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Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis

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Abstract

Since its discovery in 2007, the encephalitis associated with antibodies against the *N*-methyl-D-aspartate receptor (NMDAR) has entered the mainstream of neurology and other disciplines. Most patients with anti-NMDAR encephalitis develop a multistage illness that progresses from psychosis, memory deficits, seizures, and language disintegration into a state of unresponsiveness with catatonic features often associated with abnormal movements, and autonomic and breathing instability. The disorder predominantly affects children and young adults, occurs with or without tumour association, and responds to treatment but can relapse. The presence of a tumour (usually an ovarian teratoma) is dependent on age, sex, and ethnicity, being more frequent in women older than 18 years, and slightly more predominant in black women than it is in white women. Patients treated with tumour resection and immunotherapy (corticosteroids, intravenous immunoglobulin, or plasma exchange) respond faster to treatment and less frequently need second-line immunotherapy (cyclophosphamide or rituximab, or both) than do patients without a tumour who receive similar initial immunotherapy. More than 75% of all patients have substantial recovery that occurs in inverse order of symptom development and is associated with a decline of antibody titres. Patients' antibodies cause a titre-dependent, reversible decrease of synaptic NMDAR by a mechanism of crosslinking and internalisation. On the basis of models of pharmacological or genetic disruption of NMDAR, these antibody effects reveal a probable pathogenic relation between the depletion of receptors and the clinical features of anti-NMDAR encephalitis.

Introduction

In 2005, a syndrome of memory deficits, psychiatric symptoms, decreased consciousness, and hypoventilation was reported in four young women with ovarian teratomas.¹ Specific autoantibodies to the *N*-methyl D-aspartate receptor (NMDAR) were soon detected in these and eight other patients with similar neurological symptoms, seven of whom also had ovarian teratomas.² During the following 3 years we identified 419 other patients with this syndrome, many of them children and young adults with or without an associated tumour.

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Contributors

JD examined patients, and interviewed physicians and families. JD and RB-G provided synaptic and cell-based experimental data. EM-H collected and analysed clinical data. EL and MRR did the literature search and examined the mechanisms related to genetic and pharmacological alterations of NMDAR. JD, EL, MRR, and RB-G wrote the paper.

Conflicts of interest

A patent application for the use of NMDAR antibody determination in patients' serum samples and CSF as a diagnostic test has been filed in USA and Europe by JD. EL has a training grant from Talecris, a company that sells human immunoglobulin. None of the other authors declare any conflicts of interest.

The discovery of this disorder, termed anti-NMDAR encephalitis, has changed the diagnostic approach to clinical problems as diverse as catatonia, subacute memory disturbance, seizures, abnormal movements, and limbic encephalitis.³ It has also led to the discovery of other autoimmune synaptic encephalitides mediated by antibodies against the AMPA receptor (AMPA);⁴ the γ -amino-butyric acid-B receptor (GABA_B-R);⁵ and leucine-rich, glioma-inactivated 1 (LGI1), which is the main autoantigen of limbic encephalitis previously attributed to voltage-gated potassium channels.⁶ In addition to their clinical significance, these immune responses provide insights into the function of the neurotransmitter receptor targeted by the antibodies.⁷

In this Review we present our clinical experience in the diagnosis and management of hundreds of patients with anti-NMDAR encephalitis and also discuss reports from other investigators. We address the clinical presentation, differential diagnosis, frequency of tumour association, the cellular and synaptic mechanisms of the disease, and the process of recovery. We also discuss several confounding factors that often delay the recognition of this disorder, and propose an algorithmic strategy to guide treatment.

Frequency

The exact incidence of anti-NMDAR encephalitis is unknown, but on the basis of the rapid accrual of patients and increasing number of case reports, it seems to be more frequent than any other known paraneoplastic encephalitis. Evidence from intensive care,^{9–11} paediatric,^{12,13} and neurology departments⁸ lend support to this idea. In one retrospective analysis of encephalitis of unknown origin,¹⁰ NMDAR antibodies were identified in 1% of patients (aged between 18 and 35 years) admitted to an intensive care unit. A multicentre, population-based prospective study of causes of encephalitis in the UK¹⁴ showed that 4% of patients had anti-NMDAR encephalitis; the disorder was the second most common immune-mediated cause, after acute disseminated encephalomyelitis and before all antibody-associated encephalitis, including encephalitis attributed to voltage-gated potassium channels. In another study,¹⁵ a series of 200 patients with anti-Hu-antibody-associated encephalomyelitis was accrued over 13 years, and 500 cases of autoimmunity to proteins that interact with voltage-gated potassium channels were identified over a 6-year period.¹⁶ Thus, by comparison, our experience of 400 patients with anti-NMDAR encephalitis in just 3 years suggests a relatively frequent disorder.

The syndrome

Antibodies against the NR1 subunit of the NMDAR (NMDAR antibodies) are associated with a characteristic syndrome that develops in several stages of illness and recovery, as first reported by Iizuka and colleagues¹⁷ and Sansing and colleagues.¹⁸ About 70% of patients have prodromal symptoms consisting of headache, fever, nausea, vomiting, diarrhoea, or upper respiratory-tract symptoms. Within a few days, usually less than 2 weeks, patients develop psychiatric symptoms and many are seen initially by psychiatrists. Anxiety, insomnia, fear, grandiose delusions, hyper-religiosity, mania, and paranoia are frequent manifestations; social withdrawal and stereotypical behaviour are sometimes seen. Short-term memory loss is common but underestimated because psychiatric symptoms and speech problems often interfere with the assessment of memory.⁸ A rapid disintegration of language, from reduction of verbal output and echolalia (usually with echopraxia) to frank mutism, is frequent and cannot be attributed to cortical aphasia.

In young children, the behavioural change can be difficult to detect because they often present with temper tantrums, hyperactivity, or irritability as opposed to frank psychosis. In children, the first symptom to be recognised is often non-psychiatric—eg, seizures, status epilepticus, dystonia, verbal reduction, or mutism. Some behaviours are hypersexual and

violent (for instance, kicking and biting caregivers and parents). Because of anxiety and insomnia, some children need intense sedation.¹²

This initial phase of the illness is usually followed by decreased responsiveness that can alternate between periods of agitation and catatonia. At this stage, abnormal movements and autonomic instability are usual manifestations. Oro-lingual-facial dyskinesias are the most characteristic movements, but other types might occur simultaneously or alternate with limb and trunk choreoathetosis, elaborate motions of arms and legs, oculogyric crisis, dystonia, rigidity, and opisthotonic postures (see video recordings^{19–23}). The most frequent autonomic manifestations include hyperthermia, tachycardia, hypersalivation, hypertension, bradycardia, hypotension, urinary incontinence, and erectile dysfunction.⁸ Two women (aged 16 and 17 years) were thought to have Takotsubo cardiomyopathy (or stress cardiomyopathy) due to high blood pressure (JD, unpublished). Hypoventilation, requiring respiratory support, occurs as the patient becomes comatose but can occur earlier when the level of consciousness is relatively preserved. In some cases the central origin of hypoventilation is noted when patients cannot be weaned from mechanical ventilation. While recovering, one patient needed nocturnal ventilatory support for 3 months. Autonomic storms can fluctuate from tachycardia to bradycardia and longlasting cardiac pauses, which, in some patients, require a temporary pacemaker.¹⁸ A transient increase of intracranial pressure has been recorded in a few patients (JD, personal observation).

Motor or complex seizures develop at early stages of the disease. The overlap of abnormal movements and epileptic seizures can lead to under-recognition of the seizures or unnecessary escalation of antiepileptics for dyskinesias that are interpreted as seizures.²⁴ In general, the frequency and intensity of the seizures decrease as the disease evolves. However, seizures and status epilepticus can resurface at any time during the illness. Attempts to wean patients from sedation can result in status epilepticus.²

During such stages, in which patients are usually managed in intensive care units, dissociative responses to stimuli are noted. For example, patients often resist eye opening but show little or no response to painful stimuli.¹⁷ This dissociative state is similar to that caused by NMDAR antagonists, such as phencyclidine or ketamine, which are called dissociative anesthetics.^{25,26}

Oversimplification of the disease into cortical and subcortical stages and the suggestion that patients without a tumour have a less impaired level of consciousness than do patients with a tumour²⁷ is (in our experience) highly inaccurate. Many symptoms with which a patient presents (such as anxiety, fear, bizarre or stereotypical behaviour, insomnia, and memory deficits) cannot be classified as cortical. Clinical examination of patients reveals a diffuse encephalopathy indicating dysfunction of subcortical structures, limbic regions, amygdalae, and frontostriatal circuitry. Patients without tumours have periods of unconsciousness and confusion that can be longer or worse than are those of patients with tumours.^{8,12,28}

Diagnostic tests

Brain MRI is unremarkable in 50% of patients, and in the other 50%, T2 or FLAIR signal hyperintensity might be seen in the hippocampi, cerebellar or cerebral cortex, frontobasal and insular regions, basal ganglia, brainstem, and, infrequently, the spinal cord.² The findings are usually mild or transient and can be accompanied by subtle contrast enhancement in the affected areas or the meninges.⁸ Follow-up MRIs either remain normal or show minimum change despite the severity and duration of symptoms. Earlier reports^{2,17} of patients who had refractory seizures, or who did not recover or died, showed pronounced brain atrophy. Lesions can occur that appear demyelinating, do not usually enhance, and are transient. One patient with severe, relapsing symptoms, attributed to atypical antibody-

negative neuromyelitis optica, had anti-NMDAR encephalitis that substantially improved after aggressive immunotherapy.²⁹ A few studies that used MR spectroscopy,³⁰ fluoro-2-deoxy-d-glucose-PET,^{17,31,32} or 99mTc-d,l-hexamethyl-propyleneamine oxime (HMPAO) single photon emission computed tomography (SPECT)^{17,33} have shown variable multifocal cortical and subcortical abnormalities that change during the course of the disease, although in some cases early SPECT studies were normal.¹⁷ Reversible frontotemporal hypoperfusion and brain atrophy, not due to corticosteroid treatment, have been reported in two patients with follow-up of 5–7 years.³⁴

Electroencephalograms (EEG) are abnormal in most patients, usually showing non-specific, slow, and disorganised activity sometimes with electrographic seizures.⁸ Slow, continuous, rhythmic activity in the delta-theta range predominates in the catatonic-like stage.¹² This activity is not associated with abnormal movements and does not respond to antiepileptic drugs. Monitoring with video EEG is important to diagnose and treat seizures appropriately.²⁴ One patient had non-convulsive status epilepticus that lasted for 6 months and required a pentobarbital-induced coma.³⁵ A prophylactic oophorectomy was done and a microscopic ovarian teratoma was detected; the patient recovered afterwards.

The cerebrospinal fluid (CSF) is initially abnormal in 80% of patients and becomes abnormal later in the disease in most other patients.⁸ Findings include moderate lymphocytic pleocytosis, normal or mildly increased protein concentration, and, in 60% of patients, CSF-specific oligoclonal bands. Most patients have intrathecal synthesis of NMDAR antibodies.^{3,8,27} Of 431 patients studied (412 with paired serum and CSF), we have not encountered a patient in whom antibodies were only present in serum. If diagnosis is delayed or patients have received treatment with plasma exchange or IV immunoglobulin, antibodies might be detected only in CSF.^{10,12} Similarly, patients with a protracted clinical course or persistent symptoms might be seronegative and have persistently raised CSF titres until symptoms improve (figure 1; JD, unpublished). Less frequently, long-term follow-up reveals patients who, after recovery, still have high serum titres and absent or barely detectable titres in the CSF (any antibodies in the CSF would probably have leaked from the serum).²⁰ These findings are consistent with a disease in which the immune response is initially triggered systemically by a tumour or other unknown causes and is reactivated and expanded in the CNS.

Brain biopsy does not provide a diagnosis of anti-NMDAR encephalitis. Biopsies in 15 patients showed normal or non-specific findings, including perivascular lymphocytic cuffing (predominantly of B cells), sparse parenchymal T-cell infiltrates, or microglial activation.^{8,36} Data from autopsy studies show similar findings along with plasma cells and rare or absent neuronophagic nodules.^{2,37}

Sex, tumour association, and potential triggers of the immune response

About 80% of patients with anti-NMDAR encephalitis are women. The detection of an underlying tumour is dependent of age, sex, and ethnic background.^{8,12} Figure 2 shows the distribution of 400 patients grouped by age and the presence or absence of a tumour. When compared with a previous series,⁸ these data show that, with increased awareness of this disorder, the disease is being more frequently recognised in younger teenagers and children. Analysis of these 400 patients confirms that the younger the patient, the less likely that a tumour will be detected, and that in female patients older than 18 years, the frequency of an underlying teratoma is much the same as we initially reported (webappendix p 1).⁸ Black women are more likely to have an underlying ovarian teratoma than are patients of other ethnic groups (webappendix p 2)

Only 5% of male patients older than 18 years had an underlying tumour. Detection of tumours other than teratoma is not very common—eg, of 400 patients studied, only 7 (2%) had a tumour other than an ovarian teratoma (webappendix p 1). One patient with neuroblastoma and another with Hodgkin's lymphoma have been reported.^{38,39} The ovarian teratomas of 25 patients showed expression of NMDAR in all cases.³⁷ The expression of NR1 by other tumours has been examined in only one patient with breast cancer and proved positive (unpublished). Whether tumours other than teratomas are true associations or unrelated coincident disorders is unknown.

On the basis of these data, the first concern in female patients should be screening for an ovarian teratoma. The most useful screening tests include MRI, CT scan, and pelvic and transvaginal ultrasound (if age appropriate). Serological tumour markers (CA125, β -HCG, α -fetoprotein, or testosterone) have not been systematically assessed but are negative in many patients. High serum concentrations of testosterone and signs of virilisation were identified in a 15-year-old girl who, for 16 months, had relapsing episodes of encephalitis and psychosis. Her serum was positive for NMDAR antibodies and a large mature teratoma containing 6 L of fluid was removed, resulting in full recovery.⁴⁰ In some patients, exploratory laparoscopies and blind oophorectomies showed ovarian tumours,^{8,35} but in others no tumour was detected.²⁸

Because the presentation of anti-NMDAR encephalitis often suggests an infectious process, many patients undergo extensive blood and CSF assessments. A few patients had positive serological tests suggesting an infection (eg, positive serum mycoplasma usually in children),⁴¹ or direct evidence of a concomitant infection (eg, two patients with herpes zoster; JD, unpublished). In four patients with neurological complications attributed to influenza H1N1, one had NMDAR antibodies.⁴² The clinical picture of this patient, but not the other three, was typical of anti-NMDAR encephalitis. Moreover, none of the above mentioned patients had CSF findings indicating direct viral involvement of the CNS. The absence of detection of a consistent infectious agent makes an immune response by molecular mimicry unlikely.

Two patients developed the disorder after vaccination against H1N1 influenza (JD, personal observation), and one patient after a booster vaccination against tetanus, diphtheria, pertussis, and poliomyelitis.⁴³ A 3-year-old child had a microdeletion in the short arm of chromosome 6 that involved the HLA cluster, leading investigators to suggest a predisposition to autoimmunity.⁴⁴ A similar propensity to autoimmunity has been suggested in patients, mostly children, who had, in addition to NMDAR antibodies, antinuclear or thyroid peroxidase antibodies, or both.¹² These findings suggest that racial and genetic factors might predispose individuals to this type of autoimmunity, as shown in myasthenia gravis and Lambert-Eaton syndrome, which also occur as paraneoplastic or non-paraneoplastic syndromes.^{45–47} In this context, non-specific systemic infections or vaccinations can act as an adjuvant of the autoimmune response.

Treatment, outcome, and relapses

About 75% of patients with NMDAR antibodies recover or have mild sequelae; all other patients remain severely disabled or die.⁸ Management of anti-NMDAR encephalitis should initially focus on immunotherapy and the detection and removal of a teratoma. Most patients receive corticosteroids, intravenous immunoglobulins (IVIg) or plasma exchange as first-line of immunotherapy. These treatments have enhanced effectiveness and speed of action when patients have an underlying tumour that is removed.^{8,12,27} In patients without a tumour or with delayed diagnosis, additional treatment with second-line immunotherapy (a rituximab or cyclophosphamide, or both) is usually needed.^{12,21,48} Our experience with 105

consecutively diagnosed patients in 2009 accord with these findings (figure 3). Although 80% of patients with a tumour (mostly teratomas) had substantial improvement after tumour removal and first-line immunotherapy, only 48% of those without a tumour had a similar degree of improvement after first-line immunotherapy ($p=0.001$; unpublished) and needed second-line immunotherapy more often. Overall, second-line immunotherapy resulted in substantial improvement in 15 of 23 (65%) patients. The final outcome, substantial improvement (as previously defined⁸), was much the same in patients with or without tumour (84% vs 71%, $p=0.16$), but the five patients who died did not have a tumour and did not receive second-line immunotherapy.

Reports exist of patients with predominant psychiatric manifestations that were given electroconvulsive treatment (JD, unpublished).¹² One patient's disorder resolved without further treatment,⁴⁹ but the other patients only had a definitive improvement after immunotherapy or removal of an underlying teratoma.⁵⁰

Infrequently, the neurological response to tumour removal can be seen in a matter of hours,⁵¹ suggesting an effect of anaesthetics on NMDAR function. In one patient, induction of anaesthesia with propofol for a spinal tap produced pronounced hypotension; a repeat procedure several months later with a reduced dose of propofol was well tolerated.⁵² We are not aware of other complications related to anaesthetics.

Spontaneous neurological improvement has been reported, but usually occurs at the expense of longer hospital stay and slower recoveries. Iizuka and colleagues¹⁷ described four women with NMDAR antibodies identified in serum and CSF collected 4–7 years before the study, providing the best natural history we have of this illness. Despite an absence of consistent immunotherapy or tumour removal (tumours being identified in three patients several years after recovery), all had gradual recovery (mean 7 months in hospital, recovery of more than 3 years for two patients). By contrast, one patient who developed the disorder before it was described as a clinical entity had medical support withdrawn 3 months after the onset of symptoms because their symptoms were judged to be irreversible. Analysis of the patient's serum and CSF and a review of autopsy material showed anti-NMDAR antibodies and an ovarian teratoma.² In another case, medical support was going to be discontinued when anti-NMDAR antibodies were identified; treatment was continued and the patient recovered after treatment with rituximab and cyclophosphamide (JD, unpublished). Relapses occur in 20–25% of patients.^{8,12,27} They can be separated by intervals of months or years, usually with substantial recovery between relapses. Patients' symptoms can worsen when treatments are tapered or discontinued.

The process of recovery

Recovery from anti-NMDAR encephalitis occurs as a multistage process that happens in the reverse order of symptom presentation. Patients slowly wake from coma as their autonomic functions stabilise, respiration recovers, and dyskinesias subside; they are able to follow simple commands and can have appropriate interactions before they recover verbal functions. During this period patients can become psychotic and agitated again, calming as they recover further (JD, unpublished observations). Social behaviour and executive function symptoms are usually the last to improve, and recovery can be incomplete or delayed by many months.

For the acute stage of the disease, many patients need to be hospitalised for at least 3–4 months, followed by several months of physical and behavioural rehabilitation.^{8,12,17} Patients need close supervision to prevent incidents caused by inappropriate behaviour, impulsivity, disinhibition, and sometimes hyperphagia, hypersexuality, and hypersomnia. Patients' symptoms might resemble those of patients with Klüver-Bucy syndrome (bulimia,

hypersexuality, flat affect, memory loss, visual agnosia), Kleine-Levin syndrome (hypersomnia, compulsive hyperphagia, hypersexuality, apathy, child-like behaviour) or a persistent encephalitis lethargica (JD, personal observation).^{49,53} Counselling about long-term prognosis, even in the most disabled patients, should be done with caution.

Anti-NMDAR encephalitis during pregnancy

Three patients were diagnosed with anti-NMDAR encephalitis while pregnant, and two of them had ovarian teratomas.⁵⁴ The pregnancy was terminated in one patient who had recurrent bilateral ovarian teratomas. The two other patients carried the pregnancy to term and delivered healthy babies. One baby was thoroughly tested for antibodies in serum, cord blood, and CSF, and was shown to be negative; at diagnosis the mother had antibodies detectable only in CSF, which probably explained the absence of transfer to the fetus. During pregnancy, patients were treated safely with methylprednisolone, IVIg, or plasma exchange with mild or questionable improvement. In all three patients, recovery seemed to accelerate after delivery or termination of the pregnancy.

Milder or incomplete forms of the disorder (formes frustes)

Milder or incomplete forms of the disorder in which patients develop predominant or apparently isolated psychiatric symptoms, seizures,⁵⁵ or dystonia⁵⁶ can occur. Some of these forms represent a referral bias—eg, 5 of 6 patients with new onset epilepsy⁵⁵ also had other neurological or psychiatric symptoms. In our experience, pure monosymptomatic syndromes are uncommon and arise in less than 5% of patients.⁸ The most common scenario is that of patients with a predominant symptom and milder manifestations of other elements of the syndrome, or those who later develop other symptoms. For example, the parents of a 19-year-old man who had been diagnosed with pure mania indicated that for several weeks he had had memory problems at school. They denied abnormal movements, but when showed several forms of oculofacial dyskinesias, they indicated that, along with memory problems, the patient had profuse eye blinking, a symptom they attributed to being anxious.

Mortality and causes of death

On the basis of data for 360 patients with clinical follow-up longer than 6 months, the estimated mortality for anti-NMDAR encephalitis is 4% (15 patients died; seven of them previously reported⁸). The median time from disease onset until death was 3.5 months (ranging from 1 to 8 months). 14 patients died in intensive care units: three died of sepsis, two of sudden cardiac arrest, two of acute respiratory distress (one associated with renal failure, and one with atrial fibrillation and hyponatraemia), two of refractory status epilepticus, two of tumour progression, one after withdrawal of medical support, and two of an unknown cause. The only patient who did not die in an intensive care support unit died of unclear cause in a nursing home facility.

Differential diagnosis

The constellation of symptoms in anti-NMDAR encephalitis results in a characteristic syndrome that can suggest alternative diagnoses at different stages. Patients, particularly adults, are often diagnosed with new onset psychosis. Many patients are treated with antipsychotic medication, such as haloperidol, and then when they develop rigidity, autonomic instability, increased concentrations of muscle enzymes, or rhabdomyolysis are thought to have neuroleptic malignant syndrome.¹⁸ However, these symptoms also occur in patients who do not receive neuroleptics. Drugs that block NMDAR function, such as phencyclidine, can produce similar symptoms.^{26,57}

Rhabdomyolysis can also occur as an adverse side-effect of high-dose and long-term use of propofol (propofol infusion syndrome). Additional manifestations of propofol infusion syndrome include severe metabolic acidosis, hyperkalaemia, lipaemia, renal failure, hepatomegaly, and cardiovascular collapse.⁵⁸ We are not aware of any patient with anti-NMDAR encephalitis who developed this syndrome, but since many of these patients need protracted sedation with propofol, and also receive corticosteroids (a risk factor for propofol infusion syndrome), the possibility of this complication should be kept in mind.

Viral encephalitis is an early presumptive diagnosis, suggested by the acute neurological change, CSF pleocytosis, and occasional hyperthermia.⁵⁹ Three of our patients were suspected to have rabies because of the development of psychiatric symptoms, decreased consciousness, dystonic facial movements, hypersalivation, and autonomic instability (JD, unpublished). Ten of 20 children who had previously been enrolled in the California encephalitis project with a diagnosis of idiopathic encephalitis with psychiatric manifestations and dyskinesias had NMDAR antibodies.⁴¹ In a study⁵³ that examined patients who had previously been diagnosed with encephalitis lethargica, many with dyskinesias were shown to have NMDAR antibodies. There are several reported disorders,⁶⁰ mainly in paediatric studies,^{13,61–65} that were probably cases of anti-NMDAR encephalitis.

Pathogenic mechanisms and effects of antibodies

Compelling clinical and laboratory evidence exists that anti-NMDAR antibodies are pathogenic. As previously discussed, antibody titres in CSF and, less often, in serum relate with clinical outcome. Furthermore, the reversibility of the disorder, irrespective of the duration of symptoms, suggests an immune-mediated neuronal dysfunction rather than irreversible degeneration. These features, coupled with the paucity of brain T-cell infiltrates, places this disorder in a category distinct from those that are mediated by complement or cytotoxic T-cell mechanisms.^{66,67} Although patients' antibodies are of the IgG1 and IgG3 classes,³⁷ and therefore capable of activating complement, autopsy and biopsy studies show deposits of complement in the tumour, but not in the brain, despite the presence of IgG in brain (EM-H, unpublished).² This occurrence is probably attributable to preservation of the blood–brain barrier and low concentrations of complement in the CNS.

The first study⁸ showing that patients' antibodies altered the density of NMDAR used rat hippocampal neurons treated for 3 or 7 days with CSF or with IgG isolated from serum. The antibodies caused a pronounced decrease of surface NMDAR clusters that was reversible on removal of patients' antibodies from the culture. Subsequently, Hughes and colleagues⁶⁸ did a comprehensive assessment of the effects of patients' antibodies on synaptic NMDAR with in vitro and in vivo experiments. They showed that anti-NMDAR antibodies cause a selective and reversible decrease in NMDAR surface protein, cluster density, and synaptic localisation that is associated with CSF and serum antibody titres. The mechanism of this decrease was selective antibody-mediated capping and internalisation of surface NMDARs, because monovalent Fab fragments prepared from patients' antibodies did not decrease surface receptor density, whereas crosslinking with anti-Fab antibodies (linking two Fab fragments in a conformation much the same as unmodified antibodies from patients) recapitulated the decrease caused by patients' antibodies that were intact (figure 4). Additionally, whole-cell patch clamp recordings to assess miniature excitatory postsynaptic currents in cultured rat hippocampal neurons showed that patients' antibodies specifically decreased synaptic NMDAR-mediated currents, but did not affect AMPA receptor-mediated currents (figure 4). By contrast with these robust effects on NMDARs, patients' antibodies did not alter the localisation or expression of other glutamate receptors or synaptic proteins, the number of synapses, dendritic spines, dendritic complexity, or cell survival. Results from in-vivo experiments showed that infusion of patients' antibodies into rat hippocampus

substantially reduced NMDAR density, much the same as the decrease of these receptors seen in the hippocampi of patients on autopsy (figure 4).

These studies show that antibodies from patients with anti-NMDAR encephalitis lead to the rapid and reversible loss of surface NMDAR by antibody-mediated capping and internalisation, resulting in abrogation of NMDAR-mediated synaptic function. Our insights are based on studies by Drachman and colleagues,⁶⁹ which show that acetylcholine receptor antibodies from patients bind, cap, and internalise receptors at neuromuscular junctions as a mechanism underlying myasthenia gravis. Our studies further imply that synaptic loss of this subtype of glutamate receptors eliminates NMDAR-mediated synaptic function, resulting in patients' symptoms.

Prüss and co-workers¹⁰ reproduced the antibody-induced decrease of NMDAR concentrations in cultured hippocampal neurons. Results from a study measuring NMDA-mediated calcium internalisation in cultured granular cerebellar neurons showed that after 1 h of treatment with a patient's CSF, calcium entry substantially decreased.⁵⁶ In another study,⁷⁰ patients' antibodies were injected in the prefrontal area of rodents and the effects on the afferent facilitation for corticomotor responses were assessed in a conditioning paradigm. Patients' antibodies substantially enhanced the excitability of motor cortex, suggesting overactivity of glutamatergic pathways.⁷⁰ This glutamatergic hyperactivity has been shown in models of pharmacological or genetic reduction of NMDAR, and is the basis of the NMDAR hypofunction theory of schizophrenia discussed below.⁷¹

Patients phenotype resembles those of genetic or pharmacological disruption of NMDAR

Studies investigating the effects of phencyclidine and ketamine (non-competitive antagonists of NMDARs) in human beings show that these drugs induce behaviours that are much the same as the positive and negative symptoms of schizophrenia, along with repetitive orofacial and limb movements, autonomic instability, and seizures.^{25,72–75} In rodents, drugs that antagonise NMDAR function induce cataleptic freeze and locomotor and stereotypical behaviours.^{76–79} Mice with decreased expression of NR1 also have such behavioural deficits, whereas mice that do not express NR1 develop breathing problems and die in the perinatal period.⁸⁰ A mouse strain in which 40–50% of NMDARs in cortical and hippocampal neurons were selectively eliminated showed schizophrenia-related symptoms and social and spatial working memory deficits that emerged after sexual maturity.⁸¹

The profile of symptoms caused by antagonists of NMDAR is dose dependent and varies in much the same way as the multistage clinical course of anti-NMDAR encephalitis does (figure 5). At low doses, NMDAR antagonists cause psychosis, agitation, memory disturbance, and decreased responsiveness to pain, and at higher doses they cause dissociative anaesthesia, a state of profound unresponsiveness with catatonic features, and coma.⁸² NMDAR blockade disrupts the control of brainstem respiratory centres by higher brain regions⁸³ and the perception of pain.⁸⁴ Therefore, progressive decrease of NMDAR by patients' antibodies and gradual restoration of NMDAR after a decline in antibody titre might probably result in the multistage process of illness and recovery seen in patients with anti-NMDAR encephalitis.

All steps and resulting clinical features of anti-NMDAR encephalitis outlined in figure 6 have been shown in animal models with a pharmacological or genetic decrease of NMDAR expression.^{26,80,83} In these models, inactivation of GABAergic neurons, which express higher concentrations of NMDAR than do other neuronal subtypes, has a central role in clinical manifestations of the disease. Keeping in mind that in anti-NMDAR encephalitis the

effects of patients' antibodies on GABAergic neurons have not been studied, we postulate that an antibody-mediated decrease of NMDAR predominantly inactivates GABAergic neurons and leads to most of the clinical features of the disorder. The complexity of some abnormal movements could be explained by disinhibition of a brainstem central pattern generator.⁸⁵ Facial movements including rooting, sucking, and limb movements can occur in anencephalic newborn babies.⁸⁷ Other abnormal movements that manifest as learned sequences of motions (eg, piano playing or dancing-like motions) are probably caused by basal ganglia dysfunction. Taken together, these studies and the NMDAR-depleting effects of patients' antibodies in neurons in vitro and in the hippocampi of rats after infusion in vivo,⁶⁸ strongly suggest that an antibody-mediated decrease of NMDAR in the entire brain will probably provide a behavioural animal model that is much the same as those obtained by use of pharmacological or genetic reduction of NMDAR.

Approach to diagnosis and proposal of a treatment strategy

Anti-NMDAR encephalitis should be suspected in any individual, usually younger than 50 years and especially a child or a teenager, who develops a rapid change of behaviour or psychosis, abnormal postures or movements (mostly orofacial and limb dyskinesias), seizures, and variable signs of autonomic instability, hypoventilation, or both. Supportive findings include CSF lymphocytic pleocytosis or oligoclonal bands; electroencephalogram with infrequent spikes, but frequent, slow, disorganised, sometimes rhythmic activity that does not relate with most abnormal movements; and brain MRI that is often normal or shows transient FLAIR or contrast-enhancing abnormalities.

Antibody studies should be done in both serum and CSF. Such tests allow comparison of antibody concentrations during the course of the disease. Periodic screening of serum and CSF is useful to assess the effects of treatment, especially in the CNS. All patients should be examined for the presence of an underlying tumour, mainly an ovarian teratoma or a testicular germ-cell tumour. The very low frequency of other tumours suggests that periodic whole-body screening, as recommended for classic paraneoplastic syndromes, is unnecessary.⁸⁸ However, we do recommend periodic screening for ovarian teratomas for at least 2 years, even if patients have recovered from encephalitis.¹⁷

On the basis of previous experience and data from this Review, a proposal for treatment is shown in figure 7. Although no standard of care exists, we prefer concurrent IVIg (0.4 g/kg per day for 5 days) and methylprednisolone (1 g/day for 5 days) to plasma exchange. Plasma exchange is more difficult to do in children, poorly cooperative patients, or patients with autonomic instability. If no response is seen after 10 days, we start second-line therapy. In adults, we use rituximab (375 mg/m² every week for 4 weeks) combined with cyclophosphamide (750 mg/m² given with the first dose of rituximab), followed by monthly cycles of cyclophosphamide. This treatment is discontinued when patients have had substantial clinical recovery, which is usually accompanied by a decrease of CSF and serum antibody concentrations. Paediatricians often use only one of these drugs—mostly rituximab. After substantial improvement, antiepileptics are not needed in most patients. Because relapses occur in 20–25% of patients, often in those without teratoma, in such patients we recommend continued immunosuppression (mycophenolate mofetil or azathioprine) for at least 1 year after initial immunotherapies are discontinued.

Future studies

In this Review we have shown that anti-NMDAR encephalitis defines a new syndrome, reclassifies poorly defined disorders, and strengthens previous hypotheses, such as hypofunction of NMDAR in schizophrenia. Future studies should clarify the mechanism and timing of how the immune response is expanded in the CNS, the best treatment approach,

and strategies to accelerate the process of recovery. The frequency of the disorder suggests that multicenter clinical trials are feasible. The idea that GABAergic inactivation occurs not only in pharmacological and genetic models of decrease of NMDAR but also in patients with anti-NMDAR encephalitis needs to be confirmed. Further studies on the effects of antibodies at the cellular, synaptic, and circuit levels in animal models that recapitulate the disease and the process of recovery are necessary to fully understand how these and other synaptic antibodies affect brain function.

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Search strategy and selection criteria

References for this Review were identified by searches of PubMed from 1966 to October, 2010, with the search terms “NMDA receptor encephalitis”, “anti-NMDAR encephalitis”, and “N-methyl-D-aspartate receptor encephalitis”. Articles were also identified through searches of the authors’ own files. Papers published in English, German, and Spanish were reviewed. Data from 400 patients were obtained from clinical examination (72 cases seen by JD) and information provided by patients, their families, and physicians. Serum and CSF samples from these patients were examined by the authors by use of previously reported techniques.⁸

Figure 1. Antibody studies in a patient without tumour and extended clinical course

An 18-year-old man was transferred from another hospital after 4 weeks' of being in coma. At admission, his CSF and serum were assessed at dilution 1 in 40 for reactivity with HEK293 cells that recombinantly expressed NR1/NR2 heteromers of the NMDAR. Only the patient's CSF was positive (A). B shows the reactivity of a monoclonal antibody against NR1, and co-localises with patient's CSF reactivity (merged immunolabelling in C). D shows that the patient's serum did not react with cells expressing NR1/NR2; in E these cells are immunolabelled by use of a monoclonal antibody against NR1. F shows the merged reactivities. In C and F the nuclei of the cells are stained with DAPI. The graph shows NMDAR antibody titres in CSF over time. Titres were measured by ELISA for 13 months. CSF from control individuals with disorders other than anti-NMDAR encephalitis (eg, stroke, encephalitis suspected to be autoimmune, cerebellar degeneration, and viral encephalitis) were less than 500 relative fluorescence units (RFU; data not shown). The patient was treated initially with corticosteroids and intravenous immunoglobulin (IVIg) without improvement, and subsequently with rituximab and monthly cyclophosphamide. During the clinical course the brain MRI showed mild generalised atrophy. He is currently at home and able to take care of himself, have normal conversations, and play computer games, but is still recovering from symptoms of frontotemporal dysfunction. All techniques have been described elsewhere.⁸ CSF=cerebrospinal fluid. NMDAR=N-methyl-D-aspartate receptor.

Figure 2. Distribution of patients by age and presence or absence of tumours
Data are for 400 patients with anti-NMDAR encephalitis.

Figure 3. Treatment and outcome in 105 patients comparing presence and absence of tumour and the use of second-line immunotherapy

First-line immunotherapy consists of corticosteroids, IVIg and plasma exchange given alone or in combination (detailed below). *Second-line immunotherapy, consists of rituximab or cyclophosphamide, or both. Substantial improvement is defined as previously reported,⁸ and includes full recovery or minimum deficits estimated by physicians and family members as recovery of more than 90% of function. All other patients are judged to have little improvement or no change. In patients with tumour, first-line treatment indicates tumour removal and in most cases first-line immunotherapy. Although there was no difference between the proportion of patients who achieved substantial recovery with or without tumour (Fisher's exact test, $p=0.16$), patients with tumour responded to first-line treatment more often than did patients without tumour ($p=0.001$). Those without tumour required second-line immunotherapy more often and the 5 patients who died were in this group. Whether these patients had occult tumours is unknown.

Figure 4. Association between patients' antibodies and internalisation of NMDAR receptors and abrogation of NMDAR currents

(A) Hippocampal neurons immunostained for surface and internal (total) *N*-methyl-D-aspartate receptor (NMDAR) clusters (top row, stained with commercial NR1 subunit antibody), surface NMDAR clusters only (middle row, stained with patients' cerebrospinal fluid [CSF]) and their co-localisation (bottom row, surface NMDAR clusters in yellow). Treatment with patients' IgG for 1 day decreases surface and total NMDAR cluster density compared with control IgG. Treatment with patient Fab fragments does not affect surface or total NMDAR cluster density, whereas treatment with divalent patient Fab fragments (Fab fragments and anti-Fab secondary antibodies) decreases surface and total NMDAR cluster density to an extent similar to patients' IgG. (B) Effects of patients' IgG, Fab fragments, and divalent Fab fragments on surface and total NMDAR cluster density. (n=30 cells, four independent experiments; two samples from patients, two samples from control patients with unrelated neurological disorders with no immune system involvement). All values are mean $\pm$ SE. * = significant difference (one-way ANOVA test followed by Bonferroni's multiple comparison test, $p < 0.00071$). (C) Graphic representation of the effect of each treatment on surface receptor clusters. (D) Representative average miniature excitatory postsynaptic currents (mEPSCs) recorded in magnesium (Mg^{2+})-free physiological saline with tetrodotoxin (TTX) and picrotoxin to isolate synaptic NMDAR-mediated currents. In neurons treated with IgG from controls for 1 day, 2-amino-5-phosphonovaleric acid (APV), an NMDAR antagonist, blocks the slow decay of the mEPSC (dark green trace). The difference between the dark green traces is the slow NMDAR-mediated current. Neurons treated for 1 day with CSF from a patient (right) have no APV sensitive, NMDAR-mediated current (ie, no difference between the dark green traces). (E) Brain sections from rats infused with CSF from controls (top left) contain many NMDAR clusters in the cornu ammonis (CA1) of the hippocampus, whereas brain sections from rats infused with a patient's CSF (top right) contain substantially fewer NMDAR clusters. Presynaptic synapsin immunostaining is similar between groups (bottom left, right). (F) Effect of 2-week-infusion of patients' CSF with different antibody titres on NMDAR cluster density in CA1. Each point represents the mean NMDAR cluster density from three to five images from an infused rat, $\pm$ SE. Patients' CSF with higher antibody titres reduced NMDAR cluster density to a greater extent than did lower titre samples. These findings indicate that infusion with patients' CSF results in a titre-dependent decrease in NMDA cluster density (linear regression analysis; $R^2 = 0.32$, $p < 0.03$). All values are mean $\pm$ SE. Data are for nine rats killed after 14 days of infusion; five CSF samples from patients, and four CSF samples from controls. (G) Hippocampal section from a healthy individual (left) and from a patient with anti-NMDAR encephalitis (right) immunostained with a commercial NR1 antibody. (H) Intensity of NR1 immunostaining is substantially reduced in the hippocampi of anti-NMDAR encephalitis patients (n=2) compared with hippocampi of controls (3). The

distribution of both patient values for NR1 intensity differed significantly from the distribution of control values (paired Komolgorov-Smirnov test, $p < 0.03$). All data adapted from Hughes and colleagues,⁶⁸ with permission from the Society for Neuroscience.

Figure 5. Stages of illness and recovery

In patients with anti-NMDAR (*N*-methyl-D-aspartate receptor) encephalitis, the processes of symptom presentation and recovery develop in opposite directions (A). The clinical picture is much the same as that caused by phencyclidine, in which the profile of symptoms correlates with the circulating concentration of drug (B). Since NMDAR antibodies cause a decrease of receptors that directly correlates with the titres, we postulate that the profile of symptoms during illness and recovery depends on the intensity of antibody-mediated decrease of NMDAR (C). The green receptors are NMDAR. The blue receptors are α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA). The small round vesicles that are released in the synapse are glutamate. PCP=phencyclidine.

Figure 6. Clinical correlates of antibody-mediated decrease of NMDAR

The figure is based on data from animal models of pharmacological or genetic decrease of NMDAR (*N*-methyl-D-aspartate receptor). Each step has been shown in these models or in individuals treated with antagonists of NMDAR. The pronounced resemblance with the clinical features of anti-NMDAR encephalitis leads us to postulate that an antibody-mediated decrease of NMDAR predominantly inactivates GABAergic neurons (which are rich in NMDAR), leading to disinhibition of excitatory pathways and increase of extracellular glutamate. As a result patients develop a frontostriatal syndrome, which is characteristic of anti-NMDAR encephalitis. The complexity of orofacial and limb movements in patients with this disorder is probably explained by disinhibition of a brainstem central pattern generator that under normal conditions is tonically inhibited by the GABAergic system.⁸⁵ Because genetic disruption of NR1 causes hypoventilation,⁸⁰ a direct effect of the antibodies on the medullary-pontine respiratory network (nuclei of Kölliker-Fuse) might result in breathing dysfunction.⁸³ The presence of NMDAR in dopaminergic, cholinergic, and noradrenergic systems probably explains the autonomic manifestations (hypersalivation, hypertension, hyperthermia, cardiac dysrhythmia) that are also typical of NMDAR antagonists.²⁶ Figure adapted from Florance-Ryan and Dalmau⁸⁶ with permission from Wolters Kluwer Health. GABA= γ -amino-butyric acid.

Figure 7. Proposed algorithm for the treatment of anti-NMDAR encephalitis

*In women, ultrasound of abdomen and pelvis, or transvaginal ultrasound (if age-appropriate); in men, testicular ultrasound. †Mycophenolate mofetil or azathioprine for 1 year. ‡Consider oral or intravenous methotrexate as an alternative immunosuppressant.¹⁰ Figure adapted from Florance-Ryan and Dalmau⁸⁶ with permission from Wolters Kluwer Health.