An update on anti-NMDA receptor encephalitis for neurologists and psychiatrists: mechanisms and models

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The identification of anti-NMDA receptor (NMDAR) encephalitis about 12 years ago made it possible to recognise that some patients with rapidly progressive psychiatric symptoms or cognitive impairment, seizures, abnormal movements, or coma of unknown cause, had an autoimmune disease. In this disease, autoantibodies serve as a diagnostic marker and alter NMDAR-related synaptic transmission. At symptom onset, distinguishing the disease from a primary psychiatric disorder is challenging. The severity of symptoms often requires intensive care. Other than clinical assessment, no specific prognostic biomarkers exist. The disease is more prevalent in women (with a female to male ratio of around 8:2) and about 37% of patients are younger than 18 years at presentation of the disease. Tumours, usually ovarian teratoma, and herpes simplex encephalitis are known triggers of NMDAR autoimmunity. About 80% of patients improve with immunotherapy and, if needed, tumour removal, but the recovery is slow. Animal models have started to reveal the complexity of the underlying pathogenic mechanisms and will lead to novel treatments beyond immunotherapy. Future studies should aim at identifying prognostic biomarkers and treatments that accelerate recovery.

Lancet Neurol 2019; 18: 1045–57

Published Online July 17, 2019 http://dx.doi.org/10.1016/S1474-4422(19)30244-3

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Introduction

Anti-NMDA receptor (NMDAR) encephalitis is an immune-mediated disease characterised by a complex neuropsychiatric syndrome and the presence of CSF antibodies against the GluN1 subunit of the NMDAR.[1] Although the disease is rare, with an estimated incidence of 1·5 per million population per year, and was described only 12 years ago,[2] the impact of this disorder in neurology and psychiatry has been remarkable.[3] Patients develop a constellation of symptoms that vary according to the stage of the disease and clinically suggest the diagnosis (figure 1).[1] At onset, about 90% of patients have prominent psychiatric or behavioural symptoms that can be difficult to differentiate from a primary psychiatric disease.[5] Studies showing that patients' antibodies cause a reduction of synaptic clusters of NMDARs[6,7] have suggested similarities between the synaptic mechanisms of this disease and those related to the NMDAR hypofunction hypotheis of schizophrenia.[8]

In this Review, we first summarise the advances in diagnosis, treatment, and outcome of anti-NMDAR encephalitis, including a set of clinical features that help to recognise early psychiatric symptoms as part of the disease. We then outline potential prognostic biomarkers and describe a clinical score that predicts outcome at 1 year. We provide an overview on herpes simplex encephalitis as a trigger of autoimmune encephalitis, and on the overlap of anti-NMDAR encephalitis with demyelinating disorders. Finally, we examine the pathogenic mechanisms and how different approaches to modelling anti-NMDAR encephalitis in rodents might help understanding of the immunology and neurobiology of the disease.

Clinical features and diagnostic criteria

Many of the features of this disease, including female predominance (a female to male ratio of around 8:2), age distribution (median 21 years, range <1–85 years), variety of symptoms, frequency of tumour associations (mostly ovarian teratoma), and clinical course were outlined in initial reports[1,2,9] and confirmed later.[10–12] In 2013, a series of 577 patients detailed the frequency and variety of symptoms and highlighted some of the differences between children and adults at disease onset.[10] Whereas seizures, abnormal movements, insomnia, and irritability were more frequently identified in children, psychosis and abnormal behaviour were more common in adults. Moreover, during the course of the disease, adults showed more frequent memory impairment and hypoventilation and less frequent focal deficits (paresis, ataxia) and speech or movement disorders than children. Approximately 80% of patients improved or recovered after immunotherapy and (when needed) tumour removal.[10] Early treatment and no admission to an intensive care unit were identified as predictors of good outcome;[10] these findings have led to development of a score that predicts outcome at 1 year.[13] Within the first 2 years of the disease, 12% of patients had relapses that were usually less severe than the initial episode.[10]

As the aforementioned studies were done, other autoimmune encephalitides were identified, so that by 2015, ten additional diseases had been reported.[14] At onset and particularly in children, many of these diseases show substantial overlap (eg, irritability, confusion, and seizures) with anti-NMDAR encephalitis, emphasising the importance of neuronal antibody testing to confirm the diagnosis. In clinical laboratories, this test is a cell-based assay in which a patient's CSF or serum reactivity against NMDARs is examined using a human embryonic kidney cell line (HEK 293) that expresses the receptors. Any cell-based assay technique, either with fixed or live cells, if used without confirmatory tests (eg, brain immunostaining) might lead to false-positive or false-negative results (in 2–14% of cases).[15–17] These drawbacks are avoided if CSF is used.[16] In 2016, these problems and the necessity of improving the clinical recognition of

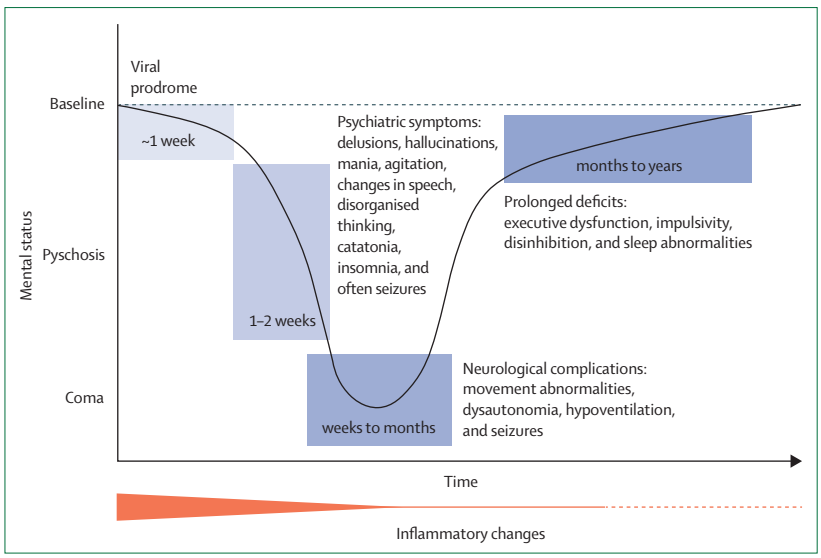

Figure 1: **Stages of illness in patients with anti-NMDAR encephalitis**
This graphic representation of the full-blown syndrome of anti-NMDAR encephalitis in teenagers and young adults shows the predominance of psychiatric symptoms at the initial phase of the disease. These symptoms are usually accompanied or followed by neurological alterations (abnormal movements, seizures, dysautonomia, or coma) that eventually improve or resolve, and lead to a prolonged phase of recovery with prominent involvement of executive functions. The intensity of inflammatory changes (which is usually reflected by the presence of pleocytosis in the CSF or suggested by the brain MRI findings), is shown by the thickness of the red line, which decreases over time until becoming a thin line and then a dotted line (minimal or undetectable inflammatory changes). Adapted from Kayser and Dalmau[4] by permission of Bentham Science. NMDAR=NMDA receptor.

Panel 1: **Diagnostic criteria of anti-NMDAR encephalitis**

Probable

- Rapid onset (<3 months) of at least four of the six major groups of symptoms:
  - Abnormal (psychiatric) behaviour or cognitive dysfunction
  - Speech dysfunction (pressured speech, verbal reduction, or mutism)
  - Seizures
  - Movement disorder, dyskinesias, rigidity, or abnormal postures
  - Decreased level of consciousness
  - Autonomic dysfunction or central hypoventilation
- And at least one of the laboratory studies:
  - Abnormal EEG (focal or diffuse slow or disorganised activity, epileptic activity, or extreme delta brush)
  - CSF with pleocytosis or oligoclonal bands
- Or three of the above groups of symptoms and identification of a systemic teratoma
- Exclusion of recent history of herpes simplex virus encephalitis or Japanese B encephalitis, which might result in relapsing immune-mediated neurological symptoms

Definite

- One or more of the six major groups of symptoms and IgG GluN1 antibodies (antibody testing should include CSF); if only serum is available, confirmatory tests should be included (eg, live neurons or tissue immunohistochemistry, in addition to a cell-based assay)
- Exclusion of recent history of herpes simplex virus encephalitis or Japanese B encephalitis, which might result in relapsing immune-mediated neurological symptoms

Adapted from Graus et al, 2016[18] by permission of Elsevier.

anti-NMDAR encephalitis led a group of experts to develop a set of diagnostic criteria[18] with sensitivity and specificity that have since been affirmed[19] (panel 1).

Psychiatric features

The severity and frequency of psychiatric symptoms had central roles in the discovery of this disease and are important in the differential diagnosis.[2,20] Whereas the first large US series of 100 patients in 2008 indicated that psychiatrists participated in the initial assessment of 77% of patients,[1] a study of 44 patients from the UK, in 2010 described that only 18% of patients presented to psychiatrists and all were managed by neurologists.[11] Differences in health-care systems probably account for these findings and should be kept in mind for the correct interpretation of systematic reviews on the psychiatric features of patients with anti-NMDAR encephalitis that often include patients assessed before 2010. In fact, more recent reports indicate that psychiatrists are increasingly involved in the diagnosis and treatment of these patients.[21–24] A retrospective study of 111 adult patients noted that 65 (59%) initially presented with psychiatric symptoms, including visual or auditory hallucinations in 26 (40%), acute schizoaffective episodes in 15 (23%), depression in 15 (23%), mania in 5 (8%) and addictive or eating disorders in 4 (6%). 45 (41%) patients were first admitted to a psychiatric institution, with a median hospitalisation of 9 days (range 0·25–239).[25] Of these 45 patients, 24 (53%) had neurological symptoms at first evaluation, and 17 (38%) developed neurological deficits within a few days. Importantly, 21 (47%) patients developed hyperthermia, muscle rigidity, coma, or rhabdomyolysis that suggested intolerance to neuroleptics. These findings illustrate the complex psychiatric manifestations of the disease, the paucity of isolated psychiatric symptoms, and the frequent intolerance to neuroleptics (panel 2). In these patients, the difference between neuroleptic malignant syndrome and genuine symptoms of the disease is challenging to determine. Indeed, sympathetic overactivity, hyperthermia, decreased level of consciousness, and increased blood concentration of creatine kinase or rhabdomyolysis can occur in neuroleptic-naive patients with anti-NMDAR encephalitis.[10] The scarcity of prospective single-centre psychiatric investigations in patients with anti-NMDAR encephalitis has led to several systematic reviews mining for a distinct psychiatric phenotype.[21,23,24] These studies rely on many, often single, case reports selected upon availability of psychiatric information, usually obtained by non-psychiatrists. Other limitations are the retrospective assessment of information from patients whose diagnosis was not always confirmed with CSF testing or beyond cell-based assay analysis.[22] Despite thorough and extensive reviews, a specific psychiatric phenotype has not emerged.[21–24] Instead, experience from multiple disciplines points to a combination of clues that should raise concern for anti-NMDAR encephalitis in patients with new-onset psychiatric symptoms (figure 2).

Separate from these studies, there are investigations focused on the prevalence of IgG NMDAR antibodies in patients with psychiatric diseases without evidence of encephalitis.[16] Most of these studies did not examine the CSF (or if examined, it was negative for NMDAR antibodies),[28] and showed that seropositive and seronegative patients had similar symptoms. A study of 228 patients with first episode of psychosis showed that seven (3%) had low serum titres of NMDAR antibodies; their clinical features and outcomes at 6 months were similar to those of seronegative cases.[29] Another study of 113 patients found four (3%) patients that were seropositive; two (2%) had classic anti-NMDAR encephalitis with ovarian teratoma, and the other two (2%) had isolated psychiatric symptoms that partially improved with immunotherapy.[30] In a cohort of 48 patients with schizophrenia, whose serum was examined after a mean duration of illness of 11 years, nine (19%) had IgG NMDAR antibodies.[31] Compared with patients with anti-NMDAR encephalitis, those with schizophrenia had lower serum antibody titres (absent in CSF), and different GluN1 epitopes. In cultured neurons, these antibodies modified the cell-surface dynamics and caused a reduction in clusters of NMDARs, suggesting a pathogenic role, although seropositive patients were clinically similar to seronegative. Other investigators using the sera of patients with schizophrenia at disease onset were unable to identify IgG NMDAR antibodies or found them only at low frequency (<2% patients).[16,32–34] This disparity could be explained by the chronic history of schizophrenia (11 years) in the indicated series, potentially leading to a secondary (mild) NMDAR immune response as a result of antigen release by the neurodegenerative process. If confirmed, the mechanism would resemble the immune activation against NMDAR caused by release of neuronal antigens in patients with herpes simplex encephalitis.[35]

Other studies investigated the prevalence of NMDAR antibodies (IgM, IgA, and less frequently IgG) in the sera of patients with a wide range of diseases.[34,36] The presence of these antibodies in all (psychiatric and non-psychiatric) diseases studied and in healthy participants[36,37] reveals a poor specificity and unclear clinical implications. Clinicians should be aware of these findings when formulating the differential diagnosis of anti-NMDAR encephalitis.[16]

A study found that, in addition to high-affinity antibodies, patients with anti-NMDAR encephalitis had low levels of unmutated NMDAR antibodies derived from activated naive B cells.[38] These unmutated antibodies could be part of a natural innate immune response occurring in all people, which, depending on different clinical presentations (eg, psychiatric disease or stroke), could impair or protect neurological function.[38] None of these possibilities were examined, and although unmutated antibodies showed functional effects at high concentration in cultured neurons,[38] their frequency and significance in humans are unknown. These findings indicate that not all circulating cell populations responsible for NMDAR antibodies derive from ongoing germinal-centre reactions as previously suggested.[39]

***Panel 2*: A patient with a delayed diagnosis of anti-NMDAR encephalitis**

A 23-year-old woman was admitted to hospital for acute paranoia and aggressiveness towards her partner. She was having auditory hallucinations and episodes of nonsensical speech. Routine CSF studies and brain MRI were normal. An EEG revealed temporal lobe seizures that responded to carbamazepine; however, her paranoia and hallucinations persisted. She also developed abnormal hand movements (grasping and clawing) and leg shaking that had no correlation with the EEG patterns. She had episodes of sweating and tachycardia, and developed insomnia with frequent night-time awakenings. She was given quetiapine and zolpidem without effect, and was empirically started on a 5-day course of methylprednisolone followed by a 3-week taper of opral prednisone, showing a slow recovery over a few weeks after discharge and while on steroid taper.

After being well for about 4 years, she presented to the emergency room of our hospital with behaviour change, paranoia, agitation, and hallucinations. She had not slept for 6 days. While being evaluated, she threw objects at the nurses and during the hospital stay she became very aggressive, requiring physical restraints. She threatened to jump from the window on several occasions. The episodes of sweating and tachycardia returned. Repeated CSF studies revealed a white blood cell count of 12 per mm^3 with normal protein concentration. A brain MRI remained normal. EEG video monitoring showed background slowing but no epileptic activity. She was admitted to the psychiatry service with the diagnosis of mania. She was initially given haloperidol but developed acute dystonia that responded to benzatropine. Over the following few months after discharge from the psychiatric service her behaviour fluctuated, sometimes giving the appearance of improvement and then worsening. These fluctuations led to multiple hospital admissions and changes in medication that included quetiapine, ziprasidone, lithium, olanzapine, and several courses of electroconvulsive therapy. During her last admission she had a low-grade fever and underwent another CSF evaluation that included neuronal antibodies, which revealed the presence of NMDA receptor (NMDAR) antibodies. No systemic tumour was identified by combined CT scan with ^{18}F-fluorodeoxyglucose PET, abdominal ultrasound, or abdominal MRI. She was started on intravenous IgG and methylprednisolone that resulted in mild improvement of her psychiatric symptoms, but she continued having cognitive deficits and bursts of agitation and aggression. Rituximab was initiated 8 weeks after the diagnosis of anti-NMDAR encephalitis, leading to substantial improvement over the following 2 months. At 6 months, her cognitive and neurological functions were almost fully recovered and the behavioural problems were resolving.

Movement disorders

Facial dyskinesias and a large variety of abnormal movements affecting the limbs and trunk are common manifestations of anti-NMDAR encephalitis and valuable clues to recognise the disease.[1,40] About 75% of adults and 95% of young children develop abnormal movements.[10] As with psychiatric symptoms, no specific movement disorder phenotype exists.[41] Oral, facial, or lingual dyskinesias, chorea, athetosis, dystonia, myorhythmia, opisthotonus, ballismus, blepharospasm, oculogyric crisis, and other features can occur in these patients.[1,40] Self-injuries of the tongue, lips, or teeth are common; tetrabenazine or focal botulinum toxin might improve some of these symptoms,[40] but the main focus should be on treating the underlying physiopathology with immune therapy. To

S	**Sleep dysfunction** Severe insomnia is more frequent than hypersomnia at disease onset;[5,24,86] by contrast, hypersomnia is more frequent during the phase of recovery (sometimes associated with hyperphagia and hypersexuality)
E	**Excitement, disinhibition, or manic behaviour alternating with depressive behaviour** Manic and bizarre behaviour, hypersexuality, or wandering are frequent at disease onset;[4] depression or suicidality are less frequent[24]
A	**Agitation or aggression** Similar in children and adults; in children, temper tantrums, kicking, biting, or hitting are common[9]
R	**Rapid onset** Symptoms develop in days or weeks; in contrast, primary psychiatric diseases usually have a slower progression of symptoms, or in cases of acute psychosis, onset is usually preceded by behavioural changes[21]
C	**Children and young adult predominance** Median age at disease onset is 21 years (37% aged <18 years, and 19% aged <12 years); female to male ratio, 8:2;[10] in contrast, mean age of schizophrenia presentation in men is 18–25 years, and in women 25–35 years (peaking after menarche and after age 40), with a female to male ratio of 0·92:1[27]
H	**History of psychiatric disease absent** In patients with history of psychosis or behavioural change, reports obtained from families or patients usually suggest that the previous episodes were caused by anti-NMDAR encephalitis
F	**Fluctuating catatonia** Catatonia can alternate with episodes of extreme agitation[21]
N	**Negative and positive symptoms at presentation** Positive symptoms (visual or auditory hallucinations; persecutory, reference, grandiose, or religious delusions; or disorganised thoughts) and negative symptoms (cognitive impairment, distractibility, decreased verbal output, or anhedonia) are usually present at onset;[5,24] in schizophrenia, positive symptoms are disproportionally more frequent than negative symptoms at disease onset[22]
M	**Memory deficit** Memory formation is impaired and examination is often difficult due to agitation, behavioural change, or speech problems; most patients do not remember large periods of their disease after recovery
D	**Decrease of verbal output or mutism** A rapid decrease of verbal output occurs, particularly in children, and it can be preceded by pressured speech[9]
A	**Antipsychotic intolerance** This pertains to typical and atypical antipsychotics; expert opinions suggest that the frequency of adverse effects is higher with typical antipsychotics[5,25]
R	**Rule out neuroleptic malignant syndrome** Hyperthermia, coma, muscle rigidity, high serum creatine kinase concentration, or rhabdomyolysis can occur in neuroleptic-naive anti-NMDAR patients; individuals considered to have a primary psychiatric disease and treated with neuroleptics can be misdiagnosed with neuroleptic malignant syndrome, missing the actual disease (anti-NMDAR encephalitis)[25]
A	**Antibodies and additional paraclinical tests (EEG, MRI, or CSF)** NMDAR antibodies are always present in CSF; 80% of patients have pleocytosis*

Figure 2: **Diagnostic clues of anti-NMDAR encephalitis in patients with new-onset psychiatric symptoms (SEARCH For NMDAR-A)**
NMDAR=NMDA receptor. *Further information and other tests are shown in the table.

prevent the patient self-injuring or fighting against the ventilator, prolonged sedation is commonly used; for example, one patient with dyskinesias refractory to ketamine, midazolam, and propofol, responded to prolonged sedation with isoflurane.[42]

Seizures and the risk of epilepsy

Seizures are a common presentation of anti-NMDAR encephalitis in children and young men.[10,12,43] Approximately 70% of patients develop seizures,[10] with frequencies of 57–82% depending on the reported studies.[1,11,43,44] Because the seizures are provoked by a specific and treatable autoimmune mechanism, the term autoimmune epilepsy is inaccurate to define the seizures during the disease.[45] A study suggested that patients with anti-NMDAR encephalitis should have a prolonged follow-up (at least 1 year) before the diagnosis of epilepsy is considered in those who remain with seizures or require antiepileptic medication.[45] Prolonged follow-up indicates that, in most patients, the seizures resolve after the encephalitis subsides. In a case series of 75 patients, 43 (57%) developed one or more of the following: tonic-clonic seizures (79%), focal seizures (74%) without impaired awareness (55%) or with impaired awareness (42%), status epilepticus (35%), and refractory status epilepticus (21%).[44] Of these 43 patients, 39 (91%) survived the disease, six (14%) had relapses (five [12%] with seizures), and all were free of seizures after a median follow-up of 31 months. Only three (8%) of the 39 patients were on antiepileptics at the last follow up. Seizure freedom was due to immunotherapy in 47% of patients and antiepileptic drugs in 16%; for the rest of the patients the cause of seizure freedom was unclear (combined effects of immunotherapy and antiepileptic drugs, or spontaneous improvement). Valproate, levetiracetam, and carbamazepine were similarly effective, although carbamazepine was associated with fewer side-effects.[44] In another case series, 88 (81%) of 109 patients developed seizures and all patients were seizure free at the 2-year follow up.[43] The duration of antiepileptic therapy did not modify seizure freedom.[43] These studies support a gradual removal of antiepileptic therapy during the process of recovery.

Intensive care challenges

About 70% of patients are admitted to intensive care units for airway protection, dyskinesias, persistent dysautonomia, a fluctuating level of consciousness, or breathing dysfunction.[10,46] Common challenges during intensive care unit admissions include differentiating true seizures from dyskinesias, and fever caused by nosocomial infections from hyperthermia due to the primary disease.[47] Most patients have tachycardia that might alternate with bradycardia, sometimes leading to prolonged cardiac pauses.[1] In a study of 76 patients admitted to intensive care units, five (7%) had dysautonomic cardiac arrest.[46] Patients with severe bradyarrhythmias require a temporary (or less frequently, permanent) pacemaker; symptoms usually resolve after the encephalitis subsides.[48] Orofacial dyskinesias and opisthotonic posturing might cause dislodging and malfunction of airway devices complicating airway management.

During the intensive care unit stage, patients receive prolonged courses of sedatives, antiepileptics, neuromuscular

blockers, empirical antibiotics, and neuroactive or psychoactive medications.[46,47] Concerns commonly arise regarding deep sedation and anaesthesia because of the potential adverse effects of the drugs (eg, ketamine, tramadol, propofol, or sevoflurane) interfering with NMDAR function. However, in most reports, the use of propofol or any of these drugs is described as uneventful.[46,49] A study suggested that anaesthesiologists should be cautious with regards to sympathetic overactivity (usually controlled with β blockade, opioids, α-2 adrenergic receptor agonists, benzodiazepines, or a combination) and ventilatory dysfunction, and that bispectral index monitoring should be used cautiously due to the complex EEG abnormalities of this disease.[49]

Treatment

The treatment approach to anti-NMDAR encephalitis involves escalation of immunotherapy, starting with first-line therapies (steroids, intravenous immunoglobulins, or plasma exchange) and transitioning to second-line therapies (rituximab or cyclophosphamide) if needed.[10,50] This approach is based on a study of 472 patients; among the 221 (47%) who did not improve at 4 weeks of initiation of first-line therapies, 125 (57%) individuals who received second-line therapies had significant improvement compared with the 96 (43%) individuals who did not.[10] No studies exist comparing first-line therapies with upfront use of rituximab. For patients who are refractory to these approaches (around 10%),[10] third-line treatments such as bortezomib (a proteasome inhibitor) or tocilizumab (an IL-6 [interleukin 6] receptor antagonist)[51] have been suggested. Bortezomib was considered effective in a few single case reports and a small case series,[52,53] and ineffective in another series.[54] A study in which treatment failure to rituximab was defined as absence of improvement 4 weeks after the last infusion showed that patients who received tocilizumab (n=10) had better outcomes at 24 months than individuals who continued on rituximab (n=10) or who received no further immunotherapy (n=6).[51] The study was retrospective, showed a substantially lower response rate to rituximab compared with other series (53% *vs* 67%),[10,51] and had some selection bias in patient assignment to the study groups. Caveats suggesting caution in the interpretation of these studies include the small number of patients, the previous or concomitant use of other immunotherapies, and the short (4 weeks) period considered to define treatment failure after second-line therapies. Thus, whether the treatment effect reported in some patients represented a delayed response to previous immunotherapies or spontaneous improvement is unclear. Similar caveats should be considered for the small number of patients reported with improvements after intrathecal or oral methotrexate[55,56] or immunoadsorption.[57] A systematic review of 87 paediatric patients treated with azathioprine, mycophenolate mofetil, or methotrexate, showed that, among individuals with assessable information, only 19 of 39 (49%) were started on one of these treatments within 6 months of disease onset. Similarly, only 35 of 58 (60%) received these treatments after the first episode of the disease, whereas for the remaining patients the treatments were introduced after one or more relapses. All patients had been previously treated with first-line or second-line therapies and 7% relapsed while being on azathioprine, mycophenolate mofetil, or methotrexate, suggesting that larger cohorts are needed to determine their efficacy.[58]

Electroconvulsive therapy was used in some patients with severe catatonia. In a systematic review of 30 cases, 21 (70%) were treated before the diagnosis of anti-NMDAR encephalitis. Among 23 assessable cases, 15 (65%) noted improvement of psychiatric symptoms (nine [39%] without previous immunotherapy); four (18%) did not improve, and the other four (18%) had electroconvulsive therapy discontinued because of seizures or neurologic deterioration.[59] Confounding factors were the previous or concomitant use of immunotherapy, and the discontinuation of antipsychotics before electroconvulsive therapy. Of note, electroconvulsive therapy can result in a brief parasympathetic-mediated bradycardia, hypotension, and asystole, followed by a more prominent sympathetic response (hypertension or tachycardia)[59] that might potentially exacerbate similar symptoms caused by anti-NMDAR encephalitis. In a case series of 577 patients,[10] 13 of 15 treated with electroconvulsive therapy had assessable outcome; one (8%) deteriorated and needed mechanical ventilation, six (46%) did not respond, and six (46%) partially improved, but five patients (38%) relapsed within 1–2 months (unpublished).

Triggers and disease associations

Two confirmed triggers of anti-NMDAR encephalitis are tumours (mostly ovarian teratomas)[1] and herpes simplex encephalitis.[60] Two studies suggested potential associations with HLA-I allele *B*07:02* and HLA-II allele *DRB1*16:02*, but the association of both alleles with disease susceptibility was weak and needs confirmation.[61,62] Earlier investigations showed that the frequency and type of associated tumours varies according to age, sex, and probably race.[9,10] Compared with teratomas of patients without anti-NMDAR encephalitis, those with encephalitis had more frequent neuroglial components and inflammatory infiltrates with over-representation of B cells, plasma cells, and dendritic cells, conforming tertiary lymphoid structures.[63] Evidence exists that tumour-infiltrating B cells are able to synthesise NMDAR antibodies in vitro.[39]

With regards to herpes simplex encephalitis, a case series of 99 patients showed that 14 (27%) of the 51 patients that were prospectively followed developed autoimmune encephalitis 2–16 weeks after herpes simplex encephalitis.[35] Detection of neuronal antibodies (64% NMDAR and 36% other) within 3 weeks of onset of herpes simplex encephalitis was a risk factor for autoimmune encephalitis. Compared with patients older than 4 years, those aged 4 years or younger were more likely to have shorter

intervals between onset of herpes simplex encephalitis and autoimmune encephalitis, choreoathetosis, a decreased level of consciousness, NMDAR antibodies, and a worse outcome at 1 year.[35] This outcome was also substantially worse than that of children with classical anti-NMDAR encephalitis. The reasons for this poorer outcome are unknown; the presence of multiple autoantibodies, cytotoxic T-cell mechanisms, disruption of the blood–brain barrier with entry of complement, increased brain vulnerability to the effects of herpes simplex encephalitis in young children,[35] or persistent inflammatory changes[64] could have had a role. This study also showed that three (6%) of 51 patients with herpes simplex encephalitis developed NMDAR antibodies without symptoms of encephalitis. None of these three patients had detectable antibodies at 1-year follow up (compared with six [67%] of nine who developed encephalitis).[35] Whether these patients are at increased risk of developing autoimmune encephalitis in the future is unclear. A rodent model of NMDAR-antibody synthesis triggered by herpes simplex encephalitis has been developed;[65] the antibodies caused a decrease of NMDAR in cultured neurons but the effects on memory and behaviour were not examined. Preliminary evidence exists that other infections, such as Japanese encephalitis virus, can lead to a similar type of NMDAR-antibody-associated postviral encephalitis.[66]

Approximately 5% of patients with anti-NMDAR encephalitis develop clinical or radiological evidence of a demyelinating disorder, such as neuromyelitis optica spectrum disorder.[67] Clinical or radiological features might precede, occur simultaneously, or develop after anti-NMDAR encephalitis; in these cases coexisting antibodies against aquaporin-4 or MOG (myelin oligodendrocyte glycoprotein) can occur.[67,68] Recognition of these associations is important to avoid misdiagnoses and refine the treatment.[67] The importance of the association of NMDAR and GFAP (glial fibrillary acidic protein) antibodies is less clear. Some studies categorise the NMDAR antibodies as accompaniments of the encephalitis with GFAP antibodies;[69] however, the syndrome is usually driven by the NMDAR immune response and the GFAP antibodies appear to be the accompaniments.[70]

Diagnostic and prognostic biomarkers

The only specific diagnostic test of anti-NMDAR encephalitis is the demonstration of IgG antibodies against the GluN1 subunit of the receptor in patient's CSF. However, the follow up of antibody titres shows an imperfect correlation with the clinical course.[15] Thus, treatment decisions during the disease should be primarily based on clinical assessment rather than on antibody titres. Here, we summarise attempts to identify other diagnostic and prognostic biomarkers (table). Although all these tests have shown some potential utility, in practice the importance of some of the findings is unclear (eg, cytokine profiling), and their interpretation has limitations because of the small number of cases, retrospective analyses, scarce longitudinal assessments, unclear specificity, and variability among tests, this variability particularly illustrated in neuropsychological studies.[86]

A study examining 382 patients with information available on their functional status after 1 year of disease onset showed that admission to an intensive care unit, treatment delay of more than 4 weeks, absence of improvement within 4 weeks of starting treatment, abnormal MRI, and CSF white blood cell count of more than 20 cells/µl were independent predictors for outcome in multivariate regression modelling.[13] These five variables were assigned one point each to construct a score, named the anti-NMDAR Encephalitis One-Year Functional Status (NEOS) score. The NEOS score strongly correlated with the probability of poor functional status at 1 year (3% for 0–1 point to 69% for 4–5 points). However, the score should not be used as a tool for guiding decisions about withdrawal of care. Indeed, 25 (32%) of 79 patients with the highest NEOS score were functionally independent 1 year after disease onset, and 25 (36%) of 70 patients with poor functional status at 1 year, recovered to good functional status at 2 years. Therefore, the NEOS score should be viewed as a tool that helps to estimate the velocity of clinical improvement rather than the expected final outcome.[13] Because the score is easy to obtain, it can be used to stratify patients for clinical trials.

Mechanisms and models

Anti-NMDAR encephalitis is a neuroinflammatory disease mainly mediated by autoantibodies against the GluN1 subunit of the receptor. With regards to clinical evidence of inflammation, there are two stages (figure 1). In the first stage (which has a duration of around 3 months or longer), patients develop severe symptoms (such as psychosis, movement disorders, seizures, dysautonomia, and coma) commonly accompanied by transient MRI abnormalities or pleocytosis that progressively decreases over several weeks while symptoms still persist (table).[4] At this stage, reports on brain biopsy or autopsy findings have shown infiltrates of B cells, plasma cells, CD4 T cells and less frequently CD8 T cells, accompanied by microglial activation, deposits of IgG, and little or no neuronal loss.[2,87,88] These findings are strikingly different from those of CD8 cytotoxic T-cell-mediated encephalitis, which is characterised by extensive neuronal loss.[3]

The second stage (which has a duration of around 6 months or longer) corresponds to the process of recovery in which the indicated symptoms have largely resolved, but patients still have alterations of behaviour, memory, cognition, and executive functions.[4] In this stage, the presence of inflammation (eg, MRI changes or CSF pleocytosis) is minimal. In both stages, antibodies are detected in CSF (less commonly in serum) and progressively decrease during symptom improvement.[14] Low titres of antibodies in the CSF and serum can persist for many months after recovery.[14]

Pathological[70,71] and immunological evidence[72,73] exists that NMDAR antibodies are synthesised systemically and within the CNS by antibody-producing cells that are able to cross the blood–brain barrier.[13] In the brain, these antibodies are pathogenic, as suggested by experiments using cultured neurons exposed to patients' antibodies,[5,6,74,75] and confirmed with models of cerebroventricular transfer of patients' antibodies to mice.[93–95] Patients' antibodies cross-link the NMDARs, altering their surface dynamics and interaction with other synaptic proteins, and causing their internalisation along with severe impairment of synaptic plasticity and NMDAR network function (figure 3A).[6,7,91,97] These effects are unrelated to complement-mediated mechanisms, as shown in human autopsies.[87,88] In mice, the antibody effects lead to memory deficits, anhedonia, depression-like behaviour, and a low threshold for seizures (figure 3B).[93–95] Moreover, the clinical features in patients and animal models resemble those caused by genetic or pharmacological attenuation of NMDAR function.[45]

Accordingly, transplacental transfer of NMDAR antibodies from pregnant patients to embryos can potentially result in neurological deficits in neonates.[98,99] In a

	Patients (n)	Results	Comments
CSF routine studies			
Dalmau et al, 2008[1]	100	Abnormal findings, 95%; pleocytosis, 91%; increased protein concentration, 32%; oligoclonal bands, 67%	In other studies, the frequency of total CSF abnormalities ranged from 79–83%,[10] and pleocytosis was around 68%[11]
CSF cytokines			
Leypoldt et al, 2015[71]	167	At disease onset, 70% of patients had increased concentrations of CXCL13 that correlated with intrathecal antibody synthesis; prolonged or secondary elevation of CXCL13 was associated with relapses or a poor response to treatment	This retrospective analysis suggested that detection of elevated CXCL13 concentrations after first-line immunotherapy support the use of second-line therapy
Chen et al, 2018[72]	66	At the acute stage, concentrations of inflammatory cytokines (TNF-α, I-L6, or IL-10), and YKL-40 (a secreted glycoprotein mostly expressed by microglia) were elevated	Changes in YKL-40 concentration correlated with mRS; unclear disease specificity
Ding et al, 2018[73]	48	CSF (and serum) concentrations of soluble Fas and FasL were increased in patients with anti-NMDAR encephalitis; the CSF concentrations correlated with the mRS score	Low number of controls (among them, only three had viral encephalitis); scarcity of clinical follow up; unclear prognostic implications
EEG			
Schmitt et al, 2012[74]	23	Continuous EEG monitoring, median 7 days, range 1–123; diffuse slowing, 91%; focal slowing, 34%; GRDA, 48%; diffuse excess beta activity (probably medication-related), 52%; electrographic seizures, 61%; EDB, 30%	EDB was associated with a more prolonged hospitalisation and increased number of days of EEG monitoring
Sonderen et al, 2018[75]	53	96% of patients (adults and children) had abnormal EEG; during the first recording, 71% had normal posterior rhythm; the first EEG was severely abnormal in 26% of patients; EDB was identified in 6% of patients at first EEG and 13% at the nadir of the disease	Although the sensitivity of abnormal EEG is high (96%), normal EEG does not exclude anti-NMDAR encephalitis
Jeannin-Mayer et al, 2019[76]	24	71% of patients had excessive beta activity; 58% had EDB; and 50% had GRDA; the median time of appearance of each pattern was 10 days (excessive beta activity), 16·5 days (EDB), and 21·5 days (GRDA); GRDA was found associated with concomitant abnormal movements	75% of patients had seizures; 21% had electrographic seizures without clinical manifestation; the rhythmic pattern of GRDA should not be misinterpreted as seizures or status epilepticus
Brain MRI			
Dalmau et al, 2008[1]	100	Abnormal MRI (55%); FLAIR changes in temporal lobes (22%), cerebral cortex (17%), cerebellum (6%), brainstem (6%), basal ganglia (5%), other (corpus callosum, hypothalamus, periventricular, or white matter, 8%); contrast enhancement in cortex, meninges, or basal ganglia (14%)	This first large series of patients might be biased towards worse clinical cases; a later study of 577 patients[10] including the first 100 showed lower frequency (33%) of abnormal MRI findings
Iizuka et al, 2016[77]	15	Median follow-up 68 months (range 10–179 months); 33% showed diffuse cerebral atrophy and two showed cerebellar atrophy; whereas the cerebral atrophy was reversible, the cerebellar atrophy was irreversible	Cerebral atrophy was associated with longer hospitalisations, ventilatory support, and serious complications, but not with poor outcome; cerebellar atrophy was associated with poor outcome
Resting-state functional MRI and connectivity			
Peer et al, 2017[78]	43	Using resting-state functional MRI, patients showed impairment of hippocampal connectivity, decoupling of the medial-temporal and the default-mode networks, and altered frontotemporal connections; memory deficits correlated with hippocampal and medial-temporal lobe network connectivity, and schizophrenia-like symptoms with frontoparietal network connectivity	72% of patients had normal MRI; the dissociation between MRI and functional connectivity studies provides an explanation for the frequently reported normal MRI in patients with severe symptoms
Finke et al, 2016[79]	40	Using multimodal structural imaging (volumetry of hippocampal subfields and microstructural integrity), patients had reduced hippocampal volumes and atrophy of input and output circuits; the findings correlated with memory performance, disease severity, and duration	The correlation between microstructural hippocampal abnormalities and memory deficits emphasise the importance of a prompt diagnosis; future long-term studies should assess the potential reversibility of findings in longitudinal assessments[77]
Phillips et al, 2018[80]	46	36 patients had neurological deficits and ten had recovered from anti-NMDAR encephalitis; using superficial white matter mean diffusivity studies, non-recovered patients showed widespread superficial white matter changes whereas recovered patients had no abnormalities; damage predominated in frontal and temporal lobes	The findings correlated with impairments in working memory, verbal memory, visuospatial memory and attention; future long-term studies should assess the potential reversibility of findings in longitudinal assessments

(Table continues on next page)

	Patients (n)	Results	Comments
(Continued from previous page)			
^{18}F-FDG PET			
Yuan et al, 2016[81]	8	18 serial FDG-PET scans from eight patients were assessed; at the acute phase of the disease, they showed severe hypometabolism in bilateral occipital lobes and relatively mild hypermetabolism in frontal lobes and basal ganglia; at early recovery phase, they showed extensive cortical hypometabolism; at late recovery phase, the FDG-PET was almost normal	The findings are similar to those of another study[101] that showed a correlation between the indicated occipital hypometabolism and the severity of patients' symptoms; unclear prognostic significance
Lagarde et al, 2016[83]	6	All six paediatric patients showed extensive, symmetrical cortical hypometabolism mainly in posterior areas, asymmetric anterior focus of hypermetabolism and basal ganglia hypermetabolism; the findings correlated with clinical severity and improvement	Four of six patients had normal MRI, showing (as with functional MRI connectivity studies[97]) the dissociation between severity of symptoms and clinical MRI results
Neuropsychological assessment			
Nicolle and Moses, 2018[86]	54	Systematic review of 10 studies that included the assessment of cognitive function in 54 adult patients; the main findings were difficulties with memory, particularly delayed verbal memory, and impaired executive functioning	Many important limitations in published studies and in this area of research are indicated by the authors, such as poor information on premorbid functioning, insufficient rationale for neuropsychological battery choice, use of samples of convenience, and limited translation of neuropsychological findings into rehabilitation
De Bruijn et al, 2018[84]	28	This study examined the long-term neuropsychological outcome in a paediatric population; 64% returned to their previous school level; in 22 with long-term (median 31 months, IQR 15–49) follow-up, there were substantial problems with sustained attention and fatigue; problems in school and work performance included word-finding difficulty (24%), dyslexia (12%), and attention or concentration deficits (18%); other problems were impulsiveness (18%), anxiety (18%), and indecisiveness (12%)	Cognitive deficits did not correlate with quality of life, but fatigue did; although follow-up is often reported as good, many patients have cognitive problems and fatigue resulting in problems in academic achievement and low quality of life; early neuropsychological counselling should be considered
Cainelli et al, 2018[85]	7	Longitudinal study of seven children, mean follow up 35 months (range 24–48); within 1 month of discharge all had deficits in attention, executive function, or visual motor functions involving executive functions; these deficits were long-lasting in about 50% of the patients; four patients developed persistent symptoms, such as impulsivity, hyperactivity, irritability, apathy, obsessive-compulsive symptoms, and difficulty to regulate their behaviour	The findings are in line with clinical and functional (MRI connectivity) studies suggesting an important role of impairment of executive functions in the cognitive disturbance of patients with this disease

TNF-α=tumor necrosis factor. IL=interleukin. mRS=modified Rankin Scale score. Fas=tumor necrosis factor receptor superfamily member 6. FasL=tumor necrosis factor ligand superfamily member 6. NMDAR=NMDA receptor. GRDA=generalised rhythmic delta activity. EDB=extreme delta brush. FLAIR=fluid-attenuated inversion recovery. ^{18}F-FDG=^{18}F-fluorodeoxyglucose.

Table: **Studies of diagnostic and prognostic tests and biomarkers for NMDAR encephalitis**

systematic review of 13 pregnant patients, nine (69%) recovered, three (23%) had moderate to severe deficits, and one (8%) died. Two patients had miscarriages and one had an abortion (all three patients had ovarian teratoma), and among the ten neonates, seven were healthy and three had neurological deficits.[100] The antibody pathogenicity is likely to be restricted to cases in which high serum antibody titres in pregnant patients coincide with the period in which the blood–brain barrier of the fetus is open;[101] this idea and the fact that serum antibody concentrations from patients are probably lowered by plasma exchange or intravenous immunoglobulin treatment might explain why no more neonates were affected.[100] These reports suggest maintaining awareness for anti-NMDAR encephalitis in patients who develop psychosis during pregnancy. Vigilance should continue in the postpartum period because some patients with postpartum psychosis were found to have anti-NMDAR encephalitis.[102]

In addition to animal models of passive antibody transfer, a model of active immunisation exists using GluN1/GluN2B heteromers of the NMDAR embedded in liposomes (figure 3C). Immunised mice developed a fulminant encephalitis characterised by infiltrates of B cells, plasma cells, microglial activation, CD4 T cells (sparse or absent CD8 T cells), rare neuronal loss, and antibodies against several epitopes of the GluN1 and GluN2 subunits of the NMDAR.[96] Different from the human disease, in which the epitopes are located in the amino-terminal domain of GluN1 and are conformational,[103] the antibodies of these mice did not target the amino-terminal domain and reacted with linear epitopes.[96] In cultured neurons, the antibodies produced a reduction of the concentration of NMDAR and NMDAR-mediated currents without affecting the number of synapses. The mechanisms of NMDAR internalisation, potential disruption of other NMDAR-interacting proteins, or impairment of synaptic plasticity in the affected mice were not described. Importantly, the resulting phenotype was characterised by dramatic hyperactivity, stereotyped motor features (tight circling), seizures, and a hunched back or lethargy, resembling some of the symptoms of the initial stage of the human disease.[96] Whether the severity of symptoms (hyperactivity, circling, or seizures) will allow studies of memory and other behaviours, or whether the symptoms are reversible is unknown. However, the findings of this model confirm that a specific immune response against NMDARs results in an ample repertoire of symptoms (eg, there is no need for antibodies against different proteins to explain each of the symptoms), and

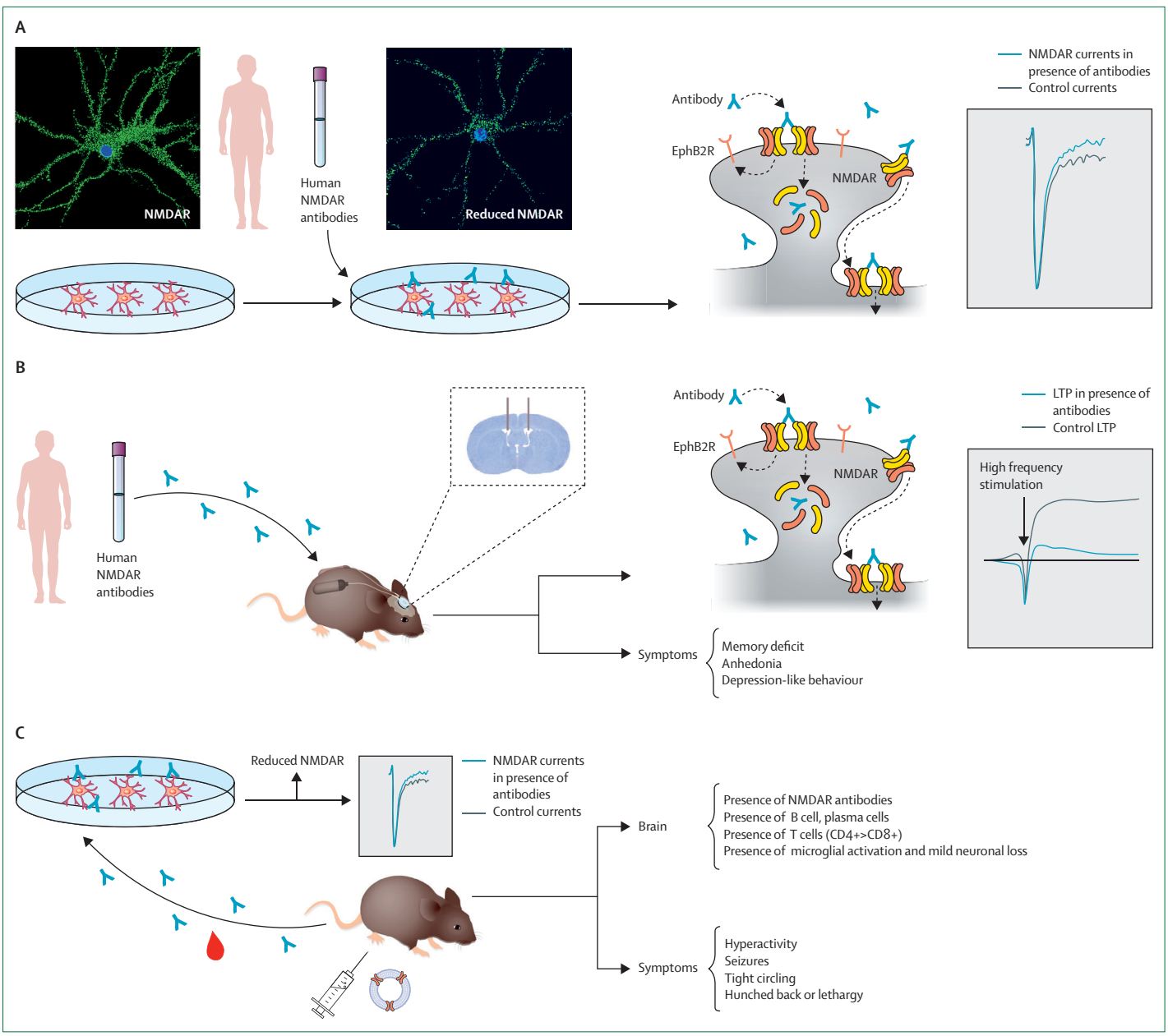

Figure 3: **Models and mechanisms of anti-NMDAR encephalitis**

(A) Effects of patient antibodies in primary cultures of rat hippocampal neurons. Cultured neurons exposed to patient antibodies (from CSF or serum) or monoclonal antibodies (derived from patients' B cells or plasma cells) cause a decrease of density of NMDARs. The fluorescence microscopy images above the Petri dishes show the clusters of NMDARs in green before and after exposure to the indicated antibodies (patients' serum or CSF, or derived from B cells or plasma cells). The cartoon and graph on the right side show the structural and functional effects of the antibodies. In brief, the antibodies bind and crosslink the NMDARs, altering the surface dynamics of NMDARs and disrupting the normal interaction with other synaptic proteins, such as EphB2R, among others. These antibody effects eventually lead to internalisation of NMDAR and interacting proteins. As a result, the NMDAR component of spontaneous excitatory postsynaptic currents (slow grey slope in the graph) is abrogated.[6,7,91] All these alterations are reversible upon removal of antibodies from the medium (not shown). (B) Mouse model of cerebroventricular transfer of patient antibodies (from CSF or serum) or monoclonal antibodies (derived from patient B cells or plasma cells). The samples containing the antibodies are chronically infused using osmotic pumps (14-day infusion) into the ventricles of mice, and the synaptic and behavioural effects are recorded during and after the infusion of the antibodies. In the brain, the antibodies cause similar synaptic alterations as those described in cultured neurons (A), leading to a reduction of synaptic NMDAR and severe impairment of long-term plasticity (reduction of LTP in the graph). These changes in synaptic function and plasticity are associated with memory deficits, anhedonia, and depression-like behaviour.[89,90,93,94] All these effects are reversible upon discontinuation of the infusion of antibodies (not shown) and can be prevented with an agonist of the EphB2R.[94] (C) Mouse model of active immunisation with GluN1/GluN2B heteromers of the NMDAR embedded in liposomes.[96] A few weeks after immunisation, mice developed antibodies against non-conformational GluN1 and GluN2 epitopes, which are different from those recognised by human antibodies (conformational and located at the amino terminal domain of GluN1). In cultured neurons, these antibodies caused a reduction of clusters of NMDAR and NMDAR-mediated currents. Pathological investigation showed extensive inflammatory infiltrates along with antibodies, microglial activation, and occasional neuronal loss.[96] All these findings were associated with a fulminant phenotype characterised by hyperactivity, seizures, tight circling, and lethargy. The exact antibody-mediated mechanisms in mouse brain and whether the symptoms are reversible are unknown.[96] LTP=long-term potentiation. NMDAR=NMDA receptor.

Search strategy and selection criteria

We searched PubMed for articles published in English from Feb 1, 2014, to April 30, 2019, using the terms "NMDA receptor", "N-methyl-D-aspartate receptor", "encephalitis", "autoimmune", and "antibodies". The final reference list was generated on the basis of relevance and originality with regard to the topics covered in this Review.

might help to explain how distinct components of the immune response (antibodies, B cells, T cells, and the inflammatory environment) contribute to the clinical stages. For example, whereas the symptoms of this model resemble those of the acute (inflammatory) stage of the human disease, the symptoms of the passive transfer model using human antibodies resemble more the second stage, with prominent memory and behavioural deficits (and absent or reduced seizures, dyskinesias, or hyperactivity). Moreover, in the active immunisation model the entire brain is affected, whereas in the passive transfer model the infusion of antibodies into the ventricles facilitates their access to the hippocampus predominantly.

Conclusions and future directions

In 12 years, anti-NMDAR encephalitis has become the most frequently recognised neuronal-antibody-mediated encephalitis, with an incidence that rivals that of some types of viral encephalitis.[3] Although the clinical advances have been remarkable, a pressing need exists to maintain rigorous clinical and immunological criteria for the diagnosis of the disease. Careful consideration to the syndrome and determination of IgG antibodies in CSF are crucial to prevent misdiagnosis. No specific biomarkers exist to guide therapy or predict outcome, only clinical assessment. Future studies might confirm some of the biomarkers we list here (table) as clinically relevant, but this confirmation will require coordinated efforts across multiple institutions using longitudinal studies with a large number of patients.

Better understanding of the immunology and neurobiology of anti-NMDAR encephalitis to develop novel therapies, achieve improved outcomes, and shorten the process of recovery is also required. Modelling the disease in vivo and in silico, has started being fruitful.[7,94] A model using super-resolution microscopy and Monte Carlo simulations emphasised the importance of disrupting synaptic NMDAR interactions with other proteins (eg, with EphB2R [ephrin-type B receptor 2] and other unknown interacting proteins) to reproduce the observed biological effects of patients' antibodies.[92] Thus, in addition to immunotherapy, we can envision therapies aimed to antagonise the effect of the antibodies and modulate the function of NMDAR, as already suggested in experimental studies.[7,94,104] A task for the future is moving these strategies to the clinics.

Contributors

JD wrote the initial draft of the manuscript, which was fully reviewed by FG and MRR. The draft was subsequently submitted to the rest of the authors who provided additional comments and suggestions until a final version was generated. Figure 3 was designed by JD and developed by JP.

Declaration of interests

JD is supported by Instituto Carlos III-Fondo Europeo de Desarrollo Regional (FEDER) (FIS 17/00234 and PIE 16/00014), Centro de Investigación Biomédica en Red para Enfermedades Raras (CB15/00010), a La Caixa Foundation Health Research Award, Agència de Gestió d'Ajuts Universitaris i de Recerca (AGAUR)-Generalitat de Catalunya, and Fundació Cellex; and also receives royalties from Athena Diagnostics for the use of anti-Ma-2 as an autoantibody test, and from Euroimmun for the use of anti-NMDA, anti-GABAB receptor, anti-GABAA receptor, anti-DPPX and anti-IgLON5 as autoantibody tests. TA is supported by Instituto Carlos III-FEDER (FIS 18–00486), a Mutua Madrileña Foundation Award (AP162572016), and Pla Estratègic de Recerca i Innovació en Salut (PERIS; SLT006/17/00362), and has received speaker honoraria from Novartis. FL works for an academic institution which also offers commercial antibody testing. EL has received grant support from Grifols, consulted for Merck, Janssen, and the US National Vaccine Injury Compensation Program. MJT is supported by the Netherlands Organization for Scientific Research (NWO/ZonMW, Veni incentive and Memorabel programme) and the Dutch Epilepsy Foundation (project 14–19), has filed a patent for methods for typing neurological disorders and cancer, and devices for use therein, and has received research funds for serving on a scientific advisory board of MedImmune, for consultation at Guidepoint Global, an unrestricted research grant from Euroimmun, and an Erasmus MC fellowship. MRR receives royalties from Athena Diagnostics for the use of anti-Ma-2 as an autoantibody test and from Euroimmun for the use of anti-NMDA receptor as an autoantibody test. FG receives royalties from Euroimmun for the use of anti-IgLON5 as an autoantibody test. JP is supported by PERIS (LT002/16/00346). CG is supported by the Deutsche Forschungsgemeinschaft (CRC-TR 166, TP B2). FM has no competing interests.

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