritis/scleritis*, uveitis, conjunctivitis, corneal ulceration, retinal vasculitis, optic neuropathy, retro-orbital mass or inflammation*
Peripheral nervous system	Mononeuritis multiplex*, cranial neuropathies*
Gastrointestional tract	Diarrhea, nausea, vomiting, abdominal pain, gastrointestinal hemorrhage; Elevated liver enzymes
Cardiovascular	Ischemic cardiac pain, cardiomyopathy, congestive heart failure, loss of pulses, valvular heart disease, pericarditis

[#]*The table is adapted from previous reviews on related topics (6, 12, 27).*
**Clinical features highly suggestive of AAV (6, 28).*
AAV, anti-neutrophil cytoplasmic antibody-associated vasculitis; CNS, central nervous system.

prognosis. Ischemic infarctions typically present as an isolated or multiple lesions affecting the white matter, since distal penetrating vessels are predominantly affected. Medullary and pontine infarctions were also reported in some cases (29, 30). Ischemic infarctions caused by AAV are typically resistant to antiplatelet therapy and tend to recur without proper immunosuppressive therapy. Patients with AAV are also at an increased risk of hemorrhagic transformation after reperfusion therapy of ischemic stroke (32). Hemorrhagic events occur less often. They more often affect the brain parenchyma (31), and sometimes the subarachnoid space (33). Brain Imaging findings usually correspond to the specific disease in each patient, involving ischemic, hemorrhagic lesions, or variable degrees of small-vessel diseases affecting both white and gray matter (34). Nonspecific white matter lesions with T2 hyperintensities can appear in the periventricular, subcortical regions, the basal ganglia, the mesencephalon and pons.

(b) Posterior reversible encephalopathy syndrome
Posterior reversible encephalopathy syndrome (PRES) is a rare yet unique complication in the late phase of AAV (35, 36). Clinically, this entity typically presents with an acute onset. Symptoms are generalized and include encephalopathy, seizures, headache and visual disturbance. Brain imaging typically reveals findings consistent with vasogenic edema, predominantly involving the bilateral parieto-occipital regions. Most patients with PRES have a dramatic improvement within days to weeks, with only the supportive therapy. Symptoms may recur when the underlying AAV is not well-controlled.

(c) Isolated parenchymal mass lesions
Isolated parenchymal mass lesions were very rarely reported in AAV (37–39), which often present with a discrete granuloma. Symptoms vary depending on the location of lesions, with seizures as the most frequent presentation (38). Brain magnetic resonance imaging (MRI) of isolated parenchymal granulomas reveals a well-delineated mass with a high signal intensity on T2-weighted images and enhancement on gadolinium-enhanced sequences (39).

(d) Cognitive impairment
Cognitive decline, though mostly subclinical and mild, can occur in AAV patients as well, with an estimated prevalence of 30% (40). According to one study of 13 AAV patients (40), the pattern of cognitive impairment, mainly affecting abstract reasoning, attention and non-verbal memory, is different from that of age-related dementia. On brain MRI, multiple white matter lesions, mainly located in the periventricular or juxtacortical areas, are often associated with the cognitive impairment (40).

Brain Meninges Involvement

Pachymeninges is affected more frequently than leptomeninges (41). The frequency of hypertrophic pachymeningitis (HP) in adult AAV ranges from 18 to 35%, depending on the methodology of studies and the sample populations selected (41, 42). Manifestations of AAV-related pachymeningitis vary depending on the location and extent of inflammation. Headache, the dominant symptom of HP, is often severe and resistant to analgesics (22). Besides, neck stiffness is not commonly seen along with headache. Cranial nerves may be compressed by the thickened dura mater and cause symptoms such as visual loss, double vision, and facial palsies. Other times the pachymeningeal inflammation may infiltrate the brain parenchyma and cause impaired consciousness and seizures (24, 42). Notably, an entity named "CNS-limited AAV" was recently proposed by Yoloseki et al. for patients with MPO-ANCA-positive hypertrophic pachymeningitis, characterized by an elderly female predominance, less severe neurological damages, and lower rates of developing into the generalized disease (24). Yet it remains unclear whether the "CNS-limited AAV" represents a novel AAV phenotype or merely a transient disease stage (24).

Imaging studies are valuable in identifying hypertrophic thickening of the dura mater, monitoring disease activity and assessing the damage of adjacent structures. On brain MRI and computed tomography (CT) scans, HP typically shows linear thickening of dura mater or a bulging mass with

enhancement. Gadolinium-enhanced T1-weighted MR imaging offers certain advantages over other sequences in identifying active inflammation of the thickened dura mater with superior spatial resolution. The brain pachymeningitis can involve the tentorium cerebelli, cranial fossa, cavernous sinus, falx cerebri, or convexity with no site preference. Additionally, brain-imaging studies can help assess the potential sinonasal and orbital involvement, a common occurrence in AAV. Additionally, the damage of adjacent bone structures is prominent on brain CT scans (41, 43).

Pituitary Gland and Stalk Involvement

Inflammation of the pituitary, termed hypophysitis, is rarely seen in AAV, yet requiring special consideration (44–46). Constitutional symptoms including fatigue, lethargy, headache, weight loss, and appetite loss frequently occur. Endocrine disturbances most commonly include diabetes insipidus, and hypogonadism (45). Other less common ones include hypothyroidism, adrenocorticotropic hormone (ACTH) deficiency and growth hormone (GH) deficiency (45, 47). Pituitary stalk compression resulting from pituitary enlargement may cause hyperprolectinemia as well (22). Visual deficits result with optic chiasm compression (45). Outcome of hypopituitarism is less favorable, despite the treatment with immunosuppressive agents. Pituitary dysfunction tends to persist, even though other systemic symptoms can come to remission after standard treatment (45, 46).

Brain MRI typically shows an enlarged pituitary gland or thickened stalk with peripheral enhancement on post-contrast sequences. Other findings include the lack of posterior pituitary hyperintensity on T1 images. Normal MRI, as reported in some cases, does not exclude pituitary involvement (47).

Spinal Cord Involvement

In general, spinal cord is rarely involved in AAV (48). The three possible mechanisms underlying spinal cord involvement include necrotizing inflammation of the spinal vasculature, compression of the spinal cord by inflamed thickened meninges as well as the formation of primary spinal granulomas (48). Clinical syndromes of the spinal cord include hypertrophic pachymeningitis (41, 48) and compressive myelopathy (49). Contrast-enhanced MRI of the spinal cord is of great diagnostic value and biopsy is often warranted to confirm the diagnosis.

Non-CNS Entities Highly Associated With CNS Involvement

(a) Cranial neuropathy

Cranial neuropathies are rarely the only manifestation in AAV, but rather coexist with other CNS symptoms such as headache and systemic symptoms. Previous investigations found a prevalence between 2 and 10% of cranial neuropathies in patients diagnosed with GPA (50) and MPA (51, 52). Commonly affected cranial nerves in AAV include cranial nerve II–VIII (50). Bulbar palsy, by contrast, is less commonly involved (53).

(b) Orbital disease

Eye involvement was reported in around 30–50% of patients diagnosed with GPA (54), with the orbit and sclera most frequently involved. MPA, by contrast, rarely impair eye movement (52). Symptoms vary and typically include proptosis, diplopia, decreased vision and orbital pain (55), resulting from compressions of ocular granuloma, granulomatous inflammation of the optic nerve and ischemic optic neuropathy due to vascular occlusion (56). MR imaging and CT can help reveal mucosal and bony lesions in the orbit and rule out continuous extension.

(c) Parasinal disease

For patients with CNS manifestations suspected of AAV, an evaluation of paranasal sinuses is a must. Findings indicative of granulomatosis in the paranasal sinuses include a soft-tissue mass, thickening of the sinus wall, or "ground-glass" material in the lumen (34). As in orbital involvement, non-contrast CT scan has its diagnostic value in evaluating the nasal cavity, paranasal sinuses, mastoids and temporal bone, due to a better resolution of mucosal and bony pathologies compared with MRI (43). Brain MRI may also aid in the evaluation of soft tissue masses within those cavities.

Differences Between ANCA Serotypes

There is an increasing consensus that the ANCA serotype, either MPO-ANCA or PR3-ANCA, has a crucial role in AAV (12). Distinctively, previous studies revealed that the ANCA serotype represents two separate groups of patients in epidemiology, genetic background, clinical features, laboratory features as well as prognosis. We summarized the differences between MPO- and PR3-ANCA positive AAV in **Table 2**. Specifically, for AAV patients with CNS involvement, the ANCA serotype matters as well (24). Though the two serotypes tended to affect the nervous system with a similar frequency (57), they differ in the pattern and severity of CNS involvement. According to one study of patients with HP in Japan, MPO-ANCA-positive HP had an elderly female predominance, more frequently had lesions limited to the dura mater and upper airways, and was less likely to have a generalized systemic progression. On the contrary, PR3-ANCA-positive HP tended to have more severe neurological damages and a generalized disease progression (24). However, evidence remains limited to patients with HP. Extrapolation of the utility of ANCA serotype in other CNS manifestations remains to be further studied.

DIAGNOSIS

The diagnosis of CNS involvement in AAV, similar to the disease overall, requires consideration of clinical, serological, radiographic, and, when available, pathological evidence (61). In patients with established AAV, new-onset neurologic deficits with abnormal radiological and cerebrospinal fluid (CSF) findings are suggestive of CNS involvement. For patients without established underlying disease, neurologic symptoms closely compatible with CNS syndromes known to arise in AAV warrant further investigations for the systemic disease. In either case, ancillary tests are of important value in making the

TABLE 2 | Comparison of PR3- and MPO-ANCA-positive AAV.

Features	PR3-ANCA-positive AAV	MPO-ANCA-positive AAV
Pathophysiology (12, 57)	Apoptosis of endothelial cells; Release of sFlt1 by monocytes; No established mouse model	Production of intracellular oxidants; No induction of release of sFlt1 by monocytes; Pathogenicity of autoantibody proved in mouse models
Epidemiology (12, 57)	Northern Europe, America and Australia	Southern Europe and Asia
Genetic background (8, 12, 57)	HLA-DP, SERPINA1, PRTN3	HLA-DQ, CTLA4
Clinical features (12, 57–59)	More ENT involvement; Cavititating pulmonary lesions, nodules and masses; More organs involved	More often renal-limited; Fibrosing pulmonary lesions and patchy infiltrates
Pathological features (12)	Granuloma and vasculitis	Granuloma and fibrosis
Response to induction therapy (12, 60)	Better response to rituximab than cyclophosphamide	Increased risk of initial treatment failure
Long-term outcome (12)	More relapses Better prognosis	Less relapses Higher risk of long-term kidney and alveolar damage Worse prognosis

PR3, proteinase 3; MPO, myeloperoxidase; ANCA, anti-neutrophil cytoplasmic antibodies; AAV, anti-neutrophil cytoplasmic antibody-associated vasculitis; HLA, human leukocyte antigen; ENT, ear, nose and throat.

Box 1 | Investigations in AAV-related CNS involvement.

ANCA immunoassays (MPO- and PR3- ANCA testing)
CBC, CMP, CRP, ESR (to evaluate the organ functions and the state of inflammation)
Autoimmune panel, complement levels (to differentiate from other inflammatory conditions)
Endocrine panel (to evaluate the pituitary function)
Screening for HIV, hepatitis, and tuberculosis
Analysis of cerebrospinal fluid (measure inflammatory mediators and degradation proteins, assess the blood-brain barrier and exclude infection)
Chest CT
Brain imaging (CT; MRI, suggested sequences include T1/T2 weighted-imaging, FLAIR, DWI, SWI and contrast enhanced T1 sequences)
Biopsy

AAV, anti-neutrophil cytoplasmic antibody-associated vasculitis; ANCA, anti-neutrophil cytoplasmic antibodies; MPO, myeloperoxidase; PR3, proteinase 3; CBC, complete blood count; CMP, comprehensive metabolic panel; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; HIV, human immunodeficiency virus; CT, computed tomography; MRI, magnetic resonance imaging; FLAIR, fluid-attenuating inversion recovery; DWI, diffusion-weighted imaging; SWI, susceptibility-weighted imaging.

diagnosis and excluding other causes of the CNS abnormalities (**Box 1**). This section describes workup that can aid in the diagnosis of AAV with CNS involvement, and with special interest, pays extra attention to the value of ANCA testing in-between.

ANCA Serology

ANCA testing is strongly recommended for patients with clinical features suggestive of AAV (**Table 1**) (6, 62). Its value lies mainly in AAV screening, and when positive, warrants further investigations for confirmative diagnosis. Positivity of the test is highly suggestive of AAV but not diagnostic by itself (6). However, the combination of ANCA positivity and certain clinical features are sufficient for AAV diagnosis, according to the widely-used classification algorithm proposed by Watts (28). A negative ANCA immunoassay, which occurs in up to half of pathologically diagnosed GPA and MPA, does not exclude AAV (6, 63). The negativity may be related to the limited sensitivity of ANCA testing, especially at the early stage of disease without systemic involvement (7). The diagnosis of AAV cannot be excluded merely based on a negative ANCA test. Therefore, biopsy of the affected organ is required for seronegative patients (6).

Regarding the testing techniques of ANCA, the most recent consensus recommended high-quality antigen-specific immunoassays for MPO- and PR3- ANCAs detection (6). ELISAs are the preferred screening methodology with a high sensitivity and specificity. Indirect immunofluorescence (IIF) for cytoplasmic ANCA (C-ANCA) and perinuclear ANCA (P-ANCA) detection is no longer prioritized as the screening test, given its large variability and poor diagnostic accuracy (6). When necessary, performing another assay or testing with another different methodology can yield higher sensitivity and specificity (6). In cases of emergency such as pulmonary-renal syndrome, rapid screening assays for ANCAs, including dot blots and biochip technology, are also available (64).

Controversy remains in the role of ANCA levels in monitoring disease activity and prediction of prognosis (63). Published studies reveal inconsistent results regarding the role of ANCA levels in predicting clinical relapse and reflecting disease activity (65–67). A meta-analysis in 2012 concluded that both a rise in ANCA and persistently positive ANCA were strongly associated with disease relapse and had a modest predictive value (66). Furthermore, results from a recent single-center study indicated that the predictive value of ANCA was only significant in renal-involved AAV, compared with those without renal involvement (68). Overall, current thinking holds that ANCA levels alone are helpful but not sufficient to determine relapse or reflect disease activity (6), and ANCA testing is not recommended to guide clinical decisions on treatment (61). Nevertheless, severe relapses are unlikely without elevated ANCA levels (69). The significance of serial monitoring remains to be proven.

Other Laboratory Investigations

A diligent workup should be ordered for patients suspected of AAV, including complete blood count (CBC), complete metabolic profile (CMP), acute phase reactants, the autoimmune panel, the endocrine panel, the complement level and investigations for potential infections. For patients with endocrine dysfunction or abnormal pituitary on MRI, levels of pituitary hormones also need to be investigated. Laboratory tests typically show elevated markers of inflammation. Leukocytosis, thrombocytosis, normochromic normocytic anemia, elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) values are indicative of the diagnosis (3, 7). Kidney functions, including serum creatinine and urinalysis, are warranted for the evaluation of renal injury. Regarding the autoimmune panel, autoantibodies other than ANCAs can be present (63), including antinuclear antibodies, rheumatoid factors, IgG4, anti-glomerular basement membrane antibodies and antiphospholipid antibodies, with unknown significance (63). Lastly, for differential diagnosis, investigations for potential infections (tuberculosis, human immunodeficiency virus, hepatitis) and complement levels are also required.

Box 2 | Conditions other than AAV with positive ANCA immunoassays#.

Vasculitis of other causes
Anti-GBM disease, IgA-vasculitis*
Gastrointestinal diseases
Ulcerative colitis, Primary Sclerosing Cholangitis, Inflammatory liver disease
Systemic inflammatory conditions
IgG4-related disease, Rheumatoid arthritis, Systemic lupus erythematous
Infection
Infective endocarditis, Tuberculosis, HIV, Amoeba infection
Malignancies
Hematological neoplasia
Drugs
Hydralazine, Propylthiouracil, Levamisole, Minocycline, Cocaine.

#The box is based upon previous reviews on related topics (6, 27). Serum ANCAs should be tested according to the algorithm proposed by the 2017 consensus on testing of ANCAs (6).
*IgA-vasculitis can show positive IgA-ANCAs in the active stage of disease, but IgG-ANCAs were rarely reported (27).
AAV, anti-neutrophil cytoplasmic antibody-associated vasculitis; ANCA, anti-neutrophil cytoplasmic antibodies; GBM, glomerular basement membrane; HIV, human immunodeficiency virus.

Cerebrospinal Fluid

Lumbar puncture is warranted for suspected patients as well. CSF analysis has a high sensitivity but low specificity in the diagnosis of AAV-related CNS disease. Most had mild lymphocyte-predominant pleocytosis, elevated protein levels and normal glucose level (7, 25, 37). Therefore, a normal CSF analysis makes the diagnosis of AAV less likely. Infectious etiology and flow cytometry for atypical cancer cells should be tailored to clinical manifestations and risk factors.

Pathology

Histopathology is the gold standard for diagnosis of small vessel vasculitis. Samples can be taken from affected organs, most commonly the kidney and the skin. Lung and nasal biopsies are rarely performed, limited by the high rate of false negatives. Brain biopsies can also be taken from corresponding structures including the dura, brain parenchyma and the overlying leptomeninges. Typically two types of pathological findings have been described: (1) necrotizing vasculitis affecting small to medium vessels; (2) granulomatosis with inflammatory cell infiltration (monocytes, plasma cells, eosinophils, and polymorphonuclear leukocytes) (41). Fibrinoid necrosis and edema were also detected in some cases. In patients of HP, fibrosis of the dura mater was always present as well (24, 41). A negative yield of biopsy, however, does not exclude the diagnosis of AAV due to its segmental nature of lesions.

Differential Diagnosis

AAV must be distinguished from ANCA-positive conditions where ANCA does not exert a direct role in pathophysiology (**Box 2**). Multiple conditions other than AAV show an elevated titer of serum ANCAs. Nonetheless, ANCAs do not mediate a direct pathogenic role, but rather indicate a chronic immune response of neutrophil cell death most times (63). Compared with the mimics, a high level and affinity of ANCAs and clinical features suggestive of AAV are important clues for the correct diagnosis (6).

Differential diagnosis can be further narrowed down to entities with both similar CNS manifestations and ANCA positivity. These mainly include systemic inflammatory diseases (IgG4 related-disease, rheumatoid arthritis, systemic lupus erythematosus, Bechet syndrome), infective diseases (tuberculosis, human immunodeficiency virus) and malignancies (lymphoma).

In particular, diagnosis of AAV can be especially difficult at an early stage with only CNS presentations and a seronegative ANCA test, which may be an under-recognized common occurrence (24). Characteristics and diagnostic criteria of this entity remain to be elucidated. Differential diagnosis is therefore protean, varying according to the specific CNS manifestation of the patient. We suggest a thorough investigation of systemic involvement to exclude alternative causes including infection and malignancy. In particular, A continued monitoring of ANCA testing may be useful for those with idiopathic hypertrophic pachymeningitis (24). Most importantly, biopsy of the lesion is highly recommended in such cases to confirm the diagnosis.

TREATMENT

Treatment should be started in a timely manner for patients highly suspected of AAV, even in the absence of pathological evidence. Steroid is an essential part of therapy, with the addition of a well-chosen immunosuppressant critical to prevent relapses and achieve remission of CNS symptoms in the long run. The treatment algorithm is shown in **Figure 2**. There are two phases of treatment, namely remission-induction and remission-maintenance. The choice of regimen in each phase depends mainly on the disease stage of the

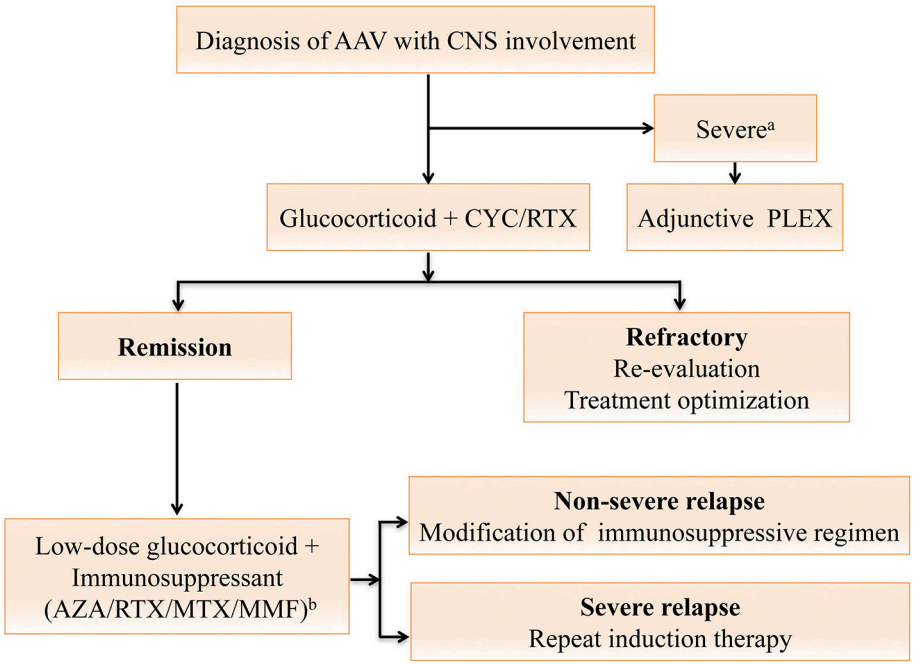

FIGURE 2 | Treatment algorithm for anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) with central nervous system (CNS) involvement. The algorithm is formulated and terms are defined according to the 2016 European league Against Rheumatism (EULAR)/European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) recommendations (61). For AAV with CNS involvement, the remission-induction therapy mainly consists of high-dose steroids and cyclophosphamide (CYC), or rituximab (RTX) for CYC-intolerant patients. Plasma exchange should be considered for those with a serum creatine level of ≥500 μmol/L or diffuse alveolar hemorrhage. Once complete remission is achieved, patients should be switched to the maintenance regimen. A combination of low-dose steroid and an oral immunosuppressive agent including azathioprine (AZA), methotrexate (MTX), mycophenolate mofetil (MMF) or RTX is used for at least 24 months (61). For patients refractory to the remission-induction therapy, referral to experts for reevaluation and treatment optimization is warranted (61). Severe relapses with organ- or life-threatening conditions are treated as per new disease, while non-severe relapses are managed with modification of the previous immunosuppressive regimen (61). [a]AAV with severe renal impairment or diffuse alveolar hemorrhage; [b]Drugs are listed in order of the strength of vote. AAV, anti-neutrophil cytoplasmic antibody-associated vasculitides; ANCA, anti-neutrophil cytoplasmic antibodies; AZA, azathioprine; CNS, central nervous system; CYC, cyclophosphamide; MTX, methotrexate; MMF, mycophenolate mofetil; PLEX, plasma exchange; RTX, rituximab.

patient, as per the European Renal Association—European Dialysis and Transplant Association (ERA-EDTA) management recommendations for AAV (61). Generally, CNS involvement is regarded as an organ-threatening manifestation in AAV, especially for those with meningeal inflammation or retro-orbital disease. Remission-induction treatment for organ-threatening AAV typically consists of high-dose glucocorticoids and oral or intravenous (IV) cyclophosphamide (CYC) (1), termed CYC-based therapy. Glucocorticoids usually start with the dose of 1g intravenous methylprednisolone on 3 consecutive days, followed with 1 mg/kg daily oral corticosteroids (up to 80 mg per day), and a gradual reduction to daily dose of 7.5 to 10 mg within 3–5 months (7, 10). CYC can be given either intravenously in pulses or orally. The intravenous CYC, at a dose of 15 mg/kg (up to 1200 mg), are prescribed every 2 weeks initially and every 3 weeks from the 4th pulse. Daily oral CYC is given at a dose of 2 mg/kg/d. The CYC-based therapy is effective in 70-90% of patients (70), and the oral regimen can better prevent relapses (71). However, the daily oral regimen, compared with intravenous CYC, also poses more safety issues due to the cumulative toxicity (71, 72) including infertility, bladder hemorrhage, severe cytopenias, serious infection, and an increased risk of malignancy. Apart from the most recognized CYC-based therapy, the identification of the important role of B cells in the pathogenesis of AAV facilitated the use of rituximab (RTX) as an alternative to CYC (73). Two large randomized trials revealed RTX (375 mg/m^2, once a week for four infusions) to be equivalent to CYC in terms of efficacy and safety in remission induction for AAV among treatment-naïve patients, and likely superior for relapsing disease (74).

Once complete remission (absence of any disease activity, usually attained after 8–12 weeks of treatment) is achieved, patients should be started with maintenance therapy to prevent further relapses, which should be continued for at least 24 months (61). In the remission maintenance phase, the induction regimen is switched to a combination of low-dose glucocorticoids and an oral immunosuppressive agent such as azathioprine (AZA), methotrexate (MTX), mycophenolate mofetil (MMF), or RTX (61). AZA (2 mg/kg/day) is the most commonly used immunosuppressive agent for remission maintenance, with MTX (20–25 mg/kg/week) as a similar alternative (72). AZA, with a lower relapse rate, is generally preferred over MMF. However, the relapse rate remains as high as 40% by 2 years despite the maintenance therapy with AZA or MTX (75). RTX is a

potentially safer maintenance drug with a higher efficacy (76). However, the utility and toxicity profile of RTX require further confirmation (76–80). In addition, the adjunctive use of plasma exchange (PLEX) (7 sessions over 2 weeks) in AAV patients with severe renal dysfunction and/or alveolar hemorrhage seems reasonable in the short-term, but remains elusive in the long run (81).

Another issue to tackle in AAV is the treatment response. Refractory to remission-induction treatment is defined as follows: (1) unchanged or increased disease activity after 4 weeks of treatment (2) <50% reduction in the disease score [e.g., Birmingham Vasculitis Activity Score (BVAS)] after 6 weeks of treatment (3) Presence of at least one major or three minor items on the disease activity score after over 12 weeks of treatment (61, 82). For AAV patients refractory to therapy, reevaluation and optimization of treatment, in close collaboration with experts, are recommended (61). Adjunctive intravenous immunoglobulin may help for those with persistent low disease activity (61, 83). Furthermore, relapses are not uncommon in AAV. Major relapses with organ- or life-threatening conditions are treated as per new disease, while non-severe relapses should be managed with an escalation or modification of the previous immunosuppressive regimen (61).

CONCLUSION AND FUTURE PERSPECTIVES

For neurologists, prompt diagnosis of AAV in patients with CNS presentations allows timely treatment and thus a dramatic improvement in prognosis. A myriad of CNS presentations including hypertrophic pachymeningitis, ischemic stroke, intracranial hemorrhage and pituitary dysfunction, combined with certain systemic symptoms, raise the suspicion of AAV. Further ancillary tests are required, among which ANCA testing yields a great diagnostic value. ANCA positivity strongly suggests the diagnosis of AAV but ANCA negativity does not rule out the diagnosis. Once diagnosed, early treatment with steroid and immunosuppressant is essential to prevent neurological relapses and sequelae.

Recent evidence suggests the presence of "CNS-limited AAV" as a distinct subset in AAV. Efforts to better elucidate its phenotypic features, optimal treatment and long-term outcome are an important focus of future research. Furthermore, accumulating studies suggest that PR3-ANCAs and MPO-ANCAs define distinctive conditions among patients with AAV. Whether the same rule applies to the neurological conditions in CNS-involved AAV, however, remains unknown. Continued attempts are needed to validate the utility of ANCA specificity in classifying CNS manifestations, guiding treatment decisions, and predicting prognosis.

AUTHOR CONTRIBUTIONS

YZ: contributed to data collection, conception of the work and drafting the manuscript. YxZ: conception of the work and revising the manuscript. MC: revising the manuscript and figures. NL: revising the manuscript and tables. ZC and MD: revising the manuscript and final approval of the version to be published.

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The Different Clinical Features Between Autoimmune and Infectious Status Epilepticus

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Objective: The prognosis of status epilepticus (SE) is highly related to the underlying etiology. Inflammation of the central nervous system (CNS), including infection and autoimmune encephalitis, is one of the treatable conditions causing SE. The initial presentation of infectious and autoimmune CNS disorders can be quite similar, which may be difficult to differentiate at the beginning. However, treatment for these entities can be quite different. In this study, we aim to identify the differences in clinical features among patients with infectious and autoimmune SE, which could help the clinicians to select initial investigation and ensuing therapies that may improve overall outcomes.

Methods: This was a retrospective study that included 501 patients with SE within a period of 10.5-years. Patients with inflammatory etiology were collected and separated into infectious and autoimmune SE. The symptoms at onset, SE semiology, status epilepticus severity score, and END-IT score at admission, treatment for SE, and outcome (modified Rankin Scale) on discharge and last follow-up were recorded. Data on the first cerebrospinal fluid, electroencephalography, and magnetic resonance imaging were also collected.

Results: Forty-six (9.2%) of the 501 patients had SE with inflammatory etiology. Twenty-five (5%) patients were autoimmune SE and 21 (4.2%) were infectious SE. Patients with autoimmune SE have younger age and female predominance. As for clinical presentations, psychosis, non-convulsive SE, and super refractory SE were more common in patients with autoimmune SE. Nevertheless, the prognosis showed no difference between the two groups.

Conclusion: The different initial clinical presentations and patient characteristics may provide some clues about the underlying etiology of SE. When inflammatory etiology is suspected in patients with SE, younger age, female sex, psychosis, non-convulsive SE, and super refractory SE are clinical features that suggest an autoimmune etiology.

Keywords: status epilepticus, inflammatory, autoimmune, infection, autoantibody

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INTRODUCTION

Status epilepticus (SE) is a neurological emergency associated with significant morbidity and mortality that usually requires admission to an intensive care unit (1–3). The goal when treating SE is to terminate the clinical and electrographic seizure activities as soon as possible (4). Even though antiepileptic drugs (AEDs) can be used to control seizures (5), the prognosis of SE is highly related to age and the underlying etiology (6–8). To further improve outcomes, targeted management of the underlying causes may be required (4, 9).

Brain inflammation can also cause SE (10, 11), including central nervous system (CNS) infections and autoimmune encephalitis (12). These conditions can be treated and may result in significantly different outcomes (13–15). Altered mental status is the most common initial presentation of inflammatory SE (12). However, it is an ambiguous sign that provides little information on the underlying etiology. Currently available investigations could help in initial differential diagnosis but have some limitations. Laboratory tests such as bacterial or viral culture, polymerase chain reaction (PCR) for specific pathogens, or autoantibody testing may not be immediately available (13, 16) and the results may take a few days or weeks to return. Cerebrospinal fluid (CSF) studies are useful to confirm the diagnose of bacterial infections, but are less effective in distinguishing between viral infections and autoimmune processes (13, 17). Magnetic resonance imaging (MRI) can provide evidence of CNS inflammation, but not the underlying cause of the inflammation (18). Electroencephalography (EEG) may sometimes show patterns that suggest a specific diagnosis, such as extreme delta brush in patients with anti-N-methyl-D-aspartate (NMDA) receptor encephalitis, but the findings are mostly non-specific (19).

Only two studies have specifically addressed the differences between infectious and autoimmune etiology. Spatola et al. were the first to report that patients with an infectious etiology were older in age and had a more severe clinical presentation at first encounter (20). Subsequently, Shin et al. found that patients with an autoimmune etiology were younger (11). Herein, we retrospectively reviewed our patients with SE and an inflammatory etiology over a 10.5-year period. We aimed to identify the presenting factors that may assist clinicians in differentiating the two entities earlier, which may lead to faster targeted treatment and better patient outcomes.

MATERIALS AND METHODS

Study Design

We retrospectively reviewed the medical records of all patients with SE admitted to the Neurological Intensive Care Unit at Kaohsiung Chang Gung Memorial Hospital between January 2006 and July 2016. This study was approved by the Chang Gung Medical Foundation Institutional Review Board.

Definitions and Criteria

SE was defined as 5 min or more of continuous clinical and/or electrographic seizure activity or recurrent seizure activity without recovery (returning to baseline) between seizures (21). Refractory SE was defined as SE not responded to first-line therapy (benzodiazepine) or second-line therapy and requiring general anesthesia (22). Super refractory SE was defined as SE continues 24 h or more after the onset of anesthesia, including those cases in which the SE recurs on the reduction or withdrawal of anesthesia (22). The semiology and etiology of SE were classified according to the International League Against Epilepsy Task Force report (23).

Inflammatory SE was defined as SE due to acute inflammation of the brain parenchyma, with or without the involvement of the meninges (12), and further divided into SE due to CNS infection and autoimmune SE. Autoimmune SE included autoimmune encephalitis and systemic autoimmune disorders causing SE (23). Patients with an identified etiology for SE such as cerebrovascular disease, intracranial tumor, head trauma, metabolic disturbance, alcohol-related, AED withdrawal, neurodegenerative disease, mitochondrial disease, and medically refractory epilepsy were excluded. Patients with an unknown etiology and those without CSF data were also excluded from this study.

Autoimmune SE was defined as suggested by previous experts' consensus (16):

1. Subacute onset (rapid progression of fewer than 3 months) of working memory deficits (short-term memory loss), altered mental status, or psychiatric symptoms.
2. At least one of the followings:
   - New focal CNS findings
   - Seizures not explained by a previously known seizure disorder
   - CSF pleocytosis (white blood cell count of more than five cells per mm3)
   - MRI features suggestive of encephalitis
3. Reasonable exclusion of alternative causes

SE patients who had positive neuronal surface auto-antibodies testing (EUROIMMUN, Autoimmune Encephalitis Mosaic 6 assay, Germany) in serum or CSF were also considered as autoimmune SE.

Infectious SE was diagnosed if microbiologic studies demonstrated an infectious agent. Those without evidence of microbiologic studies would have to fulfill one of the underlying criteria (20): (1) fever>38.5°C, (2) increased white blood cell count or C-reactive protein, (3) findings highly suggestive of a bacterial infection, such as turbid CSF, neutrophilic pleocytosis, or low CSF to serum glucose ratio (<0.5), or (4) clinical picture suggestive of a viral origin plus lymphocytic pleocytosis on CSF study with positive PCR result or serology test shows a 4-fold increase of viral antibodies 3 weeks after the onset of illness (24).

Clinical information was recorded using a standardized evaluation form, including the symptoms at onset, SE semiology and classification, status epilepticus severity score (STESS) (25) and the END-IT score (26) at admission, treatment for SE, and outcome at discharge and last follow-up. A STESS score ≥3 (25) or an END-IT score ≥3 (26) suggested a poor outcome. Data on the first acquired CSF, EEG, and MRI studies were collected. The EEG was described according to

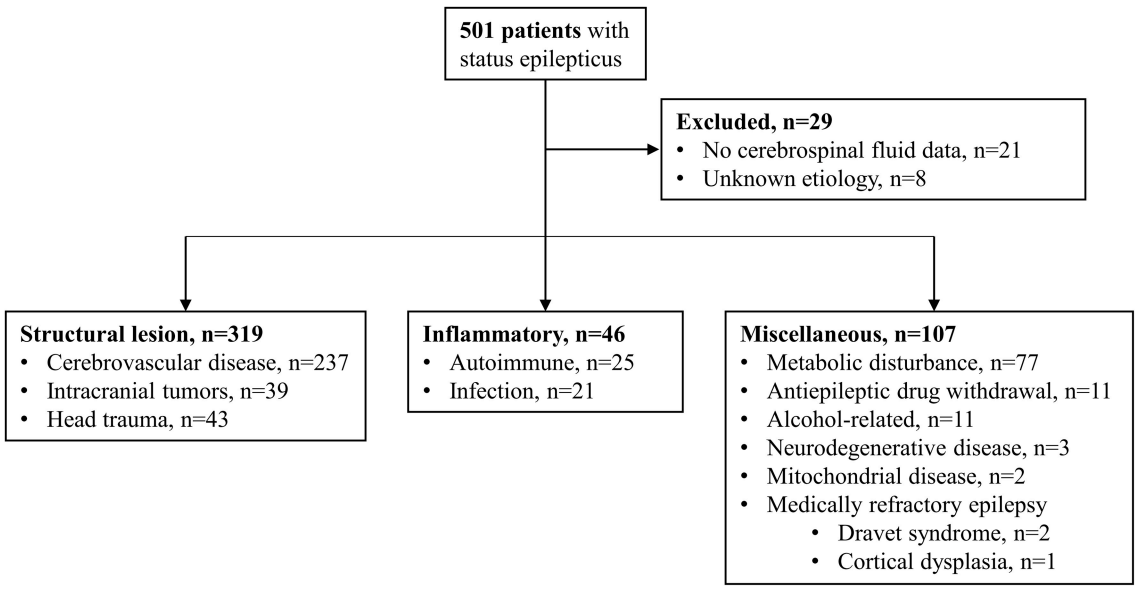

FIGURE 1 | Study population and etiologies of status epilepticus.

the 2012 American Clinical Neurophysiology Society's (ACNS) Standardized Critical Care EEG Terminology (27), which we categorized into background slowing activity, sporadic epileptiform discharge, periodic discharge, and electrographic seizures (11). MRI findings including the location and symmetry of signal changes on fluid-attenuated inversion recovery (FLAIR) and diffusion-weighted imaging (DWI) were recorded (10). Clinical outcomes at discharge and the last follow-up were graded using the modified Rankin Scale (mRS). A good outcome was defined as an mRS score <3 and a poor outcome was defined as an mRS score ≧3.

Statistical Analysis

Statistical analyses were performed using the IBM SPSS Statistics for Windows (version 22; IBM Corp., Armonk, NY, United States). To compare demographic data between infectious and autoimmune groups, categorical variables were assessed using Chi-square or Fisher exact tests, and continuous variables were compared using the Mann-Whitney *U*-test. $p < 0.05$ was considered as statistically significant.

RESULTS

During the 10.5-year study period (January 2006–June 2016), 501 patients with SE were reviewed, of whom 46 (9.2%) had an inflammatory etiology, including 25 females (54.3%) and 21 males (45.7%). Of the excluded patients, 237 had cerebrovascular disease, 77 had metabolic disturbances, 43 had head trauma, 39 had intracranial tumors, 11 had AED withdrawal, 11 had alcohol-related SE, three had neurodegenerative diseases, two had mitochondrial diseases, and three had medically refractory epilepsy. Of the three patients with medically refractory epilepsy, two had Dravet syndrome and one had focal cortical dysplasia. Patients without CSF data ($n = 21$) and those with an unknown etiology ($n = 8$) were also excluded (**Figure 1**).

The clinical characteristics of the 46 patients with inflammatory SE are presented in **Table 1**. Among the 46 patients, 25 (54.3%) had autoimmune SE, and 21 (45.7%) had infectious SE. In the patients with autoimmune SE, five were related to anti-NMDA receptor encephalitis, four were related to Hashimoto encephalopathy, one was related to CNS lupus, one was related to anti-collapsin response mediator protein 5 encephalitis, and 14 were diagnosed according to the criteria of autoimmune encephalitis (16). Of these 14 patients, five had received cell-based anti-neuronal antibody assays with negative results. The remaining nine patients did not receive anti-neuronal auto-antibody tests as the test was not available at the time of diagnosis. With regards to the patients with infectious SE, six had bacterial infections, 12 had viral infections, two had cryptococcal meningitis, and one had Creutzfeldt-Jakob disease.

The clinical features of infectious and autoimmune SE are compared in **Table 2**. The median age at onset of the patients with autoimmune SE was younger than that of the patients with infectious SE (32 vs. 56, $p = 0.015$), and more of the patients with autoimmune SE were female compared to those with infectious SE (68.0 vs. 38.1%, $p = 0.043$). The initial presentation of both groups was similar, including the STESS and END-IT score at admission, onset symptoms, and latency of seizures after the initial symptoms. Psychosis was the presenting symptom only in the autoimmune SE group (24.0 vs. 0.0%, $p = 0.025$) and non-convulsive SE was more prevalent among the patients with autoimmune SE compared to those with infectious SE (32.0 vs. 4.8%, $p = 0.027$). Refractory SE occurred more commonly in the autoimmune SE than in the infectious SE group, but the difference was not statistically significant (88.0 vs. 66.7%, $p = 0.081$). Super refractory SE was more common in the

autoimmune SE group than in the infectious SE group (41.3 vs. 19.0%, $p = 0.007$). The number of AEDs used was similar between both groups, but the use of general anesthesia was more common in the autoimmune SE group than in the infectious SE group (64.0 vs. 23.8%, $p = 0.006$). However, the duration of admission or ICU stay, mRS score at discharge, and mortality rate during admission were similar between the two groups. The sensitivity and specificity for STESS to predict the outcome at discharge were 70.6 and 44.8%, respectively, compared to 68.8 and 45.5% at last follow-up. The sensitivity and specificity for the END-IT score to predict the outcome at discharge were 9.4 and 100.0%, respectively, compared to 21.4 and 100.0% at last follow-up.

The results of CSF and EEG are presented in **Table 3** and the MRI findings are summarized in **Table 4**. Patients with infectious SE had a higher median CSF protein level (93.0 mg/dL vs. 34.8 mg/dL, $p = 0.014$), higher median white blood cell count (20 vs. 3 cell/mm^3, $p = 0.011$), higher percentage of neutrophilic predominance (52.9 vs. 15.4%, $p = 0.034$), and higher percentage of low CSF/blood glucose ratio (56.3 vs. 24.0%, $p = 0.036$) compared to the patients with autoimmune SE, who had a higher percentage of lymphocytic predominance (84.6 vs. 47.1%, $p = 0.034$). There was no significant difference in IgG index between the two groups. The autoimmune SE group tended to have a higher rate of background slowing activity in the first EEG, but the difference between autoimmune and infection was not statistically different (56.0 vs. 28.6%, $p = 0.081$). The presence of sporadic epileptiform discharge, periodic discharge, or electrographic seizure was similar among the two groups in the first EEG study. With regards to the first MRI findings, an abnormal FLAIR signal was observed in 11 patients with autoimmune SE and eight patients with infectious SE. A restricted diffusion signal on DWI was found in 14 patients with autoimmune SE and 10 patients with infectious SE. However, there were no significant differences in abnormalities in the FLAIR and DWI signals between the two groups. Detailed descriptions of the locations of the abnormal signals on FLAIR and DWI are presented in **Table 4**.

TABLE 1 | Demographic data of inflammatory SE patients.

	Patients ($n = 46$)
Onset age (years)	45 (28–60)
Female	25 (54.3)
Onset symptom	
Fever	24 (52.2)
Decreased consciousness	17 (37.0)
Seizure	10 (21.7)
Upper respiratory tract infection	8 (17.4)
Headache	6 (13.0)
Psychosis	6 (13.0)
Fatigue	3 (6.5)
Cognitive decline	1 (2.2)
Latency of seizure after onset symptoms (days)	3 (0–7)
STESS ≥3 at admission	18 (39.1)
END-IT score ≥3 at admission	**43 (93.5)**
SE with prominent motor symptoms	37 (80.4)
Generalized convulsive SE	25 (54.3)
Epilepsia partialis continua	6 (13.0)
Focal onset evolving into bilateral convulsive SE	4 (8.7)
Myoclonic SE with coma	1 (2.2)
Hyperkinetic SE	1 (2.2)
Non-convulsive SE	9 (19.6)
Non-convulsive SE with coma	6 (13.0)
Myoclonic absence status	1 (2.2)
Non-convulsive SE without impairment of consciousness	1 (2.2)
Aphasic status	1 (2.2)
Number of AEDs used	**3 (2-3)**
Refractory SE	**36 (78.3)**
Super refractory SE	**19 (41.3)**
Required general anesthesia for SE control	21 (45.7)
Death during admission	13 (28.3)
Days of admission	39 (26-79)
Days in ICU	33.5 (11-60)
More than two AEDs at discharge	17 (36.9)
Good outcome at discharge (mRS<3)	17 (36.9)
Good outcome at last follow up (mRS<3)	16 (34.8)

Continuous variables were presented as median (interquartile range)
Categorical variables were presented as n (%).
AED, antiepileptic drug; ICU, intensive care unit; mRS, modified Rankin Scale; SE, status epilepticus; STESS, status epilepticus severity score.

DISCUSSION

Inflammatory SE is a previously under-recognized subgroup of SE. In the current study, 9.2% of all cases of SE were related to an inflammatory etiology, which is in accordance with previous studies (range from 6 to 12.8%) (11, 20). Inflammatory SE has two main etiologies, infectious, and autoimmune SE, which is at times difficult to differentiate at the initial presentation. We found that younger age, female sex, the presence of psychosis, non-convulsive SE, lymphocytic predominance in CSF were more commonly observed in the patients with autoimmune SE, while a high CSF total protein level, pleocytosis, and reduced glucose ratio were more common in those with infectious SE. EEG and MRI are important tools to confirm the diagnosis of SE and exclude structural lesions (19, 28), but were not particularly helpful in the current study.

Among all patients with SE, infection accounted for 4.2% and autoimmune accounted for 5%. This suggests that autoimmune SE is as common as infectious SE (20, 29), and therefore clinical features that can distinguish the two entities are important for intensive care physicians who care for patients with SE. We observed some differences in the presenting features of those with autoimmune and infectious SE. The age at onset was younger in the patients with autoimmune SE, which has also been reported in two previous studies (11, 20). Female predominance was also observed in the autoimmune SE group in this study, which is in accordance with previous reports that reported females predominance in autoimmune encephalitis and systemic autoimmune disorders (14, 30, 31).

TABLE 2 | Comparison of the clinical features of autoimmune and infectious SE.

	Autoimmune SE ($n = 25$)	Infectious SE ($n = 21$)	*p*-value	OR (95% CI)
Onset age (years)	32 (23–49.5)	56 (36.5–68.5)	0.015	
Female	17 (68.0)	8 (38.1)	0.043	0.29 (0.09–0.98)
Onset symptom				
Fever	13 (52.0)	11 (52.4)	0.979	0.99 (0.31–3.15)
Decrease consciousness	9 (36.0)	8 (38.1)	0.883	0.91 (0.28–3.04)
Seizure	6 (24.0)	4 (19.0)	0.685	1.34 (0.32–5.58)
Upper respiratory tract infection	5 (20.0)	3 (14.3)	0.611	1.50 (0.31–7.19)
Headache	2 (8.0)	4 (19.0)	0.268	0.37 (0.06–2.26)
Psychosis	6 (24.0)	0 (0.0)	0.025	
Fatigue	1 (4.0)	2 (9.5)	0.450	0.4 (0.03–4.70)
Cognitive decline	0 (0.0)	1 (4.8)	0.806	0.41 (0.01–11.68)
Latency of seizure after onset symptoms (days)	3 (0–7)	2 (0–8.5)	0.892	
STESS ≥3 at admission	11 (44.0)	7 (33.3)	0.460	1.57 (0.47–5.23)
END-IT score ≥3 at admission	**23 (92.0)**	**20 (95.2)**	**1.000**	**1.74 (0.15–20.65)**
SE with prominent motor symptoms	17 (68.0)	20 (95.2)	0.027	0.11 (0.01–0.94)
Generalized convulsive SE	11	14		
Epilepsia partialis continua	3	3		
Focal onset evolving into bilateral convulsive SE	2	2		
Myoclonic SE with coma	0	1		
Hyperkinetic SE	1	0		
Non-convulsive SE	8 (32.0)	1 (4.8)	0.027	9.41 (1.07–83.01)
Non-convulsive SE with coma	5	1		
Myoclonic absence status	1	0		
Non-convulsive SE without impairment of consciousness	1	0		
Aphasic status	1	0		
Number of AED used	**3 (2–3)**	**3 (1–3)**	**0.159**	
Refractory SE	**22 (88.0)**	**14 (66.7)**	**0.081**	**3.67(0.81–16.59)**
Super refractory SE	**15 (41.3)**	**4 (19.0)**	**0.007**	**6.38 (1.65–24.63)**
Required general anesthesia for SE control	16 (64.0)	5 (23.8)	0.006	5.69 (1.56–20.76)
Death during admission	5 (20.0)	8 (38.1)	0.175	0.41 (0.11–1.52)
Days of admission	40 (21–91)	33 (26–77.5)	0.817	
Days in ICU	34 (10.5-63.5)	33 (15–57)	0.869	
More than two AEDs at discharge	11 (44.0)	6 (28.6)	0.280	1.96 (0.57–6.74)
Good prognosis at discharge (mRS<3)	11 (44.0)	6 (28.6)	0.280	1.96 (0.57–6.74)
Good prognosis at last follow up (mRS<3)	10 (66.7)	6 (50.0)	0.381	2.00 (0.42–9.52)

Continuous variables were presented as median (interquartile range).
Categorical variables were presented as n (%).
AED, antiepileptic drug; CI, confidence interval; ICU, intensive care unit; mRS, modified Rankin Scale; OR, odds ratio; SE, status epilepticus; STESS, status epilepticus severity score.

The onset symptoms of autoimmune SE can be various. Alteration in mental status is the cardinal symptom (12), but provides little information about the underlying etiology. In our patients, the presenting symptoms of inflammatory SE included fever, decreased consciousness, seizure, upper respiratory tract infection, headache, psychosis, fatigue, and cognitive decline. Of note, psychosis was present only in those with autoimmune SE and not in those with infectious SE. Other studies have also reported that psychosis is the dominant presenting symptom among patients with autoimmune encephalitis (14, 29, 32, 33). In addition, we found that more of the patients with autoimmune SE had non-convulsive SE compared to those with infectious SE, which was not reported in the two previous studies (11, 20). This may be due to the difficulty in recognizing non-convulsive SE clinically without EEG monitoring or because it was not specifically looked for. Super refractory SE was also more prevalent in the autoimmune SE group, which may be due to the difficulty in making a diagnosis and the ineffectiveness of traditional SE treatment to control seizure activity without immunotherapy (34). When non-convulsive SE or psychosis followed by SE occurs in patients with a young age and female sex, autoimmune SE should be considered.

CSF studies are an important tool to identify the cause of SE, however, such studies can be challenging clinically. Neutrophilic predominant pleocytosis usually points toward a bacterial infection or the early stage of viral encephalitis, especially in the first 24 to 48 hours (24). Lymphocytic predominant pleocytosis was associated with autoimmune SE in our study,

TABLE 3 | The findings of the first cerebrospinal fluid (CSF) and electroencephalography (EEG) studies.

	Autoimmune SE ($n = 25$)	Infectious SE ($n = 21$)	*p*-value	OR (95% CI)
The first CSF findings				
CSF protein (mg/dL)	34.8 (23.5–110.9)	93.0 (38.1–260.9)	0.014	
CSF WBC count (cell/mm^3)	3 (0–18)	20 (2.5–536)	0.011	
Neutrophilic predominance	2 (15.4)	9 (52.9)	0.034	0.162 (0.03–0.96)
Lymphocytic predominance	11 (84.6)	8 (47.1)	0.034	6.19 (1.04–36.78)
[a]CSF/Blood glucose ratio <0.5	6 (24.0)	9 (56.3)	0.036	0.25 (0.06–0.95)
[b]IgG index >0.6	11 (55.0)	4 (66.7)	0.612	0.61 (0.09–4.14)
The first EEG finding				
Normal	1 (4.0)	3 (14.3)	0.318	0.25 (0.02–2.61)
Background slowing activity	14 (56.0)	6 (28.6)	0.081	0.51 (0.24–1.09)
Sporadic epileptiform discharge	2 (8.0)	4 (19.0)	0.239	2.38 (0.48–11.74)
Periodic discharge	3 (12.0)	3 (14.3)	0.769	1.19 (0.27–5.29)
Electrographic seizure	5 (20.0)	5 (23.8)	0.688	1.19 (0.4–3.56)

Continuous variables were presented as median (interquartile range).
Categorical variables were presented as n (%).
CI, confidence interval; OR, odds ratio; SE, status epilepticus; WBC, white blood cell.
a The CSF/blood glucose ratio was available in 16 patients with infectious and all patients with autoimmune etiology.
b The IgG index was available in six patients with infectious and 20 patients with autoimmune etiology.

but it was also often seen in cases of viral encephalitis-related SE (17, 24). Intensive care physicians often face a dilemma over whether to use antiviral therapy or immunotherapy when the diagnosis is unclear. Other parameters of the CSF can aid in the differential diagnosis, as our data suggested that the patients with an infectious etiology usually had a higher CSF protein level, although prolonged SE itself may result in a milder elevation of lactate and/or total protein levels. This was also reported by Oyanguren et al. who found similar white blood cell count between patients with viral infections and autoimmune processes, but that the protein level was higher in those with a CNS viral infection (35). Therefore, a high protein level in patients with lymphocytic predominance pleocytosis may suggest a viral etiology.

MRI can aid in the search for the etiology of SE, but with limitations. Limbic encephalitis may present as an increased FLAIR/T2 signal or abnormal DWI in the medial temporal lobes (36–38), and it can be used in helping to make the diagnosis of autoimmune encephalitis (16). Prolonged SE itself can also cause similar changes to some viral infectious in MRI signal with DWI abnormalities in the hippocampus and pulvinar (39), particularly herpes simplex encephalitis (18). Furthermore, these MRI patterns may not be present in all types of autoimmune SE and one study reported that 60% of the MRI findings in patients with anti-NMDA encephalitis may have been normal (14). Our data showed that no specific MRI findings could differentiate autoimmune and infectious SE.

EEG is routinely used to evaluate patients with seizures or disturbed consciousness. Slow background activity was more dominant in autoimmune patients compared with other etiologies of seizure (40), although we found no statistical difference in EEG findings between the two groups. Our study showed that at an early stage of inflammatory SE, it remains difficult to differentiate the two entities using currently available para-clinical investigations. The early use of auto-antibody assays may be needed when autoimmune SE is suspected clinically.

We found that general anesthesia was more commonly used in the patients with autoimmune SE. This is in accordance with previous studies in which patients with autoimmune SE were less responsive to AEDs (11, 20, 30, 41). The reason why AEDs are less effective for autoimmune SE remains to be clarified, although it is well-known that the treatment of autoimmune SE requires prompt immunotherapy (14, 15), which may then reduce the use of general anesthesia.

The functional outcomes were similar in both infectious and autoimmune groups with a similar mRS score at discharge and similar mortality rate during admission. However, most of our patients had a poor outcome at discharge or last follow-up (63.0 and 65.2%, respectively). Our study showed that the predictive values of STESS and END-IT scores were not in the same direction. That is, STESS was more sensitive but END-IT was more specific in terms of predicting the outcomes at discharge. More studies may be needed to compare the use of these two scores. In addition to functional impairments, a recent study reported that patients also had substantial impairments in their quality of life after SE (42). Our patients with autoimmune SE had a mortality rate of 20%, which is similar to other studies ranging from 10 to 23% (20, 30, 43). A recent population-based study conducted in Germany reported a hospital mortality rate for all types of SE of 14.8% with a higher rate in those with refractory SE and super refractory SE (15.0 and 39.9%, respectively) (44). The higher mortality rate in patients with autoimmune etiology compared to those with all-cause SE may be related to the high percentage of super refractory SE among patients with an autoimmune etiology. This higher mortality rate compared to all-cause SE emphasize the need for rapid recognition of the condition and prompt treatment toward the underlying causes in addition to standard SE care.

TABLE 4 | The findings of magnetic resonance imaging study.

	Autoimmune SE ($n = 25$)	Infectious SE ($n = 21$)	*p*-value	OR (95% CI)
FLAIR and T2 abnormalities	11 (44)	8 (38.1)	0.685	1.28 (0.39–4.17)
Lateralization				
Unilateral	5 (20.0)	3 (14.3)	0.729	0.72 (0.11–4.62)
Bilateral	6 (24.0)	5 (23.8)		
Location				
Temporal lobe	9 (36)	5 (23.8)		
Mesial temporal lobe	7 (28)	4 (19)		
Lateral temporal lobe	2 (8)	1 (4.8)		
Frontal lobe	6 (24)	3 (14.3)		
Parietal lobe	7 (28)	2 (9.5)		
Occipital lobe	7 (28)	4 (19)		
Basal ganglion	0 (0)	2 (9.5)		
Multiple lobes	7 (28)	3 (14.3)	0.367	2.10 (0.41–10.66)
DWI abnormalities	14 (56)	10 (50)	0.688	1.27 (0.39–4.14)
Lateralization				
Unilateral	5 (35.7)	6 (60)	0.408	0.37 (0.07–1.97)
Bilateral	9 (64.3)	4 (40)	0.408	2.7 (0.51–14.37)
Location				
Temporal lobe	11 (78.6)	7 (70)		
Mesial temporal lobe	7 (50)	3 (30)		
Lateral temporal lobe	4 (28.6)	5 (50)		
Frontal lobe	6 (42.9)	5 (50)		
Parietal lobe	6 (42.9)	5 (50)		
Occipital lobe	5 (35.7)	5 (50)		
Basal ganglion	0 (0)	4 (40)		
Multiple lobes	11 (78.6)	6 (60)	0.393	2.44 (0.41–14.75)

Categorical variables were presented as n (%).

CI, confidence interval; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; OR, odds ratio; SE, status epilepticus.

The limitations of this study are that it was conducted at a single hospital and that the design was retrospective. In addition, the study was started before the availability of recent autoimmune encephalitis screening tests and immunotherapies, which may have affected the outcomes.

In conclusion, we observed that patients with autoimmune SE had a younger age at onset, female predominance, and often presented with psychosis, super-refractory SE and non-convulsive SE. The initial clinical investigations including EEG and MRI only provided limited information about the underlying etiology. CSF tests were helpful in diagnosing bacterial infectious-related SE but had difficulty in differentiating viral encephalitis and autoimmune SE. Since these two etiologies have different treatment strategies and the presenting symptoms are quite similar (12, 29), it is important to differentiate the two conditions as soon as possible. The patient characteristics and presenting features identified in our study may provide clinicians with some clues about the underlying etiology. Empiric treatment can be given based on these clinical clues while waiting for the results of more definitive diagnostic tests such as viral serology tests and neuronal surface auto-antibody screening.

ETHICS STATEMENT

This study is approved by the Chang Gung Medical Foundation Institutional Review Board (IRB No.: 103-3665B and 201800677B0).

AUTHOR CONTRIBUTIONS

All authors have read and approved the final manuscript. C-HL contributed to clinical data analysis and draft of the manuscript. Y-TL, C-JH, and F-YS had contributions to clinical data acquisition and analysis. M-HT had substantial contributions to the conception and design of the study, data analysis, critical revision, and final approval of the manuscript.

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REVIEW
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Application of Plasma Exchange in Steroid-Responsive Encephalopathy

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Plasma exchange has been widely used in autoimmune neurological diseases and is the standard treatment for myasthenia gravis crisis and Guillain-Barre syndrome. A growing body of research suggests that, in the clinical application of steroid-responsive encephalopathy, such as for Hashimoto's encephalopathy, limbic encephalitis, systemic lupus erythematosus encephalopathy, ANCA-associated vasculitis encephalopathy, and acute disseminated encephalomyelitis, plasma exchange is a safe, and effective option when steroids or other immunosuppressive therapies are ineffective in the short term or when contraindications are present. Additionally, plasma exchange can also be used alone or in combination with steroids, immunoglobulins, or other immunosuppressive agents to treat steroid-responsive encephalopathy. This paper reviews the clinical application of plasma exchange in steroid-responsive encephalopathy, including its indications, onset time, course, curative effects, and side effects.

Keywords: plasma exchange, steroid, clinical practice, course, onset time, side effects

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INTRODUCTION

Plasma exchange is also known as therapeutic plasma exchange (1). The seventh special issue of the Therapeutic Apheresis in Clinical Practice treatment guidelines, published in 2016 by the American Society for Apheresis, defines plasma exchange as a therapeutic procedure in which the patient's blood is separated into plasma and other blood components by medical devices, and then the plasma is removed and replaced by a replacement solution such as a colloidal solution (albumin and/or plasma) or a combination of crystal/colloidal solutions, thus eliminating or reducing unwanted substances (2). Castillo et al. (3) considered encephalopathy to be accompanied by cognitive impairment and one or more of the following: (i) neuropsychiatric symptoms (hallucinations or delusions and paranoia); (ii) myoclonus; (iii) seizure; and/or (iv) focal neurologic deficits. Steroid responsiveness refers to the complete or nearly complete return to normal neurological baseline status after steroid treatment, while steroid unresponsiveness refers to lack of improvement after at least 4–6 weeks of a sufficient dose of steroids (4). In this paper, steroid-responsive encephalopathy is a general term used to describe diseases characterized by diffuse brain injury and their responsiveness to steroids. These diseases include Hashimoto's encephalopathy, limbic encephalitis, systemic lupus erythematosus encephalopathy, ANCA-associated vasculitis encephalopathy, and acute disseminated encephalomyelitis. Plasma exchange is a rapid-onset, safe, and effective option for patients with steroid-responsive encephalopathy who fail to

respond to steroids in the short term or for patients who are unable to tolerate the side effects of steroid therapies. It can also be used as an initial treatment (see **Table 1**).

HISTORY OF PLASMA EXCHANGE

Plasma exchange dates back to 1914. Able et al. (18) described the separation of cell components and plasma from the blood of dogs with uremia. The separated components were mixed with replacement solution and then returned to the subject. Regular plasma exchange began to be used in humans in 1952. Researchers found that repeated plasma exchange reduced the amount of pathological proteins in patients with multiple myeloma (19). In 1960, Schwab and Fahey (20) reported that plasma exchange in Waldenstrom's macroglobulin and hyperviscosity syndrome achieved good therapeutic effects. Therefore, plasma exchange became the standard treatment for Waldenstrom's macroglobulin. In the 1980s, studies reported that plasma exchange was an effective treatment for systemic lupus erythematosus encephalopathy and acute disseminated encephalomyelitis; thereafter, plasma exchange began to be used as a treatment for steroid-responsive encephalopathy (4, 21).

UNKNOWN MECHANISMS OF PLASMA EXCHANGE OR POTENTIALLY INVOLVED MECHANISMS UNDER EXPLORATION

Clearing Pathogenic Antibodies From Plasma

The mechanism of plasma exchange for treating systemic lupus erythematosus encephalopathy is the rapid removal of pathogenic autoantibodies such as anti-nuclear antibodies from the blood (22). Anti-neutrophil cytoplasmic antibodies (ANCAs) play an important role in the pathogenesis of ANCA-related vasculitis encephalopathy, and the clearance of pathogenic antibodies from blood by plasma exchange can improve the therapeutic effects (2). Plasma exchange can also effectively remove pathogenic antibodies and can be combined with immunotherapy to suppress the production of autoantibodies and effectively treat limbic encephalitis (23). The mechanism of plasma exchange for treating acute disseminated encephalomyelitis is the removal of autoantibodies (antibodies against myelin oligodendrocyte glycoprotein) as well as complement components and cytokines (4).

Increasing the Susceptibility of Antibody-Producing Cells to Immunosuppressant and Chemotherapeutic Drugs

Plasma exchange can also induce proliferation of antibody-producing cells and increase the synthetic ability of antibodies as well as the susceptibility of antibody-producing cells to immunosuppressive or chemotherapy drugs (23). Studies have reported that plasma exchange can increase the synthetic activity of B cells and increase the susceptibility of antibody-producing cells to immunosuppressive agents (24).

Removing Immune Complexes From Plasma and Enhancing the Function of Macrophages and Monocytes

Plasma exchange can not only directly promote the removal of immune complexes from patients with systemic lupus erythematosus (22) but also upregulate red blood cell (RBC) complement receptors and increase the binding of RBC and immune complexes to remove immune complexes from the circulation. Steven et al. (25) studied the effect of plasma exchange on monocyte function and found that monocytes significantly increased their bactericidal effect by increasing the level of proteolytic enzymes in immune-complex-mediated diseases.

Removing Pathogenic Cytokines and Adhesion Molecules From Plasma

The concentration of soluble adhesion molecules ICAM-1 and VCAM-1 may be decreased after plasma exchange in patients with ANCA-associated vasculitis (26). Yeh et al. (27) found that double-filtration plasmapheresis can effectively remove IL-2, IL-4, IL-5, tumor necrosis factor alpha, and interferon gamma from the serum of patients.

CLINICAL APPLICATION OF PLASMA EXCHANGE IN STEROID-RESPONSIVE ENCEPHALOPATHY

Indications of Plasma Exchange for the Treatment of Steroid-Responsive Encephalopathy

Therapeutic plasma exchange is an established treatment method for known or suspected immune-mediated diseases (28). In 2016, the American Society for Apheresis published treatment guidelines for plasma exchange based on evidence-based medical research and proposed that Hashimoto's encephalopathy is a category II indication for plasma exchange and that the recommended level is 2C. Anti-N-methyl-D-aspartate receptor encephalitis is a category I indication, and the recommended level is 1C. Plasma exchange for the treatment of severe systemic lupus erythematosus, including systemic lupus erythematosus encephalopathy, is a category II indication, and the recommended level is 2C (2). Plasma exchange for the treatment of acute disseminated encephalomyelitis is a class II indication, and the recommended level is 2C (2) (See **Tables 2**, **3**).

Volume, Interval Time, and Frequency of Plasma Exchange for the Treatment of Steroid-Responsive Encephalopathy

The efficacy of plasma exchange is often related to the volume of plasma exchanged, which is dependent on the estimated plasma volume of the patient. The formula for estimating the plasma volume of the patient uses the patient's weight and hematocrit: EPV=[0.065 × wt (kg)] × [1-Hct]. This formula provides a reliable prediction of the therapeutic effect in clinical

TABLE 1 | Case reports of plasma exchange for steroid-responsive encephalopathy.

References	Diagnosis	Number	Clinical feature	Failed treatments	Process of plasma exchange	Side effects	Therapeutic effect
Nagpal and Pande (5)	Hashimoto's encephalopathy	One	52-year-old female, aphasia, memory loss, and tremor	Corticosteroids, thyroxine	Three plasma exchange procecures; the volume of Plasma exchanged per procedure was 1.8 L.	Not mentioned	After the third plasma exchange, all neuropsychiatric symptoms improved.
Gul et al. (6)	Hashimoto's encephalopathy	Two	Case 1: 8-year-old female, status epilepticus	Antiepileptic drugs, immunoglobulin, steroids	Five sessions	Not mentioned	Status epilepticus was controlled after plasma exchange.
			Case 2: 17-year-old female, status epilepticus	Immunoglobulin, Antiepileptic drugs, steroids	Five sessions	Not mentioned	After plasma exchange, epilepsy was controlled without recurrence.
Simmons and Staley (7)	Hashimoto's encephalopathy	Two	Case 1: 55-year-old female, gait ataxia, memory loss, mood change	Mycophenolate, mofetil	Five sessions; the volume of plasma exchanged per session was one times the plasma volume.	Slight citrate toxicity	Three months after plasma exchange, the patient's gait ataxia improved without obvious changes in daily activities.
			Case 2: 49-year-old female, insomnia, altered state of consciousness, mental symptoms	Steroids, immunoglobulin	Two course courses no. 1 (one times the plasma volume/session for five sessions), the second and third course were all (one times the plasma volume/session for three sessions	Transient hypotension, headache	After the first plasma exchange, orientation and daily activity improved, and the anti-thyroid peroxidase antibody was reduced from >1,000 units before plasma exchange to 286 units. The anti-thyroid peroxidase antibody was 538 units at 1 month after the first course of plasma exchange, the psychiatric symptoms were improved after the second and third courses, and the anti-thyroid peroxidase antibody was <63 units after the third course of plasma exchange.
Endres et al. (8)	Hashimoto's encephalopathy	One	55-year-old female, rapid progressive dementia, stupor, silence	Antidepressants, antipsychotics, steroids	Five sessions	Not mentioned	After plasma exchange, all symptoms were significantly improved, but verbal fluency was still lacking.
Tran et al. (9)	Hashimoto's encephalopathy	One	72-year-old female, cerebellar ataxia, cognitive dysfunction	Steroids, mycophenolate, immunoglobulin	Induction period: Two sessions/week for 6 weeks and then one procedure/week (1.5 times the plasma volume for 6 weeks, followed by 2 sessions/week (one times the plasma volume) and then 1 procedure/week. After 9.5 months, readjust to two sessions/week	Citrate toxicity somnolence lower limb spasm	Clinical symptoms were alleviated after the induction of plasma exchange, the patient could walk normally, and memory was restored. Anti-thyroid peroxidase antibody levels decreased, but when the plasma exchange sessions were reduced to one procedure/week, and the patient experienced recurrence. Therefore, plasma exchange was administered at the rate of 2 sessions/week, and the patient's gait was improved (stable and lively).

(Continued)

TABLE 1 | Continued

References	Diagnosis	Number	Clinical feature	Failed treatments	Process of plasma exchange	Side effects	Therapeutic effect
Batra et al. (10)	Anti-NMDA receptor limbic encephalitis	One	34-year-old female, abnormal mental behavior,	Acyclovir, immunoglobulin	1.2 times the plasma volume/ procedure for five sessions, once every other day, with 5% albumin as the replacement fluid	Not mentioned	Symptoms improved significantly after 1 month, and antibody tests were negative. Symptoms were significantly relieved.
Mazzi et al. (11)	Nonparaneoplastic limbic encephalitis associated with the anti-GAD antibody	One	21-year-old female, intractable epilepsy, memory loss	Antiepileptics, steroids, immunoglobulin	Sixteen sessions with 1.4 times the plasma volume replaced during each procedure	Not mentioned	Seizures were significantly reduced after the third plasma exchange session.
Martin et al. (12)	Anti-VGKC antibody-positive limbic encephalitis	One	69-year-old male, memory loss, Abnormal mental behavior	Steroids, immunoglobulin, mycophenolate, mofetil	One time the plasma volume/session (2 sessions/week) for 6 weeks	Not mentioned	Anti-VGKC antibody levels decreased, and clinical symptoms were well controlled.
Özkale et al. (13)	Two cases of anti-NMDA receptor encephalitis One case of serologic negative Autoimmune Limbic encephalitis One case of paraneoplastic limbic Encephalitis	Four	Headache, Status epilepticus psychiatric symptom	Steroid, immunoglobulin	Six sessions on average	Not mentioned	The neurological symptoms of all patients improved after plasma exchange.
Hussein et al. (14)	Systemic lupus erythematosus encephalopathy	One	17-year-old female headache, double vision, facial paralysis	Cyclosporin	Six sessions	Not mentioned	Cyclophosphamide and methylprednisolone (1 g/d for 3 days) combined with six plasma exchange resulted in significant improvement in clinical symptoms.
Bartolucci et al. (15)	Systemic lupus erythematosus encephalopathy	Ten	Average age: 30 Female: 8, male: 2 psychiatric symptoms, aseptic meningitis, cognitive decline	Not mentioned	Three sessions/week for three weeks and then two or three sessions/week, according to the clinical outcome	Not mentioned	After plasma exchange, 54% (7/13) had complete remission, and 46% (6/13) had partial remission. The European consensus lupus activity score (ECLAM) and systematic lupus activity index (SLEDAI) decreased to 1.2 and 3.9 respectively from 6.9 and 30.7.Disappeared upon head MRI examination, and consciousness level and mental state began to recover. The PR3-ANCA antibody decreased from 164 U/ml to 15.7 U/ml.
Shinozaki et al. (16)	Acute disseminated encephalomyelitis	One	Headache, confused and delirious state, no eyelash, corneal or light reflexes	Intravenous methylprednisolone (1,000 mg per day for 5 days)	Plasma exchange (PE) plus continuous hemodiafiltration using 1.5 times the circulating plasma volume, daily PE with CHDF for 3 days	Not mentioned	On the day after initiation of SPE + CHDF, the patient's corneal and bilateral light reflexes were dramatically recovered.
Balestri et al. (17)	Acute disseminated encephalomyelitis	One	An eight-year-old female, comatose and generalized tonic-clonic seizures, unable to raise her head, walk, or speak, and facial paresis	Methylprednisolone, immunoglobulin, and Interferon beta-1b	Six courses with 1,400 cc of plasma exchanged once every 2 days)	Not mentioned	Dramatic recovery was observed over the next 2 weeks, and the patient was able to walk, speak, and raise her left forearm.

TABLE 2 | Category of recommendation for plasma exchange (2).

Category for plasma exchange	Detailed description
I	Plasma exchange is used as first-line treatment alone or in conjunction with other treatments.
II	Plasma exchange is used as second-line treatment alone or in conjunction with other treatments.
III	The optimal role of plasma exchange has not been determined, and decisions should be personalized.
IV	Published evidence confirms or suggests that plasma exchange is ineffective or even harmful and that IRB approval is required if it is to be used in these circumstances.

applications. In general, macromolecular substances (immune globulin, lipoprotein cholesterol, cold globulin, etc.) inside and outside of blood vessels become slowly redistributed, achieving a gradual balance. Thus, clearance during a single treatment is limited. One is the concentration of substances in the blood vessels, while the other is the volume of plasma exchanged. Based on these two factors, the percentage of the decrease in pathogenic substances after treatment compared with the pretreatment level can be determined as follows: $X_1 = X_{0e}\text{-}V_e$ /EPV, where X_1 is the final plasma concentration, X_{0e} is the initial plasma concentration, V_e is the volume of plasma exchange, and EPV is the estimated plasma volume of patients. If the volume of plasma exchange is equal to the patient's EPV, pretreatment values will drop by 63%, and if the volume of plasma exchange is equal to 1.4 times the EPV, pretreatment values will drop by 75%. However, in the process of a single exchange, the volume of plasma exchanged is further increased. As a result, the pretreatment level decreases less, and thus, the exchange volume would increase, subsequently increasing the duration of treatment and associated costs. For most indications of plasma exchange (including Hashimoto's encephalopathy, limbic encephalitis, systemic lupus erythematosus encephalopathy, ANCA-associated vasculitis encephalopathy, acute disseminated encephalomyelitis, etc.), the volume of plasma exchanged per treatment is 1–1.5 times the plasma volume (30). For a single plasma exchange treatment, this volume will not cause reductions in the overall load of the serum levels caused by partial rebound. Several consecutive plasma exchange sessions, separated by 24–48 h, can remove a substantial percentage of the total body burden. In general, if the rate of production is moderate, then at least five sessions within 7–10 days are required to remove 90% of the patient's initial overall load, and additional sessions will be needed if the production is rapid (30).

Curative Effects

Cook et al. (31) retrospectively analyzed plasma exchange for the treatment of 10 Hashimoto's encephalopathy cases and showed that 90% of the symptoms of Hashimoto's encephalopathy significantly improved after plasma exchange. Neuwelt (32) reported the use of plasma exchange in eight systemic lupus erythematosus encephalopathy patients who failed to respond to

TABLE 3 | Recommended levels for plasma exchange (2, 29).

Recommendation	Grade 1A	Grade 1B	Grade 1C	Grade 2A	Grade 2B	Grade 2C
The quality of evidence	RCT without significant limitation or overwhelming evidence from observational studies.	RCT has important limitations (inconsistent results, methodological defects) or exceptionally strong evidence from observational studies.	Case series or observational studies.	RCT without significant limitation or overwhelming evidence from observational studies.	RCT has important limitations (inconsistent results, methodological defects) or exceptionally strong evidence from observational studies.	Case series or observational studies.
Detailed description	Strong recommendation, high-quality evidence.	Strong recommendation, moderate-quality evidence.	Strong recommendation, low-quality, or very low-quality evidence.	Weak recommendation, high-quality evidence.	Weak recommendation, moderate-quality evidence.	Weak recommendation, low-quality, or very low-quality evidence.

cyclophosphamide, among whom six were completely relieved of their clinical symptoms. In 2010, a non-blinded prospective study by Wong et al. (33) included nine cases of limbic encephalitis with positive anti-VGKC antibody, and each patient underwent five plasma exchange sessions combined with steroid and immunoglobulin treatment. After treatment, the VGKC antibody titer of all patients returned to normal within 1–4 months. After 1–3 months, clinical and cognitive tests showed that memory function had improved. After 6–9 months, the swelling subsided, and the signal was recovered on brain MRI.

Adverse Reactions

Plasma exchange is a relatively safe treatment, mostly with reports of only mild side effects, of which the most common are hypotension, hypocalcemia, urticaria, bleeding (due to loss of platelets or clotting factors), and arrhythmia. These adverse reactions are mainly related to anticoagulants, the replacement fluid used, and central venous catheterization. The incidence of hypocalcemia is 1.5–9% and is related to citrate. The main symptoms include paresthesia, muscle spasm, and arrhythmia. In addition, acid-base imbalance can be induced by citrate. The use of albumin as a replacement fluid may lead to the consumption of clotting factors and immunoglobulin and thus increase the risk of bleeding and infection. Fresh frozen plasma used as a replacement solution may cause HIV and hepatitis virus infection (34). Adverse reactions associated with central venous catheterization include infection, sepsis, thrombosis, and pneumothorax. Hemolysis and hypotension may occur, but the incidence of serious side effects such as severe hypotension, acute pulmonary edema, myocardial infarction, and death is 1.6–22% (35). In 2007, the world plasma exchange registry reported that the incidence of side effects from plasma exchange was 5.7% and that no death occurred in 838 patients who underwent plasma exchange; a plasma exchange team in Canada analyzed 91,000 sessions of plasma exchange and found that the incidence of serious side effects caused by plasma exchange was 0.4%. In addition, blood transfusion-related side effects are more common when plasma is used as the replacement fluid (36). Basic-Jukic et al. (34) studied the side effects of plasma exchange in the treatment of neurological diseases, including 152 patients from January 1982 to December 2003, with a total of 4,857 plasma exchanges performed. The incidence of side effects was 4.74% (231/4857), and the side effects were mostly mild to moderate. In summary, a few studies have reported on the side effects of plasma exchange for steroid-responsive encephalopathy, the results indicate that plasma exchange may be a safe treatment for steroid-responsive encephalopathy.

APPLICATION OF PLASMA EXCHANGE IN DIFFERENT TYPES OF STEROID-RESPONSIVE ENCEPHALOPATHY

Application of Plasma Exchange in Hashimoto's Encephalopathy

Hashimoto's encephalopathy (also known as autoimmune thyroiditis-related steroid-responsive encephalopathy) was first reported by the British scholar Brain in 1966. Hashimoto's encephalopathy is related to Hashimoto's thyroiditis, as anti-thyroid antibodies were found in serum. The patients' thyroid function can be classified as normal, hypothyroidism or hyperthyroidism (37, 38). The clinical manifestations mainly include two types: vasculitis type, mainly including recurrent stroke-like episodes, seizures, and mental abnormality, and diffuse progressive type, which manifests as cognitive dysfunction (including memory and language dysfunction) dementia, behavior change, confusion, mental derangement, and coma (5). The most common clinical manifestations are seizures, followed by psychiatric symptoms (39). Elevated levels of anti-thyroid peroxidase antibodies (anti-TPOAb) and/or anti-thyroglobulin antibodies (anti-TgAb) are important laboratory characteristics for the diagnosis of Hashimoto's encephalopathy; elevated anti-thyroid peroxidase antibody levels are most common and are observed in 86% of patients with Hashimoto's encephalopathy, while 48% of the patients with Hashimoto's encephalopathy have elevated anti-thyroglobulin antibody levels (6). Although the pathophysiological mechanism of Hashimoto's encephalopathy is still not clear, high concentrations of anti-thyroid antibodies and effective treatment with immunosuppressive agents both support the important role of autoimmune mechanisms in Hashimoto's encephalopathy (40), which is the theoretical basis of plasma exchange in the treatment of Hashimoto's encephalopathy. Although steroids are the first-line treatment for Hashimoto's encephalopathy (41), no randomized controlled trials have been performed, so the optimal dose and duration of steroids remain unclear. Steroid responsiveness is determined by the dose and administration method. Usually, intravenous methylprednisone (500–1,000 mg/d) is administered for 3–7 days, followed by oral prednisone 1–2 mg/kg/d for 6–8 weeks, and in most cases, clinical improvement is observed within the first 4–6 weeks of treatment (4). When patients are unable to tolerate the side effects of steroid or have no response to steroids in the short term, plasma exchange can be performed to improve treatment efficacy. Moreover, a few reports have demonstrated that plasma exchange can be used for the initial treatment (39).

History of Plasma Exchange as a Treatment for Hashimoto's Encephalopathy

In 2001, Boers and Colebatch (42) was the first to report that plasma exchange could effectively treat Hashimoto's encephalopathy that failed to respond to corticosteroids. The author reported a 47-year-old Uruguayan man who was treated for upper limb postural tremor and gait disorder. During hospitalization, the patient developed seizures, short-term memory impairment, visual hallucination, auditory hallucinations, and paranoid delusions. Electroencephalogram (EEG) showed diffuse slow wave activity but no epileptic discharge. Cerebrospinal fluid showed increased pressure and protein (1.06 g/l), but other cerebrospinal fluid examinations (including polymerase chain reaction of herpes simplex virus), brain magnetic resonance plain scan, and enhancement showed no abnormalities. Examinations for thyroid stimulating hormone (TSH) were normal, but the levels of microsomal antibodies and anti-thyroglobulin antibodies significantly increased, so

the diagnosis of Hashimoto's encephalopathy was established after ruling out other causes. Intravenous methylprednisolone was initiated, but 4 weeks later, the patient still experienced tremor and difficulty eating and dressing himself, so four plasma exchange sessions were performed with the exchange of 1.5–2 times the estimated plasma volume per session. After the first plasma exchange, the patient's condition improved, and after the fourth plasma exchange, the patient was able to dress, eat, talk, and work independently; in addition, his antibody levels decreased. Afterward, the patient experienced two relapses, and the symptoms were relieved after plasma exchange. Multiple studies have subsequently supported this treatment (5, 6, 40, 43–45). Nieuwenhuis et al. (45) reported a 48-year-old patient with subacute Hashimoto's encephalopathy, and the main manifestations were rapid progressive dementia, visual hallucinations, and myoclonus. Plasma exchange was used as the initial treatment of Hashimoto's encephalopathy, and clinical symptoms relieved after the first plasma exchange.

Onset Time of Plasma Exchange for Hashimoto's Encephalopathy

Most of the cases in which plasma exchange used to treat Hashimoto's encephalopathy showed positive effects after the first plasma exchange. Clinical symptoms of Hashimoto's encephalopathy were found to be improved after the first plasma exchange in a report by Boers and Colebatch (42). In addition, Bektas et al. (43) reported one Hashimoto's encephalopathy in which the patient's status epilepticus was controlled after the first plasma exchange.

The Course of Plasma Exchange for Hashimoto's Encephalopathy

Most studies on plasma exchange for Hashimoto's encephalopathy lack a specific description of the number of plasma exchange sessions used. Nieuwenhuis et al. (45) used three sessions plasma exchange to treat Hashimoto's encephalopathy successfully. Bektas et al. (43) used nine sessions plasma exchange, while Nagpal and Pande (5) and Gul Mert et al. (6) reports that the number of plasma exchange sessions for the treatment of Hashimoto's encephalopathy should be five. These results are consistent with the American Society for Apheresis, which recommends a total of 3–9 sessions plasma exchange for Hashimoto's encephalopathy, with the most common number of plasma exchange being five and exchanges being performed once every other day. The volume of plasma exchanged per treatment should be 1–1.5 times the estimated plasma volume, and albumin should be used as the replacement solution (2, 5, 31, 45).

Clinical Practice of Plasma Exchange for Hashimoto's Encephalopathy

Hussain et al. (44) reported a case of 54-year-old woman with hypothyroidism who presented with progressive cognitive impairment, gait disturbance, and seizures; based on an anti-thyroid microsomal antibody titer of 1:1,600 and the presence of head abnormalities on MRI without other reasons for cognitive impairment, a definite diagnosis of Hashimoto's encephalopathy was made. The patient began oral prednisone at a dose of 60 mg/d, and her cognitive function, apraxia, and gait disorder improved, but memory impairment remained. Because the patient could not tolerate the side effects of prednisone, the dose was gradually reduced to 15 mg/d. As the patient's cognitive function and gait disorder worsened with the reduction in the dose of prednisone, plasma exchange was performed, with five sessions per course and two courses of plasma exchange at intervals of 5 months. Four weeks after the first course of treatment, the patient's cognitive function markedly improved, and anti-thyroid microsomal antibody levels were reduced to 1:400. Cognitive function began to decline a few months later, but after the patient underwent the second course of plasma exchange, cognitive function continuously improved. Pari et al. (40) reported a 19-year-old girl who had been in good health but experienced a seizure. One month later, she had difficulty finding words and understanding language, along with symptoms of confusion, and disorientation. Electroencephalogram showed a non-convulsive status epilepticus, with a slightly elevated number of cells in CSF, with normal glucose and protein levels. PCR analysis of herpes simplex virus, adenovirus and enterovirus in cerebrospinal fluid were all negative. Brain MRI was normal. An 18F-FDG PET on the left temporal lobe, insula, temporoparietal junction, the right side of the parietal lobe metabolism reduced, diagnosis of Hashimoto's encephalopathy, intravenous methylprednisolone 1 g/d for 8 days, but no obvious improvement was observed. Electroencephalogram improved after five plasma exchange sessions, antithyroglobulin antibody, and thyroid peroxidase antibody, respectively pretreatment of >1,000 IU/ml (normal <4.1 IU/ml), 519 IU/ml (normal for <5.6 IU/ml) dropped to 462 IU/ml, 30 IU/ml. Symptoms of difficulty finding words and understanding speech also improved. In most studies, steroids work within the first 4–6 weeks, while other studies have shown that the time to complete recovery may range from 4 months to 10 years (4). However, in this case, the course of steroids was shorter. If used for a longer duration, the effect may be more pronounced. The patient may be responsive to steroid treatment, but if the clinical symptoms are severe or worsen, plasma exchange can be used to quickly relieve these symptoms. Cook et al. (31) retrospectively analyzed a study on the treatment of Hashimoto's encephalopathy with plasma exchange in 10 cases and showed that 90% of patients had significantly improved symptoms after plasma exchange. Because plasma exchange alone or with other treatments have been used as the second-line treatment for Hashimoto's encephalopathy, in 2016, the American Society for Apheresis published treatment guidelines for plasma exchange and proposed that Hashimoto's encephalopathy is a category II indication of plasma exchange. Moreover, because only observational studies or case series have reported the efficacy of plasma exchange on Hashimoto's encephalopathy and randomized controlled studies are lacking, the recommended level is 2C (2). This study was supported by Simmons and Staley (the volume of plasma exchanged per treatment was 1.0 times the plasma volume) (7) and Endres et al. (8). In addition, Tran et al. (9) found that long-term plasma exchange can be used for maintenance treatment in patients with Hashimoto's encephalopathy accompanied by cerebellar ataxia.

Plasma Exchange in Combination With Other Drugs for Hashimoto's Encephalopathy

Plasma exchange is usually combined with steroid, immunoglobulin, and antiepileptic drugs as well as immunosuppressants to treat Hashimoto's encephalopathy (5, 39, 44). Bektas et al. (43) reported a 12-year-old patient with Hashimoto's encephalopathy that mainly manifested status epilepticus, but after the first plasma exchange, his status epilepticus was controlled; subsequently, prednisone combined with a total of nine sessions plasma exchange resulted in normal mental and neurological status in 2 months. Gul et al. (6) also reported two successful cases in which plasma exchange combined with steroid, intravenous immunoglobulin, and antiepileptic drugs to treat Hashimoto's encephalopathy.

However, at present, only case reports and case analyses have shown that plasma exchange is effective at treating Hashimoto's encephalopathy, and because plasma exchange was initiated after failure to respond to steroids or immunoglobulin therapy in most of the studies, we cannot completely rule out the delayed effects of steroids. Nevertheless, because of the narrow time window between clinical symptom improvement and plasma exchange, plasma exchange can be considered for the treatment of Hashimoto's encephalopathy when steroids are ineffective in the short term or when patients cannot tolerate the side effects of steroids, and a few studies have shown that plasma exchange is effective as an initial treatment for Hashimoto's encephalopathy.

Side Effects of Plasma Exchange for Hashimoto's Encephalopathy

Plasma exchange is a relatively safe and effective treatment. The application of plasma exchange for the treatment of Hashimoto's encephalopathy is rare, and few studies have evaluated the occurrence of side effects from plasma exchange in Hashimoto's encephalopathy patients. Hussain et al. (44) reported a 54-year-old patient with Hashimoto's encephalopathy treated with plasma exchange who developed a urinary tract infection.

Application of Plasma Exchange for Limbic Encephalitis

Limbic encephalitis is a neuropsychiatric disease characterized by inflammation of the limbic system, including the hippocampus, amygdala, and less frequently the frontobasal and insular regions. The clinical manifestations are subacute onset of cognitive impairment (mainly short-term memory loss), epilepsy, and mental disorder (46, 47). Radja et al. (48) reported that 97% of VGKC-associated limbic encephalitis presented with memory impairment, 85% with seizures, and 33% with emotional change. Brain MRI may present edema or inflammation that occur selectively on unilateral or bilateral limbic systems, especially in the medial temporal region (49). Electroencephalogram usually shows focal or diffuse slow waves or epileptiform discharge (50), and cerebrospinal fluid usually shows lymphocytosis, slight protein elevation, oligoclonal band positivity, and an increase in the IgG index (51, 52). Limbic encephalitis can be divided into infectious and autoimmune limbic encephalitis according to the etiology. Infectious limbic encephalitis is usually caused by the direct invasion of the brain by pathogens such as herpes simplex virus, while autoimmune limbic encephalitis is caused by an autoimmune disorder and can be divided into paraneoplastic and non-paraneoplastic limbic encephalitis (50).

In 1968, Corsellis et al. (53) used the term "limbic encephalitis" for the first time to describe six patients characterized by progressive memory loss, confusion, and seizures. Of those patients, four had tumors, and three had bronchial carcinomas. An autopsy found that the limbic gray matter in all patients' temporal lobes exhibited inflammation and degeneration, indicating that there was a link between limbic encephalitis and tumors. Gultekin et al. (52) analyzed the relationship between 50 cases of limbic encephalitis and tumors and found that limbic encephalitis commonly occurs with small cell lung cancer (52%, 68/132), testicular cancer (11%, 14/132), and thymoma (5%, 6/132).There were also reports of paraneoplastic limbic encephalitis with non-Hodgkin's lymphoma, neuroblastoma, colon cancer, ovarian cancer, breast cancer, prostate cancer, etc. Since 1988, several studies have confirmed that patients with tumors outside the central nervous system but have neuropsychiatric symptoms have antitumor and brain tissue antibodies in their serum, including anti-Hu, anti-Yo, anti-CRMP5, anti-Ri, anti-Ma2, and anti-amphiphysin antibodies. Since 2000, studies have shown that some limbic encephalitis are detected antibodies against neuronal cell-surface antigens or antibodies against neuronal ion channels, including voltage-gated potassium channels and ligand-gated ion channels and antibodies against VGKC, NMDA, and AMPA receptors, thus providing a therapeutic basis for plasma exchange (47, 50).

History of Plasma Exchange for the Treatment of Limbic Encephalitis

Buckley et al. (54) first reported that plasma exchange successfully treated a case of limbic encephalitis. The report described a 47-year-old female stylist with myasthenia gravis. Thymoma was removed 4 years after she was diagnosed with myasthenia gravis, and after her diagnosis of myasthenia gravis for 10 years, her symptoms of myasthenia gravis recurred, the following year, the patient exhibited significant short-term memory loss, irritability, disorientation, inattention, and slowed thinking. The doses of cyclophosphamide and prednisone were reduced, and the patient started using loxapine (fourth generation antipsychotic medication), but her mental status did not improve significantly. After 7 weeks, the patient was transferred to the intensive care unit due to myasthenia crisis, and the myasthenia gravis symptoms were relieved with increased immunosuppression, but her mental status still did not improve. Brain CT and MRI were normal, while cerebrospinal fluid cytology and PCR of herpes simplex virus were negative. The electroencephalogram showed nonspecific slow waves. In the first 10 years after the diagnosis of myasthenia gravis, the VGKC antibody was normal, and significantly increased (750 pM) after the onset of psychiatric symptoms, so the patient was diagnosed with anti-VGKC receptor limbic encephalitis. The myasthenia gravis symptoms and limbic system symptoms improved after six sessions of plasma exchange. Jaben and Winters (55) studied the treatment of five anti-VGKC antibody-related diseases with

plasma exchange, of those, four were anti-VGKC antibody-related limbic encephalitis with the main clinical manifestations of memory impairment, seizures, and personality changes. All patients were given 1.0 times the plasma volume during each session every other day for a total of 5–6 sessions. Among these patients, three limbic encephalitis were treated with other immunosuppressive agents at the same time, and one significantly experienced symptom relief with plasma exchange alone. Although there have been a number of cases in which plasma exchange was used to treat limbic encephalitis, plasma exchange in combination with steroid and immunoglobulins have also been used to treat all types of limbic encephalitis. Steroid and immunoglobulin treatments are first-line therapy for limbic encephalitis whereas plasma exchange is not (56). Rather, it is implemented when steroid and immunoglobulin therapy has no obvious effect in the short term, alternatively, plasma exchange may be used in combination with steroid and immunoglobulin to treat limbic encephalitis.

Onset Time of Plasma Exchange for Limbic Encephalitis

At present, most studies that describe plasma exchange for limbic encephalitis lack a description of the onset time of plasma exchange. Schimme et al. (57) reported a 12-year-old girl with NMDA receptor encephalitis performed with eight sessions of plasma exchange over 13 days. The patient's clinical symptoms markedly improved after the second plasma exchange, and her ability to walk was partially recovered. This treatment schedule was consistent with the onset time of plasma exchange for anti-NMDA receptor encephalitis that was unresponsive to immunoglobulin (0.4 g/kg/d for 5 days) combined with methylprednisolone (1 g/d for 5 days) in the short term, as reported by Wang et al. (58) in 2015, consciousness was regained after the second plasma exchange. Mazzi et al. (11) reported a case of non-paraneoplastic limbic encephalitis with anti-GAD antibody, in which seizures were significantly reduced by the third plasma exchange. Rypulak et al. (59) reported a 23-year-old patient with NMDA receptor encephalitis who received plasma exchange, and after the third session, the patient's neurological symptoms significantly improved. The GCS score increased to 11 points from 6 points.

The Course of Plasma Exchange for Limbic Encephalitis

In the study of Batra et al. (10) and Jaben and Winters (55), the number of plasma exchange sessions used to treat limbic encephalitis ranged from 5 to 6. In 2016, the American Society for Apheresis recommended the use of plasma exchange once every other day to treat anti-NMDA receptor encephalitis, and the volume of plasma exchanged per session was 1–1.5 times the plasma volume. Albumin was used as the replacement fluid, and a total of 5–6 sessions were performed. For the treatment of paraneoplastic neuropathy (PNS), including paraneoplastic limbic encephalitis, plasma exchange is recommended once daily or every other day for a total of 5–6 sessions, and the volume of plasma exchanged per procedure should be 1–1.5 times the plasma volume (2).

Clinical Practice of Plasma Exchange for the Treatment of Limbic Encephalitis

Plasma exchange is initiated when steroid and immunoglobulin treatments fail to treat limbic encephalitis, alternatively, it can be combined with steroid and immunoglobulin treatments. Therefore, plasma exchange is usually not the first choice. However, at present, no randomized controlled trials have analyzed the therapeutic effect of plasma exchange on limbic encephalitis. In 2011, Markakis et al. (60) reported a case of a 48-year-old female who presented with mental disorders and disorientation 2 years before admission; the patient rapidly developed anterograde amnesia, irritability, hallucinations, refractory temporal lobe seizure, and obvious short-term memory loss in a few weeks. The enhanced T2 weighted sequence of brain MRI suggested bilateral temporal lobe swelling and revealed a high signal intensity in the medial temporal lobe. High concentrations of anti-GAD antibodies were found in serum and cerebrospinal fluid. A diagnosis of anti-GAD antibody-associated limbic encephalitis was established. After methylprednisolone (1 g/d for 5 days) failed, plasma exchange was initiated, each session involved the replacement of 1.2 times the plasma volume. After a total of seven sessions, the epilepsy was under control, but the patient's cognitive function did not improve. Subsequently, the patient underwent one plasma exchange session every 3 weeks along with oral prednisone (1 mg/kg, gradually reduced to 0.25 mg/kg, for at least 1 year). The seizures did not recur, and a simple intelligence test showed that language and visual memory improved, in addition, anti-GAD antibody levels were reduced at the 1-year follow-up. Mccarthy et al. (61) reported one case of a 32-year-old pregnant woman with anti-NMDA receptor encephalitis, in the first 2 weeks of pregnancy, a new symptom developed, continuous daily headache, and in the maternity clinic, the patient experienced a rapid onset of visual and auditory hallucinations, illusions, irritability, paranoid, delusional within 24 h. One week later, the patient lost consciousness, and seizures began to occur. Brain MRI was normal, EEG showed diffuse slow waves, and cerebrospinal fluid protein was elevated to 726 mg/l (normal is 150–450 mg/l). Steroids were initiated (methyl prednisolone 1 g/d for 5 days, then slowly reduced), but the patient became aggravated, and hence stayed in the intensive care unit. After plasma exchange (1.5 times the plasma volume per session), the patient's symptoms improved significantly, and after 8 weeks, the symptoms of encephalopathy were completely resolved. Van Ael et al. (62) used steroids to treat a 26-year-old woman with GAD antibody limbic encephalitis, but the treatment was unsuccessful. Plasma exchange was subsequently initiated, and marked improvements in clinical symptoms, including memory, seizures, and imaging findings were observed. At the 14-month follow-up, the level of GAD antibody, which was initially >7,000 IU, was decreased by plasma exchange to <1,000 IU. Moreover, several other studies have shown that plasma exchange is more effective than intravenous immunoglobulin and steroids for the treatment of limbic encephalitis, including in pregnant women (10, 12, 61, 63). Korff et al. (64) found that plasma exchange was the most effective at reducing antibody levels in limbic encephalitis.

Plasma Exchange in Combination With Other Drugs for the Treatment of Limbic Encephalitis

Plasma exchange is rarely used alone in the treatment of limbic encephalitis, but it is often used in combination with other immunomodulatory therapies such as steroids and/or immunoglobulin. Vincent et al. (65) analyzed the clinical features and treatment of 10 cases of anti-VGKC-antibody-associated limbic encephalitis. Among those cases, seven were treated with plasma exchange combined with steroids or immunoglobulin, and the results showed that four patients experienced a significant curative effect, two patients experienced a slight curative effect, and only one patient did not experience an effect. Desena et al. (66) analyzed the use of plasma exchange to treat 14 cases of anti-NMDA receptor encephalitis, including three adults, 10 patients began plasma exchange after failure to respond to steroids, and the results showed that 7/10 NMDA receptor encephalitis patients who underwent plasma exchange exhibited an average increase in the modified Rankin scale of 0.4, and 3/10 patients exhibited an average increase in the modified Rankin scale of 0.1 after treatment with steroids. The results indicated that plasma exchange combined with steroids was more effective than steroids alone for the treatment of anti-NMDA receptor encephalitis.

However, no randomized controlled trials have been performed to support the therapeutic effect of plasma exchange on limbic encephalitis, and plasma exchange is primarily initiated when the patient exhibits no response to steroid treatment in the short term (perhaps because steroid treatment requires a longer time period to elicit effects). Thus, the therapeutic effect of steroid treatment cannot be completely excluded, especially when it is combined with plasma exchange or immunoglobulin, so improvements in the patient's condition should not be attributed solely to plasma exchange. However, the patients receiving plasma exchange had better outcomes, and plasma exchange exhibited a time-dependent effect. The coincidence was small, and a few cases reported plasma exchange as the initial treatment of Hashimoto's encephalopathy. Therefore, plasma exchange may be considered when patients have contraindications to steroid treatment or slow onset time in the short term, but randomized controlled trials are needed for confirmation.

Side Effects of Plasma Exchange for Limbic Encephalitis

Suppiej et al. (67) analyzed the efficacy and side effects of plasma exchange for pediatric NMDA receptor encephalitis and showed two cases of transient hypotension that improved after rehydration therapy and blood vessel vasopressors, one case of allergic reaction and shock because of autonomic dysfunction, and one case of pulmonary embolism. Wong et al. (33) prospectively studied nine VGKC antibody-positive limbic encephalitis patients who underwent five sessions of plasma exchange with 50 ml/kg of plasma volume exchanged per session. Side effects associated with plasma exchange were observed in two patients: one had methicillin-resistant staphylococcus aureus septicemia and vertebral body inflammation, while the other had femoral artery puncture hematoma, deep vein thrombosis, and pulmonary embolism, which improved after treatment. Miyauchi et al. (68) reported an 11-year-old patient with anti-NMDA receptor encephalitis who developed hypotension shock ∼1 h after plasma exchange, but the patient's condition improved after rescue. Rypulak et al. (59) reported that hemodynamic instability and coagulation dysfunction occur after treatment of anti-NMDA receptor encephalitis with plasma exchange, and a prolonged interval between plasma exchange sessions can help prevent unwanted side effects. Therefore, the vital signs of patients, especially patients with anti-NMDA receptor encephalitis, should be closely monitored.

Application of Plasma Exchange in Systemic Lupus Encephalopathy

Systemic lupus erythematosus encephalopathy, also known as neuropsychiatric systemic lupus erythematosus (NPSLE), is a common neurological complication of systemic lupus erythematosus (SLE) (69), patients with NPSLE present a variety of neuropsychological symptoms, including aseptic meningitis, cerebrovascular disease, demyelination, headaches, movement disorders, seizures, confusion, anxiety, cognitive decline, and mood disorders (70), and NPSLE is the main cause of disability and death in patients with systemic lupus erythematosus. The pathogenesis of neuropsychiatric lupus involves a variety of inflammatory factors, autoantibodies, vascular lesions caused by immune complexes, and neuronal dysfunction mediated by autoantibodies (71). For many years, steroids as the first-line drug for systemic lupus erythematosus encephalopathy, often intravenous methylprednisolone (1,000 mg for 3 d), and then oral prednisone (1 mg/kg/d) gradually tapered and stopped within 3–12 months, but long-term use of the steroid has obvious side effects. When SLE encephalopathy has contraindications to steroid, or steroid is not sufficient or ineffective in the short term, plasma exchange may be a rapid-onset, safe, and effective option (72). In 2016, the American Society for Apheresis (ASFA) recommended plasma exchange as a class II indication for severe SLE, including lupus encephalopathy, and the recommended level is 2C (2).

History of Plasma Exchange for Systemic Lupus Erythematosus Encephalopathy

In 1976, Jones et al. (71) treated eight SLE patients with plasma exchange and found that plasma exchange can reduce the level of immune complexes in SLE. In 1981, Evans et al. (21) reported a 44-year-old nurse who developed systemic lupus erythematosus encephalopathy 12 years after the diagnosis of SLE, the disease mainly manifests as schizophrenia-like psychosis, personality changes, mood changes, cognitive disorders, delusions, hallucinations, and irrational thoughts and behaviors. High doses of antipsychotic medications such as thiazine, chlorpromazine, and haloperidol combined with prednisone at 200 mg/day failed to treat the patient's mental symptoms. Immune complex levels were significantly increased in the blood and cerebrospinal fluid, and electroencephalograms showed irregular delta waves of 7–8 Hz per s, hence, four sessions of plasma exchange were performed after 35–38 days.

An obvious improvement in the patient's mental status was observed 3 days after the fourth plasma exchange. Four weeks later, the dose of prednisone was reduced to 15 mg/d, and all the antipsychotic drugs were stopped at the same time, the patient's mental function and EEG performance gradually returned to normal, and the levels of immune complex and anti-neuronal antibody decreased correspondingly, indicating that plasma exchange can effectively treat lupus encephalopathy in patients with high levels of circulating immune complexes. In 1988, Unterweger et al. (73) reported a case of a 15-year-old girl with lupus encephalopathy. Three years after diagnosis of SLE, the patient manifested a severe depressive episode accompanied by suicidal ideation, disorientation, and delusional behavior, hence, steroids were initiated. After 7 days, the patient still had clinical manifestations of encephalopathy, mainly dementia, and delusions. The symptoms still did not significantly improve within 3 weeks of continued steroids. Therefore, plasma exchange was performed once every 2 days, with a total of five sessions performed over 10 days. The levels of circulating immune complexes decreased, antibody levels decreased, and the symptoms were relieved. Two weeks after the last plasma exchange session, the patient had recovered completely, and based on the results of psychological testing, the patient's attention and memory had returned to normal. Since then, studies have reported that plasma exchange can effectively treat systemic lupus encephalopathy (15, 69, 71, 74, 75). Plasma exchange has recently been reported to successfully treat one lupus encephalopathy case with catatonia as the main manifestation, avoiding the use of electroshock treatment (76). But no randomized controlled trials have confirmed the effect of plasma exchange on systemic lupus erythematosus encephalopathy.

The Course of Plasma Exchange for Systemic Lupus Erythematosus Encephalopathy

Kato et al. (77) reported three sessions of plasma exchange for the treatment of systemic lupus erythematosus encephalopathy, and Hussein et al (44) and Perisse et al (76) successfully treated systemic lupus encephalopathy using six sessions. Most studies reporting the use of plasma exchange for lupus encephalopathy lack a specific description of their methods. According to the reports on plasma exchange, for other immune mechanisms mediated neurological diseases, and according to studies reporting the plasma exchange clearance kinetics of immunoglobulin, it should be performed once daily or every other day, with the volume of plasma exchanged per procedure at 1–1.5 times the estimated plasma volume, and a total of 3–6 sessions of plasma exchange.

Clinical Practice of Plasma Exchange for the Treatment of Systemic Lupus Erythematosus Encephalopathy

Mild SLE encephalopathy needs only symptomatic treatment, but for severe SLE encephalopathy (disturbance of consciousness, seizures, severe depression, psychotic symptoms, etc.) and lupus encephalopathy in which steroids and cyclophosphamide have contraindications, high concentrations of immune complexes, and steroids have no obvious curative effect in the short term. Plasma exchange can treat lupus encephalopathy effectively, safely, and quickly (78–80). By removing pathogenic autoantibodies, immunoglobulin, immune complexes, and toxins, plasma exchange can also increase the function of regulatory T cells (23, 78). Kato et al. (77) reported a 48-year-old male with lupus encephalopathy that manifested as organic encephalopathy syndrome, specifically exhibiting mental behavior abnormalities, disorientation, memory, and intelligence impairments. Plasma exchange was performed after steroid treatment was deemed ineffective. After the first plasma exchange, the patient's consciousness improved, and their clinical symptoms were relieved. Subsequently, the steroid treatment was continued. Three days after the first plasma exchange session, a second plasma exchange session was conducted, the patient's disorientation was immediately alleviated. Quinter-Del-Rio AI et al. (79) studied a 14-year-old girl with SLE encephalopathy presenting with seizure, after steroid treatment failed, the clinical symptoms were significantly relieved with plasma exchange (1 session/d for 4 days). Gokhale et al. (69) reported three cases of lupus encephalopathy, two of which presented with status epilepticus. Plasma exchange combined with cyclophosphamide was initiated when steroid and cyclophosphamide treatment failed, and the clinical symptoms of all three patients were significantly relieved. Some scholars believe that the combination of synchronous plasma exchange and cyclophosphamide is effective for the treatment of SLE encephalopathy. Neuwelt (32) studied 26 patients who met the 1999 American Society of Rheumatology diagnostic criteria for lupus encephalopathy and treated them with plasma exchange with or without cyclophosphamide. Symptoms were relieved in 74% of patients. Euler et al (80) used plasma exchange and cyclophosphamide to treat 14 cases of severe SLE, of which 12 had complete remission of clinical symptoms within 6 years of follow-up after cessation of treatment.

SLE encephalopathy has various clinical manifestations, and its pathogenesis and pathophysiological mechanisms are still being explored. Although plasma exchange has been shown to be effective at treating SLE encephalopathy, there is a lack of randomized controlled trials to support the efficacy of plasma exchange. Thus, clinicians must weigh the pros and cons of the risk and costs, as well as other factors, to determine whether plasma exchange should be performed. In addition, large-sample, multicenter, randomized controlled trials are still needed to confirm the therapeutic effect of plasma exchange.

Side Effects of Plasma Exchange for the Treatment of Systemic Lupus Erythematosus Encephalopathy

Although plasma exchange does have a few side effects, potential life-threatening side effects are very rare, and their incidence is $<0.15\%$ (75). Bartolucci et al. (15) analyzed the side effects of plasma exchange as adjuvant treatment for lupus encephalopathy and found five cases: one case of transient hypocalcemia, one case of venous fistula of the indwelling venous catheter, one case of allergic skin reaction to albumin, and two cases of central venous catheter infection.

Plasma Exchange for the Treatment of ANCA-associated Vasculitis Encephalopathy

ANCA-associated vasculitis includes granulomatosis with polyangiitis (GPA: formerly Wegener's granulomatosis), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA: formerly Churg-Strauss syndrome), which is a group of systemic vasculitis characterized by oligovascular oligoimmune necrosis inflammation. ANCAs can be detected in the serum of most patients (81). ANCA-associated vasculitis can lead to systemic organ damage, mainly renal and lung, of which renal damage is more prevalent (70%) (81). However, the manifestations that cause central nervous system damage are not common, with an incidence of ∼5–15%. In addition, there is no significant difference in the incidence of each type of ANCA-related vasculitis-induced central nervous system damage. Usually, central nervous system damage is caused by cerebral or spinal vasculitis and granulomas, and the clinical manifestations are complex, ranging from headache to cognitive impairment, memory loss, epilepsy, disturbance of consciousness, paresthesia, etc. (81). Encephalopathy is not a disease, rather, it is a clinical syndrome that describes global brain dysfunction. Mental status alteration is the most typical manifestation, and changes in personality and/or behavior can indicate deterioration in cognitive functioning, a reduction in the level of consciousness, and specific localizing features of injury, such as seizures, ataxia, tremor, and other focal motor signs. There may also be systemic symptoms, such as headache, fever, vomiting, and loss of appetite. In summary, ANCA-associated vasculitis encephalopathy is a global brain dysfunction caused by ANCA-associated vasculitis (82).

Untreated ANCA-associated vasculitis usually leads to death, with a mortality rate as high as 90% in the natural course of 2 years, since the 1950s, when steroids became the basic treatment for ANCA-associated vasculitis, the five-year survival rate has increased to 48%, and after the 1980s, when steroids began to be combined with cyclophosphamide to treat ANCA-associated vasculitis, symptoms could be relieved in 80–90% of patients (83). Because ANCAs play an important role in the pathogenesis of disease, the use of plasma exchange to clear pathogenic antibodies from circulation, and increase the ability of the reticuloendothelial system to clear immune complexes can be combined with immunosuppressive agents for the treatment of severe ANCA-associated vasculitis (84), such as ANCA-associated vasculitis encephalopathy. However, due to the low incidence of ANCA-associated vasculitis encephalopathy, systematic studies on the treatment of ANCA-associated vasculitis encephalopathy by plasma exchange are lacking. There is currently no description of the specific dose and course of plasma exchange for ANCA-associated vasculitis encephalopathy. According to the reports on plasma exchange for other immune mechanisms mediating neurological diseases, it may be recommended once daily or every other day, with the volume of plasma exchanged per session at 1–1.5 times the estimated plasma volume, and a total of five sessions of plasma exchange should be performed.

Clinical Practice of Plasma Exchange for the Treatment of ANCA-associated Vasculitis Encephalopathy

The treatment of ANCA-associated vasculitic encephalopathy with plasma exchange is uncommon. In 2000, Deshpande et al. (85) reported a 15-year-old girl with renal failure who developed lethargy for 3 months and suffered from decreased appetite and vomiting in the week prior to admission. At 24 h after admission, renal biopsy showed that 29 of 43 glomeruli contained a mixture of fibrous crescents and cells. The patient was diagnosed with microscopic polyangiitis, and the patient was discharged after her condition improved. Three weeks after discharge, the patient had a severe headache and blurred vision, and blood pressure was 139/92 mmHg. Subsequently, the patient experienced three epileptic seizures, followed by a loss of consciousness, and irritability. Phenytoin and carbamazepine were used to control the seizures, and T2-weighted and T2 FLAIR sequences of brain MRI showed multiple increased signal intensities in the peripheral gray matter of the cerebral hemisphere, especially in the occipital cortex. Vasculitis caused widespread cerebral ischemia. EEG indicated changes consistent with encephalopathy. Headache, disturbance of consciousness, and blurred vision were relieved after the first plasma exchange session, the patient then underwent three sessions of plasma exchange, performed every other day, and after five consecutive plasma exchange sessions, cyclophosphamide was administered intravenously. After 2 months, the abnormal signals on brain MRI showed improvement. Nishio et al (86) reported reversible posterior leukoencephalopathy syndrome caused by vascular damage from Wegener's granulomatosis. A female with Wegener's granulomatosis presented severe headache, nausea, and seizures after severe intestinal complications. Blood pressure was 126/60 mmHg, brain CT showed low-density shadows in the bilateral posterior parietal and occipital lobes, and brain MRI showed high-intensity signals on the T2-weighted sequence in the bilateral occipital white matter, parietal lobe, and frontal lobe. Cerebrospinal fluid was normal. Thus, the diagnosis was reversible posterior white matter encephalopathy syndrome. Two courses of methylprednisolone combined with plasma exchange were administered, followed by intravenous cyclophosphamide at 400 mg/week. After 13 days, brain MRI showed that the abnormal signal had almost completely disappeared. The patient's consciousness and mental status also began to recover, and the concentration of PR3-ANCA antibodies decreased from 164 to 15.7 U/ml, and the intestinal symptoms were relieved. However, studies that treat ANCA-associated vasculitis encephalopathy with plasma exchange are very rare, so more studies are needed in the future to provide supporting evidence of the therapeutic effect of plasma exchange.

Plasma Exchange for the Treatment of Acute Demyelinating Encephalomyelitis

Acute disseminated encephalomyelitis is an immune-mediated single-phase acute inflammatory demyelinating disease of the central nervous system, which mainly affects the white matter of the brain, brainstem and spinal cord (87). It is common

in children and young adults, and most cases occur after viral or bacterial infections or within 2–4 weeks of vaccination (<5%) This disease can exhibit acute or subacute onset, with clinical manifestations of encephalopathy (disturbance of consciousness and behavior change) and multifocal neurological defects. In 2007, an international pediatric multiple sclerosis research group noted that encephalopathy not explained by fever is a necessary clinical manifestation of acute disseminated encephalomyelitis (87, 88), and in the prodromal stage, upper respiratory tract infection, and gastrointestinal symptoms are usually observed. The diagnosis is mainly based on clinical manifestations and imaging examination. Typical cerebrospinal fluid changes include increased pressure, increased lymphocytes, increased protein (usually <1.0 mg/l), and normal glucose. The gamma globulin and IgG levels in cerebrospinal fluid can increase, as can myelin basic protein, with a rare oligoclonal band. Electroencephalography examination presents a slow wave on imaging and is of great value in the diagnosis of acute disseminated encephalomyelitis, especially brain MRI, which can detect multiple or extensive white matter or deep gray matter lesions (thalamus and basal ganglia) within 5–14 days after the onset of symptoms (88, 89).

The pathogenesis of acute disseminated encephalomyelitis is not very clear. Cell-mediated immune dysfunction may play a main role. Humoral factors, including antibodies, complement, immune complex, and cytokines, also play an important role (78), so priority is given to immune modulators (90). No randomized controlled trials have been performed on children or adults to determine the best treatment for ADEM. Systemic intravenous large doses of corticoids are currently considered to be first-line therapy (89). Early intravenous methylprednisolone can shorten the course of the disease. Plasma exchange has been reported to be effective in the treatment of acute disseminated encephalomyelitis when the diagnosis of acute disseminated encephalomyelitis is delayed and cannot be early except for infectious diseases where steroid cannot be used, where there are contraindications to steroid, or where the effects of steroid are not obvious in the short term (90).

History of Plasma Exchange for the Treatment of Acute Disseminated Encephalomyelitis

In 1981, Newton et al. successfully treated the first case of acute disseminated encephalomyelitis caused by acute infection through plasma exchange alone (4). Subsequently, Cotter et al. (91) reported the case of a 22-year-old male with acute disseminated encephalomyelitis caused by mycoplasma pneumoniae infection. Eight days after onset, the patient improved after plasma exchange alone. Several studies have shown that plasma exchange can effectively treat acute disseminated encephalomyelitis. However, the current therapeutic effect of plasma exchange lacks the support of randomized controlled trials.

Onset Time of Plasma Exchange for the Treatment of Acute Disseminated Encephalomyelitis

Plasma exchange for the treatment of acute disseminated encephalomyelitis usually takes effect after the first plasma exchange (88). Kanter et al. (92) reported that plasma exchange for the treatment of two cases of acute disseminated encephalomyelitis, in which one improved neurological function within a few hours during the first plasma exchange. Shah et al. (93) noted, in their study of plasma exchange for the treatment of one acute disseminated encephalomyelitis, that the neurological deficit was improved after the first plasma exchange, which was supported by findings reported in the study by Yi et al. (94).

Course of Plasma Exchange for the Treatment of Acute Disseminated Encephalomyelitis

The course of plasma exchange for the treatment of acute disseminated encephalomyelitis has not been determined. Borras-Novell et al. (90) and Stricker et al. (95), in the study of plasma exchange for treating acute fulminant disseminated encephalomyelitis, included four cases of acute disseminated encephalomyelitis. The number of plasma exchange sessions was 3–10, predominantly 5, and plasma exchange was performed once daily with the volume of plasma exchanged per procedure set at one times the plasma volume, with 5% albumin used as replacement fluid, and all patients improved. Therefore, for the treatment of acute disseminated encephalomyelitis, 3–10 sessions are recommended, typically five, performed once a day or every other day, with the volume of plasma exchanged per sessions set at one times the plasma volume and albumin used as the replacement fluid.

Clinical Practice of Plasma Exchange in Acute Disseminated Encephalomyelitis

Miyazawa et al. (96) reported an eleven-year-old patient with acute disseminated encephalomyelitis. Brain MRI revealed extensive multiple high-intensity lesions in the white matter on T2-weighted imaging. Intravenous immunoglobulin (0.125 g/kg/d for 3 days) was administered after 10 days of illness, and 11 days after onset, oral prednisone was initiated at a dose of 60 mg/d, but the patient did not improve. Twelve days after onset, intravenous methylprednisolone was administered (1,000 mg/d) for 3 days. Fourteen days after onset, the patient became comatose, and spinal magnetic resonance T2 weighted images showed cervical segmental spinal cord swelling and abnormally high signal because of the patients' neurologic deterioration. At 17–20 days after onset, three plasma exchange sessions were started using 5% albumin as the replacement fluid. She regained full consciousness, and MRI improved. Lin et al. (97) described plasma exchange for the successful treatment of two cases of acute disseminated encephalomyelitis, including a 26-year-old woman who had a history of rubella vaccination, characterized by disturbance of consciousness, speech, ataxia, and myoclonus. Brain magnetic resonance T2 weighted images revealed high-intensity signals in the brain stem, cerebellum, basal ganglia, thalamus, and white matter of the cerebral ventricles. Initially, she received intravenous methylprednisolone (1,000 mg/d for 5 days and then 500 mg/d for 2 days) and then oral prednisone. However, her neurological function began to deteriorate, and one seizure occurred after 3 days of intravenous methylprednisolone. Five sessions of plasma exchange were initiated, with one session performed every 2 days, and 5% of albumin was used as

the replacement fluid. Her symptoms were alleviated after the third plasma exchange. Another a 65-year-old patient presented with acute disseminated encephalomyelitis, unconsciousness, speech disorder, emotional dissonance, and slow movement. T2-weighted images of the brain magnetic resonance showed high-intensity signals in the bilateral cerebral hemisphere, an elevated number of cells in the cerebrospinal fluid, normal glucose, and moderately elevated protein levels. She received five plasma exchange sessions (once every 2 days, with 5% albumin as the replacement fluid). After the fourth plasma exchange, her symptoms began to resolve.

Since most studies have shown that the standard dose of immunoglobulin for the treatment of acute disseminated encephalomyelitis is 0.4 g/kg/d for 5 days, steroids are usually administered intravenously at a dose of 20–30 mg/kg/d for (3–5 days), followed by oral prednisone at a dose of 1–2 mg/kg/d (87). Miyazawa and Lin et al reported that a poor response to intravenous immunoglobulin and steroids may be related to inadequate immunoglobulin and steroid dosing. Even so, the delayed effects of steroid and immunoglobulin treatments cannot be excluded as a component of symptom resolution because of the narrow time window between symptom improvement and plasma exchange, indicating that plasma exchange can effectively treat fulminant acute disseminated encephalomyelitis. In addition, Stricker et al. (95) reported four cases of acute disseminated encephalomyelitis due to delayed diagnosis and cannot exclude infection, which were significantly improved by plasma exchange alone. Keegan et al. (98) reviewed 59 cases of acute and severe central nervous system demyelination treated with plasma exchange at the Mayo clinic, including 10 patients with acute disseminated encephalomyelitis (ADEM), of whom 40% experienced symptom relief. Therefore, plasma exchange treatment for acute disseminated encephalomyelitis is effective, and few side effects have been reported. However, there is still a lack of support from randomized controlled studies.

Other types of steroid-responsive encephalopathy are very rarely reported, including hypoglycemic encephalopathy (99) and steroid-responsive encephalopathy caused by cholesterol thrombosis (100), and currently, there are no reports on the effects of plasma exchange therapy on these types.

CONCLUSION

In conclusion, plasma exchange is a widely accepted treatment method for autoimmune neurological diseases because it is safe, rapid-onset, and effective. Plasma exchange may be effective for patients with steroid-responsive encephalopathy who do not respond to treatment with steroids in the short term or those who have contraindications for steroid treatment, including patients with Hashimoto's encephalopathy, limbic encephalitis, SLE encephalopathy, ANCA-associated vasculitis encephalopathy, or acute disseminated encephalomyelitis. The main limitation of this study is the lack of systematic treatments reported in the literature. The current data are almost entirely derived from case reports and case analyses. Moreover, plasma exchange is often applied in combination with steroids and other immunosuppressive agents, hence, no high-quality evidence is available to prove the efficacy of plasma exchange on steroid-responsive encephalopathy.

AUTHOR CONTRIBUTIONS

YJ, XT, and XW provided the initial idea and outline of content for the manuscript. All authors contributed content and critically reviewed and edited the manuscript.

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REVIEW
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Neurological Involvement in Primary Systemic Vasculitis

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Primary systemic vasculitis can affect every structure in both the central and peripheral nervous system, causing varied neurological manifestations of neurological dysfunction. Early recognition of the underlying causes of the neurological symptoms can facilitate timely treatment and improve the prognosis. This review highlights the clinical manifestations of primary systemic vasculitis in the nervous system.

Keywords: primary systemic vasculitis, central nervous system, peripheral nervous system, neurological involvement, clinical manifestation

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INTRODUCTION

Primary systemic vasculitis (PSV) can be defined as a heterogeneous group of uncommon diseases characterized by blood vessel inflammation and necrosis. Unlike secondary systemic vasculitis, which usually results from infections, connective tissue diseases, neoplasms, and drugs, PSV is considered to occur with no identified etiology (1). Nevertheless, recent researches have demonstrated that PSV might be associated with farming (2), silica exposure (2, 3), solvent exposure and hydrocarbons (2, 4, 5), allergy and family history of atopy (2, 6). Despite of unknown causes, two mechanisms, deposition of immune complexes and cell-mediated immunity, were found to possibly participate in the pathophysiology of PSV by causing immunological inflammation and necrosis of the vessel wall (7). And according to the classification criteria revised in 1990 by The American College of Rheumatology (8) and in 1994 and 2012 by the Chapel Hill Consensus Conferences (9, 10), the classification of PSV is based primarily on the major size of the affected vessels, although these disease-affected arteries may have overlaps in diameter.

Many neurologists have limited knowledge of PSV because most of these patients are treated by rheumatologists. However, both the central nervous system (CNS) and peripheral nervous system (PNS) are major targets in PSV and may become involved in the earliest stages; thus, patients may be referred to a neurologist first. Since the clinical manifestations of PSV are often non-specific, the differential diagnosis may be challenging.

CNS damage was reported to occur in 24% of cases with PSV, commonly due to antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis and polyarteritis nodosa. The range of clinical expressions of PSV's CNS damage is relatively wide, including cerebrovascular manifestations such as hemorrhagic and ischemic stroke caused by intra/extra-cerebral vascular stenosis, aneurysm, and sinus venous thrombosis, meningeal and brain parenchymal involvement resulted from granulomatosis and perivasculitis, and encephalopathy due to cytokine damage.

Compared with the frequency of central vasculitic involvement, vasculitic peripheral neuropathies are more common and have been reported to occur in 37% of patients with PSV (11), and 25% of patients experience symptoms of peripheral neuropathy at initial presentation (12). Generally, vasculitic peripheral neuropathies result from the inflammation of precapillary arteries in the nerves, such as eosinophilic granulomatosis with polyangiitis (60–80% of patients),

polyarteritis nodosa (50–100% of patients), granulomatosis with polyangiitis (Wegener's granulomatosis, 13–26.6% of cases), cryoglobulinemia (70% of cases), and microscopic polyangiitis (6–18% of cases), usually presenting in a uniform pattern such as multiplex mononeuropathy (accounting for 59–85% of cases) and symmetric polyneuropathy (41% of cases) (11–13). Nerve conduction studies have revealed a much higher frequency of peripheral neurological involvement than that in clinical case series and studies. Asymptomatic vasculitic neuropathy was detected in 21 of 270 cases (7.8%) of biopsy-proven vasculitis (14).

In addition, the introduction of nerve sonography, single-photon emission computed tomography (SPECT), magnetic resonance imaging (MRI), magnetic resonance angiography (MRA), magnetic resonance spectroscopy (MRS), and apparent diffusion coefficient (ADC) have greatly improved the diagnostic rate and accuracy of vasculitic neuropathy.

SEARCH STRATEGY

We performed an advanced literature search in PubMed and EMBASE for the period January 1, 1990, through September 1, 2017, using as a search query "systemic vasculitis" "nervous system." Eligible studies were included according to the following criteria. Only human studies that were written in English were considered. All patients included in the studies were diagnosed according to the classification criteria defined by the American College of Rheumatology or the Chapel Hill Consensus Conference. Retrospective and prospective studies were included to determine the frequency of neurological manifestations. Case reports and case series were added in the reference list only when unusual features were described. Pediatric studies were excluded because the clinical features of children and newborns are different.

LARGE-VESSEL VASCULITIS

Large vessels were defined as the aorta, vena cava, and their major branches. Large-vessel vasculitis is composed of Takayasu arteritis and giant cell arteritis.

Takayasu Arteritis

Takayasu arteritis (TA) is a rare type of primary chronic inflammatory disease, causing stenosis, occlusion and aneurysm of arteries. TA mainly affects large-caliber arteries such as the aorta and its major branches in patients younger than 40 years old (more than 90% of patients are younger than 40), with a female predominance (female to male ratio is 10:1), and is more common in Asians (1). Studies have shown that more than half of patients with TA show neurological manifestations (15, 16) that range from dizziness/headaches to ischemic or hemorrhagic stroke.

Dizziness and headache are the most common complaints in patients with TA with neurological complications, accounting for ∼78.1% (214/274) and 25.5% (70/274), respectively (16). However, headache and dizziness do not necessarily indicate CNS involvement. Visual disturbances affect 4.6–59.3% of patients, and 4–21.9% of TA patients with neurological manifestations were found to have syncope as the main manifestation.

Cerebrovascular complications have always been the focus of researchers. Transient ischemic attack accounts for 3–22.2% of the nervous system manifestations caused by TA. Stroke, as the most severe complication of TA, was found to occur in 10–20% of cases (16–18). Due to lack of knowledgement, the median and average delay between symptom onset and the diagnosis of TA are 2 years (19) and 52.4 months (16), respectively, which delays the treatment of vasculitis. The majority of the strokes caused by TA are ischemic strokes, mostly due to multiple and severe stenosis or occlusive lesions in the aortic arch and its major branches. Couture and colleagues (19) evaluated the impact of stroke on the prognosis of TA patients, and after a median of seven years of follow-up, 59% of the patients had neurological deficits, 35% suffered from stroke recurrence and 24% had epilepsy. However, cerebral aneurysms and subarachnoid hemorrhage are rarely observed in TA patients. The incidence of aneurysm in TA patients is no higher than that in the general population. However, when such incidents occur, aneurysms in TA patients have a high rate of multiplicity and commonly occur in the vertebrobasilar arterial system (20). Posterior reversible encephalopathy syndrome (PRES) is an uncommon neurological complication in TA patients, mainly affecting women under the age of 30, presenting as headache, epilepsy, and neurological deficits in most patients. The pathophysiological mechanism has been suggested to be both endothelial injury and hypertension caused by TA, and the use of immunosuppressants such as cyclosporine and tacrolimus may also be a factor in the development of PRES since they can also induce endothelial dysfunction (21).

In addition, rare complications such as Horner's syndrome and intracranial granulomatosis have been reported as initial manifestations of TA. Other unusual neurological manifestations of TA that have been reported include brachial plexus palsy due to axillary artery aneurysm, unilateral sensorineural hearing loss, subclavian stealing syndrome, Moya-Moya syndrome, multiple cranial nerve palsies, cavernous sinus syndrome, and hypertrophic pachymeningitis.

Giant Cell Arteritis

Giant cell arteritis (GCA) is the most common large vasculitis in Western countries and mainly affects extracranial branches of the carotid artery and/or the aorta and its large arterial branches, usually affecting people over the age of 50 (22).

Neuro-ophthalmological manifestation is the most frequent and serious event among neurological complications of GCA, accounting for 20–28.8% of affected patients (23, 24), with 15% of them suffering from permanent visual loss (25). Visual symptoms may be caused by ischemic optic neuropathy and retinal ischemia, among which anterior ischemic optic neuropathy accounts for the largest proportion.

Cerebrovascular disease is another severe neurological manifestation, occurring in ∼5% of all GCA-related neurological complications. According to recent studies, the risk ratio of cerebrovascular accident in patients with GCA vs. non-GCA comparators was 1.40 (26), and the risk of cerebrovascular

complications was higher during the first year (or month) after GCA diagnosis (27, 28), which means that cerebrovascular events often occur during the active period of the disease. Epidemiological study shows that stroke is observed in 1–3% of patients (25), among which cerebral infarction is the most common (58%), followed by subarachnoid hemorrhage (24%), and cerebral hemorrhage (18%) (29). The main reasons are considered to be, on the one hand, ischemia or occlusion caused by direct involvement of carotid and vertebrobasilar arteries and, on the other hand, atherosclerotic changes of the vessels caused by chronic inflammation. The incidence of vertebrobasilar artery vascular accident in patients with GCA (35%) has been shown to be higher than that of the general population (which is usually <15%) (27, 28), and one study showed that audiovestibular dysfunction is not uncommon in GCA patients (30). It is interesting to note that in a retrospective study (25), researchers found that most GCA patients who experienced a vertebrobasilar stroke had neurological symptom onset after the start of corticosteroid treatment. However, it is still being debated whether this situation is due to a direct effect of vasculitis or vascular occlusion promoted by the effects of corticosteroids.

Peripheral nervous system involvement was found in 1–14% of GCA patients, presenting as cranial neuropathies, multiple mononeuropathy, or polyneuropathies (24); existing case reports include multiple cranial nerve palsy, trigeminal autonomic cephalalgia, occipital neuralgia, Horner syndrome, peroneal nerve palsy, cervical radiculopathy, brachial plexopathy, hypertrophic pachymeningitis, and cavernous sinus syndrome.

MEDIUM-VESSEL VASCULITIS

Medium vessels refer to the main visceral arteries and veins and their initial branches. Medium-vessel vasculitis consists of polyarteritis nodosa and Kawasaki disease.

Polyarteritis Nodosa

Polyarteritis nodosa (PAN) is a rare systemic necrotizing vasculitis mainly involving medium and small vessels, causing microaneurysm, stenosis, and thrombosis, therefore leading to ischemia or hemorrhage of the supplied tissues. PAN affects women more often than men, usually with an onset between 40 and 50 years of age (31). The condition may affect any organ; however, the most frequently affected organs are the peripheral nerves, followed by muscles, joints, kidneys, skin, gastrointestinal tract, and heart (32).

Involvement of the CNS has been reported to exist in 20–40% of PAN cases (33) and mainly occurs at late stages (2–3 years) (34). CNS involvement has been recognized as a sign of a poor prognosis, and the expected mortality rate at 5 years is 26% (35, 36). The most common manifestation of CNS involvement includes diffuse encephalopathy and a deficit of focal neurological function. Diffuse encephalopathy may present as new onset seizure and headache, reduced level of consciousness or altered vision, among which some of the cases also suffer from reversible encephalopathy syndrome (37–39). The main manifestations of focal CNS involvement include cerebral infarction (which occurs in 13–17% of PAN patients), hemorrhage, multifocal encephalopathy and episodes of neurological dysfunction that mimic multiple sclerosis (33, 40). Intracranial hemorrhage is a rare complication of PAN, and subarachnoid hemorrhage and intracerebral hemorrhage caused by aneurysms have been reported in PAN cases. The features of these aneurysms were found to be multiple, small in size, and equally located in the infratentorial and supratentorial arteries (41).

Reichart et al. (33) investigated early lacunar strokes complicating PAN and revealed that 33.3% (5/15) of strokes occurred within 1 month after the onset of PAN and 15% (2/13) shortly after the initiation of corticosteroids; ischemic strokes occurred during corticosteroid treatment in 77% (10/13) of the patients, 80% (8/10) of which occurred within 6 months after corticosteroid initiation and 50% (5/10) within 3 weeks. Combined with the results of prior studies showing that all strokes occurred while the patients were under adequate corticosteroid treatment, it was suggested that the promoting effect of corticosteroids in stroke might work by two mechanisms (33). For one thing, corticosteroids promote platelet aggregation in cerebral medium-sized arteries by increasing thromboxane A2, quickly causing a lacunar stroke. Lacunar strokes appearing 1 or more months after initiation of corticosteroids can be explained by the promoting effect of corticosteroids on thrombotic microangiopathies.

PNS involvement is the most common complication of PAN and occurs in 60–70% of cases; it has an onset early in the course of the disease, mostly within a few months of diagnosis (42). The common patterns of PNS involvement include mononeuropathy, polyneuropathy and mononeuritis multiplex, the pathophysiology of which has been recognized as vasculitis of the vasa nervorum. Sudden onset asymmetrical sensorimotor mononeuritis multiplex, which mainly affects the lower extremities, and insidious symmetrical peripheral neuropathy are typical and common in PAN (31). In addition, patients with PAN may also develop pachymeningitis (43) and present with headache or cranial nerve palsy. Sudden bilateral hearing loss (44) and visual alterations caused by optic neuropathy (45) have also been reported.

Kawasaki Disease

Kawasaki disease (KD) is a systemic vasculitis that mainly affects medium-sized vessels, occurring predominately in children under 5 years of age. Neurological complications of KD have been described in children, such as encephalopathy, seizures, cerebral infarction, intracranial hemorrhage, ataxia, and cranial nerve palsy (46). However, although rare cases of first onset have also been reported in adult patients, most reported cases are in young adults and the manifestations are due to late-onset sequelae instead of new-onset active disease. We found one case (47) describing a 20-year-old young adult with a history of KD suffering from subarachnoid hemorrhage due to an intracranial aneurysm with a stalk-like narrow neck, located at the trunk of the middle cerebral artery. As the researchers mentioned, coronary aneurysms in KD also arise in places where no branch exists. Therefore, non-bifurcation intracranial aneurysm might

be related to KD and might cause intracranial hemorrhage in young adults as a late sequela.

Small-Vessel Vasculitis

Small-vessel vasculitis refers to necrotizing inflammation in the wall of small intraparenchymal arteries, arterioles, capillaries, and venules, and to a secondary degree in medium-size arteries. Vascular and perivascular inflammation leads to fibrinoid necrosis and consequently vascular necrosis, occlusion and thrombosis (10). The disease consists of two major groups, ANCA-associated vasculitis and immune complex small-vessel vasculitis.

ANCA-Associated Vasculitis

ANCA-associated vasculitis is defined as necrotizing small-vessel vasculitis with few or no immune deposits, mostly associated with myeloperoxidase (MPO) ANCA or proteinase 3 (PR3) ANCA (10). Among the cases of ANCA-associated vasculitis, CNS involvement is more common in granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) than it is in eosinophilic granulomatosis with polyangiitis (EGPA) (48). Nevertheless, peripheral nerve involvement is more prevalent in EGPA than are MPA and GPA (49).

Granulomatosis With Polyangiitis (Wegener's)

Granulomatosis with polyangiitis (GPA) is characterized by necrotizing granulomatous inflammation usually associated with antibodies against PR3 and most commonly involves the upper and lower respiratory tract, and sinonasal inflammation and necrotizing glomerulonephritis are frequently present (10). Neurological complications have been shown to be present in 29–50% of all cases (50–52).

CNS involvement occurs in 7–11% of GPA patients (50, 53, 54), and when isolated cranial nerve palsies are included, the rate is 8–28% (51, 54). Since GPA can commonly involve sinonasal structures and cause granulomatous inflammation, which is capable of invading neighboring structures, the orbit, mastoid, optic nerve, chiasma, cranial nerves, meninges, and pituitary gland might be compromised, presenting as oculomotor dysfunction, mastoiditis, visual disturbances, cranial nerve palsy, headache, and endocrine dysfunction. In addition, small and medium arteries in the cranium can be involved, causing ischemia, or hemorrhage in different vascular territories (55). Cranial nerve palsy was reported to occur in 4.7–6% of GPA patients, among which the most commonly affected cranial nerves are II, VI, and VII (50, 51). The pituitary has been reported to be affected in 1.1–1.3% of GPA patients (56, 57). Meningeal pachymeningitis usually occurs i4n the early stages of GPA, with lower incidences of accompanying systemic symptoms (58), which is perhaps due to granulomatous erosion of the skull base in the early phase and may lead to a delay of diagnosis (52). The most common symptom is headache, followed by cranial nerve palsy and symptoms due to venous sinus occlusion. Vasculitis involvement can cause ischemic and hemorrhagic complications of the brain and spinal cord (58). Dysfunction of intracranial arteries may cause PRES, presenting as various symptoms (59–62). Hypophysitis has been widely reported as one of the CNS complications of GPA, and its clinical manifestations vary according to the specific sites involved. Panhypopituitarism might occur as a consequence of granulomatous inflammation of both the anterior and posterior pituitary (56). Anterior pituitary involvement may influence the release of antidiuretic hormone and present as diabetes insipidus, which was shown to occur in 47 of 58 GPA patients (81%) with sellar involvement, according to an analysis of cases performed by Peters et al. (63). Posterior pituitary inflammation may cause diminished secretion of many hormones, leading to secondary hypogonadism (occurred in 32 out of 58 sellar involved GPA patients, 55%), secondary hypothyroidism (20 out of 58 sellar involved GPA patients, 34.5%), secondary adrenal insufficiency, secondary growth hormone deficiency (19 of 58 sellar involved GPA patients, 32.8%). Compression of the pituitary stalk can result in hyperprolactinemia (5 of 58 sellar involved GPA patients, 8.6%) and galactorrhea, and visual alteration may occur if the optic chiasm is compressed (56, 57).

PNS complications have been reported to occur in 11–44% of GPA patients (54), which occurs milder and later in the course of the disease than in other ANCA-associated vasculitis (64), presenting mainly as recurrent mononeuropathies, mononeuritis multiplex, or symmetric polyneuropathy due to ischemia caused by vasculitic inflammation of the vasa nervorum. As the most frequent manifestation, distal symmetrical sensory neuropathy was reported in 7–10% of cases, followed by motor mononeuritis multiplex in 2–12% (51, 53). Commonly, peroneal (90–95%), tibial (38–55%), ulnar (35–45%), and median (26–36%) nerves are involved (29, 51).

Eosinophilic Granulomatosis With Polyangiitis (Churg-Strauss)

The characteristics of eosinophilic granulomatosis with polyangiitis (EGPA) is an eosinophil-rich and granulomatous inflammation that often involves the respiratory tract and is associated with asthma and eosinophilia (10).

Neurological involvement is common in EGPA, accounting for up to 60% of cases and usually manifesting as peripheral neuropathy that tends to present before visceral involvement (29). Therefore, early detection of peripheral nerve involvement is fundamental for early diagnosis and treatment of EGPA. The most common peripheral neurological manifestation is multiple mononeuropathy (accounting for 68% of cases with peripheral neuropathy), followed by distal symmetric polyneuropathy (28%) and asymmetric polyneuropathy (4%) (65). Since mononeuritis multiplex is typical in acute systemic vasculitis, the initial symptoms commonly present as dysesthesia, paresthesia, and edema in distal limbs, especially the lower limbs. The condition will gradually progress into asymmetrical polyneuropathy and may affect motor nerves, leading to muscle atrophy. Electrophysiological studies have shown decreases in the amplitude of sensory nerve action potentials and compound muscle action potentials, indicating the presence of axonal injury (66).

CNS involvement in EGPA is rather rare, accounting for only 6–10% of all cases (67). Cerebral infarctions and intracerebral hemorrhage resulting from intracranial vasculitis

are the most common CNS presentations of EGPA. In addition, rarer manifestations have been noted, such as subarachnoid hemorrhage, cranial nerve palsy, encephalopathy, epilepsy, hydrocephalus, headache, sinus venous thrombosis, spinal hemorrhage, meningeal involvement, and optic neuropathy.

Microscopic Polyangiitis

Microscopic polyangiitis (MPA) presents with non-granulomatous inflammation with few or no immune deposits in the walls of the affected vessels, mainly associated with antibodies against MPO. Necrotizing glomerulonephritis and alveolar hemorrhage are common complications (10). Peripheral neurological involvement occurs in 55 to 79% of cases with MPA, with no special manifestations compared with those of other ANCA-associated types of vasculitis (mainly presenting as polyneuropathy and mononeuropathy); (64). CNS involvement in MPA is rare and was reported to be able to manifest as intracerebral infarction or hemorrhage, subarachnoid hemorrhage, hypertrophic pachymeningitis, PRES or spinal cord involvement (68).

Immune Complex Small-Vessel Vasculitis

Immune complex small-vessel vasculitis is characterized by moderate to marked deposits of immunoglobulin and/or complement components in the small vessel walls.

Antiglomerular Basement Membrane Disease

Antiglomerular basement membrane (anti-GBM) disease, also called Goodpasture syndrome, is a vasculitis affecting glomerular capillaries and/or pulmonary capillaries with deposition of anti-GBM autoantibodies on GBM, accounting for 5% of adult patients with glomerulonephritis and leading to acute renal failure in approximately half of the patients. Lung involvement results in pulmonary hemorrhage, and renal involvement leads to glomerulonephritis with necrosis and crescents, which are the classic presentations of anti-GBM disease (10, 69). Neurological involvement is uncommon. According to the rare cases reported (69–73), PRES is the most frequent neurological complication. All patients reported are younger than 40 and they all manifested as hypertension, renal failure, and seizures. Destruction of the blood-brain barrier resulting from inflammatory endothelial injury and increased capillary filtration due to hypertension are important factors in the pathophysiology of PRES in GBM patients.

Cryoglobulinemic Vasculitis

Cryoglobulinemic vasculitis (CV) is defined as vasculitis with cryoglobulin immune deposits affecting small vessels (predominantly capillaries, venules, or arterioles) caused by chronic inflammation, autoimmune disorders, and lymphoproliferative disorders, frequently involving skin, glomeruli, and peripheral nerves (10). Most cases of cryoglobulinemic vasculitis result from infection, B-cell lymphoproliferative disorders and autoimmune diseases, among which hepatitis C virus infection is the cause in ∼80% of cases (74). In a study of 242 cases with non-infectious mixed cryoglobulinemia vasculitis (75), 117 patients (48%) were found to have no identified causal factor, also defined as idiopathic. However, no study has evaluated the neurological involvement of idiopathic cryoglobulinemia vasculitis alone. For patients with mixed CV, PNS involvement is not uncommon and typically starts with polyneuropathy that affects the sensory nerves initially and later the motor nerves, predominantly involving the lower limbs. CNS involvement is rare, and studies have shown that mixed CV may cause cerebrovascular events, PRES, hydrocephalus and intracranial hypertension (29, 76).

IgA Vasculitis (Henoch-Schönlein Purpura)

IgA vasculitis (IgAV) is characterized by IgA1-dominant immune deposits affecting small vessels, often involving the skin and gastrointestinal tract and frequently causing arthritis (10). The majority (75%) of cases occur in young people no more than 20 years of age (77), and CNS involvement has been reported to manifest as headache, decreased consciousness, seizures, focal neurological deficits, and visual and verbal abnormalities. However, PNS involvement has been documented as neuropathies of the brachial plexus and facial, peroneal, femoral and ulnar nerve, and in addition, Guillain–Barre syndrome and mononeuritis multiplex (78). Rare cases of IgAV-induced neurological manifestations have been reported in adult patients as ischemic stroke, axonal sensorimotor polyneuropathy (79, 80), mononeuritis multiplex (81, 82), acoustic neuritis, facial nerve palsy (83), intracerebral hemorrhage (84), anterior ischemic optic neuropathy (85), focal seizures (86), and encephalopathy (87).

Hypocomplementemic Urticarial Vasculitis (anti-C1q Vasculitis)

Hypocomplementemic urticarial vasculitis (HUV) is a kind of vasculitis accompanied by urticaria and hypocomplementemia affecting cutaneous small vessels and is associated with anti-C1q antibodies, commonly causing urticaria and multiorgan involvement such as glomerulonephritis, arthritis, obstructive pulmonary disease, and ocular inflammation (10). HUV may be induced by connective tissue diseases, infections (such as hepatitis B, hepatitis C and infectious mononucleosis), neoplasms and drugs; however, most cases of HUV are idiopathic (88). Neurological involvement has been occasionally reported as pseudotumor cerebri (89), lower cranial nerve (VIII, IX, and X) palsies (90) and peripheral nerve involvement such as asymmetrical multifocal axonal sensory neuropathy.

VARIABLE-VESSEL VASCULITIS

Variable-vessel vasculitis refers to vasculitis with no predominant type of vessel involved that can affect vessels of any size (small, medium, and large) and type (arteries, veins, and capillaries) (10).

Behçet's Syndrome

Behçet's syndrome is a vasculitis occurring in patients with Behçet's disease (BD) and can affect arteries or veins and lead to a relapsing inflammatory disorder in almost any tissue, with oral and genital ulcerations and uveitis as its most typical symptoms

(41). Neurological manifestations of BD, which are called neuro-BD (NBD), occur in 1.3–59% of all cases and usually affect patients aged between 20 and 40 years, with a male predominance (the male to female ratio is 2.8:1) (91–95). NBD commonly appears 3–6 years after other systemic involvement (92, 96, 97) and is considered to be caused by perivasculitis.

The manifestations of neurological involvement can be caused by either CNS parenchymal inflammation or vascular complications in the nervous system, with a reported prevalence of 67–76 vs. 12–20% in all NBD cases (93, 98). The former is considered to be caused by small vasculitis, leading to axonal damage and gliosis, frequently affecting the brain stem (occurs in 25–50% of all parenchymal NBD cases) (92, 93, 99, 100), thalamus and basal ganglia, and, only rarely, the white matter and spinal cord. The main clinical manifestations are subacute cranial neuropathy, ophthalmoparesis, meningoencephalitis, and alteration of cerebellar, pyramidal and extrapyramidal function. Uncommon symptoms such as subcortical dementia, stroke and transverse myelitis have also been reported (91, 101). Vascular complications mainly result from cerebral venous thrombosis (CVT) due to large vessels endothelial cell activation, and rarely, aneurysms due to perivasculitis to the vasa nervorum (91). CVT in BD mainly causes focal neurological deficits and seizures in young men (102). However, not all epileptic seizures in NBD patients result from CVT, and brainstem lesions may also lead to complex partial seizures (103).

In addition, perivasculitis to the vasa nervorum may also cause PNS involvement. However, this condition is extremely rare and was found in merely 8 out of 1,031 cases (0.8%); thus, its relationship with BD is still doubtful (91).

Cogan Syndrome

Cogan syndrome (CS) is a sequence of clinical manifestations due to a chronic immunological inflammatory multisystem disease of unknown origin, characterized by recurrent episodes of keratitis, vestibuloauditory dysfunction, and systemic vasculitis, frequently leading to visual loss, vertigo, sensorineural hearing loss, tinnitus and systemic manifestations (10). The syndrome mainly affects children and young adults with an average age at onset of 38 years (SD, 15.1 years; range, 9–70 years) (104).

It is worth noting that complications of the eyes and ears do not always occur at the same time (sometimes up to 9 years apart) (105) and in 20% of cases, vestibuloauditory symptoms can be the only presentation (104). Therefore, although the vestibuloauditory involvement in Cogan syndrome is mainly due to inflammation of inner ear structures rather than neurological involvement (105), its manifestations can be easily misdiagnosed as central acute vestibular syndrome of vascular origin, Ménière's disease or vestibular migraine, which are common in neurological out-patients. According to a study that enrolled 60 cases of CS at Mayo Clinic (104), all cases suffered from hearing loss, 90% of the cases experienced vertigo, and tinnitus (80%), ataxia (53%), and oscillopsia (25%) were also common during the course of the disease. Hearing loss is typically sudden, mainly involves bilateral high frequencies, and the decline in hearing fluctuates and progresses gradually. Vestibular function is commonly damaged bilaterally (accounting for 74% of cases that underwent a caloric test) and vestibular symptoms may last for days to weeks (sometimes indefinitely) with no resolution (104, 106). The vestibuloauditory symptoms listed above may recur in 1–13 years after onset (occurs in 22% of patients) (107).

TABLE 1 | Common CNS and PNS involvements of primary systemic vasculitis.

PSV	CNS involvement	PNS involvement
Takayasu arteritis	Dizziness (78.1%), headache (25.5%); visual disturbances (4.6–59.3%); syncope (4–21.9%); stroke (10–20%);	Rare
Giant cell arteritis	Neuro-ophthalmological damage (20–28.8%), stroke (1–3%), vertebrobasilar artery vascular accident (35%);	1–14% of cases; cranial neuropathies, multiple mononeuropathy, polyneuropathies;
Polyarteritis nodosa	20–40% of cases; Diffuse encephalopathy, cerebral infarction (13–17%);	60–70% of cases; Mononeuropathy, polyneuropathy, mononeuritis multiplex;
Granulomatosis with polyangiitis	8–28% of cases; Cranial nerve palsy (4.7–6%, mainly II, VI, and VII), pituitary damage (1.1–1.3%), meningeal pachymeningitis, ischemic, and hemorrhagic complications of brain and spinal cord, PRES	11–44% of cases; Recurrent mononeuropathies, mononeuritis multiplex, symmetric polyneuropathy
Eosinophilic granulomatosis with polyangiitis	6–10% of all cases; Cerebral infarctions and intracerebral hemorrhage	∼60% of cases; Multiple mononeuropathy (68% of PNS cases), distal symmetric polyneuropathy (28%) and asymmetric polyneuropathy (4%)
Microscopic polyangiitis	Rare	55–79% of cases; polyneuropathy, mononeuropathy
Behçet's syndrome	CNS parenchymal inflammation (67–76% of all NBD cases): subacute cranial neuropathy, ophthalmoparesis, meningoencephalitis, alteration of cerebellar, pyramidal, and extrapyramidal function; Vascular complications in the nervous system (12–20% of all NBD cases): cerebral venous thrombosis, aneurysms	Extremely rare: 0.8% of BD cases
Cogan syndrome	Ischemic stroke (2.5–3%), encephalitis (5–6%), meningitis (5–22%), encephalopathy, myelopathy, optic nerve disorders, aneurysm, and cerebral venous thrombosis	Peripheral neuropathy (1–12.5%), cranial neuropathy (1–10%, mainly II, V, VI, and VII) and myopathy

Neurological involvement was reported in 29–56% of cases and usually occurs after eye and ear manifestations (106, 108). CNS involvement may manifest as ischemic stroke (accounting for 2.5–3% of cases reported), encephalitis (5–6%), meningitis (5–22%), encephalopathy, myelopathy, optic nerve disorders, aneurysm, and cerebral venous thrombosis. PNS conditions in Cogan syndrome patients have been reported as peripheral neuropathy (1–12.5%, frequently mononeuritis multiplex), cranial neuropathy (1–10%, mainly cranial nerve II, V, VI, and VII) and myopathy (106).

CONCLUSION

Neurological involvement is a common complication of PSV (**Table 1**), and neurologists play an important role in the identification and diagnosis of PSV patients with otherwise unexplained neurological symptoms as their chief complaint. This article summarizes the neurological manifestations of PSV and hopes to improve neuroscientists' understanding of this broad range of diseases.

AUTHOR CONTRIBUTIONS

SZ conceived the article and wrote the manuscript. DY and GT reviewed and edited the manuscript. All authors read and approved the manuscript.

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Hashimoto's Encephalopathy and Seizure Disorders

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Hashimoto's encephalopathy (HE) is a rare, clinically heterogeneous condition associated with positive thyroid autoantibodies. It is increasingly recognized as an important and treatable cause of autoimmune encephalopathy. Thyroid-associated antibodies such as thyroperoxidase (TPO) antibody, thyroglobulin (TG) antibody, and thyrotropin receptor (TR) antibody were found in HE patients with seizure disorders. Although antithyroid antibodies are required for the diagnosis of HE, their role in the pathogenesis of HE remains uncertain. Instead of playing a key role in the pathophysiology processes of HE, it is suggested that thyroid-associated antibodies are hallmarks of HE. Seizure disorders were found in approximately two-thirds of HE patients, and common anticonvulsant therapy alone is usually ineffective. Some patients did not respond to any antiepileptic drugs. The use of immunotherapy can effectively control seizure disorders. Electroencephalography and imaging findings are not specific to HE patients and can also be seen in other causes of encephalopathies. However, the prognosis in the majority of patients with HE was usually good if it is diagnosed and treated correctly.

Keywords: Hashimoto's encephalopathy, seizure, immunotherapy, autoimmune encephalopathy, diagnosis

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INTRODUCTION

Hashimoto's encephalopathy (HE) is a rare clinical condition first described by Lord Brain (1). The prevalence of HE in the adult population is estimated to be 2.1/100,000 subjects in a study examining patients with unexplained encephalopathy with detectable antithyroid antibodies (2). It has become increasingly recognized in the last few years as an important and treatable cause of autoimmune encephalopathy.

The incidence of HE is higher in female (about 70–88% of female patients). The average age of onset is about 40 years old (3). Clinically, there may be various manifestations such as seizure disorders, rapidly progressive cognitive impairment, and stroke-like attack. The course of the disease may be recurrence–remission or gradual progression. Characteristically, these patients usually have high titers of thyroperoxidase antibody (TPOAb) and respond well to corticosteroid therapy. Because of these features, an acronym, steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT), was used in some research articles (4, 5). It was also called NAIM (non-vasculitic autoimmune inflammatory meningoencephalitis) because of the absence of cerebral vasculitis seen on brain biopsies in affected individuals (6). In fact, HE lacks a clear definition, and the symptoms often overlap with other neuronal antibody-associated autoimmune encephalopathies (7).

HE can be regarded as a possible immune encephalopathy due to its possible immune-mediated mechanism. The diagnosis criteria for HE remain a diagnosis of exclusion because its antibodies are not specific to HE patients. Thyroid antibodies and α-enolase antibodies (anti-NAE) have been detected in healthy people and patients with other autoimmune diseases. Although hundreds of HE

patients have been reported in the literature, the specific mechanism of HE is not fully understood.

It is suggested that HE is better termed autoimmune encephalopathy associated with thyroid antibodies because antithyroid antibodies are essential laboratory features of the diagnosis of HE (8). Seizure disorders were seen in about 60–70% patients, and many of them showed as the first manifestation of the disease. HE was often misdiagnosed with other diseases by the neurologist and pediatrician, especially doctors not majored in epilepsy. Awareness of HE has increased in the last few years, but it is still rather uncommon. HE is easy to be misdiagnosed because of the low incidence and the atypical symptoms. However, if it is diagnosed and treated correctly, the prognosis of the disease is good. Therefore, it is important to recognize the characteristics of HE. In this article, we review the characteristics of seizure disorders and the diagnostics of HE.

CLINICAL PRESENTATION OF SEIZURE DISORDERS IN HE

HE is a rare, clinically heterogeneous condition with increased antithyroid autoantibodies (9). One report divided HE into two classes: vasculitic type and indolent progressive type; the former manifested with repetitive stroke-like events, such as transient hemiparesis, aphasia, and ataxia with no or only slightly cognitive impairment. The latter shows an insidious onset of altered consciousness, seizure attacks, hallucinations, or psychotic disorders. Seizures, tremors, myoclonus, and stupor can occur in both types (10). Unusual presentations of HE like headache and peripheral neuropathy were also reported in some cases (7, 11).

Seizures are common in patients with HE. Approximately two-thirds of patients of HE experience seizure disorders. Seizure presentations include progressive focal or generalized onset seizures and new-onset status epilepticus (SE) (12–14). SE includes epilepsia partialis continua (EPC), and non-convulsive SE (NCSE) has been reported in 12% of HE patients (9, 14, 15). The most common seizure pattern was focal onset seizures with secondary generalization (4, 16). Seizure disorders are more common in children (present with seizures about 80%) than in adults and change in level of consciousness (17, 18). The type of epileptic manifestation may be generalized or focal, convulsive as well as myoclonic. EPC, a form of SE characterized by recurrent seizures that can last for hours, days, or even longer can also be found in HE individuals (19). Varassi et al. (20) describe a man with recurrent episodes of unilateral left-sided auditory hallucinations. The patient did not respond to antiepileptic drugs, such as diazepam, levetiracetam, lacosamide, and phenytoin. The patient later developed a refractory NCSE presenting with a stuporous state. Visual hallucinations were also reported before the onset of seizures in HE patients (21). Presentation of faciobrachial dystonic seizures was reported in a 58-year-old patient diagnosed with HE. Screening of autoimmune antibodies especially voltage-gated potassium channels (VGKCs)/leucine-rich glioma inactivated 1 (LGI1) antibodies were negative. Instead, the finding of high titer of serum antithyroid and the dramatic response to steroid therapy led to the diagnosis of HE (9).

POSSIBLE MECHANISMS OF SEIZURE DISORDERS IN HASHIMOTO'S ENCEPHALOPATHY

The mechanisms of seizure disorders in HE are still not fully understood. Possible mechanisms including autoimmune mechanisms may play a variety of roles in the pathophysiology of epilepsy because HE belongs to a spectrum of autoimmune encephalitis (22). Thyroid-associated antibodies such as TPOAb, thyroglobulin antibody (TgAb), thyrotropin [thyroid-stimulating hormone (TSH)] receptor antibody (TRAb or TSHRAb), and α-enolase antibody targets for cortical neurons and endothelial cells were found in HE patients with epilepsy. Although antithyroid antibodies are important when HE is diagnosed, the role in the underlying pathogenesis mechanism remains unclear, and no direct correlation between serum antibody titers and clinical state of disease severity is found. The pathogenic roles of antibodies in HE have been questioned. Rather than playing a direct role in the pathophysiology of HE, it is suggested that thyroid-associated anti-TPO is a hallmark of HE (23). Yuceyar et al. reported a case with a family history, and they hypothesized that a genetic factor may participate in the pathogenesis of HE (24). Besides, other research suggested that toxic effects of TSH, brain hypoperfusion, and edema-induced cerebral dysfunction due to autoimmune-mediated vasculitis may also play a role in the mechanisms of seizure disorders (8, 25).

EVALUATION OF SEIZURE DISORDERS IN PATIENTS WITH SUSPECTED HE

For patients with suspected HE, diagnostic testing of blood and cerebrospinal fluid (CSF), electroencephalography, and neuroimaging such as brain computed tomography (CT) scan and magnetic resonance imaging (MRI) are important in differential diagnosis from other causes of neurologic disease, such as inflammation diseases, electrolyte and metabolic disturbances, multiple sclerosis, toxins, and tumors.

LABORATORY

Thyroid hormone dysfunction ranging from hypothyroid to thyrotoxic was found in HE. Most cases occur under euthyroid and hypothyroid metabolic conditions. TPOAb in serum is one of the most frequent signs of HE, ranging from several times to several 100 times higher than normal controls. Serum TgAb also increased (71%) in some patients; however, high-titer thyroid antibodies are not HE specific. They present in about 13% of healthy subjects and even higher (27%) in white women older than 60 years. Thyroid antibodies were also found increased in patients with other autoimmune encephalitis. Some scholars found NAE autoantibodies in the serum of patients with HE and considered that it may be a specific serological biomarker for the diagnosis of HE (25).

CSF examination may be needed in order to exclude other infectious or autoimmune encephalitis. Ilias et al. found that about 75% of individuals with HE presented with CSF antibodies, which are absent in the healthy individuals (26). The main

changes of cerebrospinal fluid in patients were mild to moderate increase in protein and normal or elevated cerebrospinal fluid pressure. The increased rates in two studies were 78 and 66%, respectively (27). Lymphocytes can be slightly higher, sometimes with oligoclonal bands. Some patients might have other antibodies in addition to anti-TPO. Thus, it is necessary to detect all autoimmune antibody such as gamma-aminobutyric acid A receptor (GABAAR), N-methyl-D-aspartate receptor (NMDAR), LGi1, and antinuclear antibodies (ANA) (28).

NEUROIMAGING

MRI findings of HE varied from normal to diversified appearance, including ischemic lesions, white matter demyelination, and focal vasogenic edema (29). Many studies showed that the CT/MRI imaging of HE may sometimes simulate an ischemic stroke, multiple tumors, granulomas, or even a degenerative disease (30–32). The diverse neuroimaging features of HE may be due to different or diverse pathological process stages of HE when performing CT/MRI scan. Various and mostly unspecific abnormalities were found by MR and/or CT in about 50%. Single photon emission computed tomography (SPECT) examinations showed attenuated cerebral perfusion in cortical areas or basal ganglia (33).

ELECTROENCEPHALOGRAPHY

The etiology of epileptic seizures includes structural metabolism, immunity, inflation, trauma, and endocrine and degeneration causes, among others. To clarify the causes of seizure disorders in patients with suspected HE, electroencephalography (EEG), laboratory examination of serum and CSF, MRI, SPECT, and neuropsychological examinations need to be used.

EEG is a useful tool in the evaluation of patients suspected of HE. Abnormal EEG results were recorded in 98% of patients with HE (27). Repeated EEG or long-term video EEG increased the positive rate of examination. EEG findings usually show moderate to severe abnormalities, which are often in parallel with clinical improvement after appropriate treatment (34). The EEG abnormalities seen in HE include non-specific diffuse slowing of the background activity (delta or theta frequency wave), interictal epileptiform discharges, repetitive focal spikes or sharps, photomyogenic response, photoparoxysmal response, and generalized biphasic or triphasic waves (35). Diffuse slowing of the background activity is the most common abnormality in HE individuals. The location of epileptic activity is not always consistent with the site of lesions shown on neuroimaging or physical examination (33, 36). Myoclonus seizures were found in about half of the patients with steroid-responsive encephalopathy associated with autoimmune thyroiditis in one study (36). None of these EEG findings were specific for the diagnosis of HE and can be seen in encephalopathy due to other causes. Because of the non-specificity of the EEG examination, it seems to be a limited tool in differential diagnosis of seizure disorders and/or encephalopathy with other possible causes of encephalopathy (37). However, EEG is helpful in reflecting changes in brain functions during hospitalization and follow-up.

DIAGNOSIS

Generally, the diagnostic criteria of HE are based on the clinical features with elevated antithyroid antibodies and good response to steroids (9).

When there are unexplained episodes of focal or generalized seizures, refractory to common antiepileptic drugs, with cognitive impairment and/or neuropsychiatric symptoms, Hashimoto encephalopathy may be considered. Before the diagnosis of HE is suspected on a patient with seizure disorders, detection of neural autoantibodies, lumbar puncture for CSF examination, and brain MRI/CT are needed to exclude other etiologies such as metabolic, infectious, vascular, and other inflammatory etiologies.

We should know that positive thyroid peroxidase antibodies and good response to steroid therapy are not sufficient criteria to establish the diagnosis of HE. Diagnostic criteria of HE have been proposed by Graus et al. (38) (**Table 1**) and Castillo et al. (4). These two criteria suggested that the diagnosis of HE remains a diagnosis of exclusion.

DIFFERENTIAL DIAGNOSIS

Seizures are an extremely common symptom in HE and deserve consideration in the differential diagnosis of patients with newly onset epileptic seizures.

As all the diagnostic criteria have suggested, if the patients were diagnosed with HE, all the specific clinical syndromes of autoimmune encephalitis (with and without positive autoantibodies) and those accompanied by well-defined autoantibodies should be excluded. Due to the diversity of clinical manifestations of HE, some patients are prone to be misdiagnosed as having viral encephalitis because of their prominent psychiatric symptoms. Prominent symptoms of cognitive dysfunction, tremor, and seizure are easily misdiagnosed as Creutzfeldt-Jakob disease (CJD). If HE is characterized by a stroke-like episode, it needs to be differentiated from central nervous system vasculitis. Therefore, when clinically highly suspected to be CJD, the possibility of HE should be considered. In the literature, 53% of patients initially diagnosed with CJD were eventually diagnosed with HE (8); at the same time, HE should be distinguished from primary mental disease, metabolism, poisoning, and paraneoplastic encephalopathy. If the patients combined with peripheral nerve

TABLE 1 | Diagnostic criteria for Hashimoto's encephalopathy, from Graus et al. (38).

Diagnosis can be made when all six of the following criteria have been met:
1. Encephalopathy with seizures, myoclonus, hallucinations, or stroke-like episodes
2. Subclinical or mild overt thyroid disease (usually hypothyroidism)
3. Brain MRI normal or with non-specific abnormalities
4. Presence of serum thyroid (thyroid peroxidase, thyroglobulin) antibodies
5. Absence of well-characterized neuronal antibodies in serum and CSF
6. Reasonable exclusion of alternative causes

damage, Guillain–Barre syndrome should be excluded. Patients with HE may also have a positive ANA, thus often causing confusion with neuropsychiatric involvement in systemic lupus erythematosus. We should pay attention to the fact that psychiatric symptoms can also occur in patients diagnosed with hypothyroidism.

TREATMENT

Once the diagnosis of HE is made, immunotherapy usually brings a dramatic recovery. Seizure disorders accompanied with HE are usually refractory to antiepileptic drugs unless immunotherapy was used. Common anticonvulsant therapy alone is usually ineffective; some patients did not respond to any antiepileptic drugs, including valproic acid, phenytoin, levetiracetam, lacosamide, topiramate, midazolam, and even propofol (20). The use of immunotherapy in the acute stage of HE not only can effectively control seizure disorders but also can assist in the diagnosis of immune epilepsy.

High-dose glucocorticoids and intravenous immunoglobulin are the first-line treatment of HE. First-line treatment also includes plasma exchange. When the first-line treatment regimen is ineffective or has a poor response, second-line treatment (including rituximab and cyclophosphamide) can be used. Patients who received early immunotherapy usually had a better prognosis. Study showed that patients receiving second-line treatment also had a better prognosis than those who did not receive second-line treatment when the first-line treatment was ineffective (7). When the disease is in a stable state, the immunosuppressive agent will be kept in the lowest effective dose for a while and then tapered slowly (39). Steroid treatment leads to complete neurological recovery in most patients, but patients will not always be responsive to corticosteroids. For these patients, other alternative forms of immunity therapy should be tried.

Seizures and other neurological features can also improve dramatically after intravenous immunoglobulin and plasmapheresis, alone or in combination (9, 33). Cyclophosphamide or rituximab can be used as a second-line medication when it is encountered in patients with refractory epilepsy. In recent years, it has been found that T cell inhibitors (cyclosporine A, tacrolimus, and sirolimus) successfully applied to control seizures. Others such as methotrexate, azathioprine, and hydroxychloroquine also showed effectiveness in reported cases (40).

Often, antiepileptic drug therapies that control seizures do not need to be used in the long term in patients with HE. It should be mentioned that seizure disorders can recur especially when steroids were tapered; hence, in some patients, maintenance immunotherapy is necessary (21). For patients with recurrent symptoms, reuse of glucocorticoids, plasma exchange, or immunoglobulin therapy is still effective (33). In order to prevent recurrence, it is recommended that glucocorticoid therapy should be done in sufficient maintenance doses and tapered slowly. Second-line immunosuppressant drugs mentioned above can be used if necessary. It is inappropriate to use serum TPOAb as a marker to determine when steroid therapy should be stopped because the effect of corticosteroids on TPOAb serum levels remains controversial (2, 41). For those patients with severe sequelae, including cognitive impairment and refractory seizures, immunotherapy, and antiepileptic drugs should be used longer (42, 43). Use of immunotherapy requires a close follow-up and regular measures for prevention of side effects.

CONCLUSION

Seizure disorders are common manifestations of HE. The diagnosis of HE still mainly depends on clinical presentation and supplementary examinations (including EEG, CT and/or MRI, and neuroelectrophysiology). The exact molecular mechanism that leads to seizures is still not clear. This type of immune-related seizures is not sensitive to conventional antiepileptic drugs, but has obvious effects on immunomodulatory therapy. Immunosuppressive therapy should be used in addition to antiepileptic drugs to control seizure disorders when HE is diagnosed. However, a better prognosis can be achieved when diagnosed early and treated with immunotherapy. We suggest that the diagnosis of HE should be considered in patients with unexplained encephalopathy presenting with uncontrolled seizures because steroid therapy is highly efficacious in these patients and is reversible.

The clinical spectrum of autoimmune epilepsy syndromes is expanding. HE is a rare, progressive, and relapsing multiform disease. Numerous challenges remain with the diagnosis and exploring the mechanisms of HE. A better understanding of the specific mechanisms underlying autoimmune epilepsy in HE is needed in the future.

AUTHOR CONTRIBUTIONS

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

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Clinical Features, Treatment, and Outcomes Among Chinese Children With Anti-methyl-D-aspartate Receptor (Anti-NMDAR) Encephalitis

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Objective: Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is the most common form of autoimmune encephalitis in pediatric patients. In this study, we aimed to investigate the clinical features and long-term outcomes of pediatric patients with anti-NMDAR encephalitis in China.

Methods: We conducted a retrospective study of children (age range: 0–18 years) with anti-NMDAR encephalitis treated at Children's Hospital of Fudan University between July 2015 and November 2018. Demographic characteristics, clinical features, treatment, and outcomes were reviewed.

Results: Thirty-four patients with anti-NMDAR encephalitis were enrolled (age range: 5 months to 14 years; median age: 7 years; female: 18). The median follow- up duration was 20 months (range: 6–39 months). Eighteen (52.9%) patients initially presented with seizures and 10 (29.4%) with abnormal (psychiatric) behaviors or cognitive dysfunction. Thirty (88.2%) patients exhibited more than two symptoms during the disease course. No neoplasms were detected. Twelve (35.2%) patients had abnormal cerebrospinal fluid (CSF) findings, including leukocytosis, and increased protein concentration. Eighteen (52.9%) patients exhibited normal brain MRI findings. Electroencephalography revealed abnormal background activity in 27 (79.4%) patients, and epileptiform discharges in 16 (47.0%) patients prior to immunotherapy. All patients received first-line immunotherapy, with 30 (88.2%) and four (11.8%) patients achieving good (Modified Rankin Scale [mRS] score of 0–2) and poor outcomes (mRS score of 3–5), respectively. Initial mRS scores differed significantly between the good and poor outcome groups. Fourteen out of 18 patients (77.7%) with seizures accepted anti-epileptic drug (AED) administration, and seizure freedom was achieved in 12 out of 14 (85.7%) patients at the last follow-up. Ten of these 12 (83.3%) patients withdrew from AED treatment within 1 year.

Conclusions: Most patients achieved seizure freedom, so long-term use of AEDs may not be necessary for pediatric patients with anti-NMDAR encephalitis. Among our patients, 83.3% were sensitive to first-line immunotherapy and achieved good outcomes. Higher mRS scores before immunotherapy predicted poor outcomes, highlighting the need for a comprehensive assessment of patients with anti-NMDAR encephalitis.

Keywords: anti-NMDAR encephalitis, autoimmune encephalitis, anti-N-methyl-D-aspartate receptor, children, immunotherapy

INTRODUCTION

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is a recently recognized autoimmune disorder in which auto-antibodies mainly target the NR1 subunit of the NMDA receptor, leading to a series of complex neuropsychiatric symptoms (1, 2). Reports of anti-NMDAR encephalitis have become more frequent over recent years, shedding light on the clinical characteristics of the disease. Anti-NMDAR encephalitis is a form of autoimmune encephalitis. Patients typically present with psychiatric symptoms, behavioral dysfunction, seizures, speech impairment, cognitive impairment, movement disorders, decreased consciousness, autonomic instability, and central hypoventilation. The disease is observed in patients of different ages and genders and may or may not be accompanied by ovarian teratomas or other tumors. Increased clinical recognition of this disease has led to an increase in the number of patients diagnosed with anti-NMDAR encephalitis.

Some research groups have summarized the clinical features of autoimmune encephalitis, providing a practical clinical approach to early diagnosis of the disease, rather than completely relying on the detection of autoantibodies (3, 4). Moreover, a meta-analysis found that earlier treatment of anti-NMDAR encephalitis leads to better outcomes among children (5). However, the clinical symptoms of anti-NMDAR encephalitis are complex, especially in younger pediatric patients, and many clinicians cannot promptly distinguish them from those of other diseases such as viral encephalitis or psychological conditions. Therefore, this study aimed to summarize the demographic characteristics, clinical features, ancillary examination results, treatments, and outcomes of Chinese children with anti-NMDAR encephalitis.

MATERIALS AND METHODS

This retrospective study included 34 pediatric patients with anti-NMDAR encephalitis, who were diagnosed at the Department of Neurology at Children's Hospital of Fudan University (Shanghai, China) between July 2015 and November 2018. The study was approved by the Ethics Committee of the Children's Hospital of Fudan University, which waived the requirement for informed consent owing to the retrospective nature of the study.

All patients met the following inclusion criteria: (a) met the diagnostic criteria for definite anti-NMDA receptor encephalitis (3); (b) treatment with first-line immunotherapy during the acute phase, including methylprednisolone and/or immunoglobulin and/or plasma exchange; (c) age between 0 and 18 years; and (d) duration of follow-up exceeding 6 months, with complete medical records. We excluded patients with other possible etiologies such as viral encephalitis or psychological conditions.

Medical information was collected from medical records or via telephone interviews and follow-up was continued until the patient died or was lost to follow-up. We reviewed patients' clinical data, including age, gender, age at disease onset, follow-up duration, initial symptoms, duration between symptom onset and diagnosis, duration between symptom onset and immunotherapy, CSF examination results, brain magnetic resonance imaging (MRI) results, results of screenings for systemic neoplasms, electroencephalography (EEG) findings, and treatment strategies. Serum and CSF samples from each patient were sent to Oumeng Biotechnology Corporation (Shanghai, China) to screen for antibodies against the NMDA receptor. All samples were evaluated for anti-NMDAR IgG antibodies via indirect immunofluorescence using EU 90 cells transfected with the NMDAR1 subunit (NR1) of the NMDAR complex and immobilized on BIOCHIPs (Euroimmun AG, Lubek, Germany). CSF leukocytosis was defined as white cell count $>5/mm^3$ while elevated CSF proteins 450 >mg/L. Tumor screening (MRI and/or CT and/or ultrasound of the chest, abdomen, and pelvic cavity) was performed once each patient was diagnosed with anti-NMDAR encephalitis. All patients were screened for tumors regularly after discharge, including MRI of the chest, abdomen, and pelvic cavity (once a year for children >12 years and biennial for children <12 years of age).

Digital-video EEG records were obtained at least once before immunotherapy, three to 6 months after immunotherapy, and at the last available follow-up. EEG data were recorded for at least 30 min. All EEG recordings were retrospectively evaluated by a pediatric epileptologist familiar with the patient's age and diagnosis, but not with his/her clinical state, symptoms, or signs. EEG data were categorized as follows: background activity (normal, generalized slowing, focal slowing, and extreme delta brushes [EDB]); interictal epileptic paroxysms such as sharp waves, spike waves, polyspike waves, or generalized discharges; focal discharges; and multifocal interictal epilepticdischarges.

Brain MRI findings were obtained from all patients before immunotherapy. Abnormal brain MRI findings were defined as hyper intensities on T2-weighted images (T2WI), fluid-attenuated inversion recovery (FLAIR) images and/or hypo intensities on T2-weighted images (T1WI). The same pediatric neurologist reviewed all the brain MRI results.

Outcomes were evaluated based on mRS scores. After discharge, outcome evaluations were performed during clinical

TABLE 1 | Patients' demographic and clinical characteristics.

Item	All patients (%)	Age under 12 (%)	Age under 6 (%)
Number	34	30	14
Female: male	18:16	16:14	8:6
Median age, range(months)	86 (5–171)	81 (5–136)	32 (5–67)
INITIAL SYMPTOMS			
Psychiatric/behavior	8 (23.5%)	8 (26.7%)	4 (28.6%)
Seizure	16 (47.1%)	13 (43.3%)	10 (71.4%)
Others	10 (29.4%)	9 (30%)	0

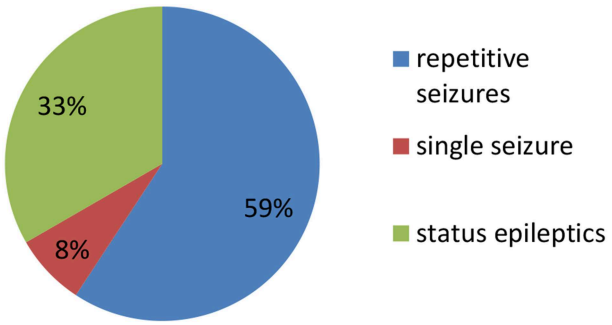

FIGURE 1 | Percentage of patients with repetitive seizures, single seizure, and status epilepticus (SE).

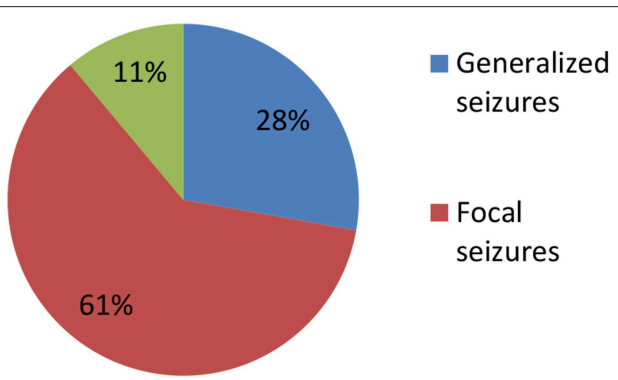

FIGURE 2 | Percentage of patients with focal, generalized, and both focal and generalized seizures epilepticus (SE).

visits to the neurologist or via telephone follow-up. The evaluation standards were as follows: full recovery, mRS score of 0; mild deficits, mRS scores of 1–2; severe deficits, mRS scores of 3–5; or death, mRS score of 6.

We used SPSS version 19.0 for all statistical analyses (SPSS Inc., Chicago, IL, USA). Continuous variables such as age, the interval from symptom onset to definitive diagnosis, and the interval from symptom onset to immunotherapy were analyzed using independent *t*-tests. Categorical variables were analyzed using Fisher's exact test, and ordinal variables were analyzed using Fisher–Freeman–Halton tests. $P < 0.05$ (two-sided) were considered significant.

RESULTS

Clinical Characteristics

Clinical characteristics of the 34 included patients are presented in **Table 1**. Patients' ages ranged from 5 months to 14 years (median age: 20 months), and 18 were female (52.9%; a female-to-male ratio of 1.125). Thirty patients (88.2%) were younger than 12 years of age, and 14 patients (41.2%) were younger than 6 years of age at symptom onset. The median follow-up duration was 20 months, ranging from 6 to 39 months. The initial presentation included seizures in 18 patients (52.9%), abnormal (psychiatric) behaviors or cognitive dysfunction in 10 patients (29.4%), a movement disorder in 3 patients (8.8%), and a decreased level of consciousness in 3 patients (8.8%). Thirty patients (88.2%) developed at least two of the six symptom categories over the course of their disease. Three patients (8.8%) were hospitalized in intensive care unit (ICU) due to central hypoventilation, coma, or refractory seizures, respectively. Each of the 18 patients who experienced seizures had onset during the acute phase of anti-NMDAR encephalitis, which was defined as <3 months after symptom onset. Seizure types included repetitive seizures (16/18, 88.8%), single seizures (2/18, 11.1%), and status epileptics (9/18, 50%) **(Figure 1).** Generalized and focal seizures were noted in 5 (27.7%) and 11(61.1%) of 18 patients, respectively **(Figure 2).** Only two (11.1%) patients reported seizures at the last follow-up. No patients developed tumors or died during follow-up.

Ancillary Examination Results

Initial CSF findings before immunotherapy are shown in **Table 2**. Eleven patients (32.4%) had CSF pleocytosis, seven (20.6%) had increased protein concentrations only, and six (17.6%) had both. Anti-NMDAR antibodies were identified in CSF obtained from 9 patients (26.5%) and both serum and CSF of 25 patients (73.5%). No patients were positive for anti-NMDAR antibodies in serum only. Brain MRI findings were normal in 19 (55.9%) of 34 patients. The remaining 15 patients (44.1%) exhibited abnormalities that included increased signal on T2WI or FLAIR images ($n = 14$, two in the temporal lobes, one in the frontal cortex, three in the thalamus, one in the parietal lobe, seven in the cerebral cortex/gray matter) and encephalomalacia ($n = 1$).

The first available EEG findings detected before immunotherapy included generalized slowing in 25/34 (73.5%) patients and focal slowing in 2/34 (5.9%). Normal background activity was observed in only 7/34 (20.6%) patients, and in 32/34 (94.1%) patients 3 months post-immunotherapy, and in all patients 9 months post-immunotherapy. Sixteen of 34 (47.1%) patients reported interictal epileptic paroxysms during the acute stage of anti-NMDAR encephalitis. This rate decreased to 14.7% ($n = 5$) 3–6 months after immunotherapy and 2.9% ($n = 1$) at the last follow-up. EDB patterns were recorded in 2/34 (5.9%) patients **(Figure 3)** and disappeared 6 months after immunotherapy **(Figure 4)**.

TABLE 2 | Results of ancillary examinations.

Examinations	All patients
Brain MRI	Numbers (%)
Total abnormal findings	18 (52.9%)
EEG	
Abnormal background	
Before immunotherapy	27(79.4%)
3–6months after immunotherapy	2(5.9%)
Last follow up	0(0%)
Interictal Epileptiform Discharge	
Before immunotherapy	16 (47.0%)
3–6months after immunotherapy	5 (14.7%)
Last follow up	2 (5.8%)
EDB	2 (5.8%)
CSF Results	
Abnormal findings	12 (35.3%)
Pleocytosis	11 (32.4%)
Increased protein concentration	7 (20.6%)
Pleocytosis and increased protein concentration	6 (17.6%)
Positive OB(Total number 11)	1 (9.1%)

EEG, electroencephalogram; EDB, extreme delta brush; CSF, cerebrospinal fluid; OB, Oligoclonal band.

Treatments and Outcomes

All patients received first-line immunotherapy, including intravenous methylprednisolone, intravenous immunoglobulin, plasma exchange, or an arbitrary combination of these treatments. The median interval between symptom onset and the start of immunotherapy treatment was 23.9 days, ranged from 7 to 42 days. The median duration of follow-up was 20 months, with a range of 6 to 39 months. Twenty-five of the 34 (73.5%) patients were treated within 30 days of first symptom appearance. Three patients (8.8%) were exclusively treated with intravenous methylprednisolone (15–30 mg/kg per day for 3–5 days), 29 patients (85.3%) with both intravenous methylprednisolone and intravenous immunoglobulin (IVIG, 0.4 g/kg per day for 5 days or 1 g/kg per day for 2 days), and two patients (5.9%) with a combination of intravenous methylprednisolone, IVIG, and plasma exchange. The median mRS score before immunotherapy was 5, which decreased to zero following 3–6 months of initial immunotherapy (**Figure 5**). By the last follow-up, 29 patients (85.2%) had fully recovered, one patient (2.9%) exhibited mild deficits (weakness on one side of the body), and four patients (11.8%) exhibited severe deficits (one with speech disturbances and memory deficits, one with dyskinesia, and two with intractable epilepsy). No deaths were noted at the last follow-up.

Comparison Between the Good and Poor Outcome Groups

Table 3 shows between-group comparisons of the good and poor outcome groups. The initial median mRS score was significantly higher in the poor outcome group than in the good outcome group ($p = 0.014$). Initial symptoms, CSF findings, the median age at the appearance of initial symptoms, the median interval between onset and diagnosis, the median interval between onset and immunotherapy, MRI findings, EEG findings, and ICU admission showed no significant between-group differences.

Comparison Between Patients Younger and Older Than 6 Years old

Table 4 shows the comparison between patients younger than 6 years old and older than 6 years. We observed no significant between-group differences for initial symptoms, CSF findings, median initial mRS score, the median interval between onset and diagnosis (d), the median interval between onset and immunotherapy (d), MRI findings, interictal epileptic discharges, or ICU admission.

DISCUSSION

Previous research has demonstrated that there are more cases of anti-NMDAR encephalitis than other kinds of autoimmune encephalitis, and that early diagnosis and aggressive medical management decrease the likelihood of morbidity and mortality (6–9). Therefore, if anti-NMDAR encephalitis is suspected and other diseases can be ruled out, treatment should begin as early as possible (10). However, there are significant differences in clinical features between pediatric and adult patients. Here we retrospectively analyzed the clinical characteristics, ancillary examination results, and outcomes of Chinese pediatric patients with anti-NMDAR encephalitis.

We observed no significant differences in sex in the present study. These findings correspond to the findings of a previous study that focused on pediatric patients with anti-NMDAR encephalitis in south-central China (11). In children, psychiatric syndromes can present as abnormal behaviors or cognitive dysfunction. This is particular true for preschool-aged children, because it is difficult for them to describe their symptoms and emotional states. Therefore, we could not make objective judgments regarding cognitive function, including the presence of memory deficits, which are independently associated with poorer outcomes (12). Instead, we attributed psychiatric symptoms and abnormal behaviors or cognitive dysfunction to a single category of symptoms. Eighteen of the 34 included patients (52.9%) initially presented with seizures, while 10 (29.4%) presented with abnormal (psychiatric) behaviors or cognitive dysfunction. We concluded that seizures and abnormal (psychiatric) behaviors and cognitive dysfunction are the most common symptoms of pediatric anti-NMDAR encephalitis, in agreement with previous findings (13–16).

Armangue et al. (9, 14) reported that younger children with anti-NMDAR encephalitis typically presented with neurologic symptoms, whereas adolescents more often presented with psychiatric symptoms. However, in our study, 75% (3/4) of adolescents presented with seizures as their initial symptom, and there was no significant difference in initial symptoms between older and younger patients (**Table 4**). This difference may be attributed to the relatively small sample of adolescents in our

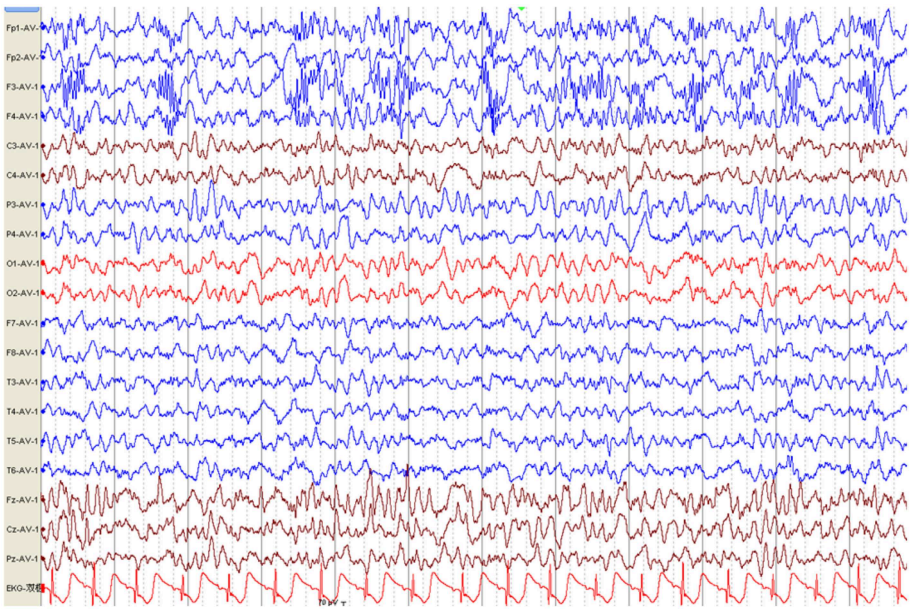

FIGURE 3 | Electroencephalography pattern of a 4-year and 5-month-old female child with anti-N-methyl-D-aspartate receptor encephalitis (Case 8), who presented with clonic seizures of her right limbs as her initial symptom. EEG was recorded 43 days after symptom onset and before immunotherapy. EEG shows bilateral frontal-predominant fast activity at 20–30 Hz riding on the generalized rhythmic delta activity (EDB).

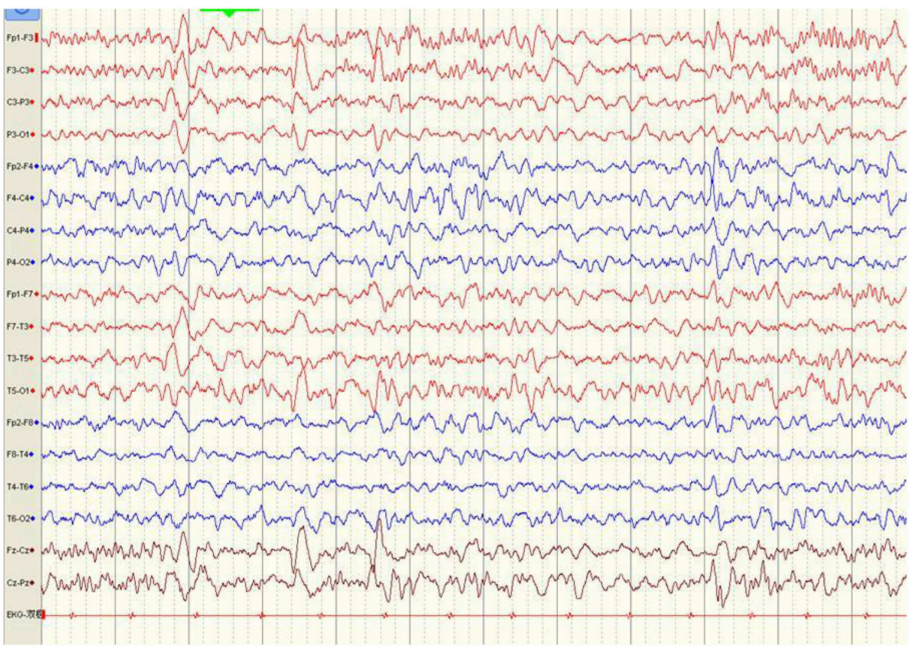

FIGURE 4 | Normal EEG was recorded six months after immunotherapy (Case 8).

study. According to the literature, adult patients more frequently present with focal seizures, while children more frequently present with generalized seizures that develop into the dominant seizure type over the course of the disease (17). In a recent study of 17 pediatric patients with anti-NMDAR encephalitis, generalized seizures were reported in 5/16 patients (31%), while focal seizures were reported in 4/16 (25%) patients, another 7/16 (44%) patients had both generalized, and focal seizures (16). In our study, among 18 patients experienced seizures, 11 (61.1%) presented with focal seizures, five (27.7%) with generalized

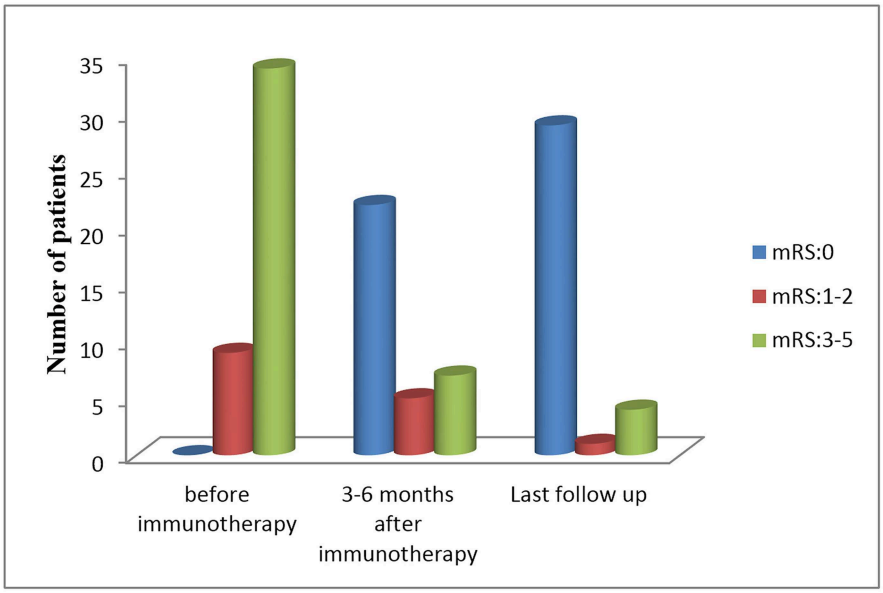

FIGURE 5 | Patients' mRS scores during the follow-up period.

seizures, and two (11.1%) with both types. Age-related differences in patients' constitutions and the use of video-EEG to determine seizure type may explain these differences.

Of the 14 patients treated with AEDs, 12 (85.7%) got seizure free during the acute stage of anti-NMDAR encephalitis, and 10 patients (71.4%) were able to withdraw from AEDs within 1 year. At the final follow-up, only two patients (14.3%) with ongoing epilepsy were treated with AEDs, indicating that long-term use of AEDs may not be necessary for pediatric patients with anti-NMDAR encephalitis. Similar results have been reported in previous studies involving both adult and pediatric patients (18). No tumors were detected in our study, which demonstrates that younger age is associated with a lower rate of teratomas (2, 11).

Although not generally helpful in diagnosing anti-NMDAR encephalitis, imaging studies play a key role in the workup of patients with suspected anti-NMDAR encephalitis because these modalities can rule out other conditions that could create a similar neurologic picture (19). A recent study demonstrated that anti-NMDA encephalitis is an autoimmune-mediated disease without specific brain MRI features. The authors categorized the brain MRI findings of patients with anti-NMDA receptor encephalitis into four types. Of these, hippocampal lesions were the most common brain abnormalities and were identified as risk factors contributing to poor prognosis (20), consistent with previous reports (21, 22). However, as with our results, some research has indicated that abnormal MRI findings do not affect prognosis as indicated by mRS scores (23). In our study, 55.9% of patients had normal brain MRI findings, and none exhibited hioppocampal lesions. This discrepancy may be due to differences between pediatric and adult patients, or to the relatively small sample size of our study. Therefore, future studies with larger samples are needed to compare brain MRI features between pediatric and adult patients.

TABLE 3 | Comparison of the good and poor outcome groups.

Item	Good outcome	Poor outcome	*P*-value
Patient number	30	4	/
Initial syndrome			/
Seizure	15	3	0.9467
Abnormal (psychiatric) behavior or cognitive dysfunction	9	1	0.7723
Others	6	0	0.5289
Abnormal CSF finding	12	2	0.8219
Median age(m)	99	24	0.1772
Median initial mRS	5	5	0.0141
Median interval between onset and diagnosis(d)	22	30	1.0000
Median interval between onset and immunotherapy(d)	20	29	0.6721
Abnormal MRI findings	12	3	0.3891
Abnormal EEG background	25	2	1.0000
Abnormal interictal epileptic discharges	14	2	0.5671
ICU stay	3	0	0.9290

Previous studies have indicated that the parietal aEEG bandwidth may separate patients with favorable and poor long-term outcomes in the early disease stages (24). In our study, the first available EEG findings that obtained before immunotherapy showed generalized slowing in 14/18 patients (77.7%), focal slowing in 2/18 patients (11.1%), and no abnormalities in 2/18 patients (11.1%), consistent with the findings of previous reports (25, 26). No patients exhibited abnormal background activity

TABLE 4 | Comparison of patients younger than 6 years old with those older than 6 years old.

Item	Age under 6 y	Age older than 6 y	*P*-value
Patient number	14	20	/
Initial syndrome			/
Seizure	10	8	0.6835
abnormal (psychiatric) behavior or cognitive dysfunction	4	6	1.0000
Others	0	6	0.0717
Abnormal CSF finding	4	8	0.7477
Median age(m)	36.5	110	0.0000
Median initial mRS	5	5	0.9830
Median interval between onset and diagnosis(d)	29.5	19	0.1010
Median interval between onset and immunotherapy(d)	27.5	17	0.0980
Abnormal MRI findings	7	8	0.8204
Abnormal EEG background	11	16	1.0000
Abnormal interictal epileptic discharges	9	7	0.1820
ICU stay	2	1	0.7450

at the final follow-up. These findings suggest that generalized slowing of EEG background activity is an important clue to diagnosing anti-NMDAR encephalitis during the acute stage, but it is not specific to anti-NMDAR encephalitis. Recent studies have demonstrated that the presence of EDB patterns is a marker of more severe disease among patients with anti-NMDAR encephalitis and corresponding with worse outcomes (27). Past researchers observed EDB patterns on EEG in 33% of patients with anti-NMDAR encephalitis (28). However, in our study, EDB patterns were detected in only 2/18 (11.1%) patients, likely due to differences in the time of EEG recording and individual differences in patients within the various study groups. Since prompt diagnosis is crucial (29), we recommend use of video-EEG monitoring for all patients with suspected anti-NMDAR encephalitis (30). Nonetheless, a recent study suggested that EDB is also not unique to anti-NMDAR encephalitis and can occur (albeit rarely) in patients with mesial temporal lobe epilepsy. While the presence of EDB should prompt suspicion of anti-NMDAR encephalitis, other possible etiologies should not be ignored (31).

Some previous studies have suggested that the prognosis is poor among patients with severe anti-NMDAR encephalitis (2, 32), but the long-term prognosis of anti-NMDAR encephalitis is good (33, 34), even in patients whose diagnoses were missed or in those with prolonged diagnostic delays who eventually recovered or substantially improved (35). Predictors of poor outcomes included younger age, decreased consciousness, memory deficits, ICU admission, treatment delay >4 weeks, lack of clinical improvement within 4 weeks, abnormal MRI, and CSF white blood cell count >20 cells/μL, etc. (2, 36–38). In our study, higher initial mRS scores predicted poor outcomes, in accordance with Anastasia Zekeridou et al. (39). However, our sample size was relatively small and further studies involving larger sample sizes are required to determine the risk factors for poor prognosis in this patient population.

According to our experience, most patients with anti-NMDAR encephalitis continue to improve within 2 years or longer, even when treated with first-line immunotherapy alone. For patients with slow clinical improvement, first-line immunotherapy can be re administered. In this study, some caretakers refused second-line immunotherapy because of cost concerns or concerns over clinical side effects, so all our patients were treated with first-line immunotherapy. Although no patients attained mRS scores of 0–2 (0%) before immunotherapy, 83.3% of them attained such scores at the final follow-up. This result indicated that first-line immunotherapy is an effective measure for pediatric patients with anti-NMDAR encephalitis. Besides, our patients' good outcomes may be associated with admission to the less intensive care unit and prompt immunotherapy after diagnosis with anti-NMDAR encephalitis.

In a recent study involving 111 patients with anti-NMDAR encephalitis, 39 (35.1%) patients were included in the severe group. Even patients with the most severe forms of anti-NMDAR encephalitis can eventually achieve good long-term outcomes after receiving early, positive, and unremitting combined immunotherapy and life support (25). Another study (40) involving 19 children with anti-NMDAR encephalitis in Thailand revealed that IVIG treatment, was associated with greater improvements in mRS scores. These findings underscore the benefits of IVIG treatment for this condition. Zhang et al. (13) analyzed the individual outcomes associated with three first-line immunotherapies and combinations of any two immunotherapies. Their findings revealed that patients treated with a combination of corticosteroids and IVIG plus second-line immunotherapy more frequently achieved full recovery than patients treated with a combination of corticosteroids and IVIG. Second-line immunotherapy with rituximab, cyclophosphamide, or both significantly improved outcomes in patients who did not respond to first-line therapy and decreased the frequency of relapses (2). Therefore, second-line immunotherapy may be necessary when patients do not achieve full recovery with first-line immunotherapy only.

Nonetheless, some recent studies have reported substantial deficits across multiple cognitive domains and behavioral problems in both adult and pediatric patients (41–44). These findings indicate that, even when good outcomes are achieved, full recovery may not be possible. Alternatively, while mRS scores are effective tools for assessing disability in patients with stroke, these scores may not be the most suitable tool for evaluating outcomes in patients with anti-NMDAR encephalitis who present with seizures and abnormal (psychiatric) behaviors or cognitive dysfunction. This is particularly true for infants who cannot walk or express their emotions. Future studies should seek to determine the most appropriate method for comprehensively assessing cognitive and social functions in patients with anti-NMDAR encephalitis at different ages.

Our study had several limitations. The functional status assessment may be susceptible to recall bias given the retrospective nature of the study. Our cohort only included

patients diagnosed and treated at the Children's Hospital of Fudan University in Shanghai, which may also have introduced a selection bias. All patients were treated with first-line immunotherapy so we could not assess differences in the effects between first-line immunotherapy and other immunotherapy measures. The relationship between anti-NMDAR antibody titers and clinical symptom severity or outcomes was not examined and should be a focus of future studies.

CONCLUSION

In our study, seizure freedom was typically achieved by the final follow-up, indicating that long-term use of AEDs may not be necessary for patients with anti-NMDAR encephalitis. More than half of the patients exhibited normal brain MRI findings. Our results further indicated that generalized slowing of EEG background activity is the main characteristic of pediatric anti-NMDAR encephalitis during the acute stage. In addition, 83.3% of our patients were sensitive to first-line immunotherapy and achieved good outcomes. Higher mRS scores before immunotherapy predicted poor outcomes among pediatric patients with anti-NMDAR encephalitis. Future studies should aim to determine the most appropriate methods for comprehensively assessing cognitive and social functions in patients with anti-NMDAR encephalitis, particularly infants.

ETHICS STATEMENT

This study was approved by the Ethics Committee of Children's Hospital of Fudan University, who waived the requirement for informed consent due to the retrospective nature of the study.

AUTHOR CONTRIBUTIONS

MZ and WL wrote the initial draft of the paper. JW and LY acquired patients' demographic and clinical data through medical records and telephone interviews. YZ guided the analysis of EEG signals. HY guided the analysis of MRI and CT results, SZ guided the study design, and LZ and YW made critical revisions to the manuscript.

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Analysis of Clinical Characteristics and Poor Prognostic Predictors in Patients With an Initial Diagnosis of Autoimmune Encephalitis

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Purpose: We aimed to retrospectively analyze the clinical features, laboratory and imaging results, and predictors of poor prognosis for patients with an initial diagnosis of autoimmune encephalitis (AE) at the Affiliated Hospital of Zunyi Medical University.

Methods: Fifty patients with an initial diagnosis of AE who were admitted to our hospital from May 2014 to May 2018 were enrolled retrospectively. Clinical characteristics and experimental test data, including the neutrophil-to-lymphocyte ratio (NLR), were collected from medical records within 24 h of admission. Independent prognostic factors were determined by multivariate logistic regression analysis. A good or poor prognosis for patients was defined based on the modified Rankin Scale (mRS). The correlation between the immunotherapy latency and prognostic mRS score was determined using the Spearman rank correlation test.

Results: Univariate analysis indicated that increased NLR ($P = 0.001$), decreased lymphocyte counts ($P = 0.001$), low serum albumin ($P = 0.017$), consciousness disorders ($P = 0.001$), epileptic seizures ($P = 0.007$), extrapyramidal symptoms ($P = 0.042$), abnormal electroencephalogram (EEG) findings ($P = 0.001$), abnormal brain magnetic resonance imaging (MRI) findings ($P = 0.003$), and pulmonary infection complications ($P = 0.000$) were associated with the poor prognosis of AE. Multivariate logistic regression analysis showed that NLR (odds ratio [OR] 2.169, 95% confidence interval [CI] 1.029–4.570; $P < 0.05$) was an independent risk factor for predicting the poor prognosis of AE. NLR > 4.45 was suggested as the cut-off threshold for predicting the adverse outcomes of AE. In addition, we revealed that there was a positive correlation between immunotherapy latency and mRS score ($r_S = 0.535$, $P < 0.05$).

Conclusions: NLR may have predictive value for the poor outcomes of AE. Early initiation of immunotherapy is associated with a good prognosis.

Keywords: autoimmune encephalitis, predictor, neutrophil-to-lymphocyte ratio, immunotherapy, modified Rankin Scale, prognosis

INTRODUCTION

Autoimmune encephalitis (AE) is a severe inflammatory disorder of the brain that is mediated by autoimmune mechanisms and characterized by prominent neuropsychiatric symptoms. AE, which is thought to be associated with antibodies against neuronal cell-surface proteins, ion channels, or receptors (1), accounts for about 20% of all adult encephalitis cases (2). Typical clinical manifestations include epileptic seizures, psychiatric and behavioral disorders, decreased levels of consciousness, memory and cognitive impairment, extrapyramidal symptoms, and central hypoventilation (3, 4). Since the discovery of anti-N-methyl-D-aspartate receptor (anti-NMDAR) antibodies by Dalmau et al. (5), more than a dozen new types of autoantibodies have been identified (6). Anti-NMDAR encephalitis is the most common type of AE, followed by anti-leucine-rich glioma-inactivated 1 (anti-LGI1) encephalitis (7) and anti-γ-aminobutyric acid B receptor (anti-$GABA_BR$) encephalitis. Other types of antibodies include anti-contactin-associated protein-like 2 (anti-CASPR2) antibody and anti-α-amino-3-hydroxy-5-methyl-4-isoxazole propionate receptor (anti-AMPAR) antibody. The presence of corresponding autoantibodies contributes to diagnosis; however, because existing criteria for AE rely on antibody testing and the response to immunotherapy, delays in diagnosis, and missed diagnosis of antibody-negative patients can occur (8). A clinical approach to the diagnosis of AE was put forward jointly by international experts, providing a basis for the early diagnosis of this disease (8). In addition, AE is a severe neurological disorder that is characterized by complicated clinical manifestations and frequent complications. Some cases are associated with tumors. Immunotherapy, intensive care unit (ICU) support, and multidisciplinary treatments can be combined to mitigate the disease (9). At present, the efficacy of immunotherapy and factors that affect patients' poor prognosis have not been determined. Thus, research on the prognostic factors of AE has great clinical and social significance.

AE is recognized as a chronic autoimmune disease characterized by the presence of antigen-specific antibodies in serum and cerebrospinal fluid (CSF) resulting from dysfunction of the immune system regulation and persistent inflammation (10). The neutrophil-to-lymphocyte ratio (NLR) is a commonly used and very significant systemic inflammation biomarker. NLR is calculated as the absolute count of neutrophils divided by the absolute count of lymphocytes (11). Moreover, NLR has been suggested as a marker for the general immune response to various stress stimuli. Prior studies have shown that increased NLR is a prognostic marker in patients with various cancers, including pancreatic cancer, lung cancer, gastric cancer, hepatocellular carcinoma, prostate cancer, and malignant mesothelioma (12–16). In addition, several reports have demonstrated that altered NLR has prognostic value in diabetes mellitus, hypertension, acute myocardial infarction, cerebrovascular disease, peripheral arterial disease, and chronic kidney disease (17–20). Recent studies have also shown that an abnormal NLR level is associated with some autoimmune diseases (21, 22). However, to our knowledge, the relationship between NLR and AE has not been studied so far. Therefore, in this study, we evaluated the association between NLR and prognosis in AE patients and whether NLR is an independent risk factor for predicting the poor prognosis of AE.

METHODS

Research Subjects

This retrospective study complied with the recommendations of the Ethics Committee of Affiliated Hospital of Zunyi Medical University. The protocol was approved by the Ethics Committee of Affiliated Hospital of Zunyi Medical University. All patients or their relatives were informed of the study and signed written informed consent in accordance with the Declaration of Helsinki. We reviewed all the medical records of patients with an initial diagnosis of AE admitted to the Department of Neurology, Affiliated Hospital of Zunyi Medical University, from May 2014 to May 2018. We reassessed the diagnosis basis and followed up with patients by telephone every 3 months after discharge. The inclusion criteria were based on the clinical diagnostic criteria for AE suggested by Mittal and Graus in 2016. Patients were categorized as "definite," "probable," or "possible" according to the adapted criteria (8). The diagnostic criteria for the "definite" group were the detection of antibodies against neuronal membrane or synaptic proteins in CSF and/or serum. Autoantibody-negative but "probable" AE did not meet the diagnostic criteria of the "definite" group but fulfilled all four other criteria supporting AE. Correspondingly, the following exclusion criteria were considered: other acute neurological diseases found during follow-up; not meeting the clinical diagnostic criteria for AE; loss to follow-up; other autoimmune diseases; and incomplete clinical data.

Data Collection

The following basic clinical data were collected: age at onset, sex, clinical manifestations, interval from onset to admission, immunotherapy latency (the time interval from onset to the initiation of immunotherapy), prodromal symptoms, pulmonary infection complications, treatment methods, and hospital stay. In addition, cranial magnetic resonance imaging (MRI) findings, electroencephalogram (EEG) data, laboratory tests, CSF examination (pressure, white blood cell [WBC] counts, and protein, glucose and chloride levels), and autoantibody tests of serum and CSF were reviewed from medical records and electronic databases. The laboratory tests included the following: WBC counts, neutrophil counts, lymphocyte counts, platelet counts, NLR, and the levels of hemoglobin, sodium (Na), potassium (K), chlorine (Cl), calcium (Ca), and albumin. These experimental examinations were recorded within 24 h of admission. NLR was defined as a simple ratio between the absolute neutrophil count and the absolute lymphocyte count. Laboratory tests except NLR were divided into low, normal, and high values based on reference intervals.

Based on previous reports on AE (3), the main symptoms were divided into the following categories: consciousness disorders; epileptic seizures; mental and psychiatric and behavior disorders; and extrapyramidal symptoms. The inflammatory CSF needed to meet at least 2 of the following criteria: an increase in

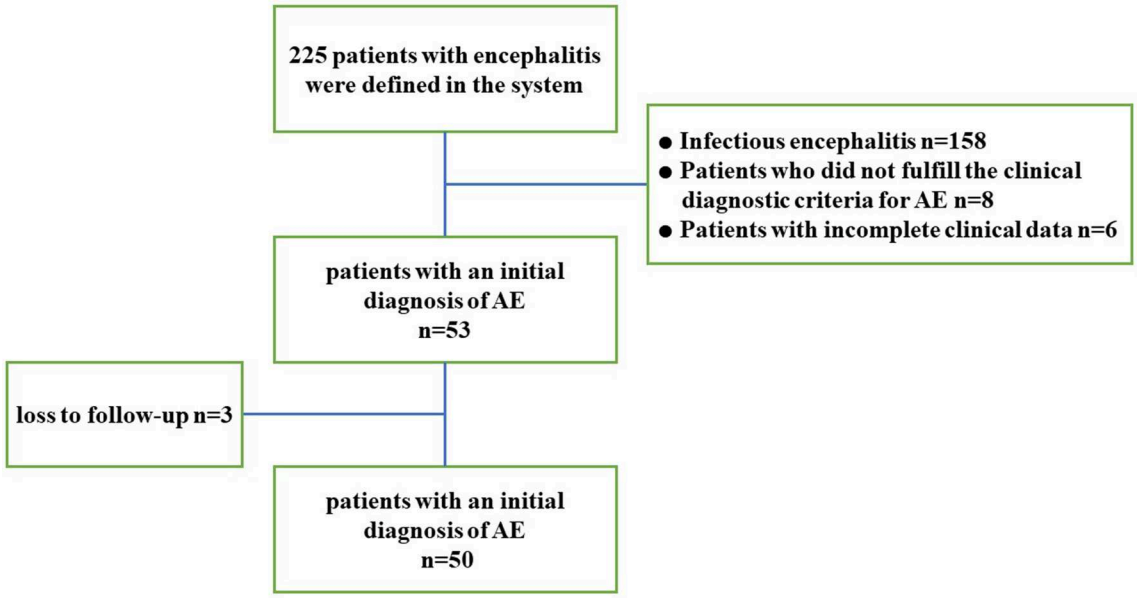

FIGURE 1 | Study flowchart. AE, autoimmune encephalitis.

the number of CSF cells ($\geq$5 leukocytes/mm^3), an increase in the rate of immunoglobulin G (IgG) synthesis, or the appearance of CSF-specific oligoclonal bands. Supportive cranial MRI included T2-weighted fluid-attenuated inversion recovery (FLAIR) hyperintensity on one or both sides of the mesial temporal lobes, multiple inflammatory lesions, or demyelination involving gray and white matter. Supportive EEG included abnormal slow-wave activity and epileptiform discharges (8). Patient serum and CSF samples were simultaneously obtained and sent to Beijing Kindstar Global Company for testing.

Disease Prognosis Evaluation

The modified Rankin Scale (mRS) was used to evaluate neurological function at the time of admission, at discharge from the hospital, and during the follow-up period. The mRS score includes 6 categories (23, 24): if patients had a full recovery (mRS 0 point); if patients had no significant functional impairment and were able to complete all daily duties and activity despite some symptoms (mRS 1 point); if patients had mild-moderate disability and were unable to complete all previous activities but could independently take care of their own affairs (mRS 2–3 points); if patients had severe disability and required others to take care of them (mRS 4 points); if patients had severe disability and required intensive care (mRS 5 points); and death (mRS 6 points). According to the mRS during the follow-up period, we divided all patients into two groups: patients with an mRS score of 0–1 were defined as "good prognosis"; patients with an mRS score of 2–6 were defined as "poor prognosis."

Statistical Analysis

All statistical analyses were performed using SPSS statistical software (version 22.0). Measurement data were presented in the form of "mean $\pm$ standard deviation" and/or "median (range)," whereas count data were presented as number (percentage). Univariate analysis was performed to compare the differences between the two groups. Independent Student's *t*-test was used for normally distributed variables, while the Mann-Whitney test was used for non-normally distributed variables. Categorical variables were compared using the chi-squared test. Logistic regression analysis was performed to determine the independent predictors of poor prognosis. The correlation between the immunotherapy latency and prognostic mRS score was determined using the Spearman rank correlation test. The optimal cutoff value for the NLR to serve as a prognostic marker for AE was determined from receiver operating curve (ROC) analysis. *P*-values < 0.05 (two-sided) were considered statistically significant.

RESULTS

Patient Profile

The search of the electronic database resulted in 225 potential encephalitis cases. A total of 50 patients with AE were included in the study (**Figure 1** provides the flowchart of patient selection). Nine cases with positive antibodies were considered "definite AE," including 7 patients positive for anti-NMDAR antibody, 1 patient positive for anti-$GABA_BR$ antibody, and 1 patient positive for anti-AMPAR antibody. Sixteen cases negative for antibodies were considered "probable AE," and 25 cases were categorized as "possible AE." All patients showed acute or subacute onset, and 33 (66%) exhibited prodromal symptoms such as headache and other clinical symptoms of non-specific upper respiratory tract infection symptoms. The average time from onset to admission was 10 days. Thirty-nine patients (78%)

were initially misdiagnosed with viral encephalitis, psychosis, cerebrovascular disease, or other diseases. Among these patients, 2 had lung tumors, 1 had thymoma, and 1 had multiple myeloma. During the entire course of the disease, 19 patients (38%) developed fever, 9 patients (18%) had central hypoventilation, 13 patients (26%) had pulmonary infection complications, and 4 (8%) had been treated in the ICU. One patient died of small cell lung cancer during follow-up. The clinical characteristics and demographic information of the subjects are summarized in **Table 1**.

TABLE 1 | Characteristics of the study population ($n = 50$).

Characteristics	Patients (%)
Sex (male/female)	31/19
Age mean, range (years)	39,14–74
Prodromal symptoms	33 (66%)
Interval between onset and Hospitalization mean, range (days)	10,1–60
Fever	19 (38%)
Initial symptoms	
Consciousness disorders	8 (16%)
Epileptic seizures	16 (32%)
Psychiatric and behavior disorders	19 (38%)
Extrapyramidal symptoms	3 (6%)
Other	4 (8%)
Consciousness disorders	25 (50%)
Epileptic seizures	25 (50%)
Psychiatric and behavior disorders	34 (68%)
Extrapyramidal symptoms	17 (34%)
Speech disturbances	5 (10%)
Memory deficits	7 (14%)
Autonomic dysfunction	1 (2%)
Mechanical ventilation	9 (18%)
Abnormal EEG results	33 (66%)
Abnormal brain MRI results	21 (42%)
Increased CSF pressure	9 (18%)
Increased CSF protein	29 (58%)
Increased CSF WBC counts	21 (42%)
Neutrophil count (10^9 /L) (median IQR)	5.30 (3.73–8.20)
Lymphocyte count (10^9 /L) (median IQR)	1.66 (1.14–2.03)
NLR (median IQR)	3.72 (2.16–5.56)
Pulmonary infection complications	13 (26%)
Tumor	4 (8%)
Immunotherapy	20 (40%)
Average hospital stay, range (days)	22.5, 5–99

IQR, interquartile range; EEG, electroencephalogram; MRI, magnetic resonance imaging; CSF, cerebral spinal fluid; NLR, neutrophil-to-lymphocyte ratio.

Auxiliary Examinations

The brain MRI, EEG, and CSF results of all patients were available. EEG findings were abnormal in 33 patients (66%), including 10 patients with epileptiform discharges (such as spike waves, sharp waves, spike slow wave complex, or sharp slow wave complex), 22 patients with unilateral or bilateral non-specific slow waves, and 1 patient with δ brushes. Brain MRI findings showed that the lesions were located in the frontal lobes, temporal lobes, parietal lobes, occipital lobes, insular lobes, hippocampus, basal ganglia, thalamus, cerebellum, cortex, and white matter. Twenty-one patients (42%) had specific T2-signal hyperintensities. These affected brain regions mainly included the medial temporal lobes, frontal and parietal lobes, and/or subcortical regions. Non-specific changes/demyelinating lesions were present in 13 patients (26%), whereas 16 patients had no abnormalities (32%). CSF findings revealed that 21 patients (42%) displayed pleocytosis, and 29 patients (58%) had high concentrations of total protein.

Treatment and Outcome

Twenty (40%) patients received immunotherapy, including eight patients with methylprednisolone (intravenous infusion, 1 g/day; 5 days); two patients with immunoglobulin (intravenous infusions, 0.4 g/kg; 5 days); nine patients with a combination treatment of IVIg and intravenous methylprednisolone; and one patient with a combination therapy of plasma exchange, IVIg, and intravenous methylprednisolone. None of our patients received second-line therapy (rituximab, cyclophosphamide, or other) due to medical insurance restrictions or drug side effects. The median follow-up time was 11 months (8–27 months). At the end of the follow-up period, 33 patients (66%) attained a good prognosis, whereas 17 patients (34%) had poor prognosis. Among all patients, 33 patients (66%) had mRS scores of 0 or 1. Meanwhile, 8 patients (16%) had mRS scores of 2, and 4 patients (8%) had mRS scores of 3. Additionally, 2 patients (4%) reached 4 points, and 2 patients (4%) received 5 points. Unfortunately, 1 patient (2%) died by the end of the study (mRS 6). Three patients relapsed during follow-up. Two patients with anti-NMDAR encephalitis also achieved a good prognosis without immunotherapy.

Predictors of Prognosis

Univariate analysis indicated that there were significant differences between the good and poor outcome groups in laboratory values, including the NLR ($P = 0.001$), lymphocyte counts ($P = 0.001$), and albumin ($P = 0.017$). We found that the median NLR was significantly higher in the poor prognosis group than in the good prognosis group. In addition, consciousness disorders ($P = 0.001$), epileptic seizures ($P = 0.007$), extrapyramidal symptoms ($P = 0.042$), abnormal EEG findings ($P = 0.001$), abnormal MRI findings ($P = 0.003$), and pulmonary infection complications ($P = 0.000$) were associated with worse prognosis of AE (**Table 2**).

All factors with a P-value < 0.20 in **Table 2** were included in a multivariate logistic regression model. Multivariate logistic regression analysis showed that NLR (odds ratio [OR] 2.169, 95% confidence interval [CI] 1.029–4.570; $P < 0.05$) was an independent risk factor associated with poor prognosis of AE (**Table 3**). ROC analysis of NLR to predict poor prognosis of AE showed that the area under the curve was 0.866 (95% CI, 0.759–0.974; $P < 0.001$). Based on the ROC curve, the optimal cutoff value was 4.45 (sensitivity, 0.824; specificity, 0.879; shown in **Table 4** and **Figure 2**).

TABLE 2 | Univariate analysis of prognostic factors associated with AE.

Variables	Good prognosis ($n = 33$)	Poor prognosis ($n = 17$)	*P*-value
Age (years), (mean ± SD)	39.06 ± 17.74	38.06 ± 19.33	0.855
Sex			
Male	19 (57.6%)	12 (70.6%)	0.369
Female	14 (42.4%)	5 (29.4%)	
Duration from onset to admission			
≤2 wk	26 (78.8%)	13 (76.5%)	0.851
>2 wk	7 (21.2%)	4 (23.5%)	
Fever			
≤ 37.5°C	21 (63.6%)	10 (58.8%)	0.740
>37.5°C	12 (36.4%)	7 (41.2%)	
Consciousness disorders			
Yes	11 (33.3%)	14 (82.4%)	**0.001**
No	22 (66.7%)	3 (17.6%)	
Epileptic seizures			
Yes	12 (36.4%)	13 (76.5%)	**0.007**
No	21 (63.6%)	4 (23.5%)	
Psychiatric and behavior disorders			
Yes	22 (66.7%)	12 (70.6%)	0.778
No	11 (33.3%)	5 (29.4%)	
Extrapyramidal symptoms			
Yes	8 (24.2%)	9 (52.9%)	**0.042**
No	25 (75.8%)	8 (47.1%)	
Brain MRI results			
Abnormal	9 (27.3%)	12 (70.6%)	**0.003**
Normal	24 (72.7%)	5 (29.4%)	
EEG results			
Abnormal	17 (48.5%)	16 (94.1%)	**0.001**
Normal	16 (51.5%)	1 (5.9%)	
CSF pressure, mmH_2O			
≥230	5 (15.2%)	4 (23.5%)	0.465
<230	28 (84.8%)	13 (76.5%)	
CSF WBC count			
Normal	19 (57.6%)	10 (58.8%)	0.933
High	14 (42.4%)	7 (41.2%)	
CSF protein level, mg/L			
≤400	13 (39.4%)	8 (47.1%)	0.603
>400	20 (60.6%)	9 (52.9%)	
CSF glucose level			
Low	1 (3.0%)	1 (5.9%)	0.655
Normal	27 (81.8%)	12 (70.6%)	
High	5 (15.2%)	4 (23.5%)	
CSF chloride level			
Low	1 (3.0%)	1 (5.9%)	0.830
Normal	29 (87.9%)	15 (88.2%)	
High	3 (9.1%)	1 (5.9%)	
Blood potassium level			
Low	5 (15.2%)	5 (29.4%)	0.232
Normal	28 (84.8%)	12 (70.6%)	
Blood sodium level			
Low	6 (18.2%)	5 (29.4%)	0.221
Normal	27 (81.8%)	11 (64.7%)	
High	0 (0.0%)	1 (5.9%)	
Blood chlorine level			
Low	2 (6.1%)	2 (11.8%)	0.277
Normal	31 (93.9%)	14 (82.4%)	
High	0 (0%)	1 (5.9%)	
Blood calcium level			
Low	12 (36.4%)	8 (47.1%)	0.465
Normal	21 (63.6%)	9 (52.9%)	
Albumin			
Low	18 (54.5%)	15 (88.2%)	**0.017**
Normal	15 (45.5%)	3 (11.8%)	
WBC count			
Normal	26 (78.8%)	12 (70.6%)	0.520
High	7 (21.2%)	5 (29.4%)	
Neutrophil count			
Normal	24 (72.7%)	9 (52.9%)	0.162
High	9 (27.3%)	8 (47.1%)	
Lymphocyte count			
Low	2 (6.1%)	8 (47.1%)	**0.001**
Normal	31 (93.9%)	9 (52.9%)	
Hemoglobin			
Low	10 (30.3%)	7 (41.2%)	0.603
Normal	22 (66.7%)	10 (58.8%)	
High	1 (3.0%)	0 (0%)	
Platelet count			
Low	1 (3%)	2 (11.8%)	0.203
Normal	22 (66.7%)	13 (76.5%)	
High	10 (30.3%)	2 (11.8%)	
NLR (median IQR)	2.92 (1.87–4.01)	5.60(4.56–11.49)	**0.001**
Mechanical ventilation			
Yes	4 (12.1%)	5 (29.4%)	0.236
No	29 (87.9%)	12 (70.6%)	
Pulmonary infection complications			
Yes	3 (9.1%)	10 (58.8%)	**0.000**
No	30 (90.9%)	7 (41.2%)	

AE, autoimmune encephalitis; SD, standard deviation; IQR, interquartile range; EEG, electroencephalogram; MRI, magnetic resonance imaging; CSF, cerebral spinal fluid; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio. Reference interval: CSF WBC count: 0–5 × 10^6/L; CSF protein level, 200–400 mg/L; CSF glucose level, 2.5–4.4 mmol/L; CSF chloride level, 120–130 mmol/L; blood potassium level, 3.5–5.3 mmol/L; blood sodium level, 137–147 mmol/L; blood chlorine level, 99–110 mmol/L; blood calcium level, 2.20–2.65 mmol/L; albumin, 40–55 g/L; WBC count, 3.5–10 × 10^9/L; neutrophil count, 1.8–6.3 × 10^9/L; lymphocyte count, 1.1–3.2 × 10^9/L; hemoglobin, 115–150 g/L; platelet count, 101–320 × 10^9/L. P values < 0.05 are considered statistically significant.

The Spearman rank correlation test was performed to analyze the correlation between the immunotherapy latency and prognostic mRS scores of 20 patients who received

TABLE 3 | Multivariate analysis of factors associated with a poor prognosis.

Variables	OR	95% CI	*P*-value
Consciousness disorders	11.995	0.173–833.456	0.251
Epileptic seizures	1.003	0.31–32.757	0.999
Extrapyramidal symptoms	10.157	0.529–195.094	0.124
EEG results	18.206	0.209–1586.043	0.203
Brain MRI results	1.189	0.53–26.628	0.913
Pulmonary infection complications	1.071	0.029–40.049	0.970
Albumin	1.792	0.100–32.115	0.692
Neutrophil count	0.089	0.002–3.640	0.201
Lymphocyte count	6.918	0.059–812.704	0.426
NLR	2.169	1.029–4.570	0.042

OR, odds ratio; CI, confidence interval; EEG, electroencephalogram; MRI, magnetic resonance imaging; NLR, neutrophil-to-lymphocyte ratio.

TABLE 4 | Receiver operating characteristic curve-related statistical indicators.

Prediction	AUC	95% CI	*P*
NLR	0.866	0.759–0.974	<0.001

NLR, neutrophil-to-lymphocyte ratio; AUC, area under the curve; CI, confidence interval.

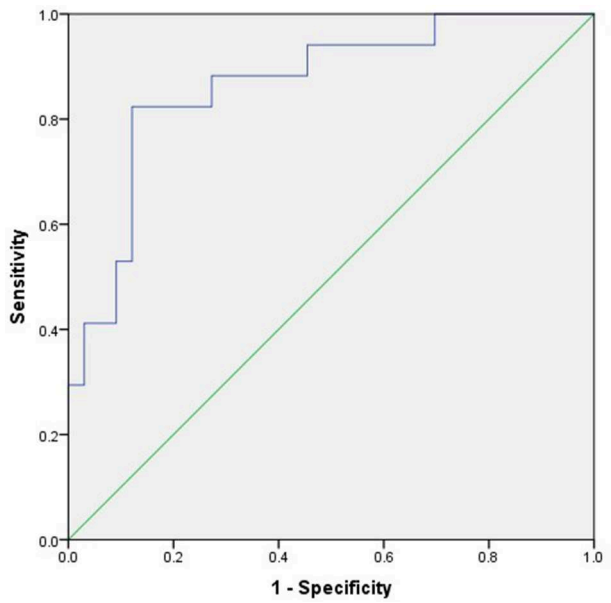

FIGURE 2 | ROC curve of the predictive value of NLR for poor prognosis of AE.

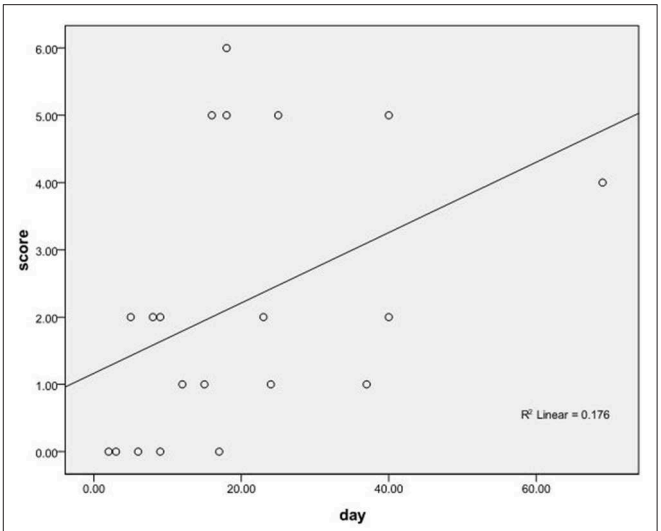

FIGURE 3 | The correlation between the immunotherapy latency and the prognostic mRS scores of 20 patients who received immunotherapy.

immunotherapy. There was a positive correlation between the immunotherapy latency and mRS score ($r_s = 0.535$, $P < 0.05$; **Figure 3**).

DISCUSSION

In this study, we retrospectively analyzed patients with an initial diagnosis of AE. We focused on clinical features, laboratory and imaging examinations, and EEG findings; moreover, we evaluated which factors are related to a poor prognosis. This study revealed that an increase in NLR was an independent risk factor for predicting the poor prognosis of AE. Prior to our study, the role of NLR in AE had not been examined, and this study presented a novel finding to predict the poor prognosis of AE.

AE is an increasingly recognized immune-mediated brain disease (10). This disease includes a heterogeneous group of encephalitic syndromes, which is divided into the following categories: new-type AE associated with antibodies to neural surface antigens and classic paraneoplastic limbic encephalitis (LE) associated with onconeural antibodies against intracellular antigens (25). It is reported that cases with surface antigen antibodies present a different immune reaction than that of cases with intracellular antigen antibodies. T cells are thought to play a cytotoxic role in cases with intracellular antigen antibodies (26), whereas antibody and/or complement-mediated mechanisms are considered to be responsible for neurodegeneration in encephalitis with surface antigen antibodies (10). Chronic inflammation, which is triggered by the overproduction of autoantibodies, inflammatory cytokine release, and deposition of the immune complex, plays an important role in the disease development process of AE (25). Abnormal immune regulation and persistent inflammation are critical pathological manifestations in the disease development process of AE.

NLR has been suggested as an indicator of systemic inflammation (11, 27). Compared with independent neutrophils, lymphocytes, and total white blood cell counts, NLR is less affected by various physiological and pathological conditions. NLR is an inexpensive, easily measurable, and widely available blood test affected by both innate immune response (mediated by neutrophils) and adaptive immune response (mediated by lymphocytes) (20). Changes in NLR may reflect the shifting balance between inflammatory activity and immune activity

(28). Inflammation is a response to acute or chronic tissue damage caused by infection, ischemic injury, physical injury, and other types of trauma. When these conditions occur, the immune system will lead neutrophils, lymphocytes and other inflammatory cells to accumulate in the site of damage (14). Under inflammatory conditions, neutrophil and lymphocyte counts present temporary changes. High levels of neutrophil infiltration may result from cytotoxicity in response to changes in the balance of pro-inflammatory and anti-inflammatory cytokines (29). The reason why NLR can predict prognosis may be summarized in two aspects: neutrophils are associated with a much quicker response, while lymphocytes are involved with more adaptive, chronic responses of the immune system (30). In the process of inflammation and immunity, neutrophils can destroy tissue directly by producing the enzyme myeloperoxidase and free radicals, and regulating the activity of other cell types (31). Moreover, some treatments such as immunotherapy can cause changes in NLR. Therefore, the routine blood results in our study were recorded within 24 h of admission to avoid interference from immunotherapy.

As an indicator of systemic inflammation, NLR has been frequently used to predict outcomes in many diseases. Prior studies have shown that altered NLR is related to decreased overall survival (OS) in various cancers. For example, Ma et al. detected that NLR is a significant predictor for recurrence in stage III melanoma patients (32). Shimada et al. suggested a high preoperative NLR as a biomarker to identify patients with a poor prognosis after resection for primary gastric cancer (33). Azab et al. found that NLR level >3.3 is an independent significant predictor of mortality in patients with breast cancer (34). Some studies have also reported that increased NLR is associated with higher rates of mortality in patients with acute heart failure or acute coronary syndrome (31, 35). In addition, a high NLR is also associated with a risk of death in critically ill patients, including patients with severe sepsis or septic shock (27, 36). Kim et al. demonstrated that NLR is a stronger independent predictor of postoperative acute kidney injury (AKI) (37). Another retrospective study of prognostic factors in patients with acute respiratory distress syndrome (ARDS) suggested that a high NLR (>14) independently predicts a poor prognosis in patients with ARDS (38). Based on recent studies, NLR is increased in patients with autoimmune diseases. In a previous study on the relationship between NLR and systemic lupus erythematosus (SLE), a high NLR was independently associated with SLE (39). In a meta-analysis on the relationship between hematological indices and autoimmune rheumatic diseases (ARDs), including ankylosing spondylitis (AS), Behçet's disease (BD), and rheumatoid arthritis (RA), NLR was recommended as a diagnostic biomarker for ARDs (22). Our study results extended previous reports on the prognostic role of NLR.

In fact, in clinical work, antibody-positive AEs are the minority, while most AEs are probable AEs or possible AEs. Several previous studies on prognostic factors of AE also evaluated different AEs, including "definite" and "probable" AE cases, in the same study (2, 40). In our study, among patients who received antibody testing, the proportion of patients with a definite diagnosis of AE (36%) was in the range reported in the literature (2, 40, 41). AE can appear as several different syndromes, classically presenting with decreased levels of consciousness (symptoms progress over a period of days or weeks) that eventually develops into coma (42). Extrapyramidal symptoms, such as dystonic seizures, chorea, or abnormal posture of the limbs, occur with anti-NMDAR encephalitis. In adults with anti-NMDAR encephalitis, facial, and limb writhing movements may be most notable in the comatose phases of the disease (43). In our data, 71% (5/7) of patients with anti-NMDAR encephalitis developed extrapyramidal symptoms. Seizures are common in AE and may occur at any stage of the disease, and studies have revealed that status epilepticus can predict a poor outcome for encephalitis (44, 45). Several studies on the death factors of encephalitis in the ICU have shown that status epilepticus, central hypoventilation, and complications (such as multiple organ dysfunction or severe pulmonary infection) are predictors of poor prognosis of encephalitis (44, 46, 47). However, in our study, consciousness disorders, epileptic seizures, extrapyramidal symptoms, and pulmonary infection complications were associated with adverse outcomes but were not independent predictors of poor prognosis. This result may be attributed to the following reason. With the development of diagnostic techniques and the availability of effective treatments, the predictors of poor prognosis may change. For example, a retrospective study of anti-NMDAR encephalitis also found that disturbance of consciousness, central hypoventilation, and complications are not independent predictors of poor prognosis (48). Another French study reported that status epilepticus in patients with anti-NMDA receptor encephalitis is unrelated to poor prognosis (49). Our results were essentially consistent with the results of previous related studies.

Serum albumin has been suggested as a prognostic factor in various diseases, including Guillain-Barre syndrome (GBS) (50). Jang et al. reported that low albumin levels are a significant indicator of AE prognosis (51). In our study, low albumin was associated with poor prognosis in univariate analysis but not in multivariate logistic regression analysis. This result may be because albumin levels in patients with low albumin have been improved during hospitalization without affecting patients' prognosis.

In most cases of AE, brain MRI shows normal or only non-specific inflammation changes (52). Some abnormal cases may present with increased signal on T2-weighted images, especially in the medial temporal lobe. In our study, abnormal MRI findings were associated with poor prognosis of AE in univariate analysis. The reason for this finding may be related to the anatomy and physiological functions of the involved brain regions. Frontal and temporal lobe lesions can easily lead to psychiatric symptoms and secondary epilepsy seizures; parietal lobe lesions are susceptible to sensory disturbances, and basal ganglia lesions are prone to causing extrapyramidal symptoms or paralysis, among other nervous system sequelae. EEG often exhibits focal or diffuse slow-wave activity associated with one or more epileptic foci in all types of AE. In addition to what may be called an "extreme triangle brush" pattern in patients with anti-NMDAR encephalitis, there are no characteristic EEG abnormalities for other forms of AE (53). However, in the acute

phase of encephalitis, aggravation of slow-wave activity is often accompanied by disturbance of consciousness, indicating that the injury is severe. Some studies have reported that EEG can predict prognosis in autoimmune or infective encephalitis, and normal EEG is a predictor of good prognosis (54). In our study, abnormal EEG was associated with poor prognosis of AE in univariate analysis. This study demonstrated that inflammatory changes in CSF are not related to prognosis. Although some patients with AE have moderately increased CSF lymphocytes, a lack of increase in cell numbers does not rule out this diagnosis (52). Most patients with AE have detectable neuronal autoantibodies in the CSF even if the CSF test is normal (8).

Immunotherapy for AE includes first-line therapy (steroids, IVIg, plasma exchange, or all) and second-line therapy (rituximab, cyclophosphamide, or other). Steroids are always the first option. Two weeks or more should be allowed for first-line therapies to work. If the patient remains very ill after first-line treatments, second-line therapy is typically administered (43). In the present study, early initiation of immunotherapy was associated with a good prognosis. Correspondingly, previous studies suggested that early immunotherapy improves the outcome of AE. A multi-institutional observational study of the prognosis of 577 patients with anti-NMDAR encephalitis showed a correlation between early immunotherapy and good prognosis, and it took more than 18 months for patients to recover (55). Another study suggested that patients who received immunotherapy within 40 days of onset had a better outcome than those who started immunotherapy after 40 days of onset (56). Our results were consistent with those of previous studies. Notably, not all patients with AE will respond to immunotherapy, but this does not mean that patients with AE cannot achieve a good outcome without immunotherapy. For example, in our study, two patients with anti-NMDAR encephalitis also achieved a good prognosis without immunotherapy. Therefore, considering the response to immunotherapy as a part of the diagnostic criteria of AE is not unreasonable. The speed of recovery, degree of residual deficit, and frequency of relapse differ greatly in different types of AE (8).

There is no known laboratory marker that predicts the poor prognosis of AE. Our study is the first to investigate the prognostic value of NLR in patients with AE. NLR has the advantage of low economic cost, no damage, and convenience. However, our study has several limitations. First, the present study was a retrospective design, thus, controlling for confounding factors was difficult. Prospective validation of NLR is required. Second, this study was conducted in a single institution, and the sample size of this study was small. Third, other inflammatory biomarkers, such as C-reactive protein (CRP), were not investigated, and the relationship between NLR and other inflammatory biomarkers could not be evaluated. Finally, there is still no consensus on the cutoff values to define the levels of NLR. The optimal cutoff value found in our study was 4.45, which is different from the values used in prior studies. The difference in cutoff points may be due to differences in the study population.

In conclusion, our study found that NLR may have predictive value for the poor outcomes of AE. Prospective validation of NLR is required. In addition, we revealed that early initiation of immunotherapy was associated with a good prognosis.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the ethical guidelines of the Declaration of Helsinki with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

XQ, HZ, CY, and ZX contributed to the conception and design of the work. XQ, HZ, and DL contributed to the acquisition, analysis, and interpretation of the data. HZ, DL, JW, PX, and JZ prepared figures and tables. XQ and HZ contributed to drafting the manuscript. XQ, ZJ, YZ, and CY contributed to statistical analysis. XQ, HZ, ZF, and ZX discussed the results. XQ and ZX revised the manuscript. XQ and HZ contributed equally and share first authorship.

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Pediatric Autoimmune Encephalitis: Case Series From Two Chinese Tertiary Pediatric Neurology Centers

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Background and purpose: We retrospectively analyzed the clinical characteristics of children with autoimmune encephalitis (AE) in two Chinese tertiary pediatric neurology centers. We also compared anti-NMDAR encephalitis with and without co-positive MOG antibody, as well as specific autoantibody-positive AE and autoantibody-negative but probable AE.

Methods: A retrospective study of children (0–18 years old) with AE in Peking University First Hospital and Children's Hospital Affiliated to Capital Institute of Pediatrics was carried out from May 2012 to January 2017. Demographics, clinical features, laboratory, and imaging findings, outcome, and co-positivity with MOG antibody were analyzed.

Results: A total of 103 children had AE, 89 (86.4%) had anti-NMDAR encephalitis, 2 (1.9%) had anti-LGI1 encephalitis, 1 (0.9%) had anti-CASPR2 encephalitis, and 11 (10.7%) were diagnosed as autoantibody-negative but probable AE. Among the 89 children with anti-NMDAR encephalitis, 35 were males and 54 were females. The follow-up time was 1–3 years. A total of 15 cases (15/89, 16.9%) with anti-NMDAR encephalitis had co-positive MOG antibody (serum or cerebrospinal fluid or both). These patients were more likely to experience relapse later in life ($P = 0.014$). We had two cases with anti-LGI1 encephalitis, that is, one with sleep disorder onset, and the other one with seizure onset, both of whom recovered after treatment. One case with anti-CASPR2 encephalitis was treated with an antiepileptic drug and fully recovered. There were 11 cases diagnosed as autoantibody-negative but probable AE who had relatively poorer outcome than those with autoantibody-positive AE (15.2%, 14/89). However, the difference was not significant ($P = 0.08$). Only one 12-year-old girl with NMDAR-antibody AE had ovarian teratoma.

Conclusion: Most subjects with AE in our Chinese cohort had anti-NMDAR AE, which had relatively good prognosis. Children with anti-LGI1 or anti-CASPR2 encephalitis were

rare and showed good response on immunotherapy. Co-positive MOG antibody was relatively common in anti-NMDAR encephalitis, which was related to high relapse rate. In our study, the prognosis of autoantibody-negative but probable AE seemed worse than that of specific autoantibody-positive AE.

Keywords: NMDAR, autoimmune encephalitis, child, prognosis, MOG

INTRODUCTION

Autoimmune encephalitis (AE) is a brain disease caused by antibodies targeting neurons in the central nervous system to generate specific immune responses. Although immune encephalitis can occur at all ages, children's AE has unique characteristics. AE associated with cell surface antigens is more common in children, the most common of which is anti-NMDAR encephalitis, and other types of AE, such as LGI1 antibody-related AE, have also been reported (1–3). The common clinical manifestations of AE include abnormal mental behavior, seizure, abnormal memory and cognitive function, and motor and consciousness disorders. Cerebrospinal fluid and serum antibody detection is crucial to determine the specific type of AE. However, some patients were diagnosed with AE clinically but were autoantibody negative. In 2016, the new diagnostic criteria about autoantibody-negative but probable AE was established (4). The immunotherapy should be given as early as possible for AE. Although there is much in the literature about AE (5–7), regarding specifically for children's AE it is still limited. Therefore, we analyze the clinical characteristics, treatment, and prognosis of children with AE in two Chinese tertiary pediatric neurology centers herein.

SUBJECTS AND METHODS

Subjects

The study was approved by the Ethics Committee of the Peking University First Hospital.

The data of children with AE who were hospitalized from May 2012 to January 2017 in the of Peking University First Hospital and children's hospital affiliated to the Capital Institute of Pediatrics were collected.

Methods

The diagnostic criteria for autoantibody-negative but probable AE and definite antibody encephalitis was proposed by Graus et al. (4) in 2016. AE was diagnosed by pediatric neurologists in each hospital on the basis of clinical findings and the presence of specific antibodies in CSF. The flow diagram of this study is shown in **Figure 1**.

The serum and CSF samples of each patient were sent to Oumeng Biotechnology Corporation, Beijing, China, or Neurological Lab, Peking University First Hospital, China, for the antibodies against the NMDA receptor and other AE-related antibodies. All samples were analyzed by indirect immunofluorescence assay using the EU 90 cells transfected method (BIOCHIPs, Euroimmun AG, Lubek, Germany).

We summarized the symptoms, such as psychiatric symptoms, seizures, speech disturbance, sleep disturbance, dyskinesia, and movement disorders, consciousness disturbance, memory deficit, and autonomic instability. Clinical data including age, gender, symptoms, CSF analysis, brain magnetic resonance imaging (MRI), electroencephalography (EEG), treatment, and follow-up were reviewed. First-line immunotherapy included intravenous (IV) methylprednisolone or intravenous immunoglobulins (IVIG), or a combination of these. Rituximab or cyclophosphamide treatment was defined as second-line immunotherapy.

All patients were followed for at least 1 year (in the range of 1–5). Epilepsy was diagnosed when seizure lasted for more than 24 months after the encephalitis (post-encephalitis epilepsy). Good outcome was defined as no sequela, and poor outcome as having any sequela.

Statistical Analysis

Statistical analysis was conducted using SPSS 25.0. Data conformance to normal distribution is described by mean ± SE. Fisher's exact test was used to compare the categorical data. All predictors were tested in univariate models, the statistically significant indicators of the univariate analysis were added to the multivariate analysis, and the indicators considered probably to be clinically meaningful based on previous literature were also included in the multivariate analysis.

Associations were described as odds ratio used in developing the outcome in patients with each predictor relative to those without the predictor with 95% confidence interval and *P*-value. $P < 0.05$ was considered statistically significant.

RESULTS

Clinical Demographics

A total of 103 children with AE, including 89 with anti-NMDAR encephalitis, two with anti-LGI1 encephalitis, one with anti-CASPR2 encephalitis, and 11 with autoantibody-negative but probable AE, were followed up (**Figure 2**).

Characteristics of Children With Anti-NMDAR Encephalitis (Table 1)

The characteristics of anti-NMDAR encephalitis are as follows: 72 patients (80.9%) presented psychiatric symptoms, 65 (73.0%) experienced seizures, 65 (73.0%) had movement disorders, 60 (67.4%) had language disorders, 57 (64.0%) had memory disorders, and 43 (48.3%) had sleep disorders, followed by consciousness disturbance, paralysis, ataxia, sensory disturbance, and central hypoventilation. All patients underwent cranial MRI.

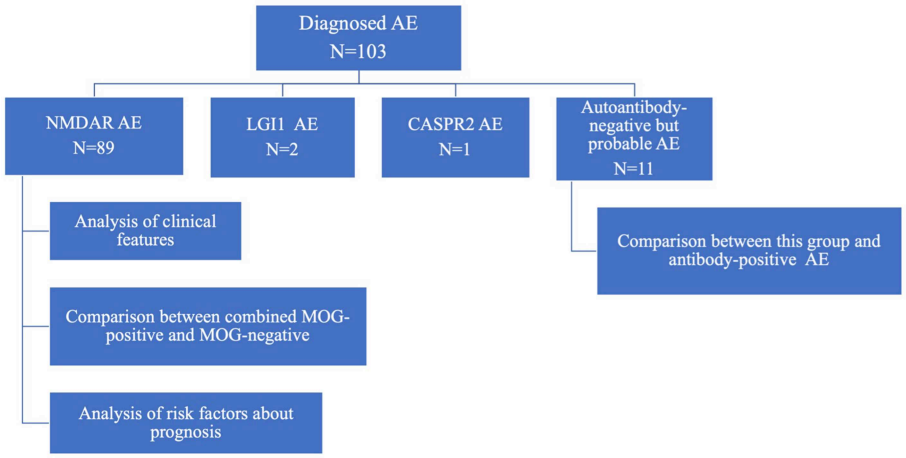

FIGURE 1 | Flow diagram of study.

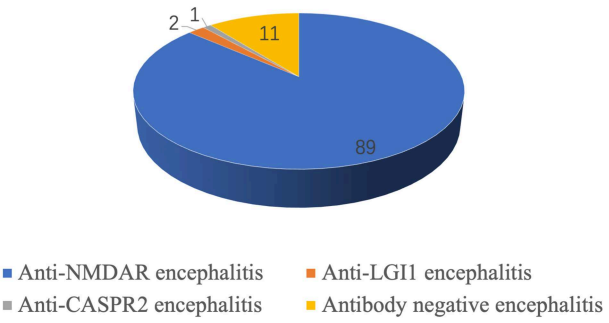

FIGURE 2 | Autoimmune encephalitis classification in children.

Radiologists reported that 29 patients (32.6%) were abnormal. The abnormal locations of cranial MRI in 21 (23.6%), 7 (7.9%), 7 (7.9%), and 5 patients (5.6%) were found in the temporal lobe, frontal lobe, parietal lobe, and basal ganglia, respectively. EEG was performed in all patients, and 79 patients (88.8%) obtained abnormal findings; 42 patients (47.2%) had generalized slow-wave, 33 (37.1%) had focal slow-wave, 55 (61.8%) had epileptic discharge, and 15 patients (16.8%) exhibited extreme delta brush. The CSF of all patients was positive for NMDAR-IgG, but 60 patients (67.4%) had positive NMDAR-IgG in serum. A total 41 patients (46.1%) had CSF leukocytosis ($>5/mm^3$). A total of 52 patients (58.4%) had oligoclonal band positive in CSF. MOG-positive serum or CSF was found in 15 patients (16.9%). For treatment, glucocorticoid therapy was performed in 87 patients (97.8%), intravenous immunoglobulin (IVIG) treatment was performed in 77 patients (86.5%), second-line drugs (rituximab and cyclophosphamide) were used in 32 patients (35.9%), and two children (2.2%) did not use immunotherapy because their parents refused to use it. Prognosis showed that 75 patients (84.3%) had complete recovery, six patients (6.7%) had epilepsy, six (6.7%) had cognitive dysfunction, one (1.1%) exhibited ataxia, and one (1.1%) died. A total of 12 patients (13.5%) experienced relapse.

Analysis of Factors Regarding Anti-NMDAR Encephalitis Outcome (Tables 2, 3)

The results of univariate analysis are shown in **Table 2**. On multivariate regression analysis, the factors associated with anti-NMDAR encephalitis outcome were admission to ICU ($P = 0.016$) and status epilepticus ($P = 0.023$, **Table 3**).

Comparison Between Combined MOG Antibody-Positive and -Negative Children With Anti-NMDAR Encephalitis (Table 4)

A higher proportion of precursor infection and relapse was found in MOG antibody-positive children than those in MOG antibody-negative ones, and the difference was statistically significant ($P < 0.05$).

Clinical Analysis of Children With Anti-LGI1 Encephalitis (Table 5)

Two patients had anti-LGI1 encephalitis, one of which was an 8-year-old boy with clinical manifestation mainly for insomnia. The cranial MRI of this patient showed left hippocampal lesions and showed positive CSF and serum LGI1 antibody. Without ICU admission, video EEG showed focal slow waves. The number of cerebrospinal fluid cells was normal. After 2 weeks of treatment with IVIG, the clinical manifestations and cranial MRI significantly improved. The second patient was a 15-year-old boy with seizure. Anti-LGI1-IgG antibody was positive (1:100) in the serum. No memory loss, cognitive impairment, mental disorder, sleep disorder, or movement disorders were reported. The prognosis was good by using IVIG (2 g/kg, for 5 days) and levetiracetam for 1 year.

TABLE 1 | Clinical characteristics of children with anti-NMDAR encephalitis.

Demographic and clinical characteristics	0–3 years old	3–6 years old	6–12 years old	12–18 years old	Total
Total	11	24	39	15	89
Seizures	8 (72.7%)	20(83.3%)	27 (69.2%)	10 (66.7%)	65(73.0%)
Seizures as initial symptom	6 (54.5%)	15(62.5%)	13 (33.3%)	7 (46.7%)	41(46.1%)
Psychiatric symptom	8 (72.7%)	21(87.5%)	31 (79.5%)	12 (80.0%)	72(80.9%)
Psychiatric as initial symptom	3 (27.3%)	8 (33.3%)	14 (35.9%)	6 (40.0%)	31(34.8%)
Movement disorders	7 (63.6%)	20(83.3%)	27 (69.2%)	11 (73.3%)	65(73.0%)
Movement disorder as initial symptom	1 (9.1%)	2 (8.3%)	4 (10.3%)	2 (13.3%)	9 (10.1%)
Speech dysfunction	3 (27.3%)	17(70.8)	30 (76.9%)	10 (66.7%)	60(67.4%)
Speech dysfunction as initial symptom	0	2 (8.3%)	5 (12.8%)	2 (13.3%)	9 (10.1%)
Sleep disorder	4 (36.4%)	14(58.3)	18 (46.2%)	7 (46.7%)	43(48.3%)
Memory disorder	5 (45.5%)	13(54.2%)	28 (71.8%)	11 (73.3%)	57(64.0%)
Consciousness disturbance	5 (45.5%)	7 (29.2%)	11 (28.2%)	6 (40.0%)	29(32.6%)
Ataxia	1 (9.1%)	4 (16.7%)	8 (20.5%)	2 (13.3%)	15(16.9%)
Sensory disorder	0	0	4 (10.3%)	0	4 (4.5%)
Paralysis	6 (54.5%)	5 (20.8%)	5 (12.8%)	1 (6.7%)	17(19.1%)
Hypoventilation	0	0	2 (5.1%)	0	2 (2.2%)
Cranial MRI with abnormal findings			29 (32.6%)		
Temporal lobe	1 (9.1%)	6 (25.0%)	12 (30.8%)	2 (13.3%)	21(23.6%)
Frontal lobe	1 (9.1%)	2 (8.3%)	4 (10.3%)	0	7 (7.9%)
Parietal lobe	0	2 (8.3%)	5 (12.8%)	0	7 (7.9%)
Basal ganglia	1 (9.1%)	2 (8.3%)	2 (5.1%)	0	5 (5.6%)
Brain stem	0	1 (4.2%)	2 (5.1%)	1 (6.7%)	4 (4.5%)
Cerebellum	0	1 (4.2%)	1 (2.6%)	1 (6.7%)	3 (3.4%)
Thalamus	0	0	1 (2.6%)	1 (6.7%)	2 (2.2%)
Occipital lobe	0	0	2 (5.1%)	0	2 (2.2%)
Deep white matter	2 (18.2%)	4 (16.7%)	1 (2.6%)	1 (6.7%)	8 (9.0%)
Subcortical white matter	1 (9.1%)	5 (20.8%)	3 (7.7%)	1 (6.7%)	10(11.2%)
EEG with abnormal findings			79 (88.8%)		
Focal slowing	2 (18.2%)	8 (33.3%)	16 (41.0%)	7 (46.7%)	33(37.1%)
Generalized slowing	6 (54.5%)	12(50.0%)	18 (46.2%)	6 (40.0%)	42(47.2%)
Epileptic form discharge	7 (63.6%)	16(66.7%)	24 (61.5%)	8 (53.3%)	55(61.8%)
Extreme delta brush	4 (36.4%)	3 (12.5%)	5 (12.8%)	3 (20.0%)	15(16.9%)
CSF pleocytosis (>5/mm^3)	2 (18.2%)	11(45.8%)	21 (53.8%)	7 (46.7%)	41(46.1%)
CSF Oligoclonal band	8 (72.7%)	13(54.2%)	24 (61.5%)	7 (46.7%)	52(58.4%)
MOG-positive (serum or CSF)	2 (18.2%)	5 (20.8%)	7 (17.9%)	1 (6.7%)	15(16.9%)
Immunotherapy					
Steroid only	10(90.9)	24(100%)	39 (100.0%)	14 (93.3%)	87(97.8%)
IVIG only	8 (72.7%)	20(83.3%)	35 (89.7%)	14 (93.3%)	77(86.5%)
Second-line drugs (rituximab or cyclophosphamide)	5 (45.5%)	11(45.8%)	14 (35.9%)	2 (13.3%)	32(35.9%)
No immunotherapy	1 (9.1%)	0	0	1 (6.7%)	2 (2.2%)
Relapse	1 (9.1%)	2 (8.3%)	7 (17.9%)	2 (13.3%)	12(13.5%)
Prognosis					
Complete recovery	10(90.9%)	17(70.8%)	35 (89.7%)	13 (86.7%)	75(84.3%)
Epilepsy	0	4 (16.7%)	0	2 (13.3%)	6 (6.7%)
Cognitive dysfunction	1 (9.1%)	2 (8.3%)	3 (7.7%)	0	6 (6.7%)
Ataxia	0	0	1 (2.6%)	0	1 (1.1%)
Death	0	1 (4.2%)	0	0	1 (1.1%)

Anti-CASPR 2 Encephalitis (Table 5)

One of the children was a 5-year-old boy who was admitted to the hospital for 1 day due to paroxysmal headache and vomiting for 2 months was diagnosed with anti-CASPR 2 encephalitis. During the course of the disease, convulsions lasted for 1 h and 30 min. Cranial MRI showed no abnormality, and EEG indicated slow waves in the occipital region. CSF test was normal, and serum anti-CASPR 2-IgG was positive. There was no ICU admission.

TABLE 2 | Factors associated with outcome of anti-NMDAR encephalitis: univariate analysis.

	Complete recovery	Incomplete recovery	OR (95% CI) or *t*-value	*P*-value
Potential predictors	75	14		
Age (mean ± SE, year)	7.92 ± 3.89	6.85 ± 4.96	−1.112	0.664
Female (%)	45 (60.0%)	9 (64.3%)	0.881 (0.269–2.891)	0.835
Status epilepticus	22 (29.3%)	9 (64.3%)	4.336 (1.305–14.411)	0.017
Consciousness disturbance	22 (29.3%)	7 (50.0%)	4.07 (1.228–13.489)	0.022
Movement disorder	52 (69.3%)	13 (92.9%)	5.396 (0.665–43.795)	0.115
CSF pleocytosis (≧5/mm^3)	34 (45.3%)	7 (50.0%)	1.072 (0.327–3.522)	0.908
Anti-NMDAR body titer ≧100	30 (40.0%)	10 (71.4%)	3.75 (1.076–13.065)	0.038
Abnormal cranial MRI	23 (30.7%)	6 (42.8%)	1.594 (0.497–5.106)	0.433
EEG with abnormal findings (slow wave or epileptic form discharge)	66 (88.0%)	13 (92.8%)	1.773 (0.207–15.217)	0.602
Extreme delta brush	12 (16.0%)	3 (21.4%)	1.97 (0.460–8.435)	0.361
ICU admission	3 (4.0%)	4 (28.6%)	9.6 (1.869)	0.007

TABLE 3 | Factors associated with anti-NMDAR encephalitis outcome: multivariate analysis.

	Odds ratio	95% CI	*P*-value
Status epilepticus	5.329	1.26–22.529	0.023
Consciousness disturbance	1.235	0.319–22.529	0.760
Movement disorder	2.944	0.302–28.696	0.353
Abnormal cranial MRI	1.455	0.331–6.388	0.619
Abnormal EEG	2.113	0.177–25.219	0.554
Anti-NMDAR antibody titer ≧ 100	1.821	0.447–7.415	0.403
ICU admission	11.494	1.569–84.2	0.016

No convulsions were observed for more than 2 years after the levetiracetam treatment, and the cognitive function of this patient was normal. Parents refused immunotherapy for this child.

Analysis of Autoantibody-Negative but Probable AE

A total of 11 patients were diagnosed with autoantibody-negative but probable AE. All patients were followed up for 1–2 years. Six patients were female, and their mean age was 6.18 ± 2.09 years old. Seizures were observed in all patients, mental symptoms were found in nine patients, and dyskinesia was presented in two patients. EEG showed generalized or focal slow-wave in all patients. Five patients exhibited epilepsy discharge, and all patients had cranial MRI abnormalities. Two patients did not receive immunotherapy. In terms of prognosis, two patients experienced epilepsy, one patient had dyskinesia, and one patient exhibited irritability. In this group, seven patients were cured, and four had sequelae.

Comparison Between Children With Autoantibody-Negative but Probable AE and With Antibody-Positive AE (Table 6)

In contrast to the antibody-positive encephalitis group, the proportions of movement disorders and CSF oligoclonal band were higher than those of the antibody-negative group ($P < 0.05$). The number of cluster seizures in the autoantibody-negative but probable AE group was higher than that in the antibody-positive encephalitis group ($P < 0.05$).

AE in Children With Tumor

All the children underwent chest- and abdomen-enhanced CT examination, and the boys underwent testicular ultrasound examination. Only one 12-year-old girl with anti-NMDAR encephalitis had ovarian teratoma (0.9%, 1/103). No tumors were found in children younger than 12 years old, and no patient with other AE had a tumor.

DISCUSSION

With the discovery of relevant antibodies, the etiology of some unknown causes of encephalitis has been clarified, and AE has become a topic receiving considerable interest in research. However, most of the published works on AE focus upon adult patients. Studies on children with AE are relatively few, or the analysis was not specific enough (5–8). Therefore, we analyze the cases of AE (including AE with known and unknown antibodies) in two Chinese tertiary pediatric neurology centers, of which both hospitals had patients from all over the country, thereby representing Chinese children with AE to some extent.

The most common clinical features of anti-NMDAR AE as the initial symptoms in our study were seizures, psychiatric symptoms, language disorders, movement disorders, and sleep disorders. Seizure is also the most common symptom in children, which is consistent with much literature (4, 5, 9–11). Children always manifested with neurological symptoms onset, adults with psychiatric symptoms (11). In the children's anti-NMDAR AE, the onset of epilepsy as the initial symptom reached 72%, and the form of epileptic attack was the most common (58%) and comprehensive attack (42%) (11). In adult patients, only 14% (12, 13) of patients are onset of seizures presented as the initial symptom. Other symptoms, such as psychiatric

TABLE 4 | Comparison between combined MOG antibody-positive and -negative children with anti-NMDAR encephalitis.

	MOG-positive	MOG-negative	X^2 or *t*-value	*P*-value
Total	15	74		
Age (mean ± SE, year)	6.31 ± 3.82	7.60 ± 3.92	−1.162	0.248
Preceding infection	8 (53.3%)	18 (24.3%)	5.075	0.024
Status epilepticus	5 (33.3%)	26 (35.1%)	1.103	0.218
Consciousness disturbance	6 (40.0%)	23 (31.1%)	0.452	0.502
CSF pleocytosis (≧5/mm^3)	7 (46.7%)	34 (43.2%)	0.002	0.964
Anti-NMDAR antibody titer ≧100	7 (46.7%)	33 (44.6%)	0.003	0.959
CSF Oligoclonal band	9 (60.0%)	43 (58.1%)	0.018	0.892
Cranial MRI with abnormal white matter	4 (26.7%)	14 (18.9%)	0.464	0.496
Extreme delta brush	1 (6.7%)	14 (18.9%)	1.336	0.248
ICU admission	1 (6.7%)	6 (8.1%)	0.036	0.850
Relapse	5 (33.3%)	7 (9.5%)	6.094	0.014
Second-line immunology	6 (40.0%)	26 (35.1%)	0.066	0.797
Sequela	2 (13.3%)	12 (16.2%)	0.078	0.780

TABLE 5 | Clinical characteristics of anti-LGI1 and anti-CASPR2 AE.

Patients	Anti-LGI1 patient 1	Anti-LGI1 patient 2	Anti-CASPR2
Age	8 years old	15 years old	5 years old
Gender	Male	Male	Male
Seizures	No	Yes	Yes
Status epilepticus	No	No	No
Psychiatric symptom	No	No	No
Movement disorders	No	No	No
Speech dysfunction	No	No	No
Sleep disorder	Yes	No	No
Memory disorder	No	No	No
Ataxia	No	No	No
Paralysis	No	No	No
Hypoventilation	No	No	No
Cranial MRI with abnormal findings	Yes	No	No
EEG with abnormal findings	Yes (focal slow waves)	Yes (focal slow waves and Epileptic form discharge)	Yes (focal slow waves)
CSF pleocytosis (>5/mm^3)	No	No	No
CSF Oligoclonal band	No	No	No
MOG-positive (serum or CSF)	No	No	No
Immunotherapy			
Steroid	No	No	No
IVIG	Yes	Yes	No
Second-line drugs (rituximab or cyclophosphamide)	No	No	No
Anti-epilepsy drugs	No	Yes	Yes
ICU admission	No	No	No
Complete recovery	Yes	Yes	Yes

symptoms, involuntary movements, language disorders, and sleep disturbances, are as common as reported in other literature.

The predictors of poor outcome were status epilepticus and ICU admission. In previous studies, the predictors of poor outcome included delayed treatment, young age, decreased consciousness, memory deficiency, high antibody titers, and ICU admission (11, 14, 15). ICU admission was a predictor of poor outcome, which was consistent with our study, whereas the status epilepticus as a predictor of poor outcome in our study is different from previous literature.

The concomitancy of anti-NMDAR antibody and MOG antibody has been reported recently (16, 17). In our cases, one patient was diagnosed with acute disseminated encephalomyelitis due to acute multiple demyelinating disease, and the test showed that the patient was NMDAR antibody-positive. Thus, we should pay attention in identifying demyelinating or acute demyelinating diseases combined with anti-NMDAR encephalitis. In the study of Titulaer et al. (18), the cohorts were divided into three groups. Group 1 included 12 patients whose anti-NMDAR encephalitis was preceded or followed by independent neuromyelitis or demyelinating syndromes (seven cases, all anti-MOG antibody-positive). Group 2 included 11 patients whose anti-NMDAR encephalitis occurred with MRI abnormality and symptoms compatible with demyelination (two MOG antibody-positive cases). Group 3 included 50 randomly selected patients with typical anti-NMDAR encephalitis (three MOG antibody-positive cases). In our cohort, MOG antibody-positive serum or CSF in 15 (16.9%) patients in anti-NMDAR encephalitis was higher than those in other reports. The reason may be that measuring positive for MOG-antibody is considerably high in children. The incidence of MOG-Ab often occurs in East Asia (19). Our patients also had increased risk of relapse later in life ($P = 0.014$) and a high proportion of preceding infection ($P = 0.024$). MOG is a specific glycoprotein in the white matter of the central nervous system. Anti-MOG antibodies can cause demyelinating lesions. In this study, 18 patients had MRI demyelinating lesions, of which 4 were positive for MOG antibodies, but 14 patients did not find any demyelinating related antibodies, including MOG and AQP4. In addition, there were 11 patients with positive MOG antibodies, but no demyelinating lesions were found on MRI. The mechanism by which MOG antibodies and NMDA antibodies are simultaneously positive is still unknown.

TABLE 6 | Comparison between children with autoantibody-negative but probable AE and antibody-positive AE.

	Negative	Positive	X^2 or *t*-value	*P*-value
Total	11	92		
Age (mean ± SE year)	6.20 ± 2.26	7.29 ± 2.87	0.017	0.334
Female (%)	6 (54.5%)	54 (58.7%)	0.227	0.634
Psychiatric symptom	8 (72.7%)	72 (78.3%)	0.109	0.742
Movement disorder	4 (36.3%)	65 (70.7%)	4.828	0.028
Cluster seizures	9 (81.8%)	42 (45.7%)	5.141	0.023
Status epilepticus	4 (36.4%)	31 (33.7%)	0.063	0.802
Consciousness disturbance	4 (36.4%)	29 (31.5%)	0.106	0.745
CSF pleocytosis ($\geqq 5/mm^3$)	5 (45.5%)	41(44.6%)	0.003	0.955
CSF Oligoclonal band	2 (18.2%)	52 (56.5%)	5.791	0.016
ICU admission	1 (9.1%)	7 (7.6%)	0.03	0.862
Relapse	1 (9.1%)	12 (13.0%)	0.057	0.746
Second-line immunology	3 (27.3%)	32 (34.8%)	0.247	0.619
Sequelae	4 (36.4%)	14 (15.2%)	3.046	0.081

A previous study Dalmau et al. (9) reported that 55% of those with anti-NMDAR encephalitis had abnormal cranial MRI, and the lesions were located in the temporal lobe, hippocampus, corpus callosum, cerebellum/cerebellum cortex, basal ganglia, and brainstem. A multicenter study Schimmel et al. (1) of 540 patients with anti-NMDAR encephalitis showed that 33% of the patients had cranial MRI abnormalities, and 80% of the abnormal signals were found in the temporal and frontal lobes. A total of 29 cases (32.6%) of children with cranial MRI abnormalities located in the temporal, frontal, and parietal lobes were reported in our study. The high proportion of basal ganglia, the incidence of cranial MRI abnormalities, and lesions in the study of this area were consistent with the results in the literature, but the pathological feature and specificity of the lesion site are lacking. A total of 79 out of the 89 patients had abnormal EEGs (88.7%), which were mainly composed of diffused slow-wave, followed by focal slow-wave. However, the extreme delta brush was rare. This finding was also reported in some previous studies (6, 20).

Autoimmune encephalitis (AE) therapy mainly includes first-line and the second-line immunotherapy. A previous work Zekeridou et al. (12) and this study showed that glucocorticoid is still the most frequently used first-line drug. Second-line drugs are always used in children with severe illness or relapse, around 20–30% of total patients. Most of the children with anti-NMDAR encephalitis had relatively good prognosis. Seventy-five patients (84.3%) achieved good outcomes, while 15 patients had poor outcomes in our study. The ratio of good outcomes was lower than those in previous research because we considered cognitive impairment an indicator of poor outcome, which was less used in previous studies. Only one (1.1%) patient died in our study, which was similar to that in previous studies, that is, the death rate in young children is low (2.7%) (11). This finding may be associated with the low proportion of cancer and autonomic instability. Twelve patients (13.5%) relapsed and improved after second-line treatment, which was consistent with the results of a previous report (12%) (11). Relapse rate can also reach 20–24% (21, 22), but the patients in those studies were adults only or both adults and children.

Our study found two cases with anti-LGI1 encephalitis and one case with anti-CASPR2 encephalitis. For two cases with LGI1 encephalitis, their first symptom was only sleep disturbance or seizure, their cranial MRI had typical characteristics, and they both responded well to immunotherapy. Only one case with anti-CASPR2 encephalitis was found, which was mainly manifested as consciousness disturbance and seizure. The seizure was controlled after antiepileptic treatment.

Some patients can be diagnosed with AE in clinical manifestation without specific antibodies. According to the proposed diagnosis criteria (4) for autoantibody-negative but probable AE, we diagnosed 11 patients [10.7% (11/103)], which was higher than that reported previously (7%) (23). These patients were given immunotherapy and were observed for 1–2 years. The outcomes showed that two cases had epilepsy, one had dyskinesia, and one had a sharp temper. The comparison between antibody-positive and -negative encephalitis groups showed that the proportion of dyskinesia and CSF oligoclonal band was higher than those of the autoantibody-negative but probable AE group ($P < 0.05$). The cluster seizures in the autoantibody-negative but probable AE group were more frequent than in the antibody-positive encephalitis group ($P < 0.05$), which were not reported in the previous study. Compared with the other AE types in this study, the prognosis of patients with autoantibody-negative but probable AE was poor. Regarding the pathogenesis of antibody-negative encephalitis, some antibodies may have not yet been discovered. However, these patients may not be associated with autoantibody but related to abnormal cellular or innate immune process (24).

In all children with AE in our study, only one 12-year-old girl had ovarian teratoma in anti-NMDAR encephalitis, thereby suggesting that children were less likely to develop tumors than older people, which was consistent with the results of a previous report on a multicenter study (9) showing that the incidence of teratoma in patients with an age of >18 years old is 56%, thereby accounting for 31% of women with the age of <18 years old and 9% in women with the age of <14 years old. In our study, we only had one case of teratoma (1.1%). Thus, in the children with AE, the incidence of tumors is low, especially for young children. Therefore, according to the characteristics of childhood illness, infectious factors may be a major inducing factor in children.

In conclusion, AE in children has its own characteristics regardless of the first sign of the disease or the condition of tumor concomitant. The shortcoming of this study is that it is not a prospective study and does not use mRS to evaluate the function. Additional research, especially prospective studies to clarify the diagnosis and treatment of anti-NMDAR encephalitis in some subgroup of children, such as the treatment of anti-NMDAR encephalitis-related epileptic seizures, is still needed in the future.

ETHICS STATEMENT

Ethics approval for this study was obtained from the Ethics Committee of the Peking University First Hospital. The parents of the patients signed written informed consent and agreed with the participation of their children in this study and allowed the use of the relevant data and information for scientific research.

AUTHOR CONTRIBUTIONS

JZ and TJ contributed in preparing the draft manuscript of this article and prepared the text. PZ and XJ prepared the figure. YJia and JY were responsible for all supervision and are the guarantor of the article. HR was responsible for the detection of specimens. Other authors have been involved in the management of the children.

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Epidemiology of Antibody-Positive Autoimmune Encephalitis in Southwest China: A Multicenter Study

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In recent years, as an increasing number of neuronal autoantibodies have been detected and used for clinical diagnosis, clinicians have become more aware of autoimmune encephalitis, causing its reported incidence to trend upward over several years. To date, however, there has been no large-scale epidemiological survey of autoimmune encephalitis in adults and children, and its epidemiological characteristics remain unclear. Six main types of antibodies are detected and used to diagnose autoimmune encephalitis in Chongqing, Southwestern China: anti-NMDA receptor antibody, anti-$GABA_B$ receptor antibody, anti-LGI1 antibody, anti-CASPR2 antibody, anti-AMPA1 receptor antibody, and anti-AMPA2 receptor antibody. From January 2012 to February 2018, 189 patients at six general hospitals in Chongqing were diagnosed with autoimmune encephalitis and were positive for neuronal autoantibodies. In this report, the epidemic situation and the antibody distribution among these patients are analyzed and described in detail. The differences in disease severity among different ages and between the sexes are evaluated, and the correlation between antibody titer and disease severity is also assessed.

Keywords: autoimmune encephalitis, epidemiology, age, sex, neuronal autoantibodies

INTRODUCTION

Encephalitis has high incidence and mortality rates worldwide (1), with a reported mortality rate of 8–18.45% (2–4). The term autoimmune encephalitis (AE) refers in general to a large group of diseases caused by an antigen-antibody reaction by the immune system to the central nervous system (5). The main clinical characteristics of AE are acute or subacute seizures of epilepsy, cognitive impairment, and mental symptoms. The disease spectrum of AE has been expanding since the first case of teratoma-related anti-N-methyl-D-aspartate (NMDA) receptor encephalitis was reported in 2007 (6). With the continuous progress and implementation of detection methods, a growing number of cases of AE with positivity for different autoantibodies have been diagnosed and reported. As an important cause of encephalitis, autoimmunity is receiving increasing attention from medical staff.

Investigations have shown that AE affects the quality of life of those affected and imposes a serious economic burden on both patients and society (7). Because the clinical manifestations of AE are very complex, the condition is difficult to diagnose, although early intervention is important for improving the prognosis of these patients (8). Neuronal autoantibodies are key for the diagnosis of AE, and changes in antibody titer are closely related to the clinical course (9). Neuronal autoantibodies identify subtypes of AE and help clinicians detect cases with atypical clinical manifestations. Therefore, antibody measurement is a critical step in the diagnosis of AE (5).

To date, there have been few epidemiological investigations of AE, and there are currently no data from large-scale epidemiological investigations. Thus, the epidemiological characteristics of the condition are still unclear. Six main types of antibodies are detected and used for the diagnosis of AE in Chongqing, Southwestern China: anti-NMDA receptor (NMDAR) antibody, anti-gamma-aminobutyric acid-B receptor ($GABA_BR$) antibody, anti-leucine-rich glioma-inactivated 1 (LGI1) antibody, anti-contactin-associated protein-like 2 (CASPR2) antibody, anti-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid 1 (AMPA1) receptor antibody, and anti-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid 2 (AMPA2) receptor antibody. In this study, the epidemiological characteristics of 189 patients with AE and antibody positivity were analyzed according to the diagnostic criteria of AE (5). The findings will provide clinicians with an improved understanding of the epidemiological characteristics of AE and contribute to speeding the diagnostic process and improving patient prognosis.

METHODS

Study Population

Data were collected from six large general hospitals in Chongqing, Southwestern China. From January 2012 to February 2018, 189 patients with AE were diagnosed with antibody positivity. The patients' medical records, laboratory results, cost information, and prognoses were reviewed and registered by a neurologist.

Inclusion Criteria

According to the AE diagnostic criteria published in *The Lancet Neurology* (5), the following four criteria were used, along with positivity for neuron surface antibodies: (1) subacute onset (rapid progression over <3 months); working memory deficits, epilepsy, or psychiatric symptoms related to the limbic system; (2) bilateral brain abnormalities highly restricted to the medial temporal lobe on T2-weighted fluid-attenuation inversion recovery MRI; (3) at least one of the following: 1) an increase in the number of cerebrospinal fluid (CSF) cells (white blood cell count exceeding $5/mm^3$) 2) EEG indicating epilepsy or slow-wave activity in the medial temporal lobe; and (4) reasonable exclusion of other diseases.

Exclusion Criteria

The exclusion criteria for the study were as follows: (1) no lumbar puncture CSF examination performed or incomplete clinical data from the period of hospitalization; (2) central nervous system infection caused by specific intracranial pathogens; (3) thyroid disease, a recent history of thyroid hormone replacement, or a lack of test results on thyroid function and antibodies; (4) an immunosuppressed state (including long-term immunosuppressive therapy due to chemotherapy, organ transplantation, or cancer); and (5) loss to follow-up.

This study was approved by the ethics committees of the six participating hospitals. All patients or their families were informed of the study and gave signed consent to allow the use of their medical records for the study.

Antibody Detection Methods

Six hospitals sent CSF and serum to the same laboratory, which began to detect AE-related antibodies in June 2011. Six types of antibodies were detected: anti-NMDAR antibody, anti-$GABA_BR$ antibody, anti-LGI1 antibody, anti-CASPR2 antibody, anti-AMPA1 receptor antibody, and anti-AMPA2 receptor antibody. The laboratory used indirect immunofluorescence (IIF) assays for antibody detection. A cell-based assay (CBA) with high specificity and sensitivity was used to analyze the CSF and serum of each patient. The initial dilution titers of CSF and serum were 1:1 and 1:10, respectively. Serum antibody titers were considered weakly positive at 1:10, positive at 1:32 to 1:100, and strongly positive at 1:320. The titers of CSF antibodies were considered weakly positive at 1:1, positive at 1:3.2 to 1:10, and strongly positive at 1:32 or above.

Statistical Analysis

The classification variables are described as percentages, and the characteristics of each subgroup are represented by the median. The chi-squared test or Fisher's exact test was used to compare differences among the subsets of classification variables. An independent-sample *t*-test was employed to compare differences among subgroups of continuous variables. The Wilcoxon signed-rank test was applied to compare differences among subgroups of hierarchical data. Spearman correlation analysis was used to analyze correlations among classified variables. SPSS 25.0 software was utilized to analyze and sort the data, with $P < 0.05$ indicating a significant difference.

RESULTS

Baseline Demography and Incidence Trends

From January 2012 to 2018, 189 patients with AE and neuronal autoantibody positivity were diagnosed at six large general hospitals in Southwestern China. Samples from 457 patients with suspected AE were analyzed for antibodies, with a positivity rate of 41.36%. Five patients died, giving a mortality rate of 2.65%. In terms of prognosis, the Glasgow Outcome Scale (GOS) was used for evaluation. Those discharged with a score of >4 had a good prognosis, those discharged with a score of 2–3 had a poor prognosis, and those with a score of 1 died.

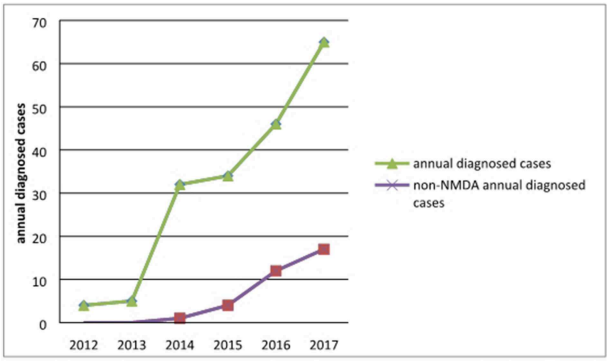

FIGURE 1 | Trends in the numbers of annual diagnosed cases of AE and non-NMDAR encephalitis.

The prognosis was good in 161 cases (85.19%). There were 41 cases (21.69%) in spring, 42 cases (22.22%) in summer, 59 cases (31.22%) in autumn, and 44 cases (24.87%) in winter. The median hospitalization time was 21 days, and the median hospitalization expenses were 4623.35 USD.

Among the 189 patients, females (116, 61.38%) outnumbered males (73, 38.62%) by a statistically significant margin ($\chi^2 = 9.783$, $P = 0.002$). The youngest patient was 1 year and 6 months old, and the oldest was 70 years old; the median age was 16 years. Among all patients, 99 (52.38%) were under 18 years old, 58 (30.69%) were 18–44 years old, 26 (7.72%) were 45–59 years old, and 6 (3.17%) were aged 60 years or older. The vast majority (83.07%) of patients were children and young adults ($\chi^2 = 213.556$, $P = 0.000$).

Of the 189 patients, 4 were diagnosed in 2012, accounting for 2.12% of all patients; 5 in 2013, accounting for 2.65%; and 32 in 2014, accounting for 16.93%; there were 34 cases (17.99%) in 2015 and 46 (24.34%) in 2016. In 2017, there were 65 cases, accounting for 34.39%. Three cases were confirmed in January and February 2018. The annual number of confirmed cases trended upward, as shown in **Figure 1**. With the development of diagnostic methods, an increasing number of autoimmune antibodies are used in clinical diagnosis. Using non-NMDAR antibodies, 1 case was diagnosed in 2014, 5 in 2015, 12 in 2016, 17 in 2017, and 2 in 2018, as shown in **Figure 1**.

Antibody Distribution

Among the 189 patients, 153 (80.95%) were positive for anti-NMDAR antibody, 14 (7.41%) for anti-$GABA_BR$ antibody, 9 (4.76%) for anti-LGI1 antibody, 5 (2.65%) for anti-CASPR2 antibody, 3 (1.59%) for both anti-NMDAR and anti-$GABA_BR$ antibodies, 3 (1.59%) for both anti-LGI1 and anti-CASPR2 antibodies, 1 (0.53%) for both anti-NMDAR and anti-CASPR2 antibodies, and 1 (0.53%) for both anti-AMPA2 receptor and anti-CASPR2 antibodies. Most of the patients were positive for anti-NMDAR antibody ($\chi^2 = 72.429$, $P = 0.000$).

Regarding the 153 patients with anti-NMDAR antibody positivity, 146 (95.42%) were CSF positive, and 123 (80.39%) were seropositive. The titer for the antibody is shown in **Table 1**.

TABLE 1 | Details of antibody titers in the CSF and serum of one antibody-positive patient.

		Negative	Weakly positive	Positive	Strongly positive
NMDAR	CSF	7	6	112	28
	Serum	30	17	98	8
$GABA_BR$	CSF	1	2	7	4
	Serum	1	4	7	2
LGI1	CSF	3	2	4	0
	Serum	1	1	7	0
CASPR2	CSF	4	0	1	0
	Serum	1	4	0	0

CSF testing was more sensitive than serum testing ($\chi^2 = 16.264$, $P = 0.000$), and the antibody titers were higher in the CSF than in the serum ($\chi^2 = 16.264$, $P = 0.000$). Among the 14 patients with anti-$GABA_BR$ antibody positivity, 13 (92.86%) were CSF positive, and 13 (92.86%) were seropositive. There was no difference in the positivity rate or titer of anti-$GABA_BR$ antibody between CSF and serum. Among the 9 LGI1-positive patients, 6 (66.67%) were CSF positive, and 8 (88.89%) were seropositive. The positive rate of serum was higher than that of CSF, but the difference was not significant. Among the 5 CASPR2-positive patients, 1 (20.00%) was CSF positive, and 4 (80%) were seropositive. Although the number of samples was small, the anti-CASPR2 positivity rate of serum was significantly higher than that of CSF.

Concurrent positivity for two types of antibodies was found in 8 patients. Further details on double-positive cases are shown in **Table 2**. Among the patients with LGI1 + CASPR2 positivity, 1 was strongly positive for CASPR2 in the CSF, whereas the antibody titers in the other patients were weakly positive or positive. In addition, only one of the five patients with anti-CASPR2 antibody positivity was CSF positive. All five patients with anti-CASPR2 antibody positivity were also positive for other antibodies, and only one of the five patients was CSF positive for anti-CASPR2 antibody. Presumably, the rate of CSF positivity for anti-CASPR2 antibody is low among AE patients in general.

Analysis of Factors Correlated With Disease Severity

Differences in Disease Severity Between the Sexes

We found that there were differences between males and females with regard to comorbid tumors and prognosis (**Table 3**). Male patients had tumors in 6 cases (8.22%), and female patients had tumors in 5 cases (4.31%). In the past, it was believed that women were more likely than men to have tumors as a comorbidity with AE, especially given the strong relationship between teratoma and anti-NMDAR encephalitis. However, in our study, male AE patients were more likely than females to have tumors, and 1/2 of males with tumors had $GABA_BR$-positive pulmonary tumors. Fifty-six male patients (76.71%) had a good prognosis, and 105 female patients (92.92%) had a good prognosis; thus, more women than men had a good prognosis, and the difference was significant ($\chi^2 = 6.766$, $P = 0.009$). Among the patients who died, 3 were (4.11%) male and 2 (1.72%) female. Although the

TABLE 2 | Details of antibody titers in the CSF and serum of patients who were positive for two antibody types concurrently.

Antibodies	Cases	Antibody titer
NMDAR + $GABA_BR$	Case 1	CSF NMDAR: weakly positive $GABA_BR$: positive Serum $GABA_BR$: positive
	Case 2	CSF NMDAR: positive $GABA_BR$: positive Serum NMDAR: positive $GABA_BR$: positive
	Case 3	CSF NMDAR: positive $GABA_BR$: positive Serum NMDAR: positive $GABA_BR$: positive
LGI1+ CASPR2	Case 1	CSF LGI1: positive CASPR2: strongly positive Serum Negative
	Case 2	CSF Negative Serum LGI1: weakly positive CASPR2: positive
	Case 3	CSF Negative Serum LGI1: weakly positive CASPR2: positive
NMDAR + CASPR2	Case 1	CSF NMDAR: positive Serum NMDAR: weakly positive CASPR2: weakly positive
AMPA2 receptor + CASPR2	Case 1	CSF AMPA2 receptor: positive Serum AMPA2 receptor: weakly positive CASPR2: weakly positive

TABLE 3 | Details regarding disease severity indicators in males and females.

	Male	Female
ICU (no.)	25	41
Ventilator use (no.)	9	9
Tumor (no.)	6	5
Surgery (no.)	1	2
Median hospitalization days	21	23
Median hospitalization costs (USD)	4622.27	5005.11
Prognosis		
GOS ≥4	56	105
2–3	14	9
1	3	2

mortality rate of males was higher than that of females, there was no significant difference ($\chi^2 = 0.990$, $P = 0.376$). Moreover, despite being more susceptible than males to AE, females had a better prognosis.

Differences in Disease Severity Among Different Age Groups

We found that there were differences in antibody distribution, combined tumors, ICU occupancy, and ventilator use between adults and children (**Table 4**). There were 34 AE cases with non-NMDAR antibody positivity (37.78%) in adults and 2 cases (2.02%) in children. Therefore, non-NMDAR antibody-positive encephalitis was more common among adults than children ($\chi^2 = 38.272$, $P = 0.000$). There were 11 adult patients and no child patients with cancer; accordingly, adults were more likely than children to have tumors ($\chi^2 = 12.848$, $P = 0.000$). Additionally, a greater number of adults (56, accounting for 62.22% of all adults) than children (fewer than 10, accounting for 10.10% of all children) were admitted to the ICU. This difference was statistically significant ($\chi^2 = 65.253$, $P = 0.000$). Among adults, 13 used ventilators, accounting for 14.44% of all adults; among children, 5 used ventilators, accounting for 5.05% of all children. Overall, adult patients used ventilators at a higher rate than children did ($\chi^2 = 4.828$, $P = 0.028$).

TABLE 4 | Details regarding disease severity indicators in different age groups.

	Adult	Children
ICU (no.)	56	10
Ventilator use (no.)	13	5
Tumor (no.)	11	0
Surgery (no.)	3	0
Median hospitalization days	22	22
Median hospitalization costs (USD)	5005.11	4623.35
Prognosis		
GOS ≥4	80	81
2–3	8	15
1	2	3

Relationship Between Antibody Titer and Disease Severity

Because the antibody status of the double-positive patients was complex, those 8 out of 189 patients were excluded from this subgroup analysis. Among the 181 patients with single antibody positivity (**Table 5**), correlation analysis showed that the antibody titer in the CSF was positively correlated with ICU admission (rs = 0.234, $P = 0.002$), with ventilator use (rs = 0.254, $P = 0.001$), and with the presence of tumors (rs = 0.200, $P = 0.007$). There was also a positive correlation between CSF antibody titers and prognosis, but it was not significant ($P = 0.135$). In addition, our analysis found that the serum antibody titer was negatively correlated with ICU admission (rs = −0.329, $P = 0.000$). Conversely, there was no significant correlation between the serum antibody titer and other indicators, such as ventilator use and prognosis.

DISCUSSION

Since Dalmau et al. (10) proposed the condition of anti-NMDAR encephalitis, an increasing number of AE-related autoantibodies have been detected and used for clinical diagnosis. To date, however, there has been no large-scale epidemiological survey of AE in adults and children, and its epidemiological characteristics remain unclear. In 2016, *The Lancet Neurology* published diagnostic criteria for AE, emphasizing the diagnostic significance of AE-related autoantibodies (5). The epidemiological characteristics of 189 patients with AE and autoimmune antibody positivity in the CSF or serum were retrospectively analyzed in this study.

The most commonly detected synaptic receptor antibodies in Southwestern China are the anti-NMDAR, anti-AMPA1 receptor, anti-AMPA2 receptor, anti-$GABA_BR$, anti-LGI1-related, and anti-CASPR2-related antibodies. In the present study, 457 patients with suspected or confirmed AE were examined for serum and CSF antibodies. The positivity rate for antibodies was 41.36%. In a study by Lai et al. (11), 35.78% of patients with AE were positive for antibodies.

TABLE 5 | Details regarding disease severity indicators in relation to different antibody titers in the CSF and serum.

	CSF				Serum			
	Negative	**Weakly positive**	**Positive**	**Strongly positive**	**Negative**	**Weakly positive**	**Positive**	**Strongly positive**
ICU (no.)	4	5	29	19	21	16	19	5
Ventilator use (no.)	0	1	7	9	6	2	6	2
Tumor (no.)	0	0	5	5	3	0	6	1
Surgery (no.)	0	0	1	2	1	0	1	1
Median hospitalization days	14	19.5	22	30	21	20	23	24.5
Median hospitalization costs (USD)	2439.89	5041.56	4676.74	6391.01	4802.69	4919.42	4700.65	4535.96
Prognosis								
GOS ≥4	13	9	107	24	28	22	95	8
2–3	2	1	14	6	5	2	15	1
1	0	0	3	2	2	1	3	1

The rate of good prognosis was 85.19%, and the mortality rate was 2.65%. This finding is consistent with previous studies, indicating that the overall prognosis of AE is good. One study of 571 patients with anti-NMDAR encephalitis by Kayser et al. (12) reported that 83% of the patients recovered completely or partially. However, in a study by Yeshokumar et al. (13), the mortality rate was 12%; the rate of good prognosis was only 53%, and the rate of poor prognosis was 34%. The differences in the results of that study and of ours may be due to differences in prognosis prediction. The previous study scored prognosis using the modified Rankin scale (mRS), whereas we used the GOS. Moderately disabled patients were classified in our study as having a good prognosis, while the study by Yeshokumar et al. classified such patients as having a poor prognosis. Some scholars have found that among all cases of encephalitis, AE has an especially poor prognosis, with 56% of AE patients dying or having severe disabilities (2, 3). The reason why patient prognosis in previous studies differs so greatly from that in the present study may be that the prognosis of AE associated with tumors is worse than that of non-tumor-related AE. As our study did not involve paraneoplastic AE, the overall prognosis was good.

In terms of the time distribution of AE, there is no previous literature specifying the incidence by season. This study found that autumn (September-November) was the most common season, accounting for 31.22% of all cases, although there was no significant difference among seasons.

With regard to sex distribution, women (61.38%) were significantly more likely than men (38.62%) to have AE. This sex distribution is consistent with previously reported statistics for AE (13). Some possible mechanisms are that estrogen enhances humoral immunity (14) and that mutation of X chromosome-linked genes leads to differential expression of pathogenic genes, leading to the occurrence of autoimmune diseases (15, 16).

In our analysis of age distribution, we observed that the majority of patients were under 45 years old (83.07%). This result is consistent with reported data on other autoimmune diseases in children and young adults. In a study by Titulaer et al. (17), 577 patients had antibody-confirmed anti-NMDAR encephalitis, 95% of whom were under 45 years old, and 37% of whom were children. However, the effect of age on autoimmune diseases is unclear. Some studies suggest that the connection may be related to changes in hormone levels after middle age and that the decrease in estrogen in females weakens the immune response (14).

From 2012 to present, the number of confirmed cases of AE has increased annually, which may be related to increasing awareness of AE among clinicians. In 2007, Dalmau et al. (10) first reported anti-NMDAR encephalitis and found that it was closely related to teratoma. In 2009, Lai et al. (11) reported anti-AMPA receptor encephalitis for the first time, presenting 10 cases associated with type 1 and type 2 glutamate receptors. In 2010, Lancaster et al. (18) first reported and described $GABA_BR$ encephalitis and found that it may be associated with small cell lung cancer. In the same year, Lai et al. (19) first reported anti-LGI1 antibody-related encephalitis and anti-CASPR2 antibody-related encephalitis associated with voltage-gated potassium channels in *The Lancet Neurology*. Since then, a variety of neuronal autoantibodies have been reported. According to the results of our study, the number of confirmed cases of non-NMDAR encephalitis is also increasing yearly, which may be related to the expansion of the known neuronal autoantibody spectrum and the gradual adoption of antibody detection.

In this study, 189 patients were diagnosed with AE and were antibody positive. The majority were positive for anti-NMDAR antibody (80.95%), followed by anti-$GABA_BR$ (7.41%), LGI1-related (4.76%), CASPR2-related (2.65%), NMDAR+$GABA_BR$ (1.59%), LGI1+CASPR2 (1.59%), NMDAR+CASPR2 (0.53%), and AMPA2 receptor+CASPR2 antibodies (0.53%). The distribution of antibodies in this study is fundamentally consistent with that of previous studies. In a study by McCracken (20), 78.82% of patients were positive for antibodies against NMDAR, followed by $GABA_BR$ (4.71%), LGI1 (4.71%), CASPR2 (2.35%), and others (9.41%). In addition, Guan et al. (21) found 12.9% of 4,106 encephalitis patients to be positive for anti-NMDAR antibody, 12.8% for anti-LGI1 antibody, 5.6% for anti-$GABA_BR$ antibody, 1.3% for anti-CASPR2 antibody, and 0.6% for anti-AMPA receptor antibody.

The present study found that CSF detection was 15.03% more sensitive than serum detection for patients with anti-NMDAR

encephalitis and that the antibody titer in the CSF was higher than that in the serum ($P = 0.000$), which was consistent with previous studies. For example, Gresa-Arribas et al. (9) found that in NMDAR encephalitis, CSF was a more sensitive sample type than blood for detecting anti-NMDAR antibodies. By comparing matched serum and CSF samples, Titulaer et al. (17) also found that the detection sensitivity of CSF was ∼15% higher than that of serum for anti-NMDAR encephalitis. However, there was no difference in sensitivity or antibody titer between serum and CSF in other types of antibody-positive AE.

In addition, although the number of CASPR2 antibody-positive patients was small, only 5 cases were CSF positive, and simultaneous detection of CASPR2 and other antibodies in the CSF was found for only one of the five patients. Thus, the positivity rate for CASPR2 in the CSF appears to be low. Bien et al. (22) found that 5 (33.33%) of 15 patients with CASPR2 receptor encephalitis were positive for anti-CASPR2 antibody in the CSF. The sensitivity of the CSF in the previous study was higher than that observed in the present study.

When we analyzed factors related to disease severity, we found that, despite significantly outnumbering male patients, female patients had a better prognosis. In a study by Harutyunyan (23), 16 (59.26%) of 27 AE patients admitted to the ICU were male whereas 11 (40.74%) were female, suggesting that males have more severe disease than females. Additionally, Murphy et al. (24) reported that when BXSB mice developed spontaneous lupus syndrome as an autoimmune disease, males tended to exhibit more severe clinical symptoms than females; the average survival time of male mice was also significantly shorter than that of female mice. Subramanian et al. (25) found that the Toll-like receptor 7 (TRL7) gene, which is related to immunogenesis and development, was heterotopic from the X chromosome to the Y chromosome and was overexpressed, which may explain the autoimmune symptoms in male mice.

The present study found that adult patients with AE are more likely than children to suffer from non-NMDAR encephalitis and to have tumors. Previous studies have shown that anti-AMPA receptor encephalitis may be associated with thymoma, small cell lung cancer, and breast cancer (19, 26, 27); anti-$GABA_BR$ encephalitis was also associated with small cell lung cancer in another report (18). These reports were consistent with the three cases of $GABA_BR$ encephalitis with lung tumors found in this study. Anti-LGI1 antibody-related encephalitis and anti-CASPR2 antibody-related encephalitis may also be associated with thymoma (19, 28). In general, adults are more likely to have non-NMDAR encephalitis because they have a higher incidence of tumors than children have (29).

In our analysis of the relationship between antibody titers and disease severity, we found that antibody titers in the CSF were positively correlated with ICU admission, ventilator use, and tumors, which reflect the severity of the disease. Gresa-Arribas et al. (9) have also indicated that antibody titers are higher in severe and teratoma patients. In addition, there was no direct correlation between CSF antibody titers and prognosis in our study, whereas Gresa-Arribas et al. (9) reported that the CSF and serum titers of patients with a poor prognosis were higher than those of patients with a good prognosis. Regardless, Broadley et al. (30) believe that the relationship between CSF titer and prognosis is not exact.

Our study has the following limitations. First, the sample size of the present study was insufficient. Nonetheless, as the number of cases is small for certain low-incidence types of AE, such as anti-CASPR2 antibody-related encephalitis, it is difficult to carry out a statistical analysis. Second, many more autoimmune antibodies are currently tested than the six antibodies mentioned in this paper. However, from 2012 to 2018, the main antibodies detected in Southwestern China were the six described herein. Therefore, we evaluated only these six antibodies. Additional antibodies could be assessed in follow-up studies.

CONCLUSION

AE is an inflammatory disorder of the brain that has very complex clinical manifestations and is difficult to diagnose. In recent years, the number of confirmed cases of AE has been increasing annually. Early intervention is very important to improve the prognosis of patients. Neuronal autoantibodies are often a key diagnostic basis in the diagnosis of AE. In our study, 41.36% of patients with suspected AE tested positive for antibodies, and their overall prognosis was good. Women outnumbered men in our sample. There were slightly more children than adults, and children and young adults accounted for the vast majority. Anti-NMDAR encephalitis accounted for the majority of cases; for this type, the sensitivity of antibody detection was higher in the CSF than in the serum, and the antibody titer was also higher in CSF than in serum. It is worth mentioning that the positivity rate for the anti-CASPR2 antibody was higher in serum than in CSF in anti-CASPR2-positive encephalitis cases, with or without concurrent positivity for other antibodies. Analysis of the factors related to the severity of the disease showed that the prognosis of women was better than that of men, that adults were more likely than children to suffer from non-NMDAR encephalitis, and that adults were more likely than children to have tumors. CSF antibody titers were positively correlated with ICU admission, ventilator use, and tumor complications, which may reflect the severity of the disease. However, there was no direct correlation between CSF antibody titers and prognosis. Understanding the epidemiological characteristics of AE can help increase the speed of diagnosis and improve the prognosis of AE patients.

AUTHOR CONTRIBUTIONS

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

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