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Review

Autoimmune encephalitis: Recent updates and emerging challenges

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ABSTRACT

The knowledge of immune dysregulation and autoimmunity in neurological disorders has expanded considerably in recent times. Recognition of clinical syndromes, reliable methods of diagnosis, and early targeted immunotherapy can lead to a favourable outcome in acute and subacute neurological disorders that may be associated with significant morbidity and mortality if left untreated. This review focuses on the rapidly expanding field of autoimmune encephalitis. We describe the differences between limbic encephalitis associated with antibodies targeting intracellular antigens, and neuronal surface antibody syndromes (NSAS) where the antigens are primarily receptors or synaptic proteins located on the neuronal cell surface. We chronologically highlight important developments in NSAS by focusing on voltage gated potassium channel complex-associated antibody mediated encephalitis, anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis, and anti-dopamine 2 receptor antibody-associated basal ganglia encephalitis. Contentious issues such as the complexities of using serum antibodies as biomarkers, the initiation of central nervous system autoimmunity, and possible pathogenic mechanisms of these antibodies will be reviewed. The therapeutic challenges that clinicians face such as the timing of therapy and the role of second-line therapy will be discussed, with crucial concepts highlighted in the form of clinical vignettes. Future directions will involve the identification of novel antigens and methods to establish their pathogenicity, as well as evaluation of the most efficacious therapeutic strategies in patients with established NSAS.

1. Introduction

The role of immune dysregulation and autoimmunity in neurological disorders has been the subject of considerable research in recent times. This review focuses on the rapidly expanding field of autoimmune encephalitis.

Limbic encephalitis (LE) was first described in the 1960s and refers to the subacute onset of episodic memory loss, confusion, and agitation [1]. LE is frequently associated with hallucinations, seizures, sleep disturbance, and signal change in the medial temporal lobe and hippocampi on imaging. LE is classically described as being paraneoplastic [1]. Antibodies to onconeural intracellular antigens which are nuclear or cytoplasmic proteins such as Hu, Ma, and Ri are associated with certain malignancies such as lung cancer and testicular tumours [1,2]. These antibodies are clearly demonstrated by standardised tests, associated with limited subtypes of malignancies, and have a variety of neurological manifestations [2]. The clinical course is usually monophasic and relentlessly progressive with a guarded prognosis, and treatment is directed to the underlying malignancy [3,4]. The antibodies targeting onconeural antigens are believed to be biomarkers of associated tumours rather than being directly pathogenic, and their detection should prompt investigation for an associated underlying malignancy [2,4,5]. Previous studies including passive transfers or active vaccination with the antigen in animal models have failed to reproduce these clinical syndromes, and newly published results have shown that neuronal cell death was due to T-cell mediated cytotoxicity, lending further weight to the contention that this group of antibodies is not directly pathogenic [2,4].

There is a second distinct group of patients with autoimmune encephalitis, where autoantibodies targeting neuronal cell surface antigenic epitopes that are extracellular rather than intracellular have been identified [2,3,6,7]. This group of antibodies are collectively referred to as "neuronal surface antibodies" (NSAbs), and the neurological manifestations associated with them as "neuronal surface antibody syndromes" (NSAS) [5]. Lancaster et al. characterised NSAbs as demonstrating five features – the epitopes are extracellular, antibody binding is visible in cells transfected with the target antigen, the antibodies should alter the function or structure of the neural antigen, the downstream effects of the antibody are

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often reversible, and the clinical picture corresponds with genetic or pharmacologic models in which the antigen is disrupted [3]. The antigens are often receptors or synaptic protein complexes intimately involved with mechanisms of synaptic transmission and plasticity [8]. Identified targets include components of the voltage gated potassium channel complex (VGKC) such as leucine-rich glioma inactivated 1 (LGI1) and contactin-associated protein-like 2 (Caspr2); the N-methyl-D-aspartate receptor (NMDAR), the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR), the γ-aminobutyric acid receptor ($GABA_BR$), and the glycine receptor [3,8,9]. NSAS collectively appear to be far more prevalent than LE, are associated with onconeural antibodies, often have a relapsing course, have an overall better prognosis, and are less commonly paraneoplastic [3,4]. The prevalence of an associated malignancy varies depending on the antibody in question, however, this is rarely more than 70% [2]. A more detailed description of the clinical and laboratory features of each of the syndromes associated with established and emerging NSAbs is outlined in Tables 1 and 2. As some NSAbs such as AMPAR, $GABA_BR$ and those identified in Table 2 have been identified in relatively small numbers of patients, it is possible that with the increasing recognition of such syndromes and greater patient numbers the clinical phenotype associated with these NSAbs will evolve and expand.

Glutamic acid decarboxylase (GAD), another antigen of interest, is dissimilar to the intracellular onconeural antigens as anti-GAD antibody associated neurological syndromes are usually non-paraneoplastic and immune responsive. Anti-GAD antibody-associated syndromes do not fulfill the criteria for a NSAS as GAD is an intracellular antigen. Anti-GAD antibodies have been identified in some patients with LE (including those with other confirmed NSAbs such as AMPAR), as well as being associated with type 1 diabetes mellitus, stiff person syndrome, temporal lobe epilepsy, and cerebellar ataxia [2,10–12]. Anti-GAD antibodies associated with neurological disorders are typically of much higher titre (>1000 international units/mL) compared with the titres found in patients with Type 1 diabetes.

2. Specific syndromes

2.1. VGKC complex-associated antibody mediated encephalitides

VGKC on cell surface membranes have been identified as being a key protein determining neuronal excitability [1]. Antibodies against this target were initially associated with disorders of the peripheral nervous system such as acquired neuromyotonia or Isaacs' syndrome, and cramp-fasciculation syndrome [13]. Subsequently, involvement of the central nervous system (CNS) in patients with VGKC complex-associated antibodies was also described such as in Morvan's syndrome where neuromyotonia is accompanied by cognitive impairment, sleep disturbance, and

Table 1
Clinical, laboratory and imaging characteristics associated with established neuronal surface antibody syndromes

Antigen	NMDAR	LGI1	Caspr2	AMPAR	$GABA_BR$	Glycine R
Age	Infancy–elderly, frequently 2–40 years	30–80 years (median 60 years)	45–80 years (median 60 years)	40–90 years (median 60 years)	25–75 years (median 60 years)	5–69 years (median 49 years)
Sex	Up to 80% female	65% male	85% male	90% female	50% female	Unknown
Neurological manifestations	Behavioural disturbance, psychosis, catatonia, seizures, aphasia, movement disorders including orolingual dyskinesias, central hypoventilation, dysautonomia	Faciobrachial dystonic seizures, limbic encephalitis, epilepsy (often tonic seizures), myoclonus, rapidly progressive dementia (can mimic CJD), sleep disorders	Peripheral nerve hyperexcitability or neuromyotonia (Isaacs' syndrome), Morvan's syndrome, limbic encephalitis (less common), sleep disorders	Limbic encephalitis, atypical pychosis	Limbic encephalitis, prominent seizures in up to 80% of patients	Progressive encephalomyelitis with rigidity, stiff person syndrome
CSF abnormalities	90% abnormal – CSF lymphocytosis, intrathecal oligoclonal bands and elevated protein	40% abnormal	25% abnormal, often bland CSF	90% abnormal, often intrathecal oligoclonal bands	80–90% abnormal, often intrathecal oligoclonal bands	Variable CSF elevated protein, lymphocytosis, and oligoclonal bands; can be normal
Imaging	Up to 50% abnormal; medial temporal lobe hyperintensity, focal cortical T2-weighted/FLAIR hyperintensity	85% medial temporal lobe FLAIR high signal	40% abnormal, medial temporal lobe FLAIR high signal	90% abnormal, medial temporal lobe FLAIR high signal	65% medial temporal lobe FLAIR high signal	Frequently normal
Tumour frequency and association	Ovarian teratomas in women >15 years, can be other tumours (thymomas, mediastinal or testicular teratomas, Hodgkin lymphoma), significant portion non-paraneoplastic (particularly children and males)	Rare, <20% (lung, thymus)	Thymomas in 20–40%	Tumours in 70% (small cell lung cancer, breast cancer, thymic cancer)	Tumours in 45–60% (small cell lung cancer)	Reported lung cancer, Hodgkin lymphoma, thymoma; usually not paraneoplastic
Relapse rate	12–25%	Uncommon	Limited experience	50–60%	Uncommon	Unknown
Other	–	Associated hyponatraemia	–	–	–	Can have concurrent GAD65–IgG antibodies

AMPAR = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, Caspr2 = contactin-associated protein-like 2, CJD = Creutzfeldt–Jakob disease, CSF = cerebrospinal fluid, FLAIR = fluid attenuated inversion recovery, $GABA_BR$ = γ-aminobutyric acid receptor, GAD = glutamic acid decarboxylase, Glycine R = glycine receptor, IgG = immunoglobulin G, LGI1 = leucine-rich glioma inactivated 1, NMDAR = N-methyl-D-aspartate receptor.
Adapted from [2,3,11], [92, 93].