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Review

Contemporary advances in anti-NMDAR antibody (Ab)-mediated encephalitis

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ABSTRACT

The study of antibody (Ab)-mediated encephalitis has advanced dramatically since the discovery of antibodies directed against the *N*-methyl-D-aspartate receptor (NMDAR) in association with a unique neuro-psychiatric syndrome, over a decade-and-a-half ago. Anti-NMDAR Ab-mediated encephalitis now represents the most well characterised form of autoimmune encephalitis. The disease most commonly manifests in young women, but all ages and both sexes can be affected. Autoantibodies may arise in the context of two well-recognised disease triggers in a proportion of patients, and ultimately facilitate NMDAR displacement from synapses. Various CSF cytokines, chemokines, and other molecules have been explored as candidate biomarkers but are limited in sensitivity and specificity. The clinical spectrum is diverse, with evolution and a combination of neuro-psychiatric abnormalities at disease nadir common. Anti-NMDAR Ab-mediated encephalitis is immunotherapy responsive, and a near-majority ultimately acquire a broadly favourable clinical outcome. The diagnosis, and more particularly, the management of the disease can still hold considerable challenges. Moreover, well-defined biomarkers remain elusive. The present review will therefore delineate pathogenic and clinical advances to date in anti-NMDAR antibody-mediated encephalitis.

1. Introduction

Following the description of four young women with ovarian teratomas presenting with a syndrome characterised by acute psychiatric disturbance, amnesia, seizures, movement disorders, altered level of conscious state and central hypoventilation in 2005 [1], antibodies against *N*-methyl-D-aspartate receptor (NMDAR) were reported shortly thereafter. In this series of patients with comparable clinical features, the disease was termed anti-NMDAR antibody (Ab) mediated encephalitis [2]. Medical knowledge has since burgeoned dramatically such that anti-NMDAR Ab-mediated encephalitis represents the most well characterised form of autoimmune encephalitis. The purpose of this review is to summarise recent advances with respect to the pathophysiology, clinical features, treatment, prognosis and outcomes of anti-NMDAR Ab-mediated encephalitis.

2. Epidemiology

The estimated prevalence of anti-NMDAR Ab-mediated encephalitis is 0.6 per 100,000 [3]. From a series of 577 patients, the median age at diagnosis was 21 years, with 37% younger than 18 years of age, and only 5% older than 45. 81% of patients were female, though male patients were more frequent in the age groups under 12 years (39%) and over 45 years of age (43%) [4]. Proportionately more male patients have been reported among Chinese patients [5,6].

3. Pathophysiology

The NMDAR is one of four families glutamate-gated ionotropic receptors, which, alongside AMPA receptors, kainite receptors and δ-receptors, are located on the post-synaptic terminal and facilitate the preponderance of excitatory neurotransmission [7,8]. The NMDAR assumes a heterotetrameric structure, comprising subunits grouped according to sequence homology into the subfamilies GluN1, GluN2 and

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GluN3. Functional receptors consist of two GluN1 subunits combined with either two GluN2 subunits, or a combination of GluN2 and GluN3 subunits [7]. Subunit composition varies throughout development, disease states, and according to neuronal activity [8]. NMDA receptors are integral to synaptic plasticity and in turn, memory, learning and cognition [9].

In anti-NMDAR Ab-mediated encephalitis, anti-NMDAR auto-antibodies target the extracellular GluN1 of the NMDAR. These can be detected via rat brain immunohistochemistry (IHC), cultured rat neurons or cell based assays (CBA's) in which cells overexpressing GluN1 are used to detect binding Abs [10]. Anti-NMDAR antibodies do not bind all CNS regions homogenously; NMDAR are most commonly found in the hippocampus, with less prominent immunohistochemical signal shown in the cortex, and minimal expression in the cerebellum [11,12]. Further, excitatory and inhibitory neurons expressing NMDAR appear to be similarly implicated in pathogenesis [12]. The antibody binding site of the NMDAR is thought to be located in the extracellular amino-terminal domain (ATD) of the GluN1 subunit [11]; subsequent work identified that the *G369I* mutation in the receptor inhibited antibody reactivity in cell based assays [13].

In cultured hippocampal neurons, incubation with patient derived antibodies results in concentration dependent reduction in NMDAR's in post-synaptic dendrites [10,14], without compromising other synaptic constituents, density of synapses, neuronal integrity or survival [14,15]. Similarly, NMDA-mediated currents, and not AMPA-mediated currents, are selectively reduced in the presence of patient antibodies [14]. A reduction in NMDAR density at the post-synaptic terminals is thought to result from antibody mediated cross-linking and internalization of the receptor [14] (Fig 1, Table 1). Conversely, removal of patient derived antibodies from the cultured neurons results in increased NMDAR clusters, highlighting reversibility [14]. Furthermore, antibody-mediated NMDAR internalization, rather than direct antibody-mediated receptor blockade, mediates functional consequences, such as reduced NMDAR-mediated currents. This was illustrated by the F(ab) component of patient antibodies alone failing to trigger significant receptor internalization or reductions in NMDAR current amplitude, as otherwise seen in the presence of patient cerebrospinal fluid (CSF) [12]. In mice infused intraventricularly with patient CSF, infusion termination resulted in clinical recovery and NMDAR reconstitution [16]. Moreover, following internalization, NMDAR-antibody endosome localisation exceeded that in lysosomes in one study [12], raising the possibility of recycling of receptors to synaptic terminals rather than degradation and thus potential clinical reversibility.

Patient antibodies can have a differential effect on NMDAR subtype. GluN2A-NMDARs are dislodged from synapses, in part through antibody-mediated interruption of NMDAR interaction with ephrin-B2

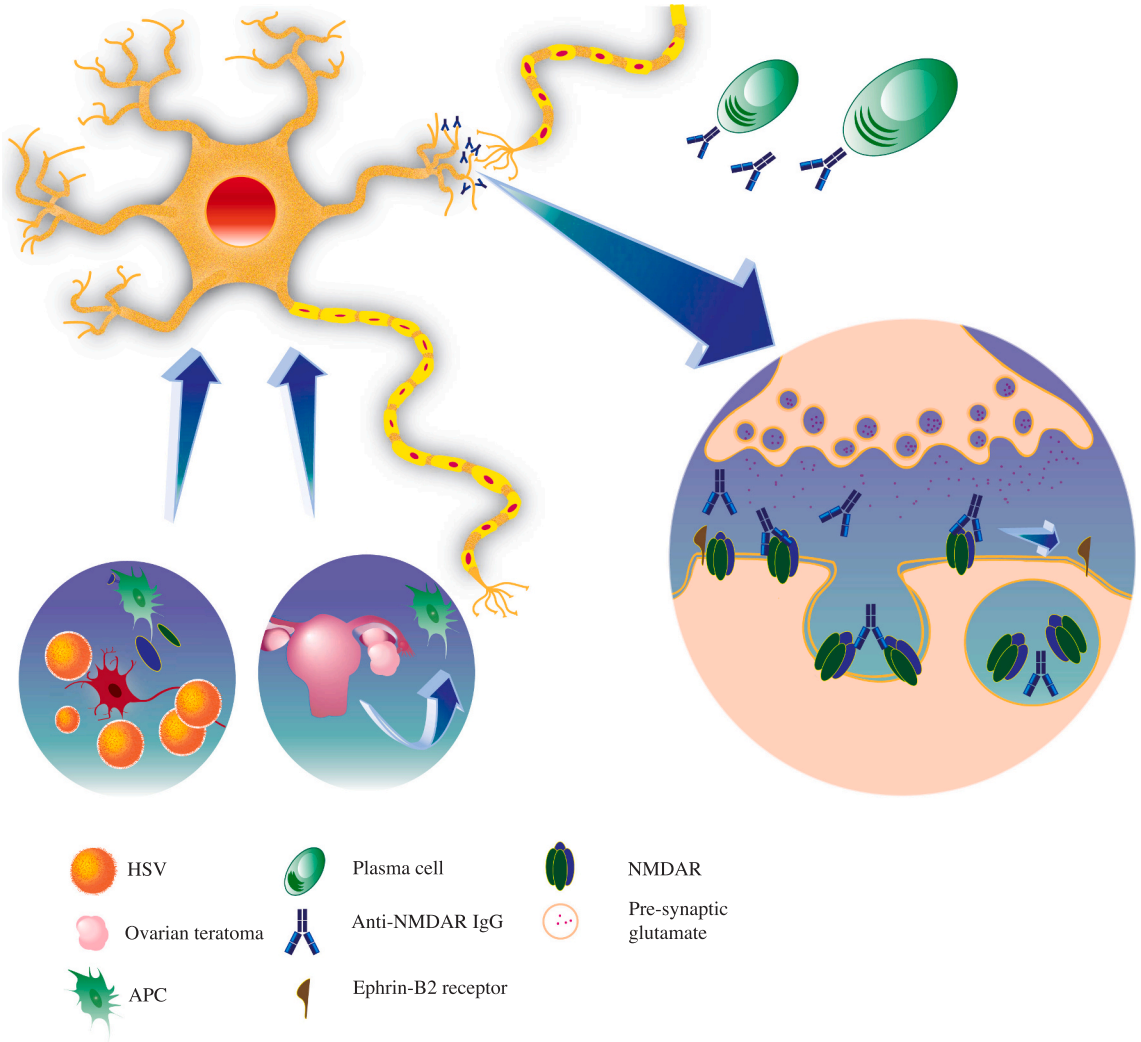

Fig. 1. Summary of salient disease mechanisms in NMDAR encephalitis. Two recognised mechanisms of immune tolerance breakdown are (a) antecedent HSV-encephalitis, and (b) ovarian teratomas. (c) Anti-NMDAR antibodies facilitate internalisation of NMDAR via cross-linking, either through CNS ingress or intrathecal autoantibody synthesis. Antibodies disrupt interaction with ephrin-B2 receptors, which normally cluster NMDAR's synaptically.
HSV, herpes-simplex virus; APC, antigen-presenting cell; NMDAR, *N*-methyl-D-aspartate receptor.

Table 1
Disease molecular and immunopathogenesis.

Characteristic	Finding	Comments	References
Disease triggers	Ovarian teratoma expressing NMDAR, HSV-encephalitis	8-38% underlying tumours, majority ovarian teratomas; antecedent HSV-encephalitis in a minority	[4–6,17] and [18]
Genetic susceptibility	HLA B*07:02, HLA DRB1*16:02; *LRRK1, ACP2, NR1H3*	Former not corroborated in larger cohort; others require confirmation in larger cohorts	[19–21]
Major IgG class	IgG1	Neuropathology does not suggest cellular cytotoxicity or complement involvement	[22,23]
In vitro antibody effects	NMDAR internalization, reduction in NMDA-mediated currents, interruption of ephrin-B2 receptor interaction		[12,14,15]
In vivo antibody effects	Behavioural, memory deficits elicited in mice, prevented with administration of ephrin-B2; psychotic-like behaviour in mice		[16,24,25]
Salient cytokines, chemokines	Elevated CSF CXCL10, CXCL13; INFγ, TNFα, IL-6, IL-7, IL-10, IL-17A and IL-15; serum and CSF BAFF, APRIL	Elevation of B-cell, as well as T-cell related chemokines and cytokines, particularly in CSF, suggesting disease compartmentalisation, though some findings not consistently shown	[26,27–29]
Neuropathology	Perivascular lymphocytic infiltration, including $CD138^+$ cells		[2,10,23,30]

NMDAR, *N*-methyl-D-aspartate receptor; CXCL-, C-X-C motif chemokine; INF-, interferon; TNF-, tumour necrosis factor; IL-, interleukin; BAFF, B-cell activating factor from the tumour necrosis factor family; APRIL, a proliferation-inducing ligand.

receptors, which normally facilitate synaptic NMDAR clustering. Conversely, GluN2B-NMDARs exhibit reduced surface diffusion in the presence of antibodies, likely due to the aforementioned auto-antibody mediated cross-linking and endocytosis [15] (Fig 1). In a separate study, increased receptor clustering was seen in the presence of autoantibodies, with greater effect seen on GluN2B-NMDARs compared to GluN2A [31]. Ultimately, glutamatergic synaptic plasticity is significantly compromised [15], as evidenced in mice exposed to patient CSF, with memory and behavioural deficits seen in parallel with a reduction in NMDAR cluster density in hippocampal neurons [16] (Table 1). In a similar experiment, co-administration of ephrin-B2 was able to antagonize the effect of patient CSF on mouse memory and behaviour, NMDAR and ephrin-B2 receptor density, and antibody-mediated impairment of synaptic plasticity [24]. More recently, in a similar mouse model, intraventricular exposure to patient-derived CSF caused a reduction and increase in dopamine 1 and 2 receptors respectively in cultured hippocampal neurons, accompanied by psychotic-like behaviour [25].

Anti-NMDAR autoantibodies are found in both serum and CSF [10,14,22]. Pathogenic antibodies are thought to be of IgG subclass [32], as illustrated in a cohort of randomly selected patients with anti-NMDAR encephalitis, schizophrenia and other conditions, where IgG, but not IgM or IgA, caused a reduction in overall NMDA receptor expression in cultured neurons [32]. Furthermore, IgG was detected exclusively in anti-NMDAR Ab-mediated cases and not controls [32]. IgG1 is the predominant subtype [22,23] (table 1). Antibodies from patient-derived CSF B cells have been shown to downregulate NMDAR receptor density and current in neuronal culture [33], indicating likely intrinsic antibody pathogenicity. Autoantibodies contain relatively low numbers of somatic hypermutations or may even assume an unmutated germline configuration [33,34]. Collectively, they reduce NMDAR-mediated currents, in a time- and dose-dependent manner [34]. Recombinant autoantibodies derived from patient CSF memory B-cells were shown to target diverse CNS epitopes, rather than the NMDAR exclusively [33]. In one study, using either rat brain immunohistochemistry or fixed CBA's, CSF sensitivity of anti-NMDAR antibodies was 100%, serum sensitivity ranged from 85.6% to 91.6% whilst specificity was 100% for both serum or CSF specimens, using either technique. Use of live CBA's did not enhance sensitivity [13].

Conversely, other studies have challenged the specificity of serum NMDAR antibodies, with seroprevalence in diverse contexts. Using live CBA's, positive and low-positive serum anti-NMDAR-IgG have been detected in patients clinically unlikely to have NMDAR encephalitis [35]. Moreover, a minority of healthy controls, patients at risk for psychosis [36] and those with first-episode psychosis were found to have anti NMDA antibodies in the serum without overt signs and symptoms of clinical anti NMDA Ab mediated AIE [37]. In another study, 18.7% of patients with psychosis, and 2.9% of healthy controls had IgG anti-NMDAR antibodies detected via live CBA in the serum but not CSF, though none of these samples tested positive using fixed CBA [38]. Using fixed CBAs, anti-NMDAR antibodies have also been detected in healthy individuals [39–41], patients with various psychiatric illnesses [41–43], neurodegenerative diseases [39,40] among other conditions [40,41], but in most instances, IgG detection appeared to be rare [39,40,43], or directed against GluN1/GluN2 [43]. Serum from 0.6% of patients with schizophrenia, using a fixed CBA, yielded positive anti-GluN1 IgG, whereas in another study, these results were subsequently negative using IHC and repeat CBA analysis [44]. Whilst potential pathogenicity of IgA and IgM has been highlighted [41], the significance of these antibody subclasses appear to be overall unclear [32,43], and taken collectively, these results indicate the importance of cross-validation testing, and crucially, concurrent CSF sample analysis [32], particularly also given approximately 15% of patients only have detectable antibodies in the CSF [13].

Early studies demonstrated anti-NMDAR autoantibody titres mirrored the disease course clinically [10,14,22,45], titres are generally higher in the serum than the CSF [22,35], and serum titres are higher in patients with an underlying teratoma [10,22,35]. An observational study assessing 250 anti-NMDAR Ab-mediated encephalitis cases yielded further salient findings [13]. Higher serum and CSF antibody titres were associated with poor outcomes as measured by the mRS scale (Modified Rankin Score) and the presence of a teratoma. Furthermore, changes in CSF antibody titres more closely reflected clinical activity during relapses than did those in serum, with early reduction in CSF titres being associated with future good outcomes. However, the majority of patients still remained seropositive in the serum and CSF after clinical recovery [13].

CSF B-cell expansion has been demonstrated in children, both acutely and during a relapse [46]. A mouse model demonstrated brain B-cell infiltration and increased CSF B-cells and plasma cells, thought to be of peripheral origin [47]. A human ex-vivo study showed reduced CD154-expressing $CD4^+$ T-cells reactive to full-length GluN1 compared to controls, and $CD4^+$ cells reactive to the ATD domain alone not significantly reduced. Further, in response to ATD or S1S2 (fusion of S1 and S2 domains) stimulation, TNFα and IFNγ responses were reduced in NMDAR encephalitis $CD4^+$ cells relative to controls. Overall, differences were thought to be unrelated to immunosuppression in the NMDAR encephalitis group, raising the possibility of ongoing autoantibody production independent of T-cell help [48].

Neuropathological data from autopsied brain specimens have generally demonstrated common features (Table 1). Macroscopic findings have included temporal lobe and hippocampal atrophy. At the microscopic level, pathological changes were more prominent in the hippocampi. The most marked pathology consists of gliosis and microglial activation, though hippocampal pyramidal neuron loss was also reported [2,10]. Other affected areas that have been reported include the neocortex, amygdala, basal ganglia, brainstem and spinal cord [2,23]. Mild to moderate perivascular lymphocytic infiltrates were generally identified, with abundant IgG immunostaining in the hippocampi, although widespread CNS deposition has been shown [2,10,23]. Further, $CD138^{+}$ cells (plasma cells, plasmablasts) were identified in perivascular and interstitial regions, and are likely responsible intrathecal autoantibody synthesis [23,30]. Complement involvement in the CNS is not seen [10,23], with exception of an atypical case where staining was exclusively observed in necrotic tissue obtained from biopsy of a region with cystic MRI changes, of uncertain pathogenic significance [30]. Therefore, antibodies, rather than cytotoxic or complement-mediated mechanisms, appear to predominantly facilitate neuronal dysfunction and disease pathogenesis.

Numerous studies have evaluated the role CSF biomarkers in anti-NMDAR encephalitis (Table 1). As expected, elevation of B-cell chemokines has been identified. In one study of 167 patients with anti-NMDAR Ab-mediated encephalitis, 70% had an elevated CSF CXCL13 (C-X-C motif chemokine 13) level, within two months of disease onset. This cytokine elevation was associated with intrathecal NMDAR antibody synthesis. None of the patients had elevated CXCL13 in the serum. Ongoing elevation of CSF CXCL13 two to six months after immunosuppression correlated with limited treatment response (modified Rankin score $\geq$ 3). Moreover, a higher proportion of relapsing patients compared to those in remission had elevated levels of CXCL13 in their CSF [26]. In another study, levels of B-cell activating factor, of the TNF family (BAFF) and a proliferation inducing ligand (APRIL), B-cell and plasma cell survival cytokines respectively [49], were measured in the serum and CSF of 40 NMDAR encephalitis patients and compared with 20 control patients [27]. The study demonstrated that significant elevations of each cytokine in the CSF, both acutely and in recovery stages, and a positive association with poor outcome [27]. These findings were in contrast to other studies, albeit with smaller numbers of patients [28,29], but nonetheless support the hypothesis of the CNS cytokine milieu promoting B-cell attraction and maturation.

Other studies have detected increased levels of the B- and T-cell chemokines CXCL13 and CXCL10 respectively, in the CSF of patients relative to controls [28,29,50,51]. In one study, CSF elevations of CXCL13 and CXCL10 were observed acutely, and CXCL10 elevations persisted during the disease course. Further, persistent elevation of T-helper-cell related cytokines, INFγ, TNFα and IL-17A and IL-15, a promoter of T-lymphocyte and NK cell differentiation and survival, were seen in the CSF but not in the serum. This supports the hypothesis of chemoattraction of lymphocytes into the CSF in the initial disease stages, and raising the question of T-cell involvement in disease pathophysiology [29]. In addition, CSF INFγ [50], TNFα [28,50,52,53], IL-6 [28,50–53], IL-7 [50] and IL-17A [28,51,52] elevation has been demonstrated in other studies comparing anti-NMDAR Ab-mediated encephalitis patients to controls. Similarly, elevation of CSF IL-10 [28,50,53], and IFNα [28], produced by lymphocytes and involved in lymphocyte activation respectively, has been demonstrated. CSF Th1 (CCL3) and Th2 (CCL1, CCL8, CCL17, CC22) chemokine elevation acutely was demonstrated in another study, and associations between treatment and declining IL-2 levels, as well mRS and CXCL10, CCL3, IL-10, CCL22 and IL-6 have been reported [50]. Further, soluble Fas and soluble Fas ligand [54], were found to be in higher concentration in the CSF of anti-NMDAR Ab-mediated encephalitis patients compared to controls, and these levels correlated with mRS at 6 months [55].

Other biomarkers include those of neuroaxonal integrity, inflammation and synaptic function. A cross-sectional study comparing the CSF of 45 antibody-mediated encephalitis patients (34 NMDAR, 11 LGI1 [leucine-rich glioma-inactivated 1]/CASPR2 [contactin-associated protein-like 2] encephalitis) to 39 cognitively normal individuals revealed elevated neurofilament light (NfL), a marker of neuroaxonal injury, in NMDAR encephalitis patients compared to controls using Simoa, while total-tau levels in CSF were unchanged between the groups. Conversely, chitinase-3-like protein (YKL-40), a marker of astroglial activation and thus neuroinflammation, was elevated in both encephalitis groups compared to controls. The ratio of YKL-40 and VILIP-1 (visinin like protein 1) in CSF discriminated antibody-mediated encephalitis patients from cognitively normal controls with 93% and 97% sensitivity and specificity respectively. Biomarkers of synaptic function, synaptosomal-associated protein-25 (SNAP-25) and neurogranin, pre- and-post synaptic proteins respectively, were significantly reduced in encephalitis patients compared to controls. In this study, longitudinal outcomes were evaluated, but limited to 10 NMDAR encephalitis and 10 LGI1/CASPR2 patients; in contrast to the aforementioned findings, higher SNAP-25 and neurogranin levels correlated to worse mRS at 12 months, along with higher YKL-40 [56]. These findings clearly warrant confirmation in a larger patient setting. Another study demonstrated acute elevation of CSF YKL-40 in anti-NMDAR Ab-mediated encephalitis patients relative to controls and correlated with IL-6 levels, and improvements in mRS at three months [53].

Collectively, these findings suggest the possibility of a predominantly B-cell driven pathogenesis, and highlight the possibility of novel biomarkers for therapeutic measures and disease monitoring. Yet, with limitations in sensitivity or specificity for anti-NMDAR Ab-mediated encephalitis, the current use of CSF biomarkers clinically is circumscribed. Further studies should examine in more detail the role of the discussed biomarkers clinically with respect to therapeutic decision making, disease monitoring and prognostication.

4. Disease triggers

Disease-initiating factors remain poorly understood. The presence of an ovarian teratoma and antecedent herpes simplex (HSV) encephalitis represent two known disease triggers [57] (Fig 1, Table 1). The disease has a strong female preponderance, and the majority of tumours are ovarian teratomas [4,10,58]. Teratomas from anti-NMDAR Ab-mediated encephalitis patients almost universally contain nervous tissue [10,23,59–61], and express NMDAR [23,60], in contrast to teratomas resected from non-encephalitic patients [23,59–61]. Nervous tissue in anti-NMDAR Ab-mediated encephalitis teratomas is more likely to contain histological features of glial tumours [60], dysplastic neurons [61] and higher proliferative indices [62]. Infiltration of lymphocytic and mononuclear phagocytic cells into teratomas was seen more commonly in anti-NMDAR Ab-mediated encephalitis patients [59–61,63], with significantly more B-lymphocyte and plasma cell infiltration a consistent finding [23,59,60,62]. Such cells were often organised into germinal centres [63,64], or tertiary lymphoid like structures, with innate antigen-presenting cells, immunoglobulin deposition and plasma cell infiltration seen in proximity to the neuroglial tissue portion of the teratoma [60]. Finally, cultured lymphocytes from anti-NMDAR encephalitis patient teratomas produce GluN1-antibodies, and in these patients, higher concentrations of GluN1-IgG are seen in teratomas compared to serum [64]. Moreover, prompt teratoma removal is associated with more favourable neurological outcomes [10]. This suggests that the tumour environment is a driver of ongoing plasma cell and auto-antibody production, despite the possibility of similar intrathecal humoral responses. Taken collectively, in a subset of patients, a breakdown in immune tolerance within ovarian teratomas could serve as a trigger for plasma cell maturation and anti-NMDAR Ab production.

In a study of HSV encephalitis, 14 of 51 prospectively recruited patients developed probable autoimmune encephalitis within 12 months following HSV encephalitis, after a median interval of only 32 days, and

de novo anti-NMDAR antibodies were detected in 9 patients of these 14 patients (8 in serum and CSF, one in CSF only) [18]. Antibody positivity was detected prior to the onset of probable autoimmune encephalitis in 6 patients. However, 11 patients who did not develop autoimmune encephalitis also developed serum or CSF antibodies against NMDAR or unidentified antigens. At 12 months follow-up, 7 of 14 and 1 of 26 patients with and without autoimmune encephalitis respectively remained seropositive.

The above study was extended by a further 48 patients of which 44 were antibody-positive, 34 anti-NMDAR positive, and 10 had unknown antigens. This cohort showed patients under 5 years of age had a worse outcome at 12 months, were more likely to be anti-NMDAR positive, had a shorter time period between HSV and autoimmune encephalitis and were more likely to have seizures, choreoathetosis or a decreased level of consciousness. Across all age groups, patients with NMDAR Ab-mediated encephalitis in this cohort had worse outcomes compared those reported for patients with disease unrelated to HSV-encephalitis [18]. More recently, two patients with a more protracted onset of anti-NMDAR Ab-mediated encephalitis at 7 and 12 months after HSV encephalitis were described [65]. Proposed mechanisms for the development of anti-NMDAR Ab-mediated encephalitis after HSV encephalitis include molecular mimicry, neuronal injury causing antigen exposure and secondary autoimmunity, or a herpes-specific autoinflammatory response [66]. A separately documented patient developed concurrent $GABA_AR$ and NMDAR antibodies in a patient after HSV-1 encephalitis, which makes the hypothesis of molecular mimicry as a mechanism of autoantibody production less likely [67]. The significance of the anti-NMDAR Abs in the subgroup of HSV-encephalitis patients not developing autoimmune encephalitis is unclear [18]. In this context, whether further factors, such as genetic risk, may be required for development of autoimmune encephalitis, or, a spectrum of subclinical pathogenicity exists, requires further elucidation.

Patients frequently undergo laboratory evaluation for infectious causes, in light of prodromal infective symptoms [58], and to exclude relevant infectious differential diagnoses. Accordingly, detection of other preceding infections has been reported, including IgM to influenza A and B, *Chlamydia pneumoniae, Legionella pneumophila, Bortedella pertussis* and *parapertusis* [45], mycoplasma IgM [22,68], streprolysin-O antibodies, *Campylobacter jejuni* IgM [22], herpes zoster [58] and *toxoplasma gondii* IgM [69]. Three cases with concomitant detection of SARS-CoV-2 via reverse-transcriptase polymerase chain reaction (RT-PCR) have been reported [70–72]. In one such case, an underlying ovarian teratoma was also found [71]. Moreover, various studies have yielded conflicting results regarding the frequency of prodromal infective symptoms in patients with an underlying teratoma [4,73]. Similarly, reports of prior vaccination include diphtheria/tetanus/pertussis [22], influenza H1N1 [58], tetanus/diphtheria/pertussis/poliomyelitis booster [74], and Japanese encephalitis [75]. Whether such relationships between antecedent infection – with exception of HSV-encephalitis – or vaccination and anti-NMDAR Ab-mediated encephalitis are purely temporal, or more directly associated, requires further elucidation.

There are some genetic susceptibility studies in anti-NMDAR Ab-mediated encephalitis patients, but power is limited (Table 1). In a German genome-wide association study (GWAS) including 96 patients with adult-onset disease, a weak association with the HLA class I allele B*07:02 was shown with anti-NMDAR Ab-mediated encephalitis [19], though this result was not reproduced subsequently when the same cohort was expanded to 178 patients [20]. A class II allele, DRB1*16:02 was identified in a Han Chinese patient population as carrying an association with the disease, and this was associated with reduced responsiveness to treatment [21]. In the prior GWAS, consisting of German and Czech patients, two risk loci were identified, both non-HLA: on chromosome 15, located in the *LRRK1* gene, and on chromosome 11, within the *ACP2* and *NR1H3* genes [20]. The aforementioned HLA-DRB1 allele could not be investigated due to the low allelic frequency in the study population [20]. Larger studies in more diverse populations are required to confirm these findings.

Ultimately, hypotheses for disease pathogenesis include tumour expression or release of NMDA receptors, or HSV-mediated neuronal destruction and NMDA receptor exposure, leading to antigen-presenting cell processing and adaptive immune recruitment, regional lymph node memory-B-cell generation. Antibody production and migration, alongside memory B-cells, into the CNS may then follow, resulting in antigen-stimulated affinity-maturation, clonal expansion and maturation into plasma cells [57]. Supportive findings include CSF and CNS parenchymal [30] B-cell and plasma cell [33] expansion and infiltration respectively, and serum-negative, CSF-positive antibody discordance in patients with clinically significant disease [13]. CNS B-cell ingress, rather than migration of serum-generated antibodies, may thus represent a major ongoing mediator of disease [57]. Within this landscape, the significance of unmutated antibodies from patient CSF warrants further clarification [34], and mechanisms of disease in patients without recognised triggers, and indeed, in those with triggers, both remain incompletely understood, noting that only a proportion of patients with teratomas or antecedent viral encephalitis subsequently develop NMDAR encephalitis.

5. Clinical features

In up to 70% of patients, neurologic manifestations are heralded by a infective-like prodrome, characterised by headache, fever, upper respiratory symptoms, nausea, vomiting and diarrhoea [58]. The median prodrome duration was seven days in two separate series [22,76], and is typically less than fourteen days [58]. Prodromal symptoms are less common in older patients [77]. In children, seizures, movement disorders, and altered conscious state are proportionately more common than in than in adults. Conversely, behavioural and psychiatric disturbance, memory disturbance and central hypoventilation more common in adults [4]. Ultimately, 87% of cases developing four or more of behavioural or cognitive deficits, memory dysfunction, speech disorder, seizures, decreased level of consciousness, movement disorder, autonomic dysfunction or central hypoventilation after one month, and only 1% remain mono-symptomatic [4,77]. Following prodromal symptoms, over the course of weeks, psychiatric features typically follow, and are often prominent. Neurological features emerge over a period of weeks to months and cognitive and behavioural deficits can persist for months to years [22,78].

Psychiatric symptoms are the most common presenting feature [79], and include anxiety, delusions, psychosis, mania, catatonia and paranoia [58]. More than 90% of patients exhibit behavioural or cognitive deficits within a month of diagnosis, and 65% of adults present initially with behavioural manifestations [4]. In one series, visual or auditory hallucinations, depressive or manic symptoms, persecutory ideation and mystical ideas were the most frequently noted psychiatric symptoms. Importantly, 51% of patients with an initial psychiatric admission had neurological features evident on initial emergency assessment, highlighting the need to consider and exclude AIE in patients presenting with a psychiatric diagnosis with concomitant neurologic deficits [80]. A minority of patients present with isolated psychiatric features [81]. Triage of these patients for diagnostic evaluation, including CSF and MRI studies, remains complex and problematic, given the impracticality of indiscriminate use of these investigations. A systematic review consisting of 464 individual adult cases was undertaken to further characterise psychopathology [82]. A complex psychopathology, encompassing catatonia, mood, behaviour and psychosis domains was highlighted. Greater consistency between patient psychopathology in literature regarded to have had psychiatry service involvement in mental state assessment was seen, raising utility for the earliest possible involvement of psychiatrists in the diagnostic work-up of suspected cases. Moreover, the combination of such features within weeks of disease onset was deemed exceptional, outside of the context of postpartum psychosis. Notably, this study did not have disease controls [82].

Movement disorders are present in approximately 70% of adults and more than 90% of children under 12 within the first month of diagnosis, proportionately more common in this age group, [4] and overall frequently an early clinical feature [83]. Moreover, in children in particular, multiple movement disorders may be identifiable [83–85]. In paediatric anti-NMDAR Ab-mediated encephalitis patients, stereotypies, consisting of pouting, chewing movements, grimacing, cycling leg movements, thrashing or rhythmic hitting limb movements, picking, "no-no" head movements, and repetitive flexion-extension and rotatory truncal movements, and perseveration were identified, but not seen in basal ganglia encephalitis patients [84]. Similarly, in a study involving video review of 34 patients, movement disorders consisted of diverse hyperkinetic phenomenologies, with marked dystonia, chorea and stereotypies the most common features – with combinations or all three commonly coexistent – in the absence of tremor or tics and rarely accompanied by myoclonus [83], consistent with prior studies [86]. The combinations of such features were considered rare in other movement disorders [83]. Other common movement disorders include parkinsonism, rigidity, opisthotonus, catatonia and myorrhythmia [22,58,83,85].

Seizures are similarly more common and more likely to be a presenting feature in children younger than 12 years [4] and males [79,87,88], seen in approximately 70% of patients overall [4], and a presenting feature in up to half of patients [89]. In one study, focal seizures were seen in 32 (74%) patients, most commonly focal motor, with impaired awareness in 18 (55%), tonic-clonic seizures in 34 (79%), status epilepticus in 15 (35%), and refractory status epilepticus in 9 (21%) patients; 5 (12%) patients had a relapse with seizures. All surviving patients (four patients died) who had seizures experienced seizure freedom at a median follow-up of 37 months, with seizure freedom significantly more likely in response to immunotherapy compared to anti-seizure mediations (ASM) [89]. Similarly, in another study, more than 80% of patients had their last seizure within 6 months of disease onset, and seizure-freedom was achieved in all within 2 years, independent of anti-seizure medication duration [88]. Moreover, of 34 patients withdrawn from ASM in another study, only 5.8% experienced seizure relapse during 1-year follow-up, with no significant difference in relation to ASM withdrawal before or after 3 months [90].

In the 2017 International League Against Epilepsy (ILAE) definitions and classifications guide, autoimmune encephalitides were deemed representative of an "immune etiology" of epilepsy [91], with some authors subsequently challenging the notion of epilepsy in the context of autoimmune encephalitis [92], given the infrequent occurrence of chronic seizures. Consequently, a framework distinguishing "acute symptomatic seizures secondary to autoimmune encephalitis" – referring to seizures occurring in the active disease stages or during a relapse – from "autoimmune-associated epilepsy," for chronic and therapy-resistant seizures, has been proposed [93]. Anti-NMDAR Ab-mediated encephalitis patients are rarely likely to be represented in the latter category.

Autonomic dysfunction may be seen in up to 50% of adult cases [4], but rarely as a presenting feature [94,95]. In one report of 91 patients, 69 had autonomic instability, with cardiac dysrhythmia, dysthermia, blood pressure instability, hyperhydriosis and sialorrhoea frequently reported. Central hypoventilation was described in 66 patients, commonly necessitating ventilatory support [10]. In another retrospective series, autonomic instability was predominantly characterised by sinus node dysfunction, with inappropriate sinus tachycardia or bradycardia, sinus pauses frequently seen, but also a single case of non-sustained ventricular tachycardia, inappropriate hypertension or hypotension, and unexplained fever observed, and nine of ten patients found to have mesial temporal abnormalities on MRI [96]. Notably, 7% of ICU-admitted cases experienced dysautonomic arrest in another series [97], whilst asystole necessitating CPR has also been described [98].

Cognitive deficits are frequent, and can manifest early in the disease course, but may be masked by prominent psychiatric features [58]. Language impairment and amnesia are frequently encountered, both observed in approximately 70% of patients within the first month of disease [4]. Characteristic language deficits include reduced verbal output, mumbling, echolalia, perseveration and frank mutism [58,86]. A case vignette of a patient with neuropsychological assessment on day 8 of disease, detailing severe global memory decline, impaired processing speed, verbal fluency, visuoconstructional abilities and executive function, highlighted the complex nature of cognitive deficits that may be seen early in the disease course [99]. Other frequent clinical features include altered conscious state, seen in almost 60% of patients, focal neurological deficits, including cerebellar ataxia and hemiparesis [4], and disorders of sleep. Sleep disorders vary during the disease course, with insomnia, often marked, as an early feature, accompanied by reduced sleep need at disease peak, followed by hypersomnia during periods of recovery [100].

Relapses are defined as new or worsening symptoms following improvement or stabilization, for two months, occur in between 12-17% of patients, though the follow-up duration varies in different studies [4–6,101]. Relapses are commonly less severe, more likely to be monosymptomatic, and more frequent in patients not treated with immunotherapy or with delays to immunotherapy [4–6,101]. Furthermore, relapses are more frequent in patients without an underlying tumour [4]. Up to 81% of relapses occur in the first 24 months, but can rarely occur many years after initial symptoms [5]. CSF Ab have been shown more likely than serum Ab to increase during a relapse [13]. In fact, the sensitivity of serum Ab rise for prediction of a relapse is poor [5,6].

An underlying neoplasm is reported in 8-38% of patients. These are almost exclusively ovarian teratomas, typically mature [4–6,17]. Neurological symptoms invariably precede tumour detection [10]. Other tumours include extraovarian and immature ovarian teratomas, lung cancer (SCLC and NSCLC), breast, testicular, ovarian cancer, thymic carcinoma and thymoma, pancreatic cancer, uterine adenocarcinoma, prostate adenocarcinoma and lymphoma [4,5,102]. The presence of an underlying tumour is of lower frequency in those 45 years and older, with ovarian teratomas proportionately less common [77].

6. Investigations

MRI abnormalities are seen in approximately 33% of patients [4]. In an initial series of 100 patients, abnormal findings did not significantly correlate with clinical severity [10]. Of 70 patients with follow-up studies, 26 with initial abnormalities showed subsequent normalisation, and 69% of these patients improved clinically [10]. Abnormalities include T2 or fluid attenuated inversion recovery (FLAIR) signal hyperintensity, in the hippocampi, cerebral cortex, basal ganglia, brainstem and cerebellum, with rare involvement in the spinal cord. Subtle overlying contrast enhancement may be detected in implicated areas of parenchyma or in a meningeal pattern [58]. In the previous study, 14 patients developed predominantly frontoparietal or generalised atrophy, of which ten had mild residual deficits, and four died [10]. Similarly, two patients with clinically severe disease courses developed frontotemporal atrophy and cerebral hypoperfusion on SPECT (single photon emission computed tomography) 7 to 12 months from disease onset, though repeat imaging 5 to 7 years later showed significant improvement, commensurate to protracted clinical improvement [103]. Both reversible and progressive cerebellar atrophy has also been described [104].

EEG abnormalities are detected in up to 90% of patients [4]. Common, albeit non-specific findings including focal or generalised slowing, in 71-80% of patients, and epileptiform discharges in 21-50% [10,22]. Epileptiform discharges and generalised slowing may have a tendency for emergence early and later in the disease course respectively [22]. In 30% of patients who underwent continuous EEG monitoring, the novel finding of an "extreme delta brush" (EDB) was described: a nearly continuous admixture of broadly-distributed, symmetric, rhythmic 1-3 Hz delta-range slowing with superimposed rhythmic 20-30 Hz fast-

beta activity [105]. This finding has been seen rarely in other disorders, suggesting it is not completely specific for NMDAR encephalitis [106].

CSF abnormalities are likewise common, evident in almost 80% of patients, with a pleocytosis in 76% and elevated protein in 17% [4]. Pleocytosis is typically lymphocytic, and CSF abnormalities may become more likely with increased disease duration [58]. Intrathecal oligoclonal band synthesis was observed in 67% in an initial series [10]. The sensitivity of anti-NMDAR antibodies in the serum and CSF are 85.6% and 100% respectively using a combination of IHC and fixed CBA, whilst the specificity of the tests in a population of patients with suspected encephalitis is 100% from either serum or CSF [13]. In a multivariate analysis, older age at diagnosis, absence of a tumour and a lower likelihood for ICU admission were independently associated with seronegative status [107].

An emerging imaging adjunct is 18-fluorodeoxyglucose positron emission tomography (FDG-PET). Whilst reports have generally been confined to small case series, they nonetheless suggest a role for FDG-PET in both diagnosis and prognostication. The occurrence of abnormalities detected in scans of patients with normal MRIs raises the possibility of a higher diagnostic sensitivity [108,109]. Early reports included isolated frontal hypermetabolism [110,111] or occipital hypometabolism [112], a combination of anterior hypermetabolism and posterior hypometabolism [113], generalised and marked unilateral cortical hypometabolism [114], and striatal hypermetabolism [115]. In one series, a description of a fronto- and temporal-to-occipital gradient was described, at a median of 10 weeks from disease onset [116]. A correlation with disease severity, and reversal with neurological recovery was observed [116]. These findings were hypothesised to reflect regional functional differences resulting from disruptions in NMDAR signalling on glucose metabolism [116]. Furthermore, in another series, early marked medial occipital hypometabolism was a feature unique anti-NMDAR Ab-mediated encephalitis, in comparison to patients with definite AE, and occipital hypometabolism correlated to greater disease severity [117]. A paediatric case series during the acute disease stages demonstrated widespread cortical hypometabolism in all patients, with concomitant basal ganglia hypermetabolism in four of six patients [118]. Evolution of findings during different stages of the disease has been demonstrated. Serial studies in one series depicted prominent occipital hypometabolism with relative anterior hypermetabolism acutely, global hypometabolism with basal ganglia hypermetabolism after 9-13 weeks, during a period of incipient clinical improvement, and near-normalisation during clinical recovery [119]. Finally, distinct metabolic patterns may relate to specific disease triggers. In another study, acutely, all cases demonstrated FDG-PET abnormalities, and paraneoplastic and idiopathic cases were more likely to show frontotemporal and basal ganglia hypermetabolism in combination with occipital hypometabolism. Cases thought to be induced by viral encephalitis demonstrated temporal hypermetabolism contralateral and hypometabolism ipsilateral to MRI changes respectively, with varying degrees of occipital hypometabolism [109]. Taken together, functional FDG-PET abnormalities may show higher anatomical correlation with clinical features compared to MRI – particularly for extra-limbic pathology – and may have an adjunctive role in delineating disease severity.

Finally, 88mTc-d,l-hexamethyl-propyleneamine oxime (HMPAO) single photon emission computed tomography (SPECT) abnormalities have been described in some patients. In some patients, early SPECT studies were normal [110], whilst accounts of frontotemporal [110], bitemporal [120], cortico-basal hyperperfusion [121] have been described. Further, in four patients, N-isopropyl-p-123 I-iodoamphetamine (^{123}I-IMP) SPECT scans were reported to show occipital hypoperfusion in all, and left frontal, parietal and temporal hyperperfusion in one patient during acute disease stages [122]. These findings suggest a role for perfusion imaging in the diagnostic evaluation of potential cases, though, along with FDG-PET, both modalities require further, larger studies to evaluate sensitivity and specificity during various disease stages.

7. Treatment

Early reports of teratoma-associated encephalitis either consistent with or confirmed to be NMDAR encephalitis highlighted responsiveness, to varying degrees, to immunotherapy, tumour removal or the combination of both [1,2]. These findings were confirmed in larger series [4,10,22], such that immunotherapy now forms the mainstay of management.

First-line therapy typically consists of high-dose methylprednisolone, intravenous immunoglobulin (IVIg) or plasma exchange (PLEx), either alone or in combination, alongside teratoma removal where applicable [58]. Typical regiments include 1g methylprednisolone for 3-5 days, 2g/kg IVIg over 2-5 days, and alternate daily plasma exchange for up to 5-7 exchanges. Second-line agents most commonly include rituximab and cyclophosphamide, with third-line options including bortezomib, tocilizumab and possibly anakinra. Accordingly, first line-immunotherapy institution has been reported in 92-99.5% of patients [4–6], with 84%, 69% and 33% receiving steroids, IVIg or PLEx respectively, and 44% of patients receiving a combination of steroids and IVIg in one series. In this study, 96% of patients with an underlying teratoma underwent excision. Immunotherapy was instituted at a median of 21 days from symptom onset. In 53% of such patients, clinical improvement occurred within 4 weeks [4]. In a more recent cohort study, 84.8% of patients exhibited clinical improvement within this period [5]. Consistent with these findings, in a recent clinician survey, when anti-NMDAR Ab-mediated encephalitis was suspected, intravenous methylprednisolone was the preferred first line therapy, followed closely by combination therapy [123]. Combination therapy was recommended *a priori* for patients with more severe phenotypes. Moreover, bridging therapy is recommended, in the form of a tapering course of steroids, maintenance IVIg or IV methylprednisolone [123]. In the prior study, of the patients without significant improvement, who subsequently received second-line immunotherapy, 78% had a good outcome, in comparison to 55% of such patients who did not receive second-line therapy [4].

Rituximab, an anti-CD20 chimeric monoclonal antibody [124], was evaluated as a second-line agent in autoimmune encephalitis in a study including 27 patients with anti-NMDAR anti-NMDAR Ab-mediated encephalitis. Patients receiving rituximab were more likely to achieve an improvement in mRS score, though no difference in the proportion of patients with a favourable outcome was seen, with rituximab well-tolerated [125]. Though further improvement can occur beyond 24 months in some patients, a subset appear refractory to conventional second-line therapies [4], thus the exploration of novel agents is warranted. In autoimmune encephalitis patients refractory to first-line therapy and rituximab, of which 27% had anti-NMDAR Ab-mediated encephalitis, a greater efficacy of tocilizumab, an IL-6R inhibitor, compared to ongoing rituximab or no additional immunotherapy was demonstrated, with respect to mRS scores [126]. Moreover, in a small uncontrolled case-series, termination of SE in new-onset refractory status epilepticus (NORSE) occurred imminently after tocilizumab administration in six of seven patients, including a single case of anti-NMDAR Ab-mediated encephalitis [127]. Evidently, retrospective study design, among other factors, limits interpretation of findings in these studies, and conclusions specific to anti-NMDAR Ab-mediated encephalitis are precluded, but nonetheless, a role for both agents are supported. Tocilizumab was further evaluated in a prospective cohort study utilising the novel Clinical Assessment Scale in Autoimmune Encephalitis (CASE) – a severity score comprising nine clinical markers [128]. In this study, of seventy-eight patients with anti-NMDAR Ab-mediated encephalitis, those who received a combination of tocilizumab and rituximab following first-line therapy experienced a greater reduction in CASE scores compared to first-line therapy with or without rituximab, with greatest efficacy following early institution. A higher proportion of

patients treated with this combination developed neutropaenia, with tocilizumab withdrawal in three patients [129].

Bortezomib, a selective proteosome inhibitor used in multiple myeloma, reversibly inhibits 26S proteosome chymotrypsin activity, with plasma cells, due to high rates of antibody synthesis, particularly sensitive [130]. Both short-lived and long-lived plasma cells are thought to be susceptible, though CNS penetration is poor [131]. A typical dosing cycle consists of 1.3mg/m2, twice-weekly, over 21 days [132]. The efficacy of bortezomib use in anti-NMDAR Ab-mediated encephalitis was highlighted in a recent systematic review, with 16 of 29 patients administered a median of 2 cycles having a good outcome, though adverse events occurred in approximately one third of patients. Reductions in serum and CSF antibody titres were reported in 85.7% and 70% of patients respectively [133]. However, no statistically significant association was seen between either serum or CSF antibody reduction and favourable outcome. As the authors noted, heterogeneity in the timing of antibody levels and dilutions used between studies limited closer interpretation [133], and nonetheless, patients with improvements reported typically demonstrate reductions in either serum or CSF antibody titres [134–137]. By contrast, in five bortezomib-treated patients followed up over eight months, no clear efficacy was seen, with an mRS of 5 maintained, and limited reductions in serum and CSF titres observed. This raises the possibility of resistance in some patients, in part potentially mediated by ASC in the CNS, resistant to bortezomib due to poor BBB penetration [138]. Potential adverse events include peripheral neuropathy, myelosuppression and infection [139]. Nonetheless, tolerability was generally favourable in most anti-NMDAR Ab-mediated cases, and bortezomib represents an attractive alternative to cyclophosphamide, with respect to gonadal toxicity [140]. The aforementioned studies were predominantly retrospective and uncontrolled, with resultant heterogeneity, and consequent inability to confidently extricate effects of prior immunotherapies and natural history of the disease on reported improvements, engendering need for caution in interpretation of respective findings. Nevertheless, a role for bortezomib for patients refractory to second-line therapy is suggested, though further clinical exploration is warranted. Indeed, a double-blinded, randomised control phase II study is currently under way [141]. Moreover, use of daratumumab, an anti-CD38 monoclonal antibody, historically also from the multiple myeloma armamentarium, represents another novel therapeutic option, and has been described in a single case with NMDAR encephalitis with a favourable outcome [142], though use in a patient with CASPR2 encephalitis was complicated by fatal sepsis [143].

Anakinra, a recombinant IL-1 receptor antagonist, used in rheumatoid arthritis, by contrast, demonstrates blood-brain barrier penetration, and was administered in mouse model of anti-NMDAR Ab-mediated encephalitis facilitated by intraventricular infusion of purified patient or monoclonal NMDAR-IgG. Anakinra was associated with reduced seizure frequency and duration, improved memory in a novel-object recognition assay, and reduced markers of astrocyte and microglial activation [144]. Further exploration of IL-1 inhibition is warranted, though immunotherapy in general is significantly more likely to effect seizure freedom compared to ASM [89].

Expeditious teratoma removal had been associated with better neurological outcomes compared to delayed removal or absence of teratoma [10], with similar findings in paediatric patients [86]. Similarly, delayed removal was associated with worse outcomes in another study [129]. Moreover, a lower risk of relapse has been demonstrated in patients with a teratoma [4,73,145], presumably due to teratoma removal. By contrast, other studies found no difference in outcome in the presence or absence of a tumour [5,17,146], with longer and more vigilant follow-up of paraneoplastic cases thought to account for the aforementioned association [10,146]. Taken together, a teratoma may not be a positive prognostic factor, but swift removal is likely warranted. Challengingly, imaging-negative cases with teratoma detection only following oophorectomy have been reported, though consideration of empirical oophorectomy may well be reserved for exceptional cases, with a unilateral approach worth considering to avoid sterilization [147,148]. The relevant mechanisms of second-line therapies and teratoma removal are summarised in Table 2.

8. Prognostic factors

From the largest available study, in multivariable analysis, avoidance of ICU admission, early treatment and longer follow-up were associated with a good outcome (mRS 0-2), the latter reflective of the prolonged recovery often seen [4]. Second-line treatment was associated with a good outcome in a multivariable analysis of first-line treatment failure. Aside from tumour presence, immunotherapy use was associated with lower relapse frequency [4]. In a multivariate logistic regression model using the same cohort, ICU admission, treatment delay beyond, and lack of improvement by four weeks, MRI abnormalities and CSF pleocytosis >20 cells/μL were associated with poor outcome at twelve months [146]. A prognostic score was coined assigning one point for each of these five variables, termed the anti-NMDAR Encephalitis One-Year Functional Status (NEOS) score, with similar predictions made if first- or second-line immunotherapy was considered [146]. As the authors noted, improvement beyond 12 months continues in a proportion of patients [4,5], thus such a score serve as a guide to the trajectory of clinical improvement, rather than a prediction of ultimate outcome

Table 2
Second-line, third-line immunotherapy and teratoma removal with relevance to pathogenesis.

Treatment	Mechanism of action	Comments	References
Second-line immunotherapy			
Rituximab	Anti-CD20 chimeric monoclonal antibody	$CD20^+$ not expressed on plasma cells	[4,124]
Cyclophosphamide	Alkylating agent, with cell-mediated and humoral immune suppression	Particularly in younger patients, potential risks of myelosuppression, haemorrhagic cystitis, bladder cancer and infertility may limit use	[4,149]
Third-line and possible prospective immunotherapy			
Tocilizumab	Anti-IL-6 receptor monoclonal antibody binding soluble and membrane-bound forms; inhibits B-cell activation, $CD8^+$ differentiation and Th17 differentiation, promotes Treg cells	May represent an option in rituximab-refractory cases.	[126,129]
Bortezomib	Selective proteosome inhibitor, inducing apoptosis in SLPC and LLPC, sparing B-cells, though poor blood-brain barrier penetration	Currently mainly used for patients refractory to other second-line agents	[131,133]
Anakinra	Recombinant IL-1 receptor antagonist	Reduced seizures, memory impairment in mouse model of disease	[144]
Concomitant therapy			
Teratoma removal	Removal of one potential source of patient antibodies	Serum antibody titres higher in the presence of a teratoma; earlier removal associated with better outcomes	[10,13]

[146]. Higher CSF and serum antibody titres have also been associated with poor outcome, though were not evaluated in the prior model [13]. Moreover, delayed immunotherapy has been associated with worse neuropsychological outcomes and increased risk of relapse [5,150].

9. Outcomes

A favourable outcome (mRS $\leq$2) was reported in 92.7% at 12 months in one study, and up to 85.7% at 24 months in others, with progressive improvement common [4,5]. Mortality occurs in approximately 7% of patients, with disease-specific causes including autonomic instability and refractory status epilepticus, and medical complications including sepsis and pulmonary embolism representing typical causes [4,5]. Epilepsy, as indicated, appears very uncommon chronically, with most patients ultimately achieving seizure-freedom [88,89,151]. Conversely, cognitive recovery is more variable. Long-term cognitive impairment has been identified over 75% of patients in a systematic review, with memory, executive function and information processing speed most commonly chronically impaired, though favourable outcomes were reported in a similar proportion of cases [150]. Further, impaired resting state functional MRI (fMRI) hippocampal functional connectivity, reduced mean hippocampal volumes and subfield atrophy on volumetric imaging and impaired hippocampal microstructural integrity as assessed by diffusion tensor imaging have been reported. These findings showed association with either cognitive deficits or disease severity [152,153]. No association of either memory measures or structural hippocampi outcomes with follow-up time were demonstrated, in contrast to clinical recovery [153]. In a subsequent study, paediatric patients at a median follow up of 31 months, despite good functional recovery and independent of treatment delay, exhibited persistence of sustained attentional deficits, long-term verbal memory and fatigue [154]. In another study, at 24 months, using a cognitive rating scale (CRS), 7.8% of patients had functional impairment preventing return to prior activities (CRS of $\geq$ 2), and residual irritability as reported via the Neuropsychiatry Inventory, in a quarter of patients, with most other neuropsychiatric symptoms mitigating [155].

10. Conclusion

Anti-NMDAR Ab-mediated encephalitis thus represents an increasingly well-characterised, proportionately common, treatable form of antibody-mediated encephalitis, often with a unique combination of clinical and paraclinical features, benefiting from rapid advances in clinical research over the past two decades. Timely diagnosis and treatment are associated with more favourable patient outcomes. As with other CNS inflammatory disorders however, avoidance of misdiagnosis is also of paramount importance, given the potential morbidity associated with treatment, consisting of immunotherapy, and where relevant, tumour resection. Thus, the importance of appropriate antibody testing in the CSF cannot be over-emphasised. Novel treatment options, particularly "third-line" therapies, offer promising efficacy and possibly favourable risk-benefit profiles, but require further evaluation in larger cohorts with more rigorous methodology. Future research directions would also entail the expansion and refinement of treatment algorithms with respect to immunotherapy, whilst exploring more disease specific therapies. Further, the characterisation and application of biomarkers in diagnosis and disease monitoring warrants ongoing exploration, given the limitations in conventional investigations, and delays in antibody results in initial diagnosis, and similar challenges in subsequent assessment of patients. To date, assessment of candidate biomarkers have revealed either limited sensitivity or specificity, or somewhat conflicting results, thus underscore the need for further work in the area, though offer insight into disease mechanisms.

Author contributions

NS performed the literature search and drafted the manuscript and tables and created the figure. MM, TO and HB reviewed, and contributed to writing and editing the manuscript.

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