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Anti-NMDA-Receptor Encephalitis and Other Synaptic Autoimmune Disorders

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Opinion statement

Synaptic autoimmunity may result in a wide variety of symptoms, including catatonia, psychosis, movement disorders, short-term memory deficits, and refractory seizures, so these patients are seen by a wide spectrum of practitioners, who need to be aware of these disorders. In some cases, these disorders occur as a paraneoplastic manifestation of an associated cancer. However, in contrast to the well-known paraneoplastic neurologic disorders of the central nervous system that predominate in older individuals, these novel disorders often affect children and young adults. Additionally, for some syndromes, the presence of a tumor does not necessarily indicate a poor prognosis. Successful treatment of the tumor and immunotherapy often result in recovery, supporting the use of surgery for severely ill patients. In all syndromes, deficits may be reversible despite the duration or severity of symptoms. For example, patients with anti-NMDA-receptor encephalitis who had been in a coma or ventilated for 6–10 months have had full recovery after appropriate treatment.

Introduction

The encephalitides associated with autoimmunity to synaptic proteins are an emerging group of immune-mediated neurologic disorders of the central nervous system (CNS) [1,2,3••, Class III]. Many of these disorders were previously considered idiopathic or of undetermined viral origin and were given descriptive names such as hyperkinetic encephalitis lethargica [4,5]. The target antigens, which play critical roles in neuronal transmission and plasticity, include the excitatory glutamate *N*-methyl-D-aspartate (NMDA) receptor and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor; the inhibitory gamma-aminobutyric acid (GABA_B) receptor; leucine-rich glioma-inactivated (LGI1) protein, a secreted neuronal protein; and contactin-associated protein 2 (CASPR2), a protein important to the normal function of voltage-gated potassium channels [1,2,3••, Class III]. The clinical spectrum of these disorders varies according to the target antigen and resembles pharmacologic or genetic models in which the corresponding receptors are disrupted. These data, the clinical responses to immunosuppressive therapies, and analyses of effects of antibodies on neuronal cultures support a direct pathogenic effect of the antibodies.

This article reviews each of the known clinical syndromes. In the absence of class I or II data regarding treatment of these patients, we present a treatment approach based on our

Disclosure

Conflicts of Interest: M.R. Rosenfeld and J. Dalmau: License fee payments from EUROIMMUN for an NMDA receptor autoantibody test; patent application for NMDAR antibody determination diagnostic test filed in USA and Europe.

experience and that of colleagues with large series of patients with anti-NMDA-receptor encephalitis.

Anti-NMDA-Receptor Encephalitis

This disorder was first described as a distinct clinical entity in 2005 in four young women who developed acute psychiatric symptoms, seizures, memory deficits, decreased level of consciousness, autonomic instability, and hypoventilation in association with the presence of an ovarian teratoma [6, Class III]. All had antibodies reacting with a neuronal cell surface protein that was shown to be the NR1 subunit of the NMDA receptor [1, Class III]. A study of 100 patients clarified that although most patients are young women (median age, 23 years), the disorder can occur in men and children [7•, Class III]. In fact, with increasing awareness of the syndrome, the number of pediatric cases has steadily grown and appears to represent about 40% of all cases [8•, Class III].

Symptoms of anti-NMDA-receptor encephalitis develop and resolve as a multistage process, with most patients experiencing a viral-like prodrome followed by the development of alterations of memory, behavior, and cognition; psychosis; seizures; dyskinesias (orofacial, limb, and trunk); and autonomic and breathing instability [7•,9•, Class III]. Most adults are initially seen by psychiatry services and can be mis-diagnosed with an acute psychotic break or drug abuse [10]. Most children are brought to medical attention because of changes in mood, behavior, or personality; seizures; or language disintegration [8•, Class III].

Autonomic instability is a common feature in adults, with about half of patients developing central hypoventilation that generally requires weeks of mechanical support. Some patients develop severe cardiac dysrhythmias requiring a pacemaker. Signs of autonomic dysfunction in children more commonly include urinary incontinence and sleep dysfunction [8•, Class III].

Most patients have abnormal CSF studies with a lymphocytic pleocytosis. About one third have increased proteins, and about 60% have oligoclonal bands. At presentation, about half of the patients have abnormal MRI findings, most commonly increased signal on fluid-attenuated inversion recovery (FLAIR) or T2 sequences in the cerebral or cerebellar cortex or medial temporal lobes. Abnormalities have been reported in other areas, such as the corpus callosum or brainstem. In some cases, faint or transient contrast enhancement of the cerebral or cerebellar cortex, overlaying meninges, or basal ganglia has been seen.

Movement disorders are common and can be misinterpreted as seizure activity. Most frequent are dyskinesias, typically orofacial dyskinesias, choreoathetoid movements of the extremities, dystonia, rigidity, opisthotonic postures, or a combination [11]. In most patients, the EEG shows generalized slow or disorganized activity without epileptic discharges. These findings may overlap with electrographic seizures.

The diagnosis of anti-NMDA-receptor encephalitis is confirmed by the detection in serum or CSF of antibodies to the NR1 subunit of the NMDA receptor. After treatment or in the advanced stages of the disease, the CSF antibodies usually remain elevated if there is no clinical improvement, whereas serum antibodies may be substantially decreased by treatments. The titer of CSF antibodies appears to correlate more closely with the clinical outcome.

Just over half of patients have an associated tumor, most commonly an ovarian teratoma that can be mistaken for a benign cyst. The detection of an ovarian teratoma is age-dependent: approximately half of female patients older than 18 years have unilateral or bilateral ovarian

teratomas, but fewer than 9% of girls younger than 14 years have a teratoma [7••, Class III]. The detection of a tumor is rare in male patients. Other tumor types in isolated cases include teratoma of the mediastinum, small-cell lung cancer (SCLC), Hodgkin's lymphoma, neuroblastoma, breast cancer, and germ-cell tumor of the testes.

Anti-AMPA-Receptor Encephalitis

Patients with AMPA-receptor antibodies develop acute limbic dysfunction that can be associated with prominent psychiatric symptoms [2•, Class III]. The disorder most commonly affects middle-aged women. Most patients present with the subacute onset of confusion, disorientation, and memory loss; seizures can also occur. About 70% of patients will have an underlying tumor in the lung, breast, or thymus [12, Class III].

CSF findings are similar to that of anti-NMDA-receptor encephalitis, with predominant lymphocytic pleocytosis. Brain MRI usually shows abnormal FLAIR signal involving the medial temporal lobes, rarely with transient signal changes in other areas. In the only series reported, five of nine patients had a history or concurrent findings of systemic autoimmunity (stiff-person syndrome, insulin-dependent diabetes, and glutamic acid decarboxylase [GAD] antibodies, hypothyroidism, and Raynaud's syndrome) [2•, Class III].

Anti-GABA_B Encephalitis

The encephalitis associated with antibodies to the GABA_B receptor usually presents with limbic encephalitis and seizures [13••, Class III]. In a series of 15 patients, the median age was 62 years (range, 24–75) and both sexes were equally affected. About half of the patients had an associated tumor, either a SCLC or a neuroendocrine tumor of the lung [14]. These patients frequently have additional antibodies to GAD and several nonneuronal proteins of unclear significance, suggesting a susceptibility to autoimmunity. The MRI and CSF findings are similar to those in other types of limbic encephalitis, with unilateral or bilateral increases in medial temporal lobe FLAIR or T2 signal consistent with limbic encephalitis and CSF lymphocytic pleocytosis.

Anti-LGI1 Limbic Encephalitis

Patients with antibodies to LGI1 develop memory disturbances, confusion, and seizures, with MRI findings that are usually typical of limbic encephalitis [3••, Class III]. Memory and cognitive deficits may be preceded by short, tonic seizures that can mimic myoclonic-type movements [15]. CSF studies in these patients are often normal or show only oligoclonal bands with normal total protein [3••,16]. This disorder was previously attributed to antibodies targeting the voltage-gated potassium channels. Some patients develop hyponatremia or rapid eye movement (REM) sleep-behavior disorders. Only 20% of cases are associated with a neoplasm, most commonly thymoma or SCLC. LGI1 is a secreted neuronal protein that interacts with presynaptic and postsynaptic receptors, and mutations of LGI1 have been associated with the syndrome of autosomal dominant lateral temporal lobe epilepsy [17,18].

Anti-CASPR2 Associated Encephalitis

This disorder represents another syndrome previously attributed to antibodies to voltage-gated potassium channels [3••, Class III]. Patients usually develop symptoms of encephalitis, peripheral nerve hyperexcitability, or both (Morvan's syndrome). CNS symptoms include cognitive impairment, memory loss, hallucinations, and seizures. Some patients have other immune-mediated disorders such as myasthenia gravis with anti-acetylcholine or muscle-specific kinase (MuSK) antibodies. The varied symptoms suggest that other proteins of the

CASPR2 complex or associated with it may actually be the target antigens for subgroups of these patients.

In some patients, the combination of symptoms has led to an initial diagnosis of an unusual form of motor neuron disease. Because anti-CASPR2 associated encephalitis responds to immunotherapy, making the distinction is critical. CASPR2 antibody-associated syndromes may occur with or without an associated tumor.

Relapses

Anti-NMDA-receptor encephalitis, anti-AMPA-receptor encephalitis, and LGI1 antibody-associated limbic encephalitis can relapse. Relapses likely occur with the other disorders as well, but the available series are too small to make any firm conclusions.

Relapses of anti-NMDA-receptor encephalitis occur in 20% to 25% of patients, with the risk of relapse associated with the presence or absence of a tumor and the timing of therapy. Patients with tumors who received tumor treatment within 4 months of the onset of neurologic symptoms, often in conjunction with immunotherapy, had fewer neurologic relapses and better overall outcomes than patients without tumors or patients with tumors that were treated later or not at all [7•,19, Class III]. Relapses can signify the presence of recurrent tumors but can be independent of tumor activity.

Similarly, relapses in patients with anti-AMPA-receptor encephalitis can occur even after successful tumor treatment and in the absence of recurrent tumor.

Outcome

Given the severity of symptoms and prolonged hospitalizations required by some patients, the frequently positive outcomes are rewarding. In a series of 100 patients with anti-NMDA-receptor encephalitis, with a median follow up of 17 months, 47 had a full recovery, 28 had mild deficits, 18 had severe deficits, and 7 patients had an illness-related death [7•, Class III]. Residual symptoms are often behavioral, and long-term follow-up shows that these residual symptoms continue to improve.

Treatment

- Recommendations for treatment derive from large series of patients with anti-NMDA-receptor encephalitis and are based on data supporting a pathogenic role of the antibodies in these disorders (Table 1). Despite the severity of symptoms, most patients will respond to treatment, but recovery can be slow and symptoms may relapse. Spontaneous recoveries have also been described in a few patients after several months of severe symptoms [9•].
- Based on the suspicion of the presence of an associated tumor, a search should be undertaken; if a tumor is found, it should be removed as soon as possible [20].
- In adults, immunomodulatory therapy with methylprednisolone and intravenous immunoglobulin (IVIg) should be initiated as soon as the diagnosis is confirmed. We start with a 5-day concurrent dosing schedule. Plasma exchange can substitute for IVIg, although it is not our preference, in part owing to the autonomic instability in some patients and difficult administration in uncooperative patients.
- If no improvement is seen after one cycle of corticosteroids and IVIg, we initiate a combination of cyclophosphamide (once every month) and rituximab (once a week for the first 4 weeks only) [21,22, Class III]. The number of monthly cycles is empiric and should be based on clinical recovery. Examination of serum and CSF

antibodies, if possible, can be helpful in guiding treatment decisions, with persistent titers in the CSF suggesting continued need for treatment.

- For patients in whom no tumor is found at initial diagnosis, yearly surveillance for 2–3 years should be considered, and we often start mycophenolate mofetil or azathioprine for 1 year at recovery because of the increased risk of relapses in this group.
- In our experience, the response of children to immunotherapy is variable [8•, Class III]. Some children have appeared to respond rapidly to IVIg or methylprednisolone, but this result was not universal and, at times, even those who responded to an initial course did not seem to benefit after repeat treatment; some of these patients continued to improve slowly, independent of the treatments used. In these patients, CSF titers usually remained elevated until the patient started to have clinical improvement. A similar experience regarding the varied response to corticosteroids, IVIg, or plasma exchange has been noted by others (personal communications). In our initial series of 32 children with a median follow-up of 4.5 months, 29% had full recovery, 45% had substantial recovery, and 26% had limited recovery [8•, Class III].
- Rituximab (with cyclophosphamide or more frequently, without it) is increasingly being used when there is no response to first-line treatments.
- It is expected that more patients will eventually improve with longer follow-up.

Supportive Care

- Patients may require prolonged stays with mechanical ventilation in intensive care units. As they recover, many will have symptoms of frontal lobe dysfunction (poor attention and planning, impulsivity, behavioral disinhibition, memory deficits), which improve over months. During this time, patients will need a multidisciplinary team approach, including physical rehabilitation and psychiatric management.

Pharmacologic Treatment

Methylprednisolone

Standard dosage	No standard has been set. The recommended dose for adults is 1.0 g intravenously per day for 5 days.
Contraindications	Documented hypersensitivity or concurrent serious infection.
Main drug interactions	Many potentially serious pharmacokinetic interactions. May increase levels of cyclosporine. Concurrent use of drugs that induce hepatic P450 enzymes can effectively decrease the steroid effects, and there are variable effects on anticoagulants.
Main side effects	Short courses of methylprednisolone are usually well tolerated, but it may cause dizziness, nausea, indigestion, increased appetite, weight gain, hyperglycemia, weakness, or sleep disturbances. More serious side effects include myopathy, hypokalemia, peptic ulcer disease, and psychosis.
Special points	Long-term treatment should be avoided because of adverse effects. Use caution with diabetic patients because of potential hyperglycemia.
Cost/cost-effectiveness	One gram of methylprednisolone is approximately \$17, and there are incremental costs for infusion and nursing care.

Intravenous Immunoglobulins

Standard dosage	No standard dose has been set. Most patients have received 0.4 g/kg intravenously per day for 5 consecutive days each month.
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Contraindications	IgA deficiency, previous hypersensitivity, hyperviscosity syndrome, vascular disease, renal insufficiency.
Main drug interactions	None.
Main side effects	Headache, nausea, fever, aseptic meningitis. Some effects are mitigated if infusions start slowly and the rate is increased as tolerated.
Special points	The use of 60 mg of intravenous methylprednisolone may decrease the severity of headache.
Cost/cost-effectiveness	Approximately \$50 to \$100 per gram an infusion can cost \$10,000, but clinical improvement likely reduces time in intensive care and inpatient facilities.

Cyclophosphamide

Standard dosage	No standard dose has been determined. We use 750 mg/m ² (body surface area calculation) infused over 1 h once every 4 weeks (longer interval based on blood counts). We recommend premedication with dexamethasone and ondansetron and post-treatment medication with prochlorperazine as needed. If patients are taking adequate oral intake, no additional hydration is needed at this dose, but for patients with reduced oral intake, hydration should be encouraged or provided. This dose of cyclophosphamide does not require mesna to prevent hemorrhagic cystitis and can be given on an outpatient basis.
Contraindications	Patients with diabetes, underlying infections, hypertension, or peptic ulcer disease need to be monitored closely.
Main drug interactions	Allopurinol.
Main side effects	Nausea, vomiting, myelosuppression, headache, dizziness, and increased risk of myeloproliferative or lymphoproliferative malignancies.
Special points	Blood counts need to be monitored for leukopenia.
Cost/cost-effectiveness	Cyclophosphamide is relatively inexpensive, but costs are increased by the need for intravenous hydration and laboratory monitoring.

Rituximab

Standard dosage	375 mg/m ² (body surface area calculation) intravenously weekly for 4 weeks.
Contraindications	Previous anaphylactic reactions to rituximab or other murine proteins.
Main drug interactions	Live-virus vaccines should not be given while receiving rituximab and for several months afterwards.
Main side effects	Infusion reactions with respiratory distress, urticaria, and hypotension can occur and are mitigated by delivering the first infusion over 90 min, with the use of diphenhydramine and acetaminophen as preinfusion medications.
Cost/cost-effectiveness	About \$600 for 100 mg. One infusion may cost over \$10,000 because of incremental infusion charges.

Mycophenolate Mofetil

Standard dosage	One gram twice a day.
Contraindications	Pregnancy, hypersensitivity to this drug or any of its components, including polysorbate 80.
Main drug interactions	Should not be given with drugs that interfere with enterohepatic recirculation. Patients should not receive live vaccines while being treated.
Main side effects	Among the many side effects are constipation, diarrhea, leukopenia, sepsis, vomiting, and increased risk of opportunistic infection and lymphoproliferative disorders.
Special points	Consult with a practitioner with prior experience with this medication for advice on safe medical monitoring.
Cost/cost-effectiveness	No data available.

Azathioprine

Standard dosage	Two to 3 mg/kg per day.
Contraindications	Pregnancy, renal impairment (use with caution), and prior use of alkylating agents.

Main drug interactions	Allopurinol; use caution with warfarin and phenytoin as the efficacy of these drugs may be decreased.
Main side effects	Multiple side effects include myelosuppression, nausea, vomiting, diarrhea, and muscle aches.
Special points	Consult with a practitioner with prior experience with this medication for advice on safe medical monitoring.
Cost/cost-effectiveness	No data available.

Antiepileptic drugs

Seizures are treated with standard antiepileptic medications. Because many of the stereotypic movements do not have an EEG correlate, however, a thorough video EEG evaluation should be done before starting these drugs.

Surgery

Tumor Resection

Standard inpatient costs will be incurred for diagnostic testing and surgery, but resection of a tumor is associated with shorter recovery times and increased likelihood of full recovery. If a malignant teratoma or other tumor is found, there will be incremental cost of tumor-directed therapy.

Interventional Procedures

Plasma Exchange

Standard procedure	One to 1.5 plasma volumes are removed at each procedure and replaced with albumin or plasma protein fractions.
Contraindications	Patient with severely compromised hemodynamic status, unstable angina pectoris, pericardial effusion, or uncontrolled sepsis or septic shock.
Complications	Hypotension, dizziness, tingling due to hypocalcemia; complications due to central venous access placement such as infection, bleeding, or thrombosis.
Cost	\$1,000 to \$2,000 per session.

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Table 1

General treatment approach to patients with synaptic autoimmunities

1	Search for and remove a tumor as appropriate for syndrome (e.g., teratoma in anti-NMDA-receptor encephalitis, systemic cancer in anti-AMPA-receptor encephalitis). ^a
2	After tumor removal or if no tumor is found, proceed with 5-day course of concurrent IVIg and methylprednisolone.
3	If clear improvement is seen within 10 days, continue with supportive care.
4	If there is no response or limited response after 1 cycle of immunosuppression, initiate cyclophosphamide (monthly) and rituximab (weekly for 4 weeks starting with the first dose of cyclophosphamide).
5	For patients with limited or no response to the approaches above, consider other forms of immunosuppression. ^b
6	For patients without tumors, continue immunosuppression with mycophenolate mofetil or azathioprine for at least 1 year after initial treatments are discontinued (to reduce the high rate of relapses after recovery).

^a Although some surgeons are hesitant to take these patients to surgery (especially those requiring intensive care, including ventilator support), tumor removal is critical in decreasing time to recovery and increasing the chance of more complete recovery

^b Single cases of responses to methotrexate have been reported [23]

(Based on series of patients with anti-NMDA-receptor encephalitis, especially Florance et al. [8••, Class III])