Could pathogenic autoantibodies in autoimmune encephalitis cross-link neurology and psychiatry?

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Abstract

The fields of neurology and psychiatry had a common origin in the 19th century, but have since drifted apart. Based on the division of ‘brain vs. mind’, diseases of the first fall within the neurological domain and disturbances of the latter are considered psychiatric. The recently emerging spectrum of autoimmune encephalitides spanning both now give a possible reason to review this divide.

Autoimmune encephalitides (AIE) are characterised by the presence of antibodies against “self” molecules expressed throughout the central nervous system. The target molecules are often involved in signal transmission and communication between neurons. In AIE, prominent psychiatric features often accompany the classical presentation of encephalitis with subacute confusion, memory loss and seizures.

The clinical studies available to date indicate that early diagnosis and aggressive immunosuppressive therapy can have significant effects on the patient’s recovery and subsequent return to full cognitive function. Smaller studies have recently also shown the presence of pathogenic autoantibodies in psychiatric patients who first presented to mental health hospitals. These findings indicate that understanding autoimmune encephalitis could also help to develop novel treatment approaches for psychiatric patients.

Looking ahead, the discovery of pathogenic autoantibodies causing diseases that span neurological and psychiatric specialties might offer new opportunities for patient treatment and management. Furthermore, understanding pathogenic autoantibodies could further increase our understanding how brain and mind are interlinked.
Historically, neurology and psychiatry have a common origin in the 19th century. Neurologists and psychiatrists were working alongside each other for decades to improve our understanding of the brain and mind and to research the microscopic details of the brain. In the last century, the two specialties began diverging and we started to separate conditions of the central nervous system (CNS) into those of the brain and those of the mind. Diseases in which a structural or molecular cause is found, were mainly considered diseases of the brain, and thus neurological. Whereas diseases that mainly affected the thoughts and mind, and we could not pin down to a structural pathology, are considered to fall within the psychiatrists’ expertise. In the NHS in Wales and England, this divide is maintained and neurology and psychiatry are often in separate trusts, and geographically separated across hospital sites.

Encephalitis, the inflammation of the brain, is a disease that is traditionally considered neurological - however, recent discoveries in the field of autoimmune encephalitis (AIE) might bring the two specialties closer together again. The emerging variety of autoantibodies, that is antibodies produced by a patient’s own immune system, against structures of the CNS might cross-link the two diverging fields. This essay will discuss some of the key findings in AIE that could bring a change to the way how neurology and psychiatry work alongside each other, and will address how the developments could have a profound impact on patients’ quality of care and the field of neuro-psychiatry as a whole.

**Autoimmune encephalitis**

The term encephalitis describes an inflammation of the brain. Encephalitis can present in many ways, but most commonly patients have headaches, are drowsy, confused and fatigued. This can then progress to the development of seizures, memory problems, and in some cases death. The term encephalitis describes a disease process that can be caused by a variety of different aetiologies: infectious encephalitis (such as herpes simplex infection), post-infectious encephalitis (as seen in the case of post-measles encephalitis) and finally autoimmune encephalitis (AIE) - caused by pathogenic self antibodies (1-3).

The neuronal network that makes up the brain communicates via electrical and chemical signals. The molecular basis of this communication are specialised ion channels that are spread along the processes of the neuron and can be found at the synapses between neurons. Ion channels are molecules that allow ions to flow across the cell membrane; they can be activated by the binding of ligands or by a change in the plasma membrane potential, effectively a change in the voltage. Binding of the autoantibody to the ion channel has been shown to set off several possible processes (see Fig. 1) that can lead to an impaired signal transduction, or communication within the neuronal network (4-8). The majority of autoantibodies identified to date are directed against ion channels (such as the N-methyl D-aspartate receptor - NMDAR), or proteins closely associated with ion channel complexes such as the voltage gated potassium channel (VGKC) complex (9-12).

Patients with AIE typically present with a subacute onset of memory loss, confusion and seizures. Although the full spectrum of autoantibodies that can cause AIE is probably not yet identified, we are beginning to understand that each particular autoantibody can cause a typical encephalitis with a slightly different clinical phenotype, or twist as you might say (see table 1). To date the subtle differences between different conditions with various autoantibody targets are probably best demonstrated by comparing patients with autoantibodies against NMDAR or different components of the VGKC-complex (for a review of the most common AIE, see (13)). Patients with NMDAR AIE often develop prominent movement disorders, can progress to the onset of mutism and often have clinical symptoms that indicate an involvement of the autonomic nervous system; all of those are not typically seen in VGKC-complex AIE.
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<td>N-methyl D-aspartate receptor, NR1 subunit</td>
<td>psychiatric features, memory loss, seizures, autonomic instability, insomnia, dyskinesia, mutism, reduced consciousness, confusion</td>
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<td>GluR1/R2</td>
<td>memory loss, seizures, psychosis</td>
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Table 1 clinical features of four autoimmune encephalitides with autoantibodies against neuronal cell surface molecules

AIE can be diagnosed using either the patient’s serum or cerebrospinal fluid (CSF), which can be obtained at a lumbar puncture. Apart from the characteristic autoantibodies in either serum or CSF, patients with NMDAR-AIE often have normal MRI scans; in up to 60% of VGKC-complex AIE patients bilateral hippocampal high intensity signal is found on MRI scans (14,15). Schmitt et al recently reported that up to a third of NMDAR autoantibody patients show a typical pattern with a so-called extreme delta brush on electroencephalogram (EEG) (16).

AIE is responsive to immunosuppressive treatment - and early intervention has been shown to correlate with better prognosis (5). The symptomatic improvement correlates with a drop in autoantibody levels, which confirms that the autoantibodies per se are likely to be pathogenic (5,10).
Psychosis and autoantibodies

Psychiatric features such as hallucinations, delusions, mood disturbance and confused thoughts have been described in the context of AIE. In Dalmau’s original case series of twelve women with NMDAR-AIE, psychiatric features were very prominent: half of the patients had first been treated by psychiatrists, and five patients had been admitted to mental health units (9). A larger case series published subsequently showed that 77/100 patients were initially seen by psychiatrists (6). VGKC-complex AIE patients have also been reported to display significant psychiatric symptoms such as hallucinations, delusions and behavioural abnormalities (10).

Although the neuropsychiatric symptoms are prominent amongst NMDAR-AIE patients, other symptoms such as seizures, reduced consciousness or movement disorders often co-exist. Kayser et al investigated how often psychiatric symptoms occurred in isolation amongst NMDAR AIE patients (17). They found that 4% (23/571 patients) of all tested NMDAR-AIE patients had isolated features of psychiatric nature, 5 of those 23 patients at their initial presentation and the remaining 18 during a relapse. It is difficult to say whether this reflects the fact that pure psychiatric episodes are rare in AIE, or whether AIE is still underdiagnosed in patients who have only psychiatric symptoms and are thus only seen by mental health physicians. Zandi et al screened 46 patients with their first psychotic episode for both VGKC-complex and NMDAR autoantibodies (18). The group showed that 1/46 and 3/46 patients had indeed detectable autoantibodies against VGKC-complex and NMDAR, respectively. This emphasises that patients might have a potentially immunotherapy-responsive condition that requires early diagnosis and treatment. Increased awareness amongst mental health professionals and a better dialogue between neurologists and psychiatrists are needed to ensure the best possible care for patients.

Figure 1 Autoantibodies can cause disease in many ways. Simplified overview of pathological mechanisms that can be caused by the binding of autoantibodies to their targets. The formation of complexes can lead to internalisation (left) of the target and possibly other proteins in the complex, effectively reducing the density of the ion channels on the cell surface. Autoantibodies can also cause disease by activating the immune system, and in particular the lytic complement cascade after binding to their target (right).
Understanding how CNS autoantibodies can cause disease

Autoantibodies can be pathogenic in many ways. The most researched site of autoantibody-mediated pathology is the neuromuscular junction (NMJ) in the peripheral nervous system, the interface between nerves and muscles. Autoantibodies against ion channels at the NMJ are found in myasthenia gravis, a disease that causes profound weakness. It was at the NMJ that it was shown that autoantibodies can act in various ways: binding of the autoantibody can result in the internalisation of the complex, but it can also lead to the activation of the lytic cascade of the complement system leading to local destruction of the structures (pathogenic mechanisms involved in myasthenia gravis are discussed in more detail by (19,20)). It was also at the NMJ where it was first discovered that autoantibodies directed against molecules that are closely associated with the ion channels in a protein complex can also be pathogenic.

Taking our understanding of autoantibody-mediated pathogenicity to the synapses of the central nervous system, all of these mechanisms have also been shown to play a role (see also Fig. 1). Research into the contribution of autoantibodies in the disease process has been done in cultured cell lines (in vitro), using animal models (in vivo) and using biopsies taken from AIE patients either during diagnostic investigations or after their death (post mortem). Both in vitro and in vivo studies confirmed that NMDAR-autoantibodies can internalise the receptor and reduce the surface density (4), VGKC-complex autoantibodies have been shown to cause complement activation in tissue biopsies (21), and finally proteins such as LGI1 and CASPR2 were identified as the autoantibody targets within components of the VGKC-complex (10,12). Other mechanisms have also been shown to play a role: Mikasova et al showed that NMDAR autoantibodies can change the trafficking of the ion channel subunits to the surface (8), and general neuronal loss and axonal injury have been found in biopsy and post mortem tissue of VGKC-complex, NMDAR and glutamic acid decarboxylase AIE (21). More and more research emerges which emphasises that the pathogenicity of CNS autoantibodies cannot be completely understood at the level of individual molecules and synapses and that we ought to research the effects of autoantibodies on the neuronal networks (22,23).

Currently, we are at a stage where we are beginning to understand more about autoimmunity of the CNS. The initial understanding was that patients who had autoantibodies against structures in their brain had raised them initially in an immune response against a cancer: in the original case series of twelve women with NMDAR AIE, the autoantibodies were raised in response to teratomas of their ovaries. However, we now know that 50-80% and 90% of NMDAR and VGKC-complex AIE patients, respectively, do not have an underlying tumour (14). It is, however, not yet understood what triggers the generation of CNS autoantibodies in the absence of tumours.

The CNS is surrounded by the so-called blood brain barrier (BBB), which strictly regulates entry to the CNS from peripheral blood. It is assumed that an intact BBB limits the access of the immune cells and antibodies present in the periphery to the CNS, and the brain is thus believed to be a site of immune privilege. How antibodies raised in the periphery against tumours, or as a response to a yet unknown stimulus, can cause symptoms is thus an area of heated debate. Recent animal studies by Hammer et al compared normal (wild type) mice with mice where the BBB was genetically modified by removing a protein called ApoE (24). They injected antibodies from patients or healthy controls into the tail vein of the animals and compared the effects on the animals’ behaviour. The results show that injection of patient antibodies into mice with an intact BBB did not result in any behavioural abnormalities, however mice with a leaky BBB showed symptoms that could be explained by an effect of the antibodies on NMDAR in the CNS. Another interesting finding by the group was that a high percentage of healthy (or rather asymptomatic) subjects carried NMDAR autoantibodies in their serum, a finding that might confirm the contribution of the breakdown of a previously healthy BBB in the development of autoantibody-mediated AIE or psychosis.
Some of the questions we need to answer now are: can CNS autoantibodies potentially be present in healthy subjects with an intact blood brain barrier without them being aware of it? What would trigger the generation of these antibodies in some of us but not others? And finally, are the assays we use to detect pathological autoantibodies perhaps not good enough and we are detecting “false positives” amongst healthy subjects? We need to investigate whether the key step is the generation of autoantibodies, or rather the breakdown of blood brain barrier integrity.

Recent studies of patients with different levels of VGKC-complex autoantibodies indicate that low levels of VGKC-complex autoantibodies might represent incidental, or non-specific, findings (25,26). More detailed studies of large healthy control cohorts will help to understand how common CNS autoantibodies are and which levels can be associated with the development of symptoms. The currently used immunosuppressive treatment regime is an aggressive approach to eliminate all autoantibodies, and thus suppresses the immune system in general. This does not come without side effects - and we need to understand in more detail, which patients could benefit from such a treatment.

**Why it matters - encephalitis treatment, and beyond**

Schizophrenia is a disease often portrayed in movies. It is a disease that fascinates, clinicians and the general public alike. It is also a disease that scares - the loss of control of one’s thoughts and mind is a daunting outlook. Whilst dementia clouds the memories and mind of the elderly, schizophrenia brings psychosis to patients who are at the peak of their lives, who have just recently graduated school, who are going to university, who think they have their life filled with opportunities lying ahead of them. The impact of schizophrenia goes further than the dramatic change in quality of life of the patients and their immediate families; it is a disease that affects the work force and thus the economy of our country. It is also a disease that usually condemns patients to life long treatment with antipsychotics, drugs with significant side effects such as gain of weight and also dyskinesia that is involuntary movements, which can be very disabling. Being able to identify even only a small subgroup of those young people who have their first psychotic episode who could improve, or even be cured, by immunosuppression would have far reaching impacts. More research is needed to fully understand how we can ensure early diagnosis and which treatment regimens are linked to the best outcome. As for VGKC-complex AIE, faciobrachial dystonic seizures (FBDS) have been recently described as brief seizures of jerk-like nature, which affect the face and arms and can pre-date the development of florid VKGC-complex AIE in 75% patients (27). The identification of such windows of treatment-opportunity before patients develop a more widespread CNS involvement could be key to ensure early treatment and to increase the chances of complete recovery to pre-morbid function.

The prognostic value of early diagnosis and aggressive immunosuppressive treatment emphasises that it is crucial to raise awareness amongst clinicians. Early diagnosis and treatment are only possible if we consider autoimmunity as a cause of first presentation of psychosis in children and adults. The formation of joint neuro-psychiatric assessment units might be able to facilitate the best patient care that is needed at such a vulnerable phase in their life. Whilst the majority of psychotic patients might not have an immuno-responsive illness, it is important to have experienced doctors who are able to make the correct diagnosis and facilitate early treatment. *Vice versa*, neurological patients who develop psychiatric symptoms late in their disease course could benefit from psychiatric input into their care. Such shared intervention units could form a novel bridge between neurology and psychiatry, and autoantibodies could indeed be the cross-link that brings the two specialties closer together again.
Summary and conclusions
Autoimmune encephalitides are an emerging new group of neurological conditions that we are currently only beginning to understand in more detail. The significance of the discovery that autoantibodies can cause CNS disease goes beyond the treatment of patients with AIE. Autoimmunity could be involved in a subgroup of mental health patients, which would offer the opportunity to use immunosuppressive therapy to improve their symptoms, and lives. But the importance of CNS autoantibodies goes even further - they are offering a new outlook on how the brain works, and that we need to understand the interaction not only between proteins and the mechanisms at individual synapses. We ought to be looking at more complex neuronal networks and the circuitry, or wiring, that we find in the brain - and once we are able to understand these processes we might be able to bring the specialties of the brain and the mind closer together. To end with the words of Stanley Cobb, one of the most inquisitive neurologists and psychiatrists of his times and a distinguished scientist: “The mind is the living brain in action” (28).
References


