Autoimmune encephalitis

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Abstract

Autoimmune encephalitis is emerging as an important and relatively common cause of encephalitis in the developed world. Crucially, early recognition and prompt initiation of a range of immunotherapies is likely to improve the outcomes of patients with autoimmune encephalitis, particularly for those with identifiable antibodies against neuronal cell surface proteins. There are a rapidly growing number of specific autoantibodies and associated syndromes, but many of these remain very rare. The majority of cases comprise anti-N-methyl-D-aspartate (NMDA) receptor encephalitis or anti-leucine-rich glioma-inactivated protein 1 (LGI1) encephalitis with the remaining cases a mixture of over 10 other specific antibodies or being seronegative. The core anti-NMDA encephalitis phenotype is a distinct symptom complex involving psychiatric and neurological features and anti-LGI1 encephalitis presents with cognitive changes and distinct seizure types. Diagnosis can be delayed owing to limited access to specialised laboratory testing or in cases with atypical or limited features.

Keywords: antibody, autoimmune, encephalitis, NMDA receptor, psychosis, seizure

Financial and Competing Interests: JAG is Chief Executive Officer and holds equity in Abaxon Biologics, a biopharmaceutical company developing novel therapies in autoimmune and other diseases. JAG and GAM have received funding from Tenovus Scotland to help establish a prospective patient register for people with autoimmune encephalitis.

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Introduction

The reported incidence of encephalitis in adults from the western world varies between 0.7 and 12.6 per 100,000.[1] Most cases of encephalitic illnesses are due to infection, but a specific cause is often not identified; for instance, in a UK multicentre study, a specific aetiology was discovered in only 63%.[2] An autoimmune aetiology is being increasingly recognised and patients with antibodies against specific neuronal cell-surface proteins are being more frequently identified in research and routine clinical settings.[3] A recent epidemiology study from Olmsted county suggested that the incidence of autoimmune encephalitis (0.8 per 100,000) nearly matched that of infective encephalitis (1 per 100,000) and that the incidence of autoimmune causes was rising over time as more antibodies are identified.[4]

Since 1968 the clinical phenotype of limbic encephalitis was recognised as a rare paraneoplastic phenomenon.[5] Patients presented with subacute behaviour and memory disturbance, along with seizures associated with a number of malignancies. Neuroimaging often revealed abnormalities in limbic areas and cerebrospinal fluid (CSF) analysis usually demonstrated a mildly raised white cell count, raised protein and unpaired oligoclonal bands. A group of antibodies usually described as antineuronal or paraneoplastic antibodies (including anti-Hu, Ma2/Ta, CRMP5 and amphyphisin) were first identified in the 1980s and 1990s.[6] These antibodies are directed against intracellular antigens and several lines of evidence suggested that they were not directly pathogenic, but were an epiphenomenon of the anti-tumour immune response. There was modest response to treatment of any tumours, but not to isolated immunotherapy in these patients. This, therefore, limited interest in the field.

Things changed in 1995 after the recognition that some patients suffering from neuromyotonia, a condition with spontaneous activity in muscles, had antibodies directed against the voltage-gated potassium channel (VGKC) and responded to immunotherapy in the form of plasma exchange.[7] Later similar antibodies were detected in patients suffering from neuromyotonia and limbic encephalitis (Morvan's syndrome)[8] and later limbic encephalitis alone.[9] The early radio-immunoassay assay (RIA) used was initially believed to identify antibodies binding to radiolabelled VGKC; so-called anti-VGKC antibody encephalitis. Attempts to confirm the antibody target and to simplify diagnostic testing were initially unsuccessful and the RIA remained the gold standard for several years.

In 2010, two major research groups independently demonstrated that for the majority of patients with anti-VGKC encephalitis, the antibodies actually bind not to the VGKC protein itself but to leucine-rich, glioma-inactivated

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protein 1 (LGI1), which is linked to VGKCs in a multiprotein complex in vivo and which was actually also present in the RIA.[10,11] A smaller proportion of anti-VGKC antibody positive patients have antibodies directed against contactin-associated protein-like 2 (CASPR2), a cell-surface protein also linked to the VGKC complex.[12] Following this realisation, relatively simple commercial cell-based assays (CBAs) were introduced in which the antigen of interest is expressed at the cell surface of commercial cell lines and can be used as a substrate to identify autoantibodies with a high degree of sensitivity and sensitivity.

Several of the initial cases of anti-VGKC encephalitis occurred as a paranoeoplastic phenomena, but once the antibody test was available and increasingly utilised, a number of non-paraneoplastic cases were identified[13] and current data suggests malignancy is seen only in a minority of patients.

In 2005, Dalmau and colleagues identified four patients presenting with a distinct encephalitis associated with an ovarian teratoma.[14] Thereafter, they were able to identify pathogenic antibodies binding the NR1 sub-unit of the N-methyl-D-aspartate receptor (NMDAR). These antibodies were shown to bind to rat hippocampi and interact directly with a cell-surface channel and subsequent in vitro experiments demonstrated that the antibodies can cross-link NMDARs leading to their removal from the cell surface and disruption of numerous cortical and subcortical networks.[15,16] Thus, they are widely accepted as being directly pathogenic. By 2008, a case series of over 100 cases of encephalitis associated with NMDAR antibodies (NMDAR-e) was published, confirming the condition was not that rare and it is currently the most commonly recognised form of autoimmune encephalitis. Interestingly in this series 60% of patients had no tumour detected and further work has identified preceding herpes simplex virus encephalitis as a trigger for developing NMDAR-e in a number of patients.[14]

By the late 2000s the identification of anti-VGKC antibody encephalitis and NMDAR-e had established immunotherapy-responsive, antibody-mediated encephalitis as a nosological entity and fuelled increasing interest in identifying other autoantibodies and reshaped how clinicians managed suspected encephalitis. Additional autoantibodies directed against novel neuronal cell-surface proteins have since been identified, with several novel autoantigens being identified each year.

The relative incidences of the different forms of antibody encephalitis are difficult to assess. The relative incidence of positive antibodies sent to a tertiary neuroimmunology service in 2011 was 50% NMDAR, 30% LGI1, 3% CASPR2, 5% α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA), 3% gamma-aminobutyric acid type B ($GABA^B$) and 1% glycine antibodies, respectively.[15] This is not epidemiological data, as the samples will have been sent from multiple populations and the pattern of investigation will likely differ considerably on this basis. Nonetheless, cases of NMDAR-e and anti-LGI1 encephalitis appear to make up the majority of clinical cases reported in the published literature and this is in agreement with our experience.

Typical presentations of most common phenotypes

General clinical features

Many of the different antibody-mediated syndromes have distinct clinical features, but these may only be in a proportion of patients either at a very early stage of the illness or alternatively at a late stage when ideally therapy should have already been commenced. In many cases, there are not any pathognomic features, but instead the patients have a phenotype that could include one of several of the antibody-mediated encephalitides. Table 1 contrasts the general findings in patients with autoimmune encephalitis and clinically important differential diagnoses.

Specific antibody phenotypes

Anti-NMDAR-e

Anti-NMDAR-e is the most commonly identified cause of autoimmune encephalitis. The clinical spectrum is wide, with challenges in diagnosis early in the disease course and in those with limited forms. Nonetheless, there is a core phenotype that is distinctive as the archetypal form of NMDAR-e.

The seminal case series comprised four young females with a distinct neuropsychiatric syndrome and ovarian teratomas.[16] They presented with acute psychiatric symptoms, seizures and memory impairment, and progressed to decreased levels of consciousness with central hypoventilation requiring ventilatory support. Three patients improved with immunotherapy or treatment of the teratoma. One died. The patients' sera and CSF showed a distinct pattern of autoreactivity on hippocampal sections and subsequent work identified NMDAR antibodies as the relevant autoantibody.[17–19] The recognised clinical phenotype subsequently widened to include male and females, cases without tumours, children, and a wide range of psychiatric and neurological features.

A large multicentre observational study highlights the core features of NMDAR-e.[20] In this study patients were predominantly younger (95% under 45 years), female (female to male ratio of 4:1), with tumours in 5% of children under 12 years, in 58% of females over 18 years and only in 23% of adults over 45 years.

In adults the presentation usually comprises an initial period of complex psychopathology, including psychosis, delusions, hallucinations, agitation or catatonia.[21] This then evolves to include orofacial dyskinesias, memory impairment, and in many cases to autonomic dysfunction and a decreased conscious level. Seizures are common and can be frequent, focal or generalized, and treatment resistant.

Table 1 General features distinguishing autoimmune encephalitis from important differential diagnoses

Feature	Autoimmune encephalitis	Infective encephalitis	Neurodegenerative disease	Primary psychiatric	Nonencephalitic encephalopathy
Fever	-	+	-	-	+/-
Systemic response/sepsis	-	+	-	-	+
'Infective' prodrome	+/-	+	-	-	+/-
Temporal onset	Days to weeks	Hours to weeks	Months to years	Weeks to months	Days to weeks
Course	Deterioration with fluctuations	Deterioration with fluctuations	Deterioration	Fluctuations	Fluctuations
Frequency of seizures	High frequency from onset	Variable	None	None	Variable, usually infrequent or none
CSF white cell count	Usually <100	Usually 100s–1,000s	Normal	Normal	Normal or mild increase
CSF protein	Mild elevation	Mild-to-high elevation	Normal	Normal	Normal-to-mild elevation
CSF oligoclonal bands	Negative Paired Unpaired Polyclonal	Negative Paired Unpaired Polyclonal	Negative	Negative	Negative Paired Polyclonal
MRI brain	Often normal Focal 'inflammatory' lesions Enhancement	Often significant abnormalities	Atrophy	Normal or nonspecific changes	Normal or nonspecific changes

CSF: cerebral spinal fluid

Within a month of onset, the vast majority of patients develop four or more core symptoms comprising abnormal behaviour and cognition, memory impairment, speech disorder, seizures, abnormal movements, decreased consciousness or autonomic dysfunction, central hypoventilation, and cerebellar ataxia or hemiparesis. Probably around 1% of patients have a purely monosymptomatic manifestation of the disease, such as an isolated psychosis, after a few months. Thus, while the full clinical spectrum is quite varied, the hallmark is the above *symptom complex* developing over weeks to months.

Early immunotherapy is associated with better outcomes in NMDAR-e patients, as is instigation of second-line therapy if first-line therapies fail.[20] Aggressive immunotherapy carries significant risks of serious side-effects and a challenge for treating clinicians is, therefore, in identifying patients most likely to benefit from escalating treatments and those likely to do well with more conservative management. In 2019, the anti-NMDAR Encephalitis One-Year Functional Status (NEOS) score was developed from a cohort of 382 patients in order to provide an early clinical tool for predicting prognosis.[22] This simple five-point prediction score correlates well with 1-year functional outcome and may be helpful in the early selection of patients who should be treated with second- or third-line immunotherapies.

Anti-LGI1 encephalitis

Anti-LGI1 encephalitis has a median age of onset of about 60 years, and usually presents in one of two ways: rapidly progressive cognitive decline or as new-onset, high-frequency, focal seizures.[23] Anti-LGI1 encephalitis is extremely rare in children.

Rapid cognitive decline

Most patients with anti-LGI1 encephalitis develop some cognitive impairment at some stage and this can be severe and early in the illness, leading to a rapid deterioration in cognitive function. If untreated this can progress over weeks or months to marked impairment in multiple cognitive domains and an overt dementia picture. Often there is also a history of new-onset seizures, either focal or generalised, which is an important clue to a potential autoimmune aetiology.

New-onset, high-frequency, focal seizures

With anti-LGI1 encephalitis, there are at least three distinct phenotypes of new-onset, high-frequency, seizures.

Firstly, and most specific for anti-LGI1 encephalitis, around 20% of cases present with a highly distinct seizure semiology known as facio-brachial dystonic seizures, which are considered pathognomic for the condition.[24] These consist of very brief, sudden, shock-like movements of one or more limbs, neck and facial muscles. Awareness is usually preserved. Characteristically, they rapidly progress in frequency over a few days from onset to occur dozens or hundreds of times per day and are usually very sensitive to steroids but less so anti-epileptic medications.

A second common presenting seizure semiology manifests with autonomic features. Typically, the patient reports highly stereotyped events that again characteristically occur with very high frequency. There can be a wide range of reported symptoms, such as an abnormal sensation in the abdomen, often rising upwards, palpitations, fear or panic, sensory disturbances, temperature changes or other autonomic symptoms. Commonly there are accompanying physiological changes, such as tachycardia, blood pressure fluctuations or 'goosebumps'. Given how closely these patients' symptoms mimic anxiety attacks or arrhythmias, diagnosis is often delayed until cognitive impairment develops or MR imaging or CSF analysis suggests an encephalitic disorder.

Thirdly, anti-LGI1 encephalitis can manifest as new-onset, highly frequent seizures of almost any semiology, either focal or generalised, depending on where the initial inflammatory focus is developing.[25] In this context the most characteristic features are the abrupt onset of a very high frequency of seizures that are often resistant to initial anti-epileptic drugs.

Finally, there are some other less common clinical features that can be seen in anti-LGI1 encephalitis and may prompt the initial consideration of the diagnosis. Patients with cognitive dysfunction often have a hyponatraemia in a syndrome of inappropriate antidiuretic hormone secretion-type pattern. Occasionally patients can have ictal arrhythmias, including benign electrocardiogram changes through to complete heart block,[26,27] which can be mistaken as a primary cardiac disorder.

Anti-GABA^{B} receptor encephalitis

Antibodies against the GABA^{B} receptor are probably the third most commonly identified anti-neuronal cell-surface protein antibodies, however, they are considerably rarer than NMDAR or anti-LGI1 antibodies (personal observations). This has a less distinctive phenotype, usually presenting as typical limbic encephalitis. Anti-GABA^{B} receptor encephalitis can present primarily with highly frequent focal seizures that are treatment resistant with less pronounced psychiatric and cognitive issues. Tumours are common, with around 50% of patients having a small-cell lung cancer.[28]

Other anti-neuronal cell-surface receptor antibody-associated syndromes

Other specific antibodies in autoimmune encephalitis are significantly rarer than the aforementioned syndromes and are reviewed in Table 2.

Challenges for the future

Increasing number of reported antibodies associated with encephalitis

Two or three new antibodies are being reported in association with encephalitic presentations annually. The most clearly established antineuronal cell surface antibody-mediated syndromes, such as NMDAR-e, were initially described as distinct clinical syndromes with subsequent identification of the autoantibody. An expansion of the clinical phenotype then followed as more cases were identified with the availability of diagnostic tests. In recent years, antineuronal cell-surface antibodies have been identified by screening large numbers of samples from otherwise seronegative cases in specialised neuroimmunology centres. Using a variety of laboratory screening methods to screen large numbers of samples, small numbers of patients have had unique putative autoantibodies identified and an argument made for these as distinct disease entities. The evidence of pathogenicity is more limited for some of the more recently identified antibodies. Thus, for clinicians it is becoming increasingly difficult to be clear what the best strategies are for immunological testing and to maintain an awareness of newly recognised antibodies and the reported associated phenotypes.

Broadening phenotype associated with established antibodies

Another challenge is the tendency for the clinical spectrum of particular autoantibodies to expand with increasing awareness of and testing for any given particular disorder. Undoubtedly for most of these syndromes the clinical spectrum has been convincingly shown to be wider than in the initial small case reports; however, the limits to the full phenotypes are very difficult to determine.

Without a 'gold standard' test or diagnostic criteria other than the presence of the antibody in question, it can prove very difficult to determine whether an autoantibody found in a particular patient is a true or a false positive. Thus, the nosological limits of particular antibody syndromes tend to be hard to define, making clinical interpretation of antibody results complex and nuanced.

For example, many of these antineuronal cell surface antibodies have been described in cases with certain clinical features commonly seen in other contexts where they are not usually considered as autoimmune phenomena. Isolated psychosis or epilepsy, for instance, are frequently seen with nonautoimmune aetiologies.

There are a number of significant ongoing studies being led from Cambridge and Oxford looking at autoantibodies in psychosis in particular. The prevalence of pathogenic autoantibodies in psychosis study is looking at the incidence of antibodies that have been associated with encephalitis in adults with a first presentation of psychosis across a number of UK sites. That these antibodies are pathogenic in causing psychosis is far from proven. Indeed as Table 3 demonstrates there is actually a fairly high incidence of antibodies generally in this population,[29] although this study used a lower cutoff threshold for anti-VGKC antibodies than has been shown to be clinically useful.[30,31] Less specific antibodies, such as anti-VGKC and anti-neuronal antibodies, had a much higher rate than the control population. It had previously been noted that less specific NMDAR assays, detecting the NR2 epitope rather than NR1, which is felt to be more specifically involved in autoimmune encephalitis, were detected in 5% of patients

Table 2 Antibodies currently reported in association with encephalitis

Antibody	Clinical presentation	Largest series of reported cases	Frequency of associated malignancy (%)	Common associated tumours	Level of evidence of direct pathogenicity
NMDAR	Psychiatric onset, orofacial dyskinesia, seizures, coma	577 patients[20]	40	Ovarian teratoma	Pathogenic
LGI1	Limbic encephalitis, hyponatraemia, fasciobrachial dystonic seizures	76 patients[35]	5–10	Thymoma, thyroid, lung, renal	Pathogenic
CASPR2	Limbic encephalitis, Morvan's syndrome, neuromyotonia	27 patients with LE or Morvan's syndrome[36]	25–50	Thymoma	Uncertain
$GABA^B$	Limbic encephalitis, psychosis, refractory seizures	20 patients[28]	50	SCLC	Likely pathogenic
$GABA^A$	Refractory seizures, encephalitis	26 patients[33]	17	Thymoma, SCLC	Uncertain
AMPA	Limbic encephalitis, psychosis	22 patients[37]	60–70	SCLC, breast, thymoma	Uncertain
Glycine	Limbic encephalitis, PERM, rigidity	Literature review of 187 patients[38]	5–10	Thymoma, lymphoma, breast	Likely pathogenic
mGluR5	Encephalitis, myoclonus, cerebellar syndrome	11 patients[39]	70	Hodgkin's lymphoma, SCLC	Uncertain
DPPX	Encephalitis, PERM, hyperekplexia, gastrointestinal symptoms	9 patients[40]	<10	Lymphoma	Uncertain
DR2	Encephalitis, movement disorder, sleep disturbance	17 patients[41]	0	Nil	Uncertain
IgLON5	Sleep disorder, bulbar symptoms, cognitive dysfunction (14%)	22 patients[42]	0	Nil	Uncertain
Neurexin-3α	Limbic encephalitis, orofacial dyskinesia, central hypoventillation	5 patients[43]	0	Nil	Uncertain

AMPA: α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid; CASPR2: contactin-associated protein-like 2; DPPX: dipeptidyl-peptidase-like protein 6; DR2: dopamine receptor 2; $GABA^A$: gamma-aminobutyric acid type A; $GABA^B$: gamma-aminobutyric acid type B; LE: limbic encephalitis; LGI1: leucine-rich glioma-inactivated protein 1; mGluR5: metabotropic glutamate receptor 5; NMDAR: N-methyl-D-aspartate receptor; PERM: progressive encephalomyelitis with rigidity and myoclonus; SCLC: small-cell lung cancer

with schizophrenia. Therefore, detection of such a range of antibodies may indicate that the immune system plays a role in the pathogenic processes seen in active psychosis as a downstream phenomenon, rather than necessarily being directly causal in the way we see with autoimmune encephalitis. At present, the assumption is that LGI1 and N-methyl-D-aspartate NR1 antibodies in this setting represent rarer phenotypes of encephalitis.

There has been a small published series of 18 patients with psychosis who were found to have NMDAR antibodies.[32] It was reported that nine patients improved with standard care, but that nine patients were refractory and received immunotherapy. All nine received steroids, six plasma exchange, two immunoglobulin infusions and two rituximab. Six of these nine were said to go into clinical remission. Limited clinical and investigation information was given to establish if there were other features of more typical NMDAR-e. At present, however, the SINAPPS2 (Study if ImmuNotherapy in Antibody Positive Psychosis) study is underway. This is a multisite randomised control trial looking to recruit patients with either a first presentation of psychosis of over 2 weeks duration or relapsing having been in remission for 6 months. The aim is for patients to

Table 3 Prevalence of anti-neuronal cell-surface protein antibodies in first-episode psychosis.[29] Note that the cutoff value for VGKC antibodies in this study was >150 pM but other studies establish a cutoff value of >400 pM as the clinically useful threshold[34,44]

Antibody	No (%) of first psychosis patients (n = 228)	No (%) of controls (n = 105)	Odds ratio (95% CI)
NMDAR (NR1 IgG)	7 (3)	0	5.4 (p = 0.02)
LGI1	3 (1)	0	2.3 (p = 0.13)
CASPR2	2 (1)	3 (3)	0.3
$GABA^AR$	8 (4)	1 (1)	3.8 (0.5–30.7)
AMPA	0	0	–
Anti-neuronal	20 (9)	4 (4)	2.4 (0.8–7.3)
VGKC >150 pM	11 (5)	3 (3)	1.7 (0.5–6.3)
ANA >1/160	7 (3)	9 (9)	3.6 (1–13.6)

AMPA: α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid; ANA: antinuclear antibodies; CASPR2: contactin-associated protein-like 2; CI: confidence interval; $GABA^AR$: gamma-aminobutyric acid type A receptor; LGI1: leucine-rich glioma-inactivated protein 1; NMDAR: N-methyl-D-aspartate receptor; VGKC: voltage-gated potassium channel

be treated either with placebo or immunoglobulin followed by rituximab with clinical monitoring thereafter to determine efficacy. The results will likely be very influential in the direction of management of such patients in the future. If negative, this may indicate the detection of these antibodies is an epiphenomenon. If positive, it will be important to try and determine if the antibodies are truly pathogenic or if the immune system may play an important downstream role after clinical onset in disease progression. Thus, immunotherapy may prove to have a role in treatment, but an understanding of its role in altering the pathogenic processes will still need to be determined.

Controversies surrounding antibody testing

Diagnostic testing strategies

Autoantibody testing in autoimmune encephalitis has developed from the work of a few select and highly expert laboratories around the world. These centres have established antibody-mediated encephalitis as an important, relatively common and treatable disease entity, and have advanced our knowledge in the area tremendously. Routine diagnostic testing of patient samples has historically been carried out by these laboratories, given their expertise and use of advanced diagnostic and research techniques, which are not otherwise widely available. As interest in this area has grown, so has the demand for rapid access to diagnostic testing, which cannot reasonably be expected to be met by such a small number of laboratories. In addition, as new and often rare autoantibodies are identified, it remains in the domain of highly expert laboratories to adapt their techniques to screen for these in addition to the more established antibodies. It is clear that these reference laboratories continue to play a central role in identifying new antibodies and in diagnostic testing for many of them.

Nonetheless, with commercialisation of relatively simple and quick diagnostic assays for several of the commoner autoantibodies, it has become feasible for less specialised laboratories to begin to implement a degree of local testing. It is now possible for local laboratories to test for the common autoantibodies, which will identify the majority of antibodies in seropositive cases, and to refer on for further testing for the rarer antibodies in patients testing negative with the initial screen.

Commercial assays for NMDAR antibodies and for anti-LGI1 and anti-CASPR2 antibodies are available that are rapid, reliable and accurate. The costs are relatively high (£35–£80 per test depending on the assay) compared to most routine laboratory tests; however, the ability to offer patients rapid and accurate screening for the most common autoantibodies can transform the investigation and management of this patient group. In neurological centres where all testing is routinely referred on to highly specialised laboratories, there is often a delay of several weeks in obtaining results. During this time empirical immunotherapy may have been commenced depending on how convincing the clinical picture is, but many clinicians feel uncomfortable initiating such first- or second-line therapies without clearer and more specific supporting laboratory evidence. In contrast, neurological centres with access to local testing can offer results within a few days, or same day if clinically urgent, of screening for autoantibodies that make up the vast majority of seropositive cases. This allows early initiation and escalation of therapies, or indeed re-focuses investigations and management along other lines.

Undoubtedly, the highly specialised laboratories offer a range of diagnostic assays not available in local laboratories with limited commercial assays and are far better positioned to use more advanced techniques, such as live cell assays or to screen for much rarer antibodies. The reluctance of clinicians to amend their investigation strategies to send samples to their closer services for fear of the available assay being less sensitive is likely unfounded, but poses the clearly proven risk of a significant delay in samples reaching the more distant quaternary laboratory services and being processed. Given that the commercialised assays will detect a very high proportion of autoimmune encephalitis patients it makes sense to test these quickly at regional laboratories and for the quaternary services with more detailed assays to be performed when these tests are negative, but there

remains a high clinical suspicion of encephalitis. This more detailed screening is now shifting from serial testing for individual, select antibodies, to a process of testing for a large number of antibodies using a commercially available mosaic panel of multiple antigens that can include NMDAR, LGI1, CASPR2, GABA^{B}, AMPA, dipeptidyl-peptidase-like protein 6 (DPPX), IgLON5, glycine receptor, metabotropic glutamate receptor 5 (mGluR5) and others.

In many cases the broad diagnosis of autoimmune encephalitis will be readily apparent from the initial clinical presentation and initial CSF profile, imaging and other parameters. In this context it is vital that clinicians begin empirical immunotherapy before confirmatory autoantibody testing. Early treatment in both NMDAR-e[33] and LGI1 encephalitis[24] is likely to lead to improved outcomes and the same is likely to be true of the remaining autoantibody-associated syndromes. Some very practical clinical guidelines to how to approach the initial investigation and treatment of autoimmune encephalitis have recently been developed.[34]

Assay technique

An additional ongoing debate is of which assay techniques should be employed for testing for antibodies against neuronal cell-surface receptor antibodies.[34] The use of fixed animal brain tissue slices has a long history in this field and is commonly used as a relatively crude screening technique in routine clinical diagnostics and also forms the basis of identifying most of the anti-neuronal cell-surface receptor antibodies now recognised. This technique is limited in that it requires experienced interpretation, is very sensitive to the tissue preparation process and does not yield a specific autoantibody result. The technique also detects antibodies against intracellular antigens, which are not always clinically relevant, and can fail to detect antibodies against antigens that have been modified by the fixative.

More specific tests include the CBAs that comprise either live neuronal cell cultures or fixed cells expressing relevant antigens of interest. The live CBA is perhaps the most sensitive and flexible diagnostic technique but is labour intensive, expensive and few centres have the expertise required to perform them. The fixed CBAs are now commercially available for most antigens and can be performed rapidly using equipment available in most laboratories. The CBAs have the further advantage of utilising the antigen of interest in its native conformation. This avoids the complication of detecting antibodies against irrelevant intracellular antigens or denatured proteins sequences that can occur with other techniques, such as tissue immunochemistry or immunoprecipitation assays.

At present there is no complete consensus on the ideal testing technique. Some laboratories will use multiple techniques to reach a consensus on any given result, e.g. brain slice immunochemistry or live CBAs to detect a likely antibody, followed by confirmatory specific testing with a fixed CBA expressing defined antigens. Other laboratories prefer to use one technique, be it a live CBA or multiple fixed CBAs.

The need for prospective patient registries

Much of what we know about the clinical and immunological behaviour of these disorders comes from retrospective identification of cases by testing large numbers of samples referred to highly specialised laboratories. This is an efficient way to identify new autoantibodies and continues to drive the field forward. However, with this referral bias there is often very limited clinical information available on the affected patients, their management or longer-term outcomes. There has, therefore, been a shift to develop prospective registers of proven cases to more fully inform our understanding of the clinical features and outcomes in these disorders. Establishing transparent registers to allow clinicians to more consistently feedback their patients' responses to treatment, outcomes and the rates of alternative diagnoses should better inform future patient care. Registries should inform the best acute and longer-term investigation and treatment strategies, as well as how best to monitor for associated malignancies.

Conclusion

While we are lucky enough to live in an era where we can now recognise and effectively treat patients with autoimmune encephalitis there remain important uncertainties. It is crucial that clinicians have an awareness of the common patterns of presentation and investigation findings to enable early treatment. Immunological testing strategies need to keep evolving to improve diagnosis and patient outcome. Where possible near-site testing of the more common antibodies is preferable. Prospective registries should inform clinicians on the incidence of false-positive results with different antibodies and assays.

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