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Neuronal surface autoantibodies, encephalitis, and psychosis: from neurology to psychiatry

Autoimmune encephalitis in the 2000s

It has been over a decade since the first description of an encephalitis presenting with psychosis, occurring in young women with ovarian teratoma.[1] This disorder, now known to be caused by autoantibodies which recognise the NR1 subunit of the N-methyl-D-aspartate (NMDA) receptor (NMDAR), has had a profound effect on the neurological landscape. NMDAR-antibody encephalitis has also had an effect on the cultural landscape, with Susannah Cahalan's bestselling account of her experience of the disorder, *Brain on Fire*, topping the *New York Times* bestseller list and being made into a Hollywood movie.

But why was the impact of this newly described disorder so great? After all, it was in the 1960s that Brierley, Corsellis and colleagues first penned their seminal descriptions of limbic encephalitis. All of the original case descriptions, like Cahalan herself, presented with psychiatric symptoms before going on to develop various neurological symptoms including seizures and cognitive dysfunction.[2]

Unlike these original cases, however, NMDAR-antibody encephalitis is highly responsive to immunotherapy. We now know that this is because NMDAR antibodies attach to the neuronal surface (unlike the classical 'onconeural' antibodies associated with paraneoplastic limbic encephalitis) and are therefore accessible *in vivo* to antibody-directed immunomodulatory therapies. This was not a novel paradigm as such, having been well established in myaesthenia gravis. However, this disorder was occurring within the central nervous system, thereby challenging the notion that antibodies or antibody-secreting cells could not cross the blood brain barrier and that the brain was an immune privileged site.

Further, as the number of reported cases began to increase, it became apparent that a minority of patients presented *solely* with psychiatric symptoms throughout the course of their illness.[3] What was novel was not the fact that CNS inflammation can cause an immunotherapy-responsive isolated psychiatric phenotype – indeed, neurologists have been treating psychosis due to SLE and other CNS inflammatory disorders for years, despite little understanding of the mechanisms underlying psychotic symptoms in these disorders. The real breakthrough lies in the fact that a relatively straightforward laboratory test has enabled the identification of an entirely new repertoire of neuronal autoantibodies that target relatively well-characterised membrane proteins involved in neurotransmission, offering a mechanistically plausible pathway from antigen to symptoms and indeed to psychopathology.[4] In 2017, many of these novel autoimmune encephalitides – associated with antibodies targeting the AMPA, glycine, GABA-A and –B receptors or other membrane proteins such as leucine-rich glioma inactivated 1 (LGI1) and contactin-associated protein-like 2 (CASPR2) – are now familiar to most UK neurologists. New antigenic targets – mostly extracellular, although occasionally intracellular/cytosolic – are being reported every few months (IgLON5, dipeptidyl-peptidase-like protein-6 [DPPX], and neurexin 3α encephalitis have all been described in the last few years)[5] (see Table 1). Unlike with syndromes associated with the classical onconeural antibodies, only a minority of patients have an associated tumour, such as an ovarian teratoma in NMDAR-antibody encephalitis; if a tumour is present, resection appears to expedite recovery.

The technology that has enabled this explosion of discovery of immunotherapy-responsive disease in an ever-growing number of patients is the development of cell-based assays (CBAs) for the detection of neuronal surface autoantibodies. CBAs are cell lines, transfected with a genetic construct containing the target antigen of interest. This leads to surface expression of the antigen, thereby avoiding exposure of pathogenically irrelevant intracellular epitopes and also maintaining the native conformation of the target protein. This is a crucial feature of this group of antibodies to which previous detection methods such as ELISAs and western blots are largely insensitive.

The impact on psychiatry

If the impact on neurology has been great, the impact on psychiatry has been no less profound. Of the original 100 cases of NMDAR encephalitis described by Dalmau and colleagues, 77% presented to psychiatric services, the majority with largely psychotic symptoms.[6] That proportion is perhaps smaller in the UK today, partly due to greater awareness amongst clinicians, but the fact remains that in its early stages, autoimmune encephalitis can be a *mimic* of first episode psychosis (FEP).

Antigen	Antigen description/epitope	Main encephalopathy syndrome; which possible psychiatric features?	Other associated neurological disorders
NMDAR (NR1 subunit)	Ligand gated ion channel subunit	Encephalopathy (usually extralimbic). Psychiatric features include anxiety, agitation, bizarre behaviour, catatonia, delusional or paranoid thoughts, and visual or auditory hallucinations. Also movement disorder, seizures, autonomic instability.[3,24,25]	Post-herpes simplex encephalitis relapse with chorea; idiopathic epilepsy; immunotherapy-responsive dementia.[26,27]
LGI1	VGKC- and AMPAR-associated secreted molecule	LE with or without faciobrachial dystonic seizures (FBDS). Psychiatric features include confusion, hallucinations, depression.[28]	Morvan's syndrome, NMT, epilepsy, REM sleep behaviour disorder[28]
CASPR2	VGKC-associated adhesion molecule	LE and Morvan's syndrome. Psychiatric features include confusion, hallucinations, agitation, delusions.[29]	NMT, epilepsy[28]
AMPAR	Ligand gated ion channel	LE. Psychiatric features include confusion, personality change, psychosis, apathy, agitation, confabulation. [30-32]	
$GABA_AR$	Ligand gated ion channel	LE with refractory seizures. Psychiatric features include confusion, affective changes (inc depression), hallucinations[33]	Varied presentations.[34]
$GABA_BR$	Ligand gated ion channel	LE with refractory status epilepticus. Psychiatric features include psychosis, agitation, catatonia.[30,35]	Opsoclonus-myoclonus; cerebellar ataxia; PERM[35,36]
D2R	Metabotropic receptor	'Basal ganglia encephalitis' with prominent movement disorder (dystonia, parkinsonism, chorea, tics). Psychiatric features include agitation, depression, psychosis, emotional lability.	SC, PANDAS[37]
DPPX	Auxiliary subunit of Kv4.2 potassium channels	LE with enteropathy. Psychiatric features include amnesia, delirium, psychosis, depression[38,39]	PERM[40]
MGluR5	Metabotropic receptor	'Ophelia syndrome': LE in association with Hodgkin lymphoma. One case of LE without lymphoma. Psychiatric features include depression, anxiety, delusions, visual and auditory hallucinations, anterograde amnesia.[41]	
IgLON5	Neural cell adhesion molecule of unclear function	Characteristic sleep disorder preceded or accompanied by bulbar symptoms, gait abnormalities, oculomotor problems and cognitive decline; a tauopathy, strongly associated with HLA-DRB1*10:01.[42,43]	
Neurexin 3α	Synaptic molecule involved in formation and maturation of synapses	Infectious prodrome followed by cognitive dysfunction, seizures, reduced consciousness, and orofacial dyskinesias; sometimes severe clinical course; mimic of NMDARE but with less prominent psychiatric symptoms.[44]	
ARHGAP26	A multidomain protein involved in regulation of endocytosis	Autoimmune cerebellar ataxia with dizziness and dysarthria; also memory dysfunction and depression.[45,46]	One patient reported with immunotherapy-responsive psychosis with suicidality, aggression, mutism.[47]
Synapsin	A synaptic vesicle-associated protein involved in regulation of neurotransmitter release.	69-year-old man with confusion, disorientation, seizures, and left hippocampal hyperintensities on MRI.[48]	Synapsin IgG also found in patients with neurological and psychiatric disorders (including psychosis, depression and bipolar disorder).[49]
AK5	An intracellular (cytosolic) nucleoside monophosphate kinase, expressed exclusively in the brain.	>50 yo; subacute pure anterograde amnesia, occurring in most cases after a prodromal phase of asthenia, anorexia, and depression. Hippocampal atrophy on MRI. Prominent anxiety, but seizures not reported.[50]	
GFAP	An intracellular (cytosolic) glial intermediate filament protein.	Corticosteroid-responsive meningoencephalitis or encephalitis, with or without myelitis. Presents with subacute onset of memory loss and confusion. Co-occurs with autoimmune endocrinopathy in one third, and with tumour in one third. Psychiatric symptoms reported in 29%.[51,52]	

adenylate kinase 5; ARHGAP26: Rho GTPase activating protein 26; ATD: amino terminal domain; BPAD: bipolar affective disorder; CBA: cell-based assay; ELISA: enzyme-linked immunosorbent assay; GFAP: glial fibrillary acidic protein; LE: limbic encephalitis; MDD: major depressive disorder; NMT: neuromyotonia; PERM: progressive encephalomyelitis with rigidity and myoclonus; RIA: radioimmunoassay; SC: Sydenham's chorea; PANDAS: paediatric autoimmune neuropsychiatric disorders associated with Streptococcal infections. Table reproduced and updated with permission from Pollak et al. [4]

Similarities between NMDAR-antibody encephalitis and psychosis are not limited simply to delusions and hallucinations. Patients with psychotic disorders, even if antipsychotic-naïve, can present with catatonia, autonomic instability including hyperthermia, extrapyramidal signs including tremors and dyskinesias, hypersomnolence or acute insomnia, hyponatremia and even a delirium-like picture.[7]

In *Brain on Fire*, Cahalan is initially diagnosed with schizoaffective disorder by a psychiatrist, before she develops a frank encephalopathy and NMDAR-antibody encephalitis is diagnosed by her neurologist, Dr Najjar. Musing on her diagnostic journey, she asks a simple question: "*how many people currently are in psychiatric wards and nursing homes denied the relatively simple cure of steroids, plasma exchange, [or] more intense immunotherapy…?*". Cahalan was not alone in wondering whether encephalitis was just the tip of the autoimmune iceberg. By 2011, psychiatrists had begun to search for NMDAR and other neuronal surface autoantibodies in patients with so-called 'primary' psychotic disorders – those in which causation is thought to be complex or unknown. The first study to look for these antibodies in FEP found NMDAR and voltage-gated potassium channel complex antibodies in 7% of patients presenting to a community psychosis service in Cambridge. Importantly, one NMDAR autoantibody-positive patient was given plasmapheresis and made a full psychiatric recovery that was sustained at seven months follow-up.[8]

Reports of brain-reactive antibodies in psychosis are nothing new, dating back as far as the 1930s, but in looking for antibodies strongly suspected to be pathogenic by virtue of their role in the various newly-described autoimmune encephalitides, the argument for plausible antibody pathogenicity in psychotic disorders is strengthened. Most recently, Lennox and colleagues conducted the largest ever prospective study of neuronal surface autoantibodies (NMDAR, LGI1, CASPR2, GABA-AR) in first episode psychosis, involving 230 young people from 14 sites around the UK. We found that 8% of subjects had a neuronal surface autoantibody detectable in peripheral blood, and for NMDAR-antibodies the difference versus healthy control prevalence was statistically significant. Crucially, seropositive subjects were not distinguishable from seronegative subjects on the basis of clinical features alone.[9]

Other recent studies, using various assays and confirmatory testing methods, have identified potentially disease-relevant antibodies in patients with a variety of psychosis diagnoses, including chronic psychosis,[10] childhood-onset psychosis,[11] and postpartum psychosis.[12]

For psychiatrists, these developments are exciting and parallel similar discussions in neurology regarding the relevance of these antibodies in epilepsy, movement disorders and memory syndromes. They come at a time when psychiatry is increasingly looking towards neuro-immune interaction as a putative disease mechanism in psychotic and other severe mental illnesses. Genome-wide association studies suggest immune-related SNPs confer schizophrenia risk, raised inflammatory markers appear to characterise acute illness stages, and considerable epidemiological overlap with autoimmune disorders is attracting attention.[13] For decades, there has been little progress in the pharmacological treatment of psychosis, and we still largely rely on dopamine D2 receptor antagonism, which is the same mechanism of action as that of chlorpromazine, introduced in 1952. The possibility that even a subset of patients with psychosis may have an immunotherapy-responsive autoimmune basis to their disorder has therefore attracted considerable enthusiasm.

But is this enthusiasm premature? So far, there have been numerous case reports of good immunotherapy-responses in patients with psychosis, and the largest open-label case series to date demonstrated improvement in symptoms concomitant with reduction in antibody titre in each of 9 patients with acute psychosis and NMDAR antibodies who received immunotherapy.[14] But selection bias, placebo response to a dramatic, highly medicalised intervention, and regression to the mean cannot be ignored as potential factors here.

Current controversies

Biological psychiatry is replete with false dawns, and some authors are sceptical of the relevance of neuronal autoantibodies in psychotic disorders.[15] Critical debate tends to centre around two themes:

1) Serum neuronal surface autoantibodies are sometimes found in healthy people and in other, non-encephalitis diseases – therefore they can only have disease-relevance when there is a phenotype typical of classic descriptions of autoimmune encephalopathies.
2) Serum antibodies without associated detectable CSF antibodies are unlikely to represent an antibody-mediated brain disease.

There continues to be active discussion around these points which cannot be adequately summarised here, but the following comments point towards some relevant considerations:

1) Different CBAs appear to have different sensitivities and specificities. One theoretical factor contributing to this variation is that the fixation process may affect protein structure and permeabilisation may expose intracellular antigens allowing antibodies to bind that have a lower chance of pathogenic potential. One recent study in a first episode psychosis cohort demonstrated that live CBAs are more sensitive than fixed CBAs. Furthermore, single molecule imaging demonstrated to a high degree of likelihood that that even antibodies from weakly positive sera, far from being 'false positive', targeted the NMDAR.[16]
2) Whereas CSF antibodies, and evidence of intrathecal synthesis are frequently observed in typical NMDAR-antibody encephalitis, CSF positivity rates are much lower in other types, such as LGI1 or CASPR2-antibody encephalitis.[17] Further, in animal models it has been demonstrated that at relatively low titres the brain can act as an 'immunoprecipitator' of NMDAR antibodies (and by extension presumably other neuronal surface autoantibodies) meaning that unless the brain becomes saturated due to an excess of antibody, as may be the case when there is intrathecal synthesis and active, florid encephalitis, absence of detectable CSF antibody does not necessarily exclude a CNS-binding surface antibody.[18] Indeed, cases of seropositive but CSF-negative NMDAR encephalitis have been reported using a live CBA in the UK.[19]

Ultimately, despite these important scientific questions, as more patients are tested for these antibodies clinicians need a clearer evidence base regarding treatment decisions. A placebo-controlled double blinded randomised controlled trial, currently recruiting in the UK will help. The SINAPPS2 trial will randomise 80 patients with acute psychosis and neuronal surface autoantibodies to receive either active immunotherapy (IVIG and rituximab) or sham immunotherapy in addition to psychiatric treatment as usual [clinicaltrials.gov NCT03194815 / www.sinapps.org.uk].

Clinical best practice

Until the results of this RCT are known, which patients should be tested and what should neurologists make of a positive neuronal surface autoantibody test in a patient whose symptoms are largely, or indeed wholly, psychiatric in nature? Crucially, one would not wish to miss making a diagnosis of autoimmune encephalitis as soon as possible, and potentially allowing intervention before the disease progresses to a more florid neurological picture. 'Red flag' signs, then, are those which suggest a greater or lesser degree of encephalopathy:[7,20]

- Acute/subacute onset
- Autonomic instability
- Language disorder
- Impairment of consciousness
- Significant cognitive dysfunction
- Seizures
- Neuroleptic sensitivity

Patients with a positive serum autoantibody test should be investigated with EEG, MRI and CSF analysis and diagnosis of autoimmune encephalitis made with current guidelines in mind.[21] Where appropriate, the possibility of co-occurring tumour should be excluded. Ideally care should be shared between neurology and psychiatry; indeed throughout the UK, these disorders have heralded the development of innovative models co-working between neurology and psychiatry, both in inpatient and an outpatient settings.

In terms of psychiatric treatment, there is mounting evidence that patients with NMDAR-antibody encephalitis may respond poorly to antipsychotic treatment, with high rates of rhabdomyolysis and even development of a neuroleptic malignant syndrome (NMS)-type picture.[22,23] For this reason, benzodiazepines are preferred for initial management of behavioural disturbance and catatonia. If antipsychotics are required, sedating atypical antipsychotics such as olanzapine may be preferable.

With a considerable research effort now ongoing at an epidemiological, mechanistic, clinical and trial level, the identification of neuronal surface autoantibodies has re-energised biological psychiatry, suggesting new aetiological insights, and potentially offering new treatment avenues for a group of disorders affecting millions worldwide.

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