The expanding spectrum of clinically-distinctive, immunotherapy-responsive autoimmune encephalopathies

O espectro em expansão das encefalopatias autoimunes clinicamente distintas e que respondem à imunoterapia

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ABSTRACT

The autoimmune encephalopathies are a group of conditions that are associated with autoantibodies against surface neuronal proteins, which are likely to mediate the disease. They are established as a frequent cause of encephalitis. Characteristic clinical features in individual patients often allow the specificity of the underlying antibody to be confidently predicted. Antibodies against the VGKC-complex, mainly LGI1(leucine-rich glioma-inactivated 1), CASPR2 (contactin-associated protein 2), and contactin-2, and NMDA (N-methyl, D-aspartate) -receptor are the most frequently established serological associations. In the minority of cases, an underlying tumour can be responsible. Early administration of immunotherapies, and tumour removal, where it is relevant, offer the greatest chance of improvement. Prolonged courses of immunotherapies may be required, and clinical improvements often correlate well with the antibody levels. In the present article, we have summarised recent developments in the clinical and laboratory findings within this rapidly expanding field.

Key words: autoantibody, encephalitis, leucine-rich glioma-inactivated 1, contactin-associated protein 2, N-methyl, D-aspartate.

RESUMO

As encefalopatias autoimunes constituem um grupo de condições associadas à presença, no soro, de anticorpos contra proteínas de superfície neuronais. Acredita-se que esses anticorpos sejam mediadores da ocorrência da doença, sendo reconhecidos atualmente como causas frequentes de encefalite. Apresentações clínicas características permitem, muitas vezes, predizer o grupo específico de anticorpos subjacentes. Anticorpos contra o complexo VGKF, especialmente LGI1 (leucine-rich glioma-inactivated1), CASPR2 (contactin-associated protein 2) e contactina-2, e contra o receptor NMDA(N-methyl, D-aspartate) são as associações sorológicas mais frequentemente estabelecidas. Na minoria dos casos, pode ser detectado um tumor subjacente. As maiores chances de melhora estão relacionadas à administração precoce de imunoterapia e à remoção do tumor, quando presente. A duração da imunoterapia pode se prolongada e a melhora se correlaciona, muitas vezes, com os níveis séricos de anticorpos. Neste artigo, estão resumidos os avanços recentes nos achados clínicos e laboratoriais neste campo que está em tão rápida expansão.

Palavras-Chave: autoanticorpos, encefalite, leucine-rich glioma-inactivated1, contactin-associated protein 2, N-methyl, D-aspartate.

For around 30 years, it has been recognised that limbic encephalitis (LE) can be associated with a distant cancer. Such paraneoplastic LE is often refractory to even aggressive immunotherapies and tumour removal. Using brain-section immunohistochemistry and western blotting techniques, a number of encephalitis-associated autoantibody targets was subsequently discovered. Some showed relatively specific associations with the type of underlying tumour, for instance, Ma2 antibodies and testicular tumours[1]. As these techniques employed denatured neural antigens, and revealed intracellular targets, it was difficult to conceive that the detected antibodies were directly pathogenic[2]. They are still considered likely bystanders in a predominantly T-cell mediated syndrome.

More recently, a number of antibodies have been discovered targeting the extracellular domain of neural proteins in their native conformations[3,4]. Most frequently, these antibodies are directed against the voltage-gated potassium channel (VGKC)

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Support: S.R.I was supported by the National Institute for Health Research (NIHR), Department of Health, UK. This work has been supported by the NIHR-funded Oxford Biomedical Research Centre.

Conflict of interest: A.V. and the Department of Clinical Neurology in Oxford receive royalties and payments for Ab assays. A.V. is the inventor on patent application WO/2010/046716 entitled "Neurological Autoimmune Disorders". S.R.I is a co-inventor. The patent has been licensed to Euroimmun AG for the development of assays for Lgi1 and other VGKC-complex Abs. A.V and S.R.I. may receive royalties for testing of VGKC complex Abs.

Received 11 January 2012; Accepted 18 January 2012

complex and the N-methyl, D-aspartate (NMDA) receptor[3-6]. These antibodies are likely to be pathogenic, the diseases are typically immunotherapy-responsive, and they are only associated with cancer in a minority of patients. The antibodies and related clinical features will be the focus of this article.

THE VGKC-COMPLEX: LGI1, CASPR2, AND CONTACTIN-2

LE is a term often used to describe the triad of amnesia, disorientation, and seizures. A minority of patients may develop additional features such as delusions, hallucinations, and sleep-cycle disturbances. The onset is typically over a few days or weeks and the main differential diagnoses include viral encephalitis and metabolic derangements[3]. The most common serological association is with VGKC-complex antibodies. It often predicts a <10% risk of an underlying tumour and a good response to early immunotherapies, typically with a parallel reduction in VGKC-complex antibody levels[7]. A useful clue to VGKC-complex antibody positivity is serum hyponatraemia and around half of the patients show T2/FLAIR high-signal in the medial temporal lobes[7,8].

Morvan's syndrome (MOS) represents another encephalopathy associated with VGKC-complex antibodies[9]. Neuromyotonia (NMT) is a peripheral nerve hyperexcitability disorder, which was the first syndrome to be associated with VGKC-complex antibodies[10]. NMT is a critical part of MOS. When compared with LE, patients with MOS have more frequent tumours and psychiatric features, with fewer seizures and magnetic resonance image (MRI) changes (SRI and AV, unpublished observations). Despite the higher frequency of tumours, many cases present a clear response to immunotherapies accompanied by a paralleled reduction in antibody levels in the few cases examined prospectively.

A highly-distinctive seizure semiology has been observed in association with VGKC-complex antibodies. Firstly described in three cases, in 2008[11], and subsequently in 26 additional cases, in 2011[12], faciobrachial dystonic seizures (FBDS) manifest as frequent, brief, dystonic epileptic events that typically affect the arm and the ipsilateral face[12]. Importantly, patients are commonly (anti epileptic drugs) AED-refractory and AEDs are associated with significant side effects. By contrast, the FBDS are immunotherapy-responsive, often exquisitely (Fig 1)[12]. Importantly, in at least 75% of cases, FBDS seem to precede the onset of amnesia and confusion that typify VGKC-complex antibody LE[12]. Therefore, we have proposed that clinical recognition of FBDS may allow initiation of immunotherapies which prevent LE. Prospective studies are awaited to examine such hypothesis.

The four clinical syndromes (NMT, MOS, LE and FBDS) show consistencies in their subacute onset and immunotherapy-responses. However, the individual phenotypes appear distinct from one another. Therefore, a key question has arisen: how can one antibody mediate the four syndromes? To address the question, the concept of the 'VGKC-complex' was first established in 2009[13]. Experiments have shown that VGKCs found within the mammalian brain membranes used to define the antibodies are tightly-complexed with a number of other proteins. Some of these proteins – leucine-rich glioma-inactivated 1 (LGI1), contactin-associated protein 2 (CASPR2) and contactin-2 – were identified as targets of the patient antibodies (Fig 2)[8,13,14]. LGI1-antibodies are predominantly observed in patients with LE and FBDS[8,14,15], and CASPR2-antibodies in MOS and NMT[8,13,14]. There is some overlap with LGI1-antibodies in some patients with MOS and, less frequently, NMT. Also, CASPR2-antibodies are found in few patients with LE[8].

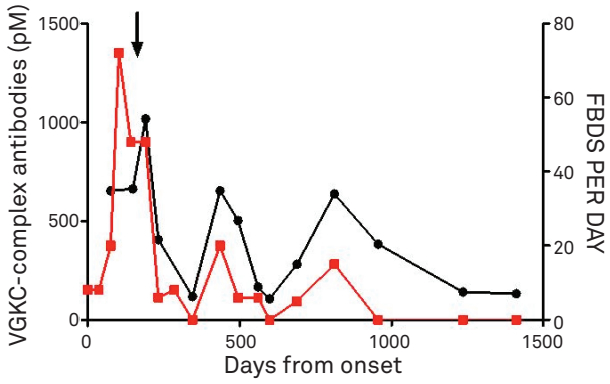

Fig 1. Close correlation between faciobrachial dystonic seizure (FBDS) frequency and VGKC-complex antibodies in a single patient. Clinical relapses are associated with discontinuation of immunotherapies, which were commenced as depicted by the downward arrow. Adapted from Irani et al.[12].

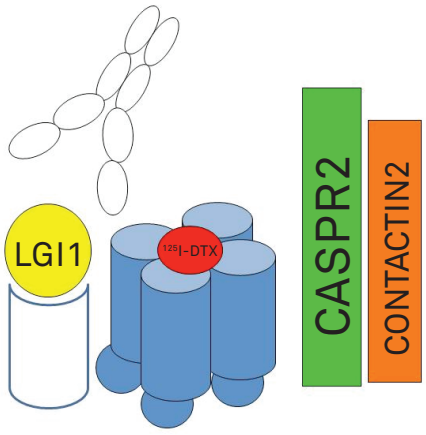

Fig 2. The VGKC-complex. leucine-rich glioma-inactivated 1 (LGI1), contactin-associated protein 2 (CASPR2) and contactin-2 are tightly associated with VGKCs in mammalian brain membranes and are co-immunoprecipitated in the radioimmunoassay. These proteins are commonly targeted by the patient antibodies (white). ^{125}I-DTX = radioiodinated dendrotoxin, a Kv1 antagonist.

Contactin-2 antibodies were least commonly detected[8]. As LGI1 is almost exclusively expressed in central nervous system neurons, and CASPR2 in both the central and peripheral nervous systems, the antibodies are considered likely mediators of the diseases. While careful correlations between antibody levels and clinical outcomes in individual patients, in combination with passive transfer experiments in animals, are required to formally assess VGKC-complex antibody pathogenicity, it has been proven that LGI1-antibodies can generate seizure activity in hippocampal slice cultures[16]. Interestingly, further evidence for the disease relevance of these proteins come from known genetic variations. Human LGI1-mutations produce a lateral temporal lobe epilepsy syndrome[17] and mice lacking LGI1 show a variety of motor semiologies[18]. Humans with CASPR2 mutations present autism, seizures, and peripheral neuropathy[19].

THE NMDA-RECEPTOR

A different characteristic set of clinical features has been linked to another autoantibody (Table). On this occasion, the antibodies are directed against an ion-channel: the NMDA-receptor. The initial article described antibodies in young females with ovarian teratomata[20]. Patients showed clinical improvements with a combination of tumour removal and immunotherapies. Since this important finding, it has become clear that the disease affects both males and females and it is more commonly non-paraneoplastic[21-23]. Tumours are most frequently detected in women between 20 and 40 years-old, and they are almost always ovarian teratomata.

The typical disease appears to progress though two major, well-characterized stages[21]. The first one is associated with prominent psychiatric features, such as delusions, behavioural change, wandering, and hallucinations. In addition, patients develop language difficulties, amnesia, disorientation, and seizures[21,24]. After a lag of 10 to 20 days, patients develop movement disorder, decreased level of consciousness, and florid dysautonomia. The latter two features frequently take patients to the Intensive Care Unit (ICU), where this disease is not an uncommon diagnosis[25]. The movement disorder characteristically involves orofacial dyskinesias and choreoathetoid limb movements. However, akinetic-rigid-mute presentations can predominate. Many of these patients are reminiscent of von Economo's encephalitis lethargica (EL) cases and, indeed, around half of the children originally given a diagnosis of EL have NMDAR-antibodies[26]. In children, the movement disorder may be the presenting feature[27], there is a very low frequency of tumours and often a preceding infection, which is associated with a variety of organisms[21].

Therapy for NMDAR-antibody encephalitis should involve early removal of a tumour, if present, and early institution of first-line immunotherapies[21,24]. These two measures have seemed to improve outcomes when contrasted to delayed intervention. Therefore, clinical confidence in disease recognition is critical. Ancillary investigations, such as cerebrospinal fluid (CSF) and MRI may help, as CSF frequently shows a prominent lymphocytosis early in the disease and MRI is typically normal. This is often surprising in the face of florid and severe multimodal neurological dysfunction.

Table. Differences between VGKC-complex and NMDAR-antibody associated encephalitis (modified from Irani and Vincent, Discovery Medicine 2011; 11(60):449-458. With permission from Discovery Medicine).

	VGKC-complex antibody (usually LGI1 antibody)	NMDAR-antibody
Gender ratio (M:F)	2:1	1:3
Age	Usually >50 years-old	Usually <50 years-old
Target antigen	LGI1>>>CASPR2	NR1 subunit of NMDAR
Is there tumour associated?	Rarely (<10%). If so, SCLC and thymoma.	Ovarian teratoma (20 to 50%), others rarely.
Clinical features	Amnesia, disorientation, and medial temporal lobe seizures.	Psychiatric features, amnesia, disorientation, and seizures progress to movement disorder, dysautonomia, and central hypoventilation.
Distinctive clinical features	Faciobrachial dystonic seizures, typically precede amnesia and confusion.	Choreoathetoid movement disorder, usually starting days to weeks after the psychiatric features.
Blood tests (other than antibody)	Hyponatraemia (consistent with SIADH, in around 60%).	Nil
MRI	Bilateral hipocampal high signal (in around 60%). In remaining 40%, changes can be unilateral or absent.	Often normal. Occasionally, non-specific high signal or medial temporal lobe high signal.
CSF	Most commonly no cells or oligoclonal bands. Positive antibodies in many patients.	Early lymphocytic pleocytosis and later oligoclonal bands. Antibodies detected in majority of patient CSFs.
Immunotherapy regime	Usually good response to one to two immunotherapies (steroids +/-Ivlg/plasma exchange).	Slow response, often over months; typically requires >2 immunotherapies.

MRI: magnetic resonance imaging; CSF: cerebrospinal fluid; SCLC: small cell lung cancer; SIADH: syndrome of inappropriate antidiuretic hormone.

Taken together, this disease appears to involve predominantly cortical regions early in the disease and later subcortical areas, such as the brainstem pattern generators, basal ganglia, ascending activating reticular system, and hypothalamus. Indeed, when combined with data from sequential EEGs and MRIs, the disease progression could be explained by a cortical-to-subcortical transition in the burden of the pathology[21,28]. This appears to involve a lymphocytic pleocytosis, however the lack of evidence of inflammation on imaging suggests that NMDA-receptor downregulation, without complement fixation, is the predominant pathophysiological mechanism[24].

OTHER ANTIGEN TARGETS

Additionally, a variety of other autoantibody targets has been discovered in rarer encephalopathic syndromes. These are directed against the glycine, $GABA_B$ and AMPA receptors. Progressive encephalomyelitis with rigidity and myoclonus (PERM) has long been associated with GAD-antibodies, however as GAD is an intracellular enzyme, these antibodies are unlikely to be causative. Therefore, it is more disease-relevant that PERM has recently been associated with antibodies that target the extracellular domain of the glycine receptor[29]. A few patients with LE, without VGKC-complex antibodies, may have antibodies directed against the glycine, $GABA_B$ or AMPA receptors. Although in a recent unselected screen, the latter two are very rarely found in cases with autoimmune encephalitis[6]. Furthermore, there remain a minority of LE cases without an associated antibody identified to date: further antibodies will surely be discovered in many of these cases.

ANTIBODY DETERMINATION AND SERUM-TO-CSF RATIOS

For all the antibodies discussed, the most able method to mimic the native antigen is the cell-based assay (CBA). This achieves surface expression of the antigen and in non-permeabilized mammalian cells, it only permits the antibody access to the extracellular domain of the antigen[3,4,20,30]. All antibodies can be measured in this manner. However, there are still antibodies that target the VGKC-complexes, which do not have a known antigenic target[8]. Therefore, for sensitivity, we still recommend using the traditional VGKC-complex radioimmunoassay. Conversely, the CBAs may detect CASPR2 and LGI1-antibodies when the radioimmunoassay is negative (Irani and Vincent, unpublished observations), and it may be that a combination of both assays offers optimal coverage.

It is a consistent finding (>95% of cases), for all the conditions described, that antibody concentrations in the serum are higher than in the CSF[8,21,28]. This implies that using the relatively concentrated serum offers the most sensitive diagnostic assay. However, as intrathecal synthesis of antibody is established in some of these conditions[21,24], it may be that the measurement of CSF antibodies plays a role in the follow-up of patients, and this possibility needs to be investigated.

CONCLUSIONS

In summary, there is a growing number of CNS-disorders which are associated with potentially pathogenic autoantibodies. Many of these antibodies are directed against CNS receptors (e.g. NMDA, glycine, AMPA, and $GABA_B$), but also non-ion channel proteins (LGI1, CASPR2 and contactin-2) are being established as antigenic targets. As shown in the Table, consistent and distinctive disease features appear to segregate with the individual antibodies. In the established syndromes, these clinical features are sufficiently characteristic to be highly predictive of an underlying antibody. As early treatments offer optimal outcomes, confident clinical recognition should be encouraged. The ongoing expansion in the number of autoantibody associated clinical syndromes is likely to continue in the coming years.

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