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Cognition and Psychopathology in Autoimmune Encephalitides – a focus on risk factors and patient outcomes.

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Abstract

Neurocognitive compromise, neuropsychiatric symptoms, and psychopathology are all evident in the acute stages of autoimmune encephalitides (AE). These factors considerably affect functional independence after discharge. Drawing on psychometric assessments and qualitative descriptions, this review will explore the nature, extent, and diagnosis of cognitive disorder in AE. Potential pathophysiological and neuroanatomical architecture related to neurocognitive compromise in the acute and chronic stages of this illness is examined. In regards to outcomes, the review highlights clinicodemographic factors currently known to be associated with poorer cognitive outcome. Finally, the review delves into neuropsychiatric symptomology and psychological concerns that should be considered at diagnosis and during follow up of these patients.

Keywords: Autoimmune, Cognition, Encephalitis, Outcomes, Psychopathology

Introduction

Autoimmune encephalitides (AE) are a rare and diverse group of neurological conditions, which are characterised by an immune mediated inflammation of the brain and associated neuronal circuitry dysfunction (1). The prevalence of AE in the USA is estimated at 13.7/100,000, while the incidence is estimated to be 0.8/100,000 person-years (2). While these rates are not significantly different from infectious encephalitis, the rates of disease relapse, disease progression, and recurrent hospitalisation has been reported to be higher in AE than infectious encephalitis, indicative of increased disease burden associated with AE (2).

Neurocognitive compromise, neuropsychiatric symptomology, and psychological distress contribute significantly to the burden of this disease (3,4). These symptoms and signs of AE are evident during the acute stage and also feature as chronic sequelae. Such symptoms range in severity from minor fluctuations in

attention, to severely incapacitating cognitive impairment, and debilitating neuropsychiatric and psychological features that can limit functional independence. In this review, we provide an update on the nature and extent of cognitive and psychopathological aspects of AE, from the acute to chronic stages of the illness. Our findings emphasise the need to assess and monitor neurocognitive and psychopathological manifestations of AE, as these can be associated with increased patient morbidity, and worsened long-term outcome.

Current diagnosis of AE

To expand the diagnostic criteria for AE, guidelines moved from criteria that were reliant on antibody testing and response to immunotherapy, towards a syndrome-based diagnostic approach (5). Emerging from these guidelines is a three-tier diagnostic system of clinical evidence; 'possible or probable' (where antibody status is not needed in many cases), and 'definite' (where the autoantibody status is often required). Diagnosis of AE can be made without presence of detectable or known autoantibodies – the so called 'seronegative' AE. Neurocognitive and neuropsychiatric symptoms form a fundamental part of the latest diagnostic criteria as outlined in the position paper which emphasises that *"patients with autoimmune encephalitis could present* with memory or behaviour deficits without fever or alteration in the level of consciousness, or with normal *brain MRI or CSF results"* (p.5, (5)).

While the identification of autoantibodies in serum or CSF is not required for diagnosis, disease-associated antibodies have been used in defining clinical syndromes (5,6). There have been several novel autoantibodies detected, broadening the spectrum of AE subtypes over the past two decades. The current review examines AEs with autoantibodies targeting neuronal surface antigens expressed within the CNS as this AE subgroup have lower associations to underlying cancer than AEs that are associated with antibodies targeting intracellular antigens, and as such they differ in their pathophysiology and response to immunotherapy (1). A summary of clinical manifestations of seropositive AE is available in Table 1. Where possible, this paper will integrate evidence from cohort studies with neuropsychological data available, however given the rare incidence of AE (compounded by fewer neuropsychological published studies), case studies with and without raw data are also referenced. Of note, steroid-responsive encephalopathy with autoimmune thyroiditis (SREAT, previously referred to as Hashimotos Encephalopathy) and Rasmussen Encephalitis are not covered in this review as they fall outside the realm of 'classical' AE in terms of currently known pathogenicity, but the reader can resort to the following references for further input (7,8). Also of note are the clinical diagnosis of autoimmune epilepsy and autoimmune psychosis, of which there is overlap with existing criteria for AE, with the respective clinical presentation emphasising common symptomatology between AE and autoimmune epilepsy and autoimmune psychosis. For example, patients with autoimmune epilepsy usually present with new onset refractory seizures with one or more coexisting features of AE(9). Similarly those with'possible AE' criteria as per Graus et position paper(5) can present with psychotic symptoms, but there needs to be additional clinical signs/symptoms and paraclinical evidence of AE based on investigations (ie lumbar

puncture, MRI). (10). On the other hand those with acute psychosis can have a primary psychiatric disorder until further investigations reveals underlying autoimmunity which would trigger a search for AE. Given the search for autoimmune epilepsy and autoimmune psychosis relies on the same testings as for 'classical' AE, the neuropsycholocial literature often does attempt to capture those with presence of autoantibodies even if their underlying illness was purely seizures or purely psychosis. Of course more research and ongoing efforts in delineating key and distinguishing cognitive profiles are warranted.

Acute Cognitive Functioning & Psychopathology

Across the AE spectrum and in the early stages of the illness, patients often present with an insidious onset of anterograde amnesia, along with working memory deficits, mood and behavioural changes (5). These presentations range in severity from minor memory difficulties to severe attentional, amnestic and psychiatric presentations (5). It is imperative to highlight that in the acute stages, AE patients may have impairments in fundamental cognitive functions, such as basic attention and arousal, leading to a more global profile of reduced "higher cognitive" functions, such as memory, executive and language function. Consequently, acute AE presentations can make the cognitive assessment process challenging, impacting the state of current research. In addition, clinicians must be cautious not to overcall the apparent reduced "higher cognitive" functions that are a reflection of impairments in these fundamental cognitive functions.

Psychiatric symptomology is a fundamental diagnostic feature of the of the anti-NMDAR ab mediated AE syndrome. Al-Diwani and colleagues summarised the psychopathology/neurobehavioral presentation in the acute stage as 'polymorphic' and noted that it did not respect conventional psychiatric classifications (11). The anti-NMDAR ab mediated AE phenotype was described to encompass features of catatonia, behavioural alterations, and psychosis (11). This phenotype was closely represented by a cluster of seven discrete symptomatology: agitation, aggression, hallucinations, delusions, mutism, irritability or a mood disorder. Psychosis is recognised broadly among other AE subtypes including anti-CAPSR2 ab mediated AE (12), anti-LGI1 ab mediated AE (13), anti-AMPAR ab mediated AE(14) and anti-IgLON5 ab mediated AE (15) Delusional thoughts and visual hallucinations have also been reported in case studies of anti-DPPX ab mediated AE (16) and anti-GABA B ab mediated AE (17). However the assumption that only severe psychiatric symptoms characterise the psychopathology in AE patients may hinder diagnosis. Clinicians should be alert to generalised neuropsychiatric symptomology, as this is commonly reported in acute stages of AE. Reported symptomology has included apathy and lethargy, increased irritability, aggressiveness and agitation, adynamic behaviour, and indifference, as well as new onset anxiety and depressive symptomology (11,12,18–28). Consequently, detailed assessment of psychopathology should be performed as standard practice when AE is suspected. Such assessment should encompass questioning of the individual but noting an informative history is essential to determine onset and natural history of symptom progression.

Episodic memory impairments are at the forefront of acute neurocognitive deficits across the AE clinical syndrome spectrum (3,4,20,27,29–33). These findings are consistent with the clinical syndrome of limbic encephalitis (LE) – a syndrome associated with several cell surface or synaptic autoantibody mediated AE subtypes, including LGI1, AMPAR and CAPSR2. LE is characterised clinically by rapid development of confusion, focal seizures, working memory deficits, psychosis and behavioural disturbance. Radiologically there is increased signal on T2-weighted fluid attenuated inversion recovery (FLAIR) MRI imaging in the medial aspect of the temporal lobes (5). These clinical and paraclinical features are believed to be the manifestation of dysfunction of the mesial temporal networks. In the AE, the dysfunction is postulated to be associated with disruption to neuronal circuity secondary to disruption to receptor systems, as observed in models of anti-NDMAR AE (discussed below). It is important to note however that acute memory impairments have also been noted in patient with unremarkable or non-specific clinical imaging (3,15,18,21,34).

In addition to memory dysfunction, psychometric investigations have revealed impairments across a number of domains in the acute stage of the AEs, as indicated by poor performance on cognitive tests. Significantly reduced cognitive proficiency (e.g. attention and processing speed) is the most commonly reported impairment (3,15,33,35,36). In regards to language, performances on confrontation naming appear to be binary, with patients presenting either with significant anomia or performing within expected ranges (33,37–41). In the acute stages of AE, executive functions are commonly impaired as their effectiveness is dependent on fundamental cognitive processing being intact, particularly cognitive proficiency. In patients that have been well enough to engage in cognitive testing, performances have been reduced on tests assessing planning, organisation, reasoning, problem-solving, set-shifting and maintenance, and verbal fluency (33,35–38). Topographical disorientation both with and without amnesia has also been reported in AE patients (39,42).

Taking the evidence together, it is clear that there is cognitive variability at an individual level, as well as across the AE clinical syndromes. Therefore, when formal cognitive testing cannot be performed due to severity of acute illness itself, documenting clinical observation, brief cognitive screening test, and informant reports will assist with characterising the acute neurocognitive compromise. From a research perspective, this will assist with advancing the understanding and cognitive phenotyping of the AE syndromes.

Neural Systems of acute AE

On the basis of experimental models, neuronal dysfunction due to the pathogenic role of the antibodies is suggested to lead to disruption to neuroanatomical networks and to the acute cognitive symptomology observed in patients with AE (41, Figure 1). The most persuasive evidence for this lies in research examining anti-NDMAR Ab mediated AE and anti-LGI1 Ab mediated AE. As we noted previously (4), the memory impairments reported in anti-LGI1 Ab mediated AE are consistent with anti-LGI1 antibodies predilection to target limbic structures, particularly the hippocampus in this illness (44). This finding is consistent with rodent

studies (45). Although the mechanisms underlying the effects of antibodies on the target are unknown, there is evidence that the disease causes pathogenic changes in the hippocampus, driving the memory impairments observed in these patients (46). Similarly, the episodic memory deficits observed in anti-NMDAR ab mediated AE patients are consistent with NMDAR expression and the known role of the NMDAR system in memory. NMDARs are highly expressed in the temporal association cortices within the neuronal presynaptic terminals (47). As such NMDAR and its functioning have been implicated to play a crucial role in learning and memory (48). Administration of NMDAR antagonists such as ketamine have been shown to disrupt frontal and hippocampal signalling contributing to disruption of encoding and retrieval of new memory formations in humans (48). In the acute stage, in anti-NMDAR Ab mediated AE, the NMDAR system is significantly interrupted via the reversible anti-body mediated capping and internalisation of the receptor, possibly leading to the observed amnestic syndrome. In addition, NMDARs are highly concentrated in the frontal cortex, likely explaining the deficits in executive function and psychiatric presentations of this patient population (49). The literature of the hypothesised mechanisms inducing cognitive deficits in antiAMPARs, anti CAPSR2, and anti $GABA_A$Rs ab mediated AEs is very limited and is summarised in Gibson et al. (2020).

Cognitive and Psychological Sequelae

While cognitive impairments due to neuronal dysfunction (secondary to the pathogenicity of the associated antibody) is likely ubiquitous in patients in the acute stages of AE, the long-term cognitive outcomes following treatment are highly variable. Although experimental models suggest that the pathogenic effects of antibodies gradually resolve after treatment, the persistent ongoing cognitive impairments (even when neuroimaging reveals no clinically relevant 'macroscopic' changes) suggests that either a) there are other yet to be discovered pathophysiological mechanisms or b) there is damage that is not readily apparent on standard clinical imaging (50). This is supported by research imaging, where widespread superficial white matter damage post-treatment has been associated with a number of ongoing cognitive difficulties, including attention and memory dysfunction (51,52)**.**

Chronic Cognitive Compromise

Neurocognitive compromise varies across the clinical syndromes and is often associated with the type of autoantibody. Although cognitive impairments are not universal, clinical signs and symptoms of neurocognitive or psychiatric/psychopathological sequelae occur in many patients with AE. Primarily, patients with anti-LGI-1 ab mediated AE and anti-NMNDAR ab mediated AE appear to be more likely to experience ongoing neurocognitive compromise (4,37). Impairments in anti-AMPAR ab mediated AE, anti-VGKC (unspecified) ab mediated AE and seronegative patients are highly variable, with outcomes ranging from severe cognitive deficits to apparent recovery. To note, the variability in findings between anti-VGKC (unspecified) Ab mediated AE patients is likely attributable to the presence of different antibodies that were a) unable to be identified at the time, b) were non-pathogenic bystander antibodies or b) are antibodies whose pathogenesis is still unknown. Thus it is not unreasonable to suggest that patients who suffered from ongoing

memory problems in the anti-VGKC (unspecified) ab mediated AE literature may have had anti-LGI1 antibodies present that were unable be detected at the time of the research, resulting in the significant variability in patient outcomes reported in these papers. Neurocognitive compromise is less commonly reported in anti-CASPR2 ab mediated AE. There is a paucity of cohort studies relating to patients with anti-DPPX ab mediated AE,anti-GABA (A&B) ab mediated AE, IGLON-5 ab mediated AE, mGluR ab mediated and thus it is difficult to comment broadly on these patients. The lack of neurocognitive research outside LGI-1 and NMDA encephalitis limits the understanding of outcome in these populations.

Principally, episodic verbal memory impairments have been heavily examined in the research literature, likely due to their debilitating impact on everyday life. In Anti-NMDAR ab mediated AE, Nicolle & Moses demonstrated that patients had ongoing impairments on tasks assessing verbal learning, immediate and delayed recall (37). Similarly, in a systematic analysis McKeon and colleagues concluded that 55.3% of their patients demonstrated memory impairment against a background of preserved intellect, with performances ranging from subtle to severe, suggesting a significant divide in memory outcomes (3). In anti-LGI1 ab mediated AE, patients appear to present with a similar picture with a proportion presenting with severe memory impairments (4). However, the contribution of higher functions, e.g. frontal lobar functions to poor memory psychometrically have been difficult to disentangle in the literature. Ongoing memory dysfunction is less commonly reported in anti-CASPR2, anti-DPPX,anti-GABA (A&B) ab mediated AE and IGlon5 ab mediated AE

Uncommon memory profiles have also been reported in AE patients. There are case reports of temporally ungraded retrograde amnesia of autobiographical memory dating back decades in anti-VGKC ab mediated encephalitis and anti-LGI1 ab mediated encephalitis (39,53). Clinicians should be aware that this specific deficit relies on a careful history accurately demarking the extent of remote autobiographical loss as standard psychometric analysis maybe unrevealing.

Examination of the factors associated with poorer memory outcomes has focused on the anti-NMDAR and anti-LGI1 mediated AE groups. Nevertheless, some of these factors can be extrapolated to other AE syndromes. With respect to the association between the integrity of memory structures and performances on memory tasks, anti-NMDAR ab mediated AE patients who present with significant memory impairments in the chronic stage are likely to display hippocampal subfield atrophy and impaired microstructural integrity of the hippocampus (50). Notably, Finke and colleagues also illustrated with hippocampal volumetry that both the input (dentate gyrus) and output structures (subiculum and presubiculum) of hippocampal circuitry are bilaterally affected in anti-NMDAR AE. Both the CA4/DG and subiculum subfields of the hippocampus play a crucial role in memory formation and storage and their volumes were reduced in their cohort of patients. As these findings mirror the neuroanatomical findings of other patient populations who present with memory impairments, this damage is likely the cause of the memory impairments in the chronic stage of anti-NMDAR antibody mediated AE. Finke and colleagues also noted that damage to the hippocampal subfield consisting of atrophy and impaired microstructural integrity was associated with disease severity and duration. This likely

explains the variability in the severity of outcomes and suggests that patients with a serve disease course and/or a long duration of disease are more likely to present with chronic memory impairments. This persistent structural damage goes beyond the antibody capping and internalisation suggesting there are other unknown pathophysiological mechanisms (49,50).

From a functional network perspective, anti-NMDAR patients have demonstrated reduced functional connectivity between the hippocampus and the anterior default mode network (DMN) (54). This network is a set of brain regions that increase their activity during internally directed tasks (e.g. recalling emotionally neutral or recent autobiographical memories) and decrease activity during top-down goal-directed behaviour (e.g. thinking about the external world) (55). The medial temporal lobes are key structures within this network, along with the medial prefrontal cortex (mPFC), and changes in this network have been reported in other neurological and psychiatric diseases and implicated with depression and memory retrieval (56,57). Correspondingly the decreased functional connectivity of the anterior DMN was correlated with poorer memory performance (54). Further, as previously noted, whole brain superficial white matter damage is evident in some AE patients, and importantly these changes have been correlated with deficits in verbal and visuospatial memory (51).This decreased functional connectivity and white matter damage may provide insight into the memory deficits in this population who do not present with structural damage or atrophy on clinical imaging.

As seen in anti-NMDAR ab mediated AE, anti-LGI1 ab mediated AE case studies and cohort studies have demonstrated selective hippocampal atrophy in patients (44,53,58–60), which has been associated with episodic memory impairments on testing (53,58,60). As reviewed by Griffith and colleagues, studies have demonstrated that patients can have atrophy of hippocampal CA3 region, decreased volume of left CA2/3 subfield, and smaller CA4/denudate gyrus volume, all of which have been associated with poorer performances on specific aspects of verbal memory tasks(4). Even without overt structural damage visible on MRI, the hippocampus in these patients can be damaged (at the microscopic level) and this is potentially associated with memory abnormalities on testing (60).

In regards to outcomes related to treatment variability, the latency between disease onset and initiation of immunotherapy has been correlated with worse verbal and visuospatial episodic memory performance (60). Patients who have received second-line therapy (likely a manifestation of poorly controlled underlying disease) are reported to have significantly worse verbal memory performance on delayed recall (60). Higher levels of disability have been associated with worse verbal memory performance (specifically delayed recall and recognition on a word list task) (60).

Persistent impairments in some aspects of executive functioning (EF) have been reported in anti-LGI1 ab mediated AE and anti-NMDAR ab mediated AE (3,37). Anti-NMDAR Ab mediated AE group performances on tasks of EF have been reported to be significantly poorer compared to healthy matched controls on tasks of visuospatial organisation and planning, and problem-solving (61). Similarly, on a task of inhibition, there were substantial group differences (54). Poor performances on tasks measuring mental

flexibility, disinhibition and orthographical lexical retrieval have been noted in anti-LGI1 ab mediated AE (4). Broadly, the evidence for other AE (when available) suggests moderate impairments in the early stages of the disease, with improvements after immunotherapy for many patients. While higher levels of disability have been associated with poorer EF outcomes in anti-NDMAR AE, further research is required to confirm the strength of these claims and their generalisability to other AE syndromes (3).

The neuroanatomical substrate of poorer EF in these patients is yet to be explored. While not evident on clinical MRI, it has been observed that AE patients can have white matter damage (54). White matter changes in these patient populations are most prominent in the cingulum bundle, an integral fibre tract that connects the cingulate cortex to areas of the limbic system (54). To note, the cingulate cortex has been associated with impairments in EF and, as hypothesised by Finke and colleagues, this link may provide an understanding to ongoing executive dysfunction in AE patients, however additional research is necessary (54). There is also clinical and radiological evidence for the involvement of non-limbic subcortical structures in AE subtypes (62,63). For example, a prominent clinical manifestation of anti-LGI1 mediated AE is the presence of faciobrachial dystonic seizures prior to the onset of limbic encephalitis (64). Imaging of case studies, including FLAIR MRI, Positron emission tomography (FDG-PET) and Single Photon Emission Tomography (SPECT) have demonstrated involvement of the basal ganglia (62). This evidence implicates the involvement of frontal-striatal circuits, which have been related to cognitive, behavioural, and personality changes in other neurological diseases, (65,66). Together, the implication of these frontal networks suggest they may form the basis of certain non-amnestic deficits, such as impaired frontal lobar functions.

Across the AE subtypes there is variability at the individual level on tasks of attention and working memory. At a group level, however, the evidence suggests a broad picture of improvement. Nevertheless, given the significant variability in cognitive domains, inclusion of these tests during neuropsychological assessment is prudent. There are several factors that may need to be considered at the individual level for patients who are experiencing ongoing attention and working memory difficulties. Related to AE specifically, the literature suggests a trend towards the more severe course of acute illness being associated with increased severity of ongoing cognitive impairments across the domains. Other factors to be considered include; ongoing seizure activity, current medication regime and associated side effects, and severity of ongoing neuropsychiatric symptoms, including anxiety.

There is little evidence exploring ongoing language deficits, and thus patients should be considered on a case by case basis when clinically suggestive (3,4,37). Visual perceptual/constructional not secondary to executive function deficits are not commonly reported in patients (3,4,37).

Finally, while rarely explored psychometrically, social cognitive deficits have been briefly touched upon in the adult literature. McKeon and Colleague's anti NMDAR mediated AE cohort demonstrated when

compared to controls, the cohort performed poorly on judging the severity of interpersonal violations and using mental state information to make sense of social situations (47). These findings are consistent with subjective findings, which suggest social dysfunction in some patients (61,67).

Examining neuropsychological outcomes broadly, patients have up to eight times the odds of adverse neuropsychological outcomes when treatment was initiated more than three months after the onset of encephalitis (3). When exploring other factors, McKeon and colleagues did not find any significant relationships between cognitive outcome and the following factors: gender, age, MRI abnormalities, EEG abnormality, seizures, ICU admission, nature of treatment, and aetiology (idiopathic or paraneoplastic). Antibody titres in cerebrospinal fluid and serum at onset have not been significantly correlated with cognitive outcome as yet (68).

Chronic Psychopathology

Persistent neuropsychiatric issues following AEs are an important source of long-term morbidity for patients who have suffered an AE, which weigh heavily on patients and their loved ones alike. Not only do these factors influence cognition day to day, but they also play a significant role in psychosocial outcomes and quality of life. Long term prognosis varies considerably across the AE spectrum and neuropsychiatric outcomes incorporate depressive and anxiety symptomology. In addition, psychological concerns also include symptoms of adjustment disorder and challenges to personal identity (69,70).

The anti-NMDAR AE research has demonstrated that patients experience ongoing neuropsychiatric issues (including psychiatric comorbidities, cognitive changes and emotional/impulse control disorders), as well as seizures and sleep difficulties, and that these factors are strongly associated with poorer psychosocial outcomes (69). Quality of life assessments have revealed reduced quality of life in several domains including current situation, future prospects, mood, ability to carry out daily activities, social life and cognitive function (67). Notably, one third of patients do not resume their prior work or schooling after illness, and despite patients experiencing persistent neuropsychiatric symptoms only one third of this group report having psychiatric follow up (69).

Although there is a lack of research exploring neuropsychiatric outcomes in the other AE clinical syndromes, what is reported in the anti-NMDAR AE ab mediated AE literature, and in the encephalitis and the acquired brain injury literature should be used to highlight neuropsychiatric issues. At the forefront of this body of research are the raised levels of depression and anxiety in these populations, which can be attributed to both neurobiological changes as well as adjustment difficulties associated with the sequelae of the disease (70). In regards to the latter, adjustment difficulties may arise as patients come to fully comprehend the impact of residual cognitive deficits and neuropsychiatric issues on everyday life, and the realisation of an inability to return to their prior life (71). As emphasised by Easton, distinctive to encephalitides is the uncertainty that arises secondarily to the lack of memories surrounding the illness (71). Patients are unable to rely on their own recollections of illness (and often for the few days or weeks prior to hospital admission) and are often

informed by others about the course of the illness a course which can be marked by stressful events, including ICU stays, seizures, and disorientation/confusion of the patients. These events are often retold to the patient by distressed family and loved ones, who themselves often have yet to process the events, and thus the patient's understanding of their own illness can be marred by the lens of others, which may be disconcerting when one has little or no recollection of the events themselves. Relatedly, narrative studies have highlighted the impact of identity issues and the concept of a 'loss of self' – particularly when there are comparisons to the 'pre-illness' and 'post-illness' self, loss of self in the eyes of others, and discontinuation of identity when there are memory disruptions (71,72).

Notably, many of the neuropsychiatric and psychological sequelae can be addressed through various pathways, including psychopharmacological means as well as psychotherapy. Although there is a paucity of research on the efficacy of psychological interventions in this population directly, interventions have been shown to be beneficial in a multitude of populations with traumatic and other forms of brain injuries. Consequently, ensuring that all of these patients are appropriately screened and managed across multiple follow-ups is vital to maximising the quality of life in AE patients.

Conclusions

The past two decades of research has advanced our understanding of the nature and course of AE, improving patient survival rates and minimising disease burden from a physical standpoint. What has become apparent, however, is that the neurocognitive compromise, neuropsychiatric symptoms and compromised psychological outcomes across the syndromes of AE. In the acute stages poor episodic memory, psychomotor slowing, fluctuations in attention and variability in cognitive control are commonly reported, however the cognitive syndromes of AE have yet to emerge. At this time, it also appears that neuropsychiatric symptomology arises in the prodromal phases of many AE syndromes. In the post-treatment phases of many subsets of AE, chronic sequalae vary significantly, ranging from minor attention fluctuations, to severely incapacitating neurocognitive compromise and debilitating neuropsychiatric and psychological profiles that affect functional independence. The current research broadly suggests poorer outcomes in the domains of episodic memory and cognitive control, perhaps reflecting the influence of disrupted frontotemporal networks critical to these cognitive functions. Considerable work remains to be done in clarifying the cognitive mechanisms underpinning these findings, as well as identification of post-treatment cognitive syndromes in different AE subtypes and clarification of factors associated with worse cognitive outcomes. What is becoming clear, however, are the ongoing neuropsychiatric and psychological symptomology evident in this population. Given the impact of these symptoms on quality of life, efforts should be made to ensure that AE patients are thoroughly assessed throughout their recovery journey, and interventions made when necessary. Ultimately, research in AE associated cognitive syndromes and psychopathology will likely assist in cognitive profiling according to disease subset. It will also inform what cognitive architectures are compromised which can aid in the development of personalised cognitive and psychological interventions, aimed at lessening the

morbidity associated with the disease. Cognitive and neuropsychological manifestations of AE lead to significant impairments in functional independence, and ongoing research in this area is crucial.

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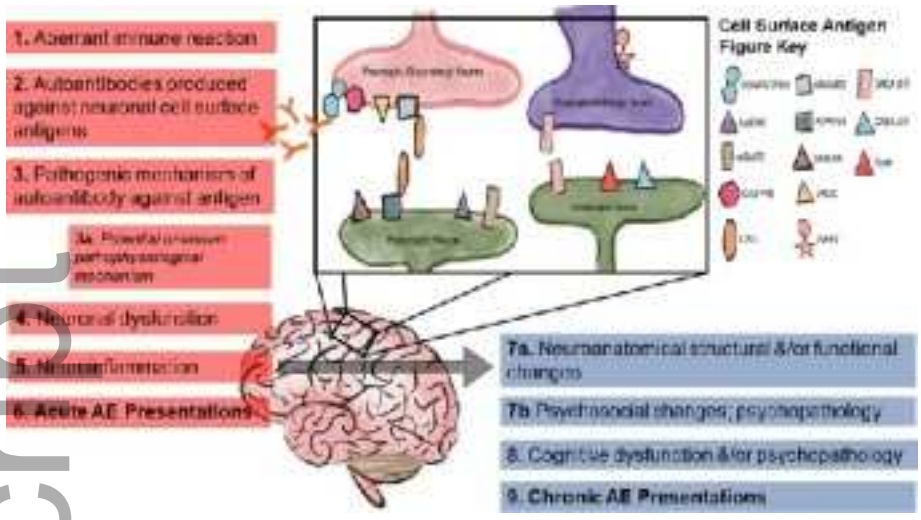
622 Table 1. Clinical features of Autoimmune Encephalitis with autoantibodies targeting neuronal surface
623 antigens

	Associated Clinical Syndrome
NMDAR	– Non-specific prodromal symptoms, described as 'flu-like' – Followed by an acute onset of behavioural and mental state disturbances including psychiatric symptoms: hallucinations, delusions, mania, agitation, changes in speech, disorganised thinking, catatonia, insomnia and often seizures. – Without treatment clinical course can include dysautonomia, hypoventilation, and movement abnormalities(73)
LGI1	– Faciobracial dystonic seizures – Cognitive disturbances fundamentally characterised as amnesia – Behavioural changes, sleep disturbances and hyponatraemia – Paraclincal features of limbic encephalitis (74)
CASPR2	– Rapid development of confusion, working memory deficit, mood changes and, in 53% of these patients, seizures – Additional symptoms have also been reported in these patients beyond the limbic system, including cerebellar dysfunction and neuropathic pain. – Patients can also present with Morvan syndrome – a clinical presentation of a combination of cognitive symptoms or seizures as well as peripheral nerve hyperexcitability and dysautonomia or insomnia (12)
DPPX	– Severe prodromal weight loss of diarrhoea – Followed by cognitive dysfunction (primarily memory deficit), – CNS hyperexcitabilty or brainstem or cerebellar dysfunction (75)
GABA A	– Heterogeneous clinical presentations. – Features of limbic encephalitis can be present. – Cognitive and behavioural changes noted in 2/3 of patients, primarily memory deficits(76)
GABA B	– Prominent seizures along with classic features of limbic encephalitis, including memory deficits, psychiatric symptoms, and behavioural and personality changes(77,78)
AMPAR	– Heterogeneous clinical presentations. including behavioural, cognitive, motor and sensory manifestations (32) – Dysexecutive features are also noted as a potential feature, with other extralimbic symptoms noted including movement disorders, cerebellar signs and sleep disorders.

IgLON-5	– Heterogeneous clinical presentations. Sleeping dysfunction is commonly reported, along with "cognitive disturbances" (33)
MGluR	– Heterogeneous clinical presentations. – Behavioural changes including depression, anxiety as well as cognitive dysfunction primarily memory loss has been commonly reported in cases (79)
Seronegative	– Heterogeneous clinical presentations. Often present with cognitive (memory dysfunction has been commonly reported in cases) which resolve with immunotherapy. (5)(80)

Abbreviations: NMDAR = N-methyl-D-aspartate receptor; LGI1 = leucine-rich glioma inactivated 1; CASPR2: contactin-associated protein 2; DPPX = dipeptidyl peptidase-like protein 6; GABA = gamma-Aminobutyric acid; AMPAR: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; IgLON-5 = immunoglobulin like cell adhesion molecule 5
mGluR = metabotropic glutamate receptor 5; GlyR = Glycine Receptor; VGKC = voltage-gated potassium channels

Figure 1. Neural Systems of AE leading to the acute and chronic cognitive AE presentations. **1**. An aberrant immune reaction occurs. This produces **2.** an antibody response where autoantibodies are produced against neuronal cell surface antigen targets. These antibodies have a **3.** pathogenic mechanism against the targeted antigen. Given there is ongoing cognitive dysfunction in some patients, hypotheses suggest there are also **3a.** unknown pathophysiological mechanisms. The pathogenic mechanism results in **4.** neuronal dysfunction, directing a cytotoxic response against neuronal issue resulting **5.**neuroinflammation and the **6.** acute AE presentations. This can all lead to **7a**. neuroanatomical structural and/or functional changes on clinical and/or research imaging which is correlated to cognitive dysfunction. The neuroanatomical changes along with **7b.** psychosocial changes and psychopathology, lead to the **8.** cognitive dysfunction and/or psychopathology seen in **9.** chronic AE presentations. AE = Autoimmune Encepahilitis; NMDAR = N-methyl-D-aspartate receptor; LGI1 = leucine-rich glioma inactivated 1; CASPR2: contactin-associated protein 2; DPPX = dipeptidyl peptidase-like protein 6; GABA = gamma-Aminobutyric acid; AMPAR: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; mGluR = metabotropic glutamate receptor 5; GlyR = Glycine Receptor; VGKC = voltage-gated potassium channels



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