Perspective

Autoimmune Encephalitis: An Expanding Frontier of Neuroimmunology

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Introduction

Discovery of the spectrum of autoimmune encephalitis (AIE) is among the most attractive events of neurology in the past decade. AIE includes a heterogeneous group of encephalitic syndromes, which generally include two major categories: classic paraneoplastic limbic encephalitis (LE) associated with the so-called well-characterized onconeural autoantibodies against intracellular neuronal antigens (e.g., Hu, Ma2, etc.) and new-type AIE associated with autoantibodies to the neuronal surface or synaptic antigens.[1] Paraneoplastic LE occurs in the context of malignant tumors and results from an immunological response to tumor antigens, which mimic intracellular antigens expressed in neurons. The autoantibodies in this situation might not be pathogenic but can serve as diagnostic markers for paraneoplastic LE. The new-type AIE occurs in association with pathogenic autoantibodies against synaptic receptors or membrane antigens, and the binding of autoantibodies to their targets causes neuronal dysfunction, usually irreversibly. Over a dozen new-type autoantibodies have been identified since the discovery of anti-N-methyl-D-aspartate receptor (NMDAR) antibody by Dalmau *et al.* in 2007.[2] Most of these autoantibodies associated with specific and well-characterized symptoms and the detection of these autoantibodies confirm the diagnosis. Since the introduction and establishment of the diagnostic test for anti-NMDAR antibody in China in 2010,[3] hundreds of cases of AIE have been diagnosed and treated, which has changed our clinical approach to encephalitis management. The following sections will focus on a few recent advances as well as related clinical research on AIE in China.

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Epidemiology

Autoimmune encephalitis is not a rare cause of encephalitis. However, it is still difficult to estimate its incidence. Anti-NMDAR encephalitis is the major component of the disease spectrum. According to the UK-based prospective surveillance study in children, the incidence of anti-NMDAR encephalitis is 0.85 per million children annually.[4] No data about incidence in adults is available. Gable *et al.*[5] reported that the frequency of anti-NMDAR encephalitis surpassed that of individual viral etiologies in young individuals enrolled in the California Encephalitis Project. Increasing numbers of AIE cases have been identified in China since the autoantibody assay was introduced to some neurological centers after 2010. The frequency of AIE also surpassed that of viral encephalitis in our project in Peking Union Medical College Hospital (PUMCH). A total of 4106 cases of encephalitis of unidentified etiology were registered to PUMCH encephalitis and paraneoplastic neurological syndrome project for autoantibody assay between May, 2013 and December, 2014. A total of 531 cases (12.9%) were positive for autoantibodies, including 423 cases (10.3%) with anti-NMDAR antibodies, 68 cases (1.66%) with anti-leucine-rich glioma-inactivated 1 (LGI1) antibodies, thirty cases (0.73%) with anti-γ-aminobutyric acid B

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receptor ($GABA_BR$) antibodies, seven cases (0.17%) with anti-contactin associated protein 2 (CASPR2) antibodies, and three cases (0.073%) with anti-α-amino-3-hydroxy-5-methyl-4-isoxazole propionate receptor (AMPAR) antibodies. The relative frequencies of the NMDAR, LGI1, $GABA_BR$, CASPR2, and AMPAR antoantibodies were 79.7%, 12.8%, 5.6%, 1.3%, and 0.6%, respectively, in patients with AIE [Figure 1]. Our findings indicate that AIE associated with autoantibodies is one of the major causes of encephalitis. Anti-NMDAR encephalitis is the most common cause of AIE, followed by anti-LGI1 encephalitis. However, the frequency of anti-LGI1 encephalitis may be underestimated due to potentially unrecognized cases with insidious onset in elderly patients which mimic neurodegenerative disorders.

Pathogenic Mechanism

Understanding the pathogenic mechanisms is critical for research and clinical management of AIE. Most data focus on anti-NMDAR antibodies, which recognize an extracellular epitope in the GluN1 subunit of the NMDAR. The autoantibodies crosslink the NMDARs and promote internalization of the receptors, which reduces the receptor density on the neuronal surface, resulting in neuronal dysfunction.[6] This process is reversible after removal of autoantibodies and may explain the good recovery of patients after immunotherapy.[7] The internalization of receptors was also described as an effect of autoantibodies in AMPAR encephalitis.[8] Other autoantibodies may work through different mechanisms. For example, anti-LGI1 antibodies block the binding sites of LGI1, which results in a decrease of AMPAR via unknown mechanisms.[9] Anti-$GABA_BR$ antibodies influence receptor function and block the inhibitory effects of baclofen on the spontaneous firing of cultured neurons.[10]

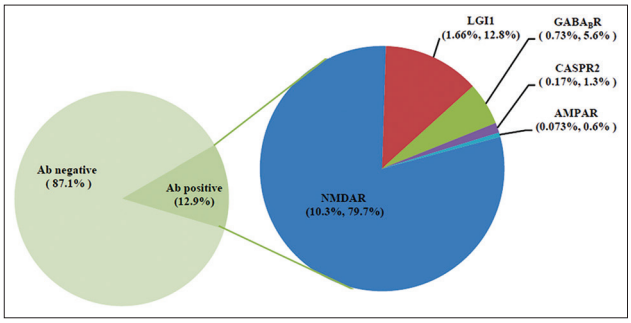

Figure 1: The laboratory experience of PUMCH encephalitis and paraneoplastic neurological syndrome project. A total of 4106 cases with encephalitis of unidentified etiology were test for antibodies against neuronal cell-surface or synaptic protein: 531 cases (12.9%) were positive for autoantibodies, including 423 cases (10.3%) with anti-NMDAR antibodies, 68 cases (1.66%) with anti-LGI1 antibodies, thirty cases (0.73%) with anti-$GABA_BR$ antibodies, seven cases (0.17%) with anti-CASPR2 antibodies and three cases (0.073%) with anti-AMPAR antibodies. PUMCH: Peking Union Medical College Hospital; Ab: Antibody; NMDAR: N-methyl-D-aspartate receptor; LGI1: Leucine-rich glioma-inactivated 1; $GABA_BR$: γ-aminobutyric acid B receptor; CASPR2: Contactin-associated protein 2; AMPAR: α-amino -3-hydroxy-5-methyl-4-isoxazole propionate receptor.

Pathological studies on anti-NMDAR encephalitis indicated that the intrathecal antibody synthesis in the disease is associated with the colonization of B-cells and plasma cells in the central nerve system (CNS). Analysis of the inflammatory infiltrates in brain samples from autopsy or biopsy demonstrated numerous plasma cells ($CD138^+$) in perivascular, interstitial, and Virchow–Robin spaces, and B- and T-cells predominantly located in perivascular regions. Complement-mediated mechanisms did not play a substantial pathogenic role in anti-NMDAR encephalitis.[11]

Tumors and infections may trigger the onset of AIE. According to Dr. Dalmau *et al.*, 46% of female patients with anti-NMDAR encephalitis had tumors, mainly ovarian teratoma and Asian patients were more likely to have a teratoma (45%) than Caucasians (31%) or Hispanics (27%).[7] However, in our series of 115 Chinese patients with anti-NMDAR encephalitis, only 26.5% (18/68) of female patients had ovarian teratoma, while the series reported by other centers in China showed even lower percentages of related tumor.[12] The CNS is an immune-privileged organ. Neuronal cell surface antigens do not activate the immune system under physiological conditions. However, the activation can be induced elsewhere either by a systemic tumor or an infection. Neural tissues with NMDAR are always present in teratoma and represent potential autoantigens. Tabata *et al.*[13] reported a pathological observation of neuronal tissues obtained from ovarian teratoma in patients with anti-NMDAR encephalitis. Lymphocyte infiltration was more frequent in the encephalitis group than in the nonencephalitis group. Dense B-lymphocyte infiltration near neural tissues was observed in the encephalitis group. Differences in lymphocyte infiltration in ovarian teratoma between anti-NMDAR encephalitis and nonencephalitis patients underscore the immunological importance of the ovarian teratoma as the site of initial antigen presentation in anti-NMDAR encephalitis.

Herpes simplex virus encephalitis (HSVE) is a triggering factor for anti-NMDAR encephalitis.[14] The so-called post-HSVE choreoathetosis in children is confirmed now as post-HSVE anti-NMDAR encephalitis due to the fact that patients with relapsing symptoms had no evidence of viral reactivation but harbor NMDAR antibodies and respond well to immunotherapy. Other viral infections are suspected to play a role in triggering anti-NMDAR encephalitis and still need further confirmation.[15]

However, the triggering factor remains unknown for a considerable percentage of patients with AIE. We recently reported two female cases with tumor-negative anti-NMDAR encephalitis after resection of melanocytic nevus.[16] Our observation suggests a possible link between AIE and melanocytic nevus. Melanoblasts migrate from the neural crest to the epidermis and hair follicles, where they differentiate and become mature melanocytes that synthesize melanin. Hoogduijn *et al.*[17] found that cultured

melanocytes express NMDAR. Therefore, NMDAR in melanocytic nevus may be a potential autoantigen in the pathogenesis of anti-NMDAR encephalitis. It might be reasonable to pay attention to prominent melanocytic nevus in patients with relapsing anti-NMDAR encephalitis without detectable tumor.

Clinical Presentation

The degree of syndrome specificity should not be overlooked because each of the neuronal cell-surface autoantibodies is associated with a relatively specific syndrome [Table 1].[1,18] For example, the manifestations of anti-NDMAR encephalitis can be categorized into eight groups: behavior and cognition, memory, speech, seizures, movement disorder, loss of consciousness, autonomic dysfunction, and central hypoventilation.[7] Fever and headache have been suggested as prodromal symptoms without specificity. However, the cerebrospinal fluid (CSF) pleocytosis and meningeal enhancement in magnetic resonance imaging (MRI) in some cases indicate meningeal involvement which is consistent with neuropathological findings of this disorder. Persistent fever in the active phase of anti-NDMAR encephalitis may result from CNS dysfunction or sympathetic hyperactivity when infection can be ruled out. The presentation of anti-NDMAR encephalitis differs from classical LE in its diffuse CNS involvement and represents a unique type of AIE.[1] On the other hand, AIE associated with autoantibodies against LGI1, $GABA_BR$, and AMPAR often presents with limbic syndrome, for example, epilepsy, short-term memory loss, and psychiatric symptoms.

The so-called autoimmune epilepsy is another frontier of AIE. Faciobrachial dystonic seizures and temporal lobe epilepsy with amygdala enlargement may be the characteristic type of seizure in anti-LGI1 encephalitis.[19-21] Recently, Li *et al*.[22] described a negative myoclonus in a Chinese child with anti-NMDAR encephalitis. Our study[23] demonstrated that most Chinese patients with anti-$GABA_BR$ antibody-associated LE presented with prominent refractory epilepsy, which usually improved neurologically with immunotherapy.

Diagnostic Approach

Different techniques are available for the diagnosis of neuronal cell-surface antibodies. Most laboratories in China use the cell-based assay (CBA, Euroimmun, Germany) commercially available for the diagnosis of neuronal cell-surface autoantibodies, which is a highly sensitive and specific assay. Tissue-based assays (TBAs, Euroimmun, Germany) are used in confirmative tests in addition to CBA if only serum is available. TBA can also be used as a screening method to reveal yet-to-be-identified autoantigens when so-called unknown fluorescence object (UFO) is observed. However, resources for identification of new autoantigens underlying the UFO are still limited in China. Timely diagnosis of AIE is usually hindered by the lack of laboratory resources in some areas of China.

The rule of "CSF ONLY" has been emphasized in the diagnosis of anti-NMDAR encephalitis because the autoantibodies always exist in CSF and the determination of serum autoantibodies alone carries the risk of diagnostic errors. The sensitivity of NMDAR antibody testing is higher in CSF than in serum. However, it may not be true for anti-LGI1 antibodies or anti-$GABA_BR$ antibodies which might be more prevalent in serum than in CSF. Titers of

Table 1: Autoimmune encephalitis with antibodies against neuronal cell-surface or synaptic protein

Antigen	Clinical syndrome	Tumor
NMDAR	Diffuse encephalitis Prodromal symptoms, psychiatric, seizures, amnesia, movement disorders, catatonia, autonomic instability, and coma	10–45% female adult patients; ovarian teratoma
LGI1	Limbic encephalitis, hyponatremia, and occasional FBDS	Rare
$GABA_BR$	Limbic encephalitis and prominent seizures	30–50%; SCLC
AMPAR	Limbic encephalitis and psychiatric symptoms	70%; lung, breast, and thymoma
Caspr2	Encephalitis, Morvan syndrome, and neuromyotonia	0–40%; thymoma
mGluR5	Limbic encephalitis (reported in less than ten patients)	Frequent; Hodgkin lymphoma
D2R	Basal ganglia encephalitis and Sydenham chorea	Infrequent
DPPX	Diarrhea, encephalitis with CNS hyperexcitability Confusion, psychiatric symptoms, tremor, myoclonus, nystagmus, hyperekplexia, PERM-like symptoms, and ataxia	No tumor association
$GABA_AR$	Refractory seizures, status epilepticus, or epilepsia partialis continua, stiff-person, opsoclonus	Infrequent
GlyR	Stiff-person, PERM, limbic encephalitis, ataxia	Infrequent
IgLON5	Abnormal sleep movements and behaviors, obstructive sleep apnea, stridor, dysarthria, dysphagia, ataxia, and chorea	No tumor association

Modified according to autoimmune encephalopathies by Leypoldt *et al*.[1] NMDAR: N-methyl-D-aspartate receptor; LGI1: Leucine-rich glioma-inactivated 1; $GABA_BR$: γ-aminobutyric acid B receptor; FBDS: Faciobrachial seizures; SCLC: Small cell lung cancer; CASPR2: Contactin-associated protein 2; AMPAR: α-amino-3-hydroxy-5-methyl-4-isoxazole propionate receptor; mGluR5: Metabotropic glutamate receptor 5; D2R: Dopamine-2 receptor; DPPX: Dipeptidyl-peptidase-like protein 6; $GABA_AR$: γ-aminobutyric acid B receptor; GlyR: Glycine receptor; IgLON5: IgLON family member 5; CNS: Central nerve system; PERM: Progressive encephalomyelitis with rigidity and myoclonus.

anti-NMDAR encephalitis in CSF and serum were higher in patients with poor outcome or teratoma than in patients with a good outcome or no tumor. The titer change in CSF was more closely related with relapses than was that in serum. Our laboratory at PUMCH always requires serum-CSF pairs for autoantibody assay to minimize errors of interpretation and misleading diagnoses.[24]

A recent report of anti-NMDAR antibodies after plasma exchange and removal of ovarian teratoma in a patient with encephalopathy suggested that the antibodies may be undetectable in an early phase in some cases.[25] We also experienced two female patients with encephalitis and ovarian teratoma without detectable autoantibodies either on CBA or TBA (no UFO identified) but showed good recovery after immunotherapy and teratoma resection. Under these circumstances, the anti-NMDAR antibodies which were produced by the localized plasma cells and cause neuronal dysfunction may not reach a detectable level in lumbar CSF due to a concentration gradient.

Other CSF findings of anti-NMDAR encephalitis include increased CSF pressure and mild elevation of white cell counts and protein.[26] Mild lymphocytic inflammation with activated lymphocytes and plasma cells was identified in CSF cytology studies of anti-NMDAR encephalitis [Figure 2]. The presence of oligoclonal bands and plasma cells in CSF indicates intrathecal immunoglobulin synthesis. The clinical significance of the co-existence of multiple anti-neuronal antibodies in single patients is an interesting question. This immunophenotype affects clinical manifestation resulting in variation or overlap of neurological syndromes. For example, the co-existence of anti-AQP4 antibodies in anti-NMDAR encephalitis may contribute to additional demyelination features and tendency to relapse. The presence of additional onconeural antibodies (e.g., anti-Hu antibodies) warrants investigation for occult tumor and indicates a poor prognosis.[27]

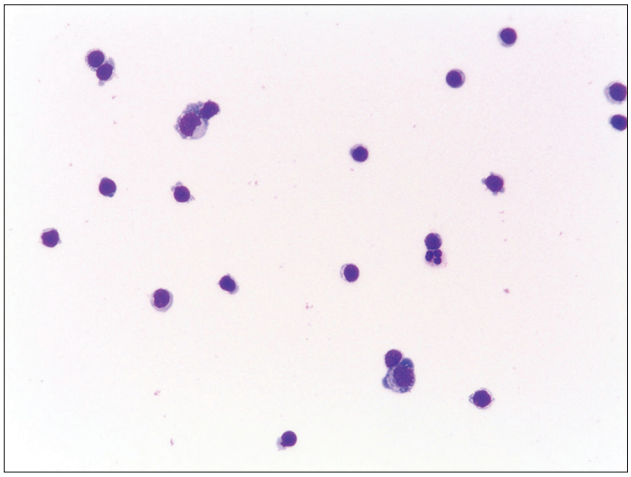

Figure 2: CSF cytology of a patient with anti-NMDAR encephalitis. Lymphocytic inflammation is typical CSF findings of anti-NMDAR encephalitis, and plasma cells are often identified in CSF. CSF: Cerebrospinal fluid; NMDAR: N-methyl-D-aspartate receptor (May-Grunwald-Giemsa stain, original magnification ×200).

A recent study demonstrated CXCL13, a B-cell-attracting chemokine produced by plasma cells and monocytes/macrophages, as a potential biomarker for anti-NMDAR encephalitis. Seventy percent of patients with new onset of anti-NMDAR encephalitis showed elevated CXCL13 levels in the CSF. Prolonged or secondary elevation of CXCL13 was associated with limited response to treatment and relapses.[28]

Neuroimaging findings of mesial temporal involvement are significant for the diagnosis of LE related to $GABA_BR$ or LGI1 antibodies. Though routine MRI may not aid diagnosis in most cases of anti-NMDAR encephalitis [Figure 3]. Positron emission tomography (PET) provides evidence of cerebral functional change underlying the clinical manifestation. PET results of patients diagnosed with anti-NMDAR encephalitis showed inconsistent results. However, relative hypometabolism of the bilateral occipital lobes and hypermetabolism of the bilateral frontal, temporal, and parietal lobes are characteristic findings in the acute phase of the disease.

Treatment

Underlying tumors are the major trigger for AIE, and therefore, patients should be screened for systemic tumors during diagnosis. The ovarian teratoma, once detected, should be

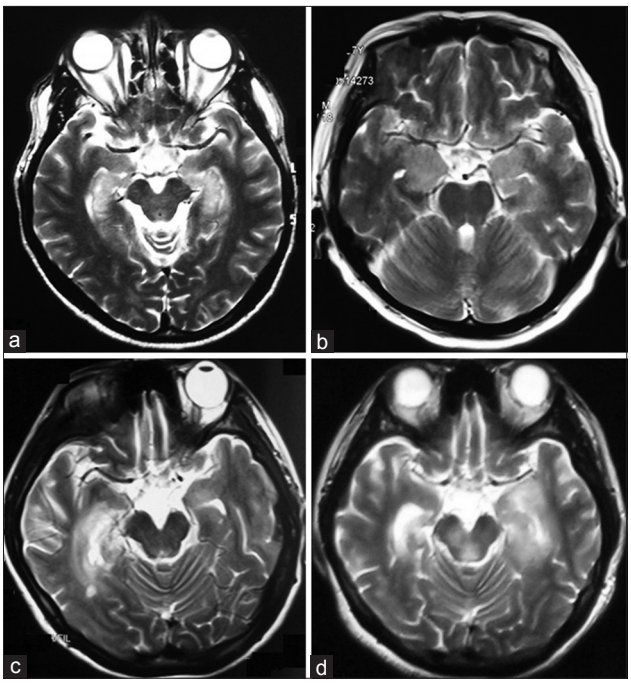

Figure 3: Brain MRI of autoimmune encephalitis. (a) High signals on bilateral mesial temporal lobe in a patient with limbic encephalitis associated with anti-$GABA_BR$ antibodies. (b) High signals on the bilateral mesial temporal lobe and right amygdala enlargement in a patient with limbic encephalitis associated with anti-LGI1 antibodies. (c) Abnormalities in the right mesial temporal lobe in a patient with anti-NMDAR encephalitis during her initial episode. (d) New lesions more prominent at left mesial temporal lobe and brain stem during her relapse. MRI: Magnetic resonance imaging; $GABA_BR$: γ-aminobutyric acid B receptor; LGI1: Leucine-rich glioma-inactivated 1; NMDAR: N-methyl-D-aspartate receptor.

removed promptly in patients with anti-NMDAR encephalitis. Critical neurological and systemic complications should not be looked as contraindications for surgery. First-line immunotherapy for anti-NMDAR encephalitis includes steroids, intravenous immunoglobulin, or plasma exchange; second-line immunotherapy includes rituximab or cyclophosphamide. The protocol suggested by Dalmau *et al.* emphasizes the indications of the second-line therapy and long-term immunotherapy.[7] The systemical review by Nosadini *et al*.[29] demonstrated that patients given immunotherapy do better and relapse less than patients given no treatment and second-line therapy, for example, rituximab improves outcomes and reduces relapses. However, administration of rituximab is limited in China due to an off-label indication of the medicine. The retrial of first-line therapy is still an option in resource-limited settings [Figure 4]. On the other hand, according to the study by Zekeridou *et al*.[30] despite a higher rate of second-line immunotherapy in their case series, the outcome in their series was very similar to the outcome reported in the previous series. Randomized clinical trial is needed to determine the optimal treatment of anti-NMDAR encephalitis.

Intrathecal administration of methotrexate (MTX) was reported to be effective in a few pediatric cases with anti-NMDAR encephalitis.[31] We recently used intrathecal therapy in three patients refractory to first-line and second-line immunotherapy. The patients demonstrated remarkable clinical improvement and decrease of anti-NMDAR antibody titers after 4–5 cycles of intrathecal administration of MTX and dexamethasone. Intrathecal immunotherapy might be a promising option for refractory cases since it may directly affect intrathecal antibody synthesis in anti-NMDAR encephalitis.

Cases with relapsing AIE represent a new challenge to neurologists. Relapse of anti-NMDAR encephalitis is defined as the new onset or worsening of symptoms after at least 2 months of improvement or stabilization. Dalmau *et al.* reported that 12% of patients showed clinical relapses during a 24-month follow-up.[7] Our observations in a Chinese series suggest a higher relapse among patients (23.5%) in our series, with multiple relapses in half of relapsing cases.[32] Inadequacy of second-line and long-term immunotherapy, absence of teratoma, and potential demyelinating mechanism might contribute to the relapse of anti-NMDAR encephalitis.[7]

Specific symptomatic treatment for anti-NMDAR encephalitis might play a role based on the mechanism of NMDAR dysfunction in this disorder. D-cycloserine, known as anti-tuberculotic medicine, has been widely used in neuropsychiatric studies, since it acts as a partial NMDA-agonist at low doses, at the glycine-binding site of NR1 subunit.[33] We recently observed clinical improvement in one refractory case with anti-NMDAR encephalitis after administration of D-cycloserine (125–250 mg/d).

In conclusion, the discovery of AIE broadens the horizons of neuroimmunology and alters the strategies for diagnosis and treatment of encephalitic syndrome. The characteristics of Chinese patients with AIE need to be fully defined based on multicenter clinical studies in the future. Further studies focusing on the antibody – receptor interaction and intrathecal antibody synthesis will contribute to our understanding of the immune mechanisms and developing more specific and effective treatment.

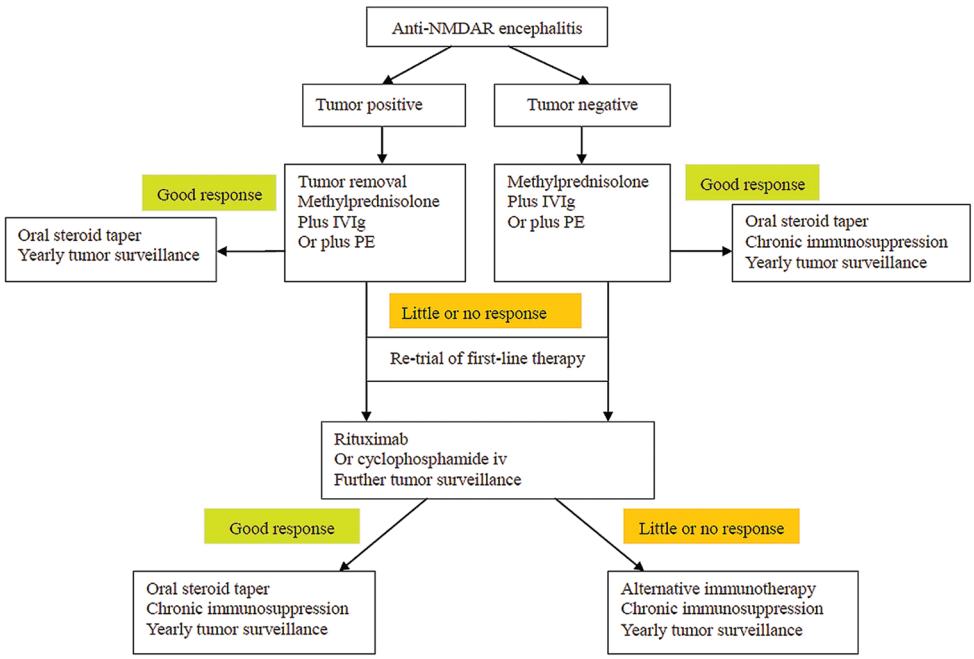

Figure 4: Proposed pathway for the treatment of anti-NMDAR encephalitis. The algorithm demonstrates indications of first-line, second-line, and chronic immunotherapy. The retrial of first-line therapy is an option in patients with little or no response to the initial immunotherapy. Chronic immunosuppression: mycophenolate mofetil or azathioprine for 1 year. NMDAR: N-methyl-D-aspartate receptor; IVIg: Intravenous immunoglobulin; PE: Plasma exchange.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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