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Editorial

Antibody-mediated encephalitis: a treatable cause of schizophrenia

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Summary
Psychiatrists need to be vigilant for the newly recognised and treatable disorder of antibody-mediated encephalitis. Psychiatric symptoms are common, and individuals with the disorder often present initially to psychiatric services. We describe the clinical features of the disorder and make recommendations for further investigations.

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Psychiatry has been progressively demedicalised in the UK. The speciality has separated from the rest of medicine and there has been discussion about the relevance of biological models of psychiatric illness among some psychiatrists.[1] This dangerous position is now exposed as new brain disorders have been described that are affecting patients currently under our management, which require medical investigation and management.

N-methyl-D-aspartate receptor antibody enchephalopathy

The most relevant disease is that associated with antibodies to the *N*-methyl-D-aspartate (NMDA) receptor. This was first described in young women who presented with a rapidly progressive neurological illness characterised by prolonged psychosis or disturbed behaviour, followed by a life-threatening state of autonomic instability, coma and dystonic movement disorder and with an underlying ovarian teratoma.[2] The antibodies are highly specific, demonstrably absent in large numbers of healthy and disease controls,[3,4] and there is *in vitro* and *in vivo* evidence for their pathogenicity.[4] Since 2007 there has been a large case series from a tertiary neurooncology centre in the USA[5] and the first 44 cases from a neuroimmunology service in the UK,[3] as well as many individual case reports.[6] These studies have broadened the clinical picture to include a wider age (5–80) and gender distribution (66–80% female) of patients, and showed that only a percentage (20–50%) of individuals had a detectable underlying paraneoplastic cause (usually an ovarian teratoma). The disorder has caused a high level of interest because of the severity of the clinical picture at nadir and the encouraging response to treatments if offered early in the course of the illness. In those with teratomas the removal of the tumour is essential, and even in the absence of tumour the disorder is usually substantially improved with immunotherapy. In both cases treatment is time critical – the sooner treatment is started the better the prognosis;[3] thus early diagnosis is the key.

Even in the first case series, seizures and cognitive dysfunction were usually present but were dominated by the psychiatric features. The most common initial presentation (68–80%) was with symptoms of psychosis, with hallucinations, delusions, social withdrawal and thought disorder.[3,5] There was then an inevitable progression, usually within a month, onto the second stage of more overt neurological features with movement disorder, characteristically of orofacial and choreoathetoid dyskinesias, epilepsy, autonomic disturbance and impaired consciousness often requiring admission to intensive care.

Subsequently, individuals with less severe progression have been identified and the clinical phenotype associated with these antibodies has expanded further. Individuals who were initially diagnosed as having encephalitis lethargic, neuroleptic malignant syndrome, catatonia or Hashimoto encephalopathy have had NMDA receptor antibodies.[3]

Voltage-gated potassium channel antibody enchephalopathy

The other condition that is of relevance is associated with antibodies against components of the voltage-gated potassium channel complex. These individuals usually present with amnesia and seizures, but they may also first present to psychiatric services with symptoms of agitation, hallucinations or behaviour change.[7] In a few cases, these individuals have been diagnosed initially as having a primary psychotic illness with the voltage-gated potassium channel complex antibodies only discovered following the development of hyponatraemia or seizures.[8] An increasing number of patients with these antibodies also have brief, dystonic faciobrachial dystonic seizures that can be misinterpreted as myclonic jerks.[6]

Antibodies in cases of schizophrenia

In addition, we have described four cases of individuals with a DSM-IV diagnosis of schizophrenia with serum NMDA receptor or voltage-gated potassium channel complex antibodies, without a history of seizures, movement disorder or dysautonomia, even over 2 years of follow up.[9] On this basis 6.5% (1.9–18.9% with 95% confidence intervals) of those with first-episode psychosis may have a psychiatric disorder associated with specific antibodies that are amenable to immunotherapy. In a review of all requests for NMDA receptor and voltage-gated potassium channel complex antibodies over the last 12 months through one tertiary

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neurological centre (Addenbrookes Hospital Cambridge, UK), the strongest predictor of a positive test result was a history of psychosis. Furthermore, 8 of the 16 individuals who were detected to be antibody-positive over this time have been under the management of psychiatric services. They had received diagnoses of schizophrenia ($n=6$) and first-episode psychosis ($n=2$). In addition, a novel but less common antibody directed against α-amino-3- hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors has been associated with atypical forms of psychosis and, in some cases, an underlying tumour.[6] The individuals with neurological conditions described in the literature to date could therefore represent the tip of the iceberg, although further work is needed to replicate findings and the clinical relevance of their cases.

Mechanisms of action

The mechanisms by which these antibodies produce a psychiatric phenotype is not clear but NMDA receptor dysfunction, in particular, has been a plausible explanation as the underlying mechanism for schizophrenia over the last 20 years. Kraepelin in his seminal classification of psychotic illnesses described a fluctuating confusional state and catatonic movement disorder alongside the psychotic symptoms and rapid cognitive deterioration in the disorder that he characterised as the catatonic form of dementia praecox,[10] mirroring many of the symptoms seen in NMDA receptor antibody encephalitis. Indeed, NMDA-receptor blockade *in vivo* produces a range of schizophrenia-like symptoms in healthy individuals.[11] Ion channel disturbance and hyponatraemia have also been described as features of schizophrenia, previously attributed to medication-induced or psychogenic polydipsia.

Implications for clinical practice

There is, therefore, growing evidence that a proportion of schizophrenia may be antibody mediated and psychiatrists need to start to consider this aetiology in each presentation of first-episode psychosis. If positive, these patients should be considered for treatment with immunotherapy and have an underlying tumour excluded. This should be done, initially at least, in a centre that has experience in managing individuals with antibody-mediated disorders. Current recommendations, if paraneoplastic causes are excluded, are that individuals are aggressively treated with intravenous methylprednisolone and early reduction in the antibodies with plasma exchange, intravenous immunoglobulin or both, and combined with longer-term high-dose steroids or another immunosuppressive drug.[2,3]

Neurologists have already embraced and adopted this new clinical practice. Antibody screening in young people presenting with psychosis, seizures and cognitive disturbance is now part of routine clinical practice in neurological and intensive care settings. In the USA and the UK, antibody-associated encephalitis is now recognised to account for a significant minority of all cases of encephalitis and intensive care admissions.[2] The recognition of this cause of psychiatric presentations has required a shift in behaviour, with new collaborations with plasma exchange facilities, gynaecologists for ovarian teratoma removal and a challenge to nursing skills to manage the change in profile of patients on neurology wards. These changes have been managed because of the recognition of the treatment responsiveness of the condition, and facilitated by the co-location of these specialties. Psychiatry in contrast has been slow to respond, with current clinical practice being a long way removed from that of neurologists. Individuals with acute psychosis do not always see a psychiatrist for assessment in the UK, let alone have access to investigation. This is an untenable position, when there is the potential for detecting such a treatable disorder in a percentage of our patients. The physical and cultural separation of psychiatry from the rest of medicine makes it difficult for us now to adequately investigate and manage our patients.

Recommendations

We therefore recommend that all individuals with a first presentation of psychosis, or people with psychosis and features of autonomic disturbance, movement disorder, disorientation, seizures, hyponatraemia or rapid deterioration should be assessed with the possibility of antibody-mediated encephalitis in mind. This assessment should include, as a minimum, a neurological and cognitive examination and early serum testing for antibodies against the NMDA receptor and voltage-gated potassium channel. All patients testing positive for these serum antibodies should be referred to neurological centres with expertise in managing these cases. Cerebrospinal fluid is not usually required but the local immunology service should be consulted for advice. While awaiting antibody results, an electroencephalogram can be useful: encephalopathic features should prompt early referral. Magnetic resonance imaging of the brain may well be normal (although the finding of temporal lobe signal change on imaging is very suggestive of an antibody-mediated encephalopathy). The aim of these recommendations is the early identification and improved treatment for patients with this disorder and to bring medical investigation and management back to psychiatric practice.

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psychiatry in 19th-century literature

Post-trauma symptoms in Dickens' *Our Mutual Friend*: better Abel than Cain

Alistair Stewart

The long shadow cast by traumatic experiences on many people who live through them has been well described. Some attention has been paid more recently to the ways in which people who commit violent assaults can be affected psychologically as a consequence of their own actions. However, it requires an imaginative leap to enter the mind of the perpetrator of violence who has not yet been detected, or otherwise made themselves available for interview. Charles Dickens does this, in a forceful and convincing way, in a chapter towards the end of his novel *Our Mutual Friend*, written in the 1860s.

Bradley Headstone, a conscientious and humourless schoolteacher with a 'slowly labouring expression', discovers that Lizzie Hexham, the young woman on whom he has set his heart, has affections for a frivolous and selfish upper-class waster, Eugene Wrayburn. Driven by hatred for this man, Headstone follows him late one night along the banks of the Thames, clubs him over the head and throws him in the river.

He does not know for certain that he has killed his victim. His crime undiscovered, he feels no guilt or regret. He does not thereby escape the anguish of the compulsion to return.

First, he fears discovery:

> 'there are fifty doors by which discovery may enter. With infinite pains and cunning, he double locks and bars forty-nine of them, and cannot see the fiftieth standing wide open.'

Second, the doubts in his mind tie him fast to the recollection of his deeds:

> 'now, too, was he cursed with a state of mind more wearing and more wearisome than remorse. He had no remorse; but the evil doer who can hold that avenger at bay, cannot escape the slower torture of incessantly doing the evil deed again and doing it more efficiently . . . The state of that wretch who continually finds the weak spots in his own crime, and strives to strengthen them when it is unchangeable, is a state that aggravates the offence by doing the deed a thousand times instead of once; but it is a state, too, that tauntingly visits the offence upon a sullen unrepentant nature with its heaviest punishment every time.'

In detail this means:

> 'supposing his head had been held down under water for a while. Supposing the first blow had been truer. Supposing he had been shot. Supposing he had been strangled. Suppose this way, that way, the other way. Suppose anything but getting unchained from the one idea, for that was inexorably impossible.'

On returning to his classroom duties, Headstone finds no respite.

> 'He was doing it again and improving on the manner, at prayers, in his mental arithmetic, all through his questioning, all through the day.'

Research has shown that many young men convicted of violent offences are affected by intrusive memories and ruminations. Of course, the same research shows that many offenders are not troubled in that way. Or perhaps they simply do not want to discuss the matter at the relevant time.

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