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Editorial

Autoimmunity in psychiatry†

Kenneth Davison

Summary
Current knowledge of the role of autoimmunity in the pathogenesis of the main psychiatric disorders is briefly outlined. The significance of immunological effects on synaptic transmission and associated neuropsychiatric syndromes is emphasised. Clinical psychiatrists are encouraged to keep abreast of developments in this increasingly important area.

Declaration of interest
None.

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Two articles in this issue[1,2] and a report[3] and editorial[4] in recent issues of the *Journal*, draw attention to the possible role of autoimmunity in the pathophysiology of psychiatric disorders. Autoimmunity, which has been known since the early years of the 20th century, is the failure of an organism to recognise its constituent parts as self, resulting in a series of immunological responses to its own cells and tissues, thought to be the result of a loss of immunological tolerance to autoreactive immune cells. The mechanisms of autoimmunity are complex; they involve a number of immunocytes and the cell-surface and serum mediators that they express.[5] The acute injury and potential ensuing damage inflicted by these processes on particular organs or systems produce a variety of autoimmune-related diseases of which more than 150 are listed by the American Autoimmune Related Diseases Association, affecting around 3% of the population.[6] Broadly, the factors predisposing to the development of autoimmunity include genetic, infectious, neoplastic and environmental influences.

As the central nervous system may be affected by autoimmune processes, for example in multiple sclerosis and, more recently, autoimmune limbic encephalitis (discussed below), there seems no reason why autoimmunity should not be a possible basis for some psychiatric disorders. The occurrence of a variety of psychiatric syndromes in the course of some autoimmune physical diseases, such as systemic lupus erythematosus[7]and antiphospholipid syndrome,[8] is also suggestive of a connection.

Schizophrenia

Most attention has been focused on schizophrenia but, since the 1930s, efforts to substantiate autoimmunity as a major pathogenetic factor have met with conflicting results. In this issue of the *Journal*, in a study noteworthy for the size of its database, Chen *et al*[1] demonstrate a positive association between in-patients with schizophrenia and several autoimmune diseases, and confirm the long-recognised negative association of schizophrenia with rheumatoid arthritis. The latter observation is now thought to be the result of two alleles of the same gene, one of which confers a predisposition to schizophrenia and the other to rheumatoid arthritis, that thus become mutually exclusive. These results are similar, albeit from an Asian perspective, to the analysis from the Danish National Registers by Eaton *et al*[9] who observed that a personal history of any autoimmune disease was associated with a 45% increase in risk for schizophrenia. Additionally, 9 autoimmune diseases were more prevalent among patients with schizophrenia, and 12 had a higher prevalence among parents of people with schizophrenia than parents of controls.

These observations are, of course, indirect evidence of autoimmune involvement in the pathogenesis of schizophrenia. Efforts to find more direct evidence, such as cerebral antibodies and other immunological abnormalities specific to schizophrenia, have produced inconsistent and contradictory results in past decades. The recent recognition of autoimmune limbic encephalitis, however, has directed attention to autoantibodies that antagonise proteins involved in synaptic function, with positive findings in some patients with first-episode schizophrenia.[10] It has recently been estimated that antibody-mediated encephalitis accounts for around 6.5% of incidents of first-episode psychosis, and hence should be considered in the differential diagnosis.[4]

Therapeutic trials studying individuals with schizophrenia on immunosuppressive medication, including steroids, azathioprine, and, more recently, the cyclo-oxygenase-2 (COX-2) inhibitor, celecoxib, have produced conflicting results. The inconsistent research and treatment findings have been attributed to the heterogeneous pathogenesis of schizophrenia and the confounding effects of antipsychotic drugs, many of which themselves affect the immune system.[11]

Mood disorders

Major depressive disorder is reported to be associated with increased levels of pro-inflammatory cytokines found both in the blood and in cerebrospinal fluid; in the brain they influence neurotransmitter metabolism and neuroendocrine function. An excess of a subset of T-helper lymphocytes known to be involved in the pathogenesis of autoimmune diseases (Th17) has also been found. As similar changes also occur in other physical diseases, it is thought that they may account for the development of comorbid depression in some physically ill patients. It is difficult to decide whether these findings are indicative of an exaggerated normal immune response or evidence of autoimmunity. Nevertheless, the employment of the immunosuppressive drug, celecoxib, as adjuvant therapy with fluoxetine has been reported to have a greater antidepressant effect than fluoxetine with placebo.[12]

In a further study from the Danish National Registers, which also included bipolar disorder, Eaton *et al*[13] confirmed their earlier findings for schizophrenia but, in contrast, found that an increased risk for bipolar disorder was associated only with a

†See pp. 374–380 and 381–386, this issue.

personal history of Guillain–Barré syndrome, Crohn's disease, autoimmune hepatitis and a family history of pernicious anaemia. In contrast to schizophrenia, bipolar disorder was not negatively associated with rheumatoid arthritis. The results for 'non-affective psychosis' were similar to schizophrenia. Bipolar disorder and schizophrenia, however, have been shown to share a similar immune profile, although an increased prevalence of organ-specific autoantibodies has been reported in bipolar disorder only.

Obsessive–compulsive disorder and related conditions

In the past decade, the concept of 'paediatric autoimmune neuropsychiatric disorders associated with streptococcal infection' (PANDAS)[14] has developed as an offshoot of Sydenham's (rheumatic) chorea, which is thought to have a similar aetiology. PANDAS refers to the development in children of motor tics and obsessive–compulsive disorder (OCD) and sometimes Tourette syndrome, after streptococcal infections, with a relapsing course after further infections. Although this concept has encountered some opposition, anti-basal ganglia autoantibodies have been identified[15] and treatment with plasmapheresis and intravenous immunoglobulins is reported to be effective. These observations have prompted a search for neuronal antibodies, especially directed against the basal ganglia, in adult OCD and Tourette syndrome with positive results in a proportion of cases.[2] Interestingly, although Nicholson *et al*[2] found anti-basal ganglia antibodies in almost 20% of their participants with OCD, they failed to find immunological evidence of previous streptococcal infection. Such results raise the possibility of other triggers for the production of anti-basal ganglia antibodies in the pathogenesis of OCD.

Autoimmune limbic encephalitis

Limbic encephalitis, an inflammatory process involving mainly the hippocampi and amygdalae, has been recognised since the 1960s and was regarded as rare and invariably associated with carcinoma, especially of lung, breast and ovary. There is considerable evidence of an autoimmune basis for this condition, involving anti-neuronal antibodies directed against both the cell body and the neuronal membrane. The latter affect synaptic transmission, which is thought to be responsible for the psychiatric symptoms (see below).

In the past decade several forms of limbic encephalitis that are not invariably paraneoplastic have been described, associated with anti-neuronal antibodies. The latter principally target components of the voltage-gated potassium channel (VGKC) complex, γ-aminobutyric acid (GABA) receptors, and *N*-methyl-D-aspartate (NMDA)-type and amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA)-type glutamate receptors.[16] This disrupts synaptic transmission, which is thought to be principally responsible for the psychiatric symptoms. These include cognitive impairment, depression, hallucinations and behavioural disturbance.

These disorders are of interest to psychiatrists because, alongside a variety of neurological features, psychiatric symptoms are a prominent part of the clinical picture and sometimes the presenting ones. For example, in one series of 100 patients with anti-NMDA receptor encephalitis almost 75% presented initially to psychiatrists.[17]

Although the psychiatric clinical picture can be extremely varied, some characteristic syndromes have been described. For instance, anti-NMDA receptor encephalitis is reported to occur mainly in children or young women who display paranoid delusions, hallucinations, agitation, speech abnormalities and bizarre behaviour, whereas the typical presentation of VGKC encephalitis is said to be a person of middle age with memory deficits, confusion, apathy and irritability, often accompanied by excessive sweating and salivation. Patients with anti-AMPA receptor limbic encephalitis are mostly women aged 50–70 with subacute memory loss and confusion, although agitation, aggression and atypical psychosis have also been described.[17] These disorders usually respond to immunotherapy, including intravenous immunoglobulin, plasmapheresis and steroids, although recovery may be incomplete.

A significant consequence of interest in these disorders has been the impetus it has given to immunological research into psychiatric disorders in general. Other synaptic receptor and intracellular neuronal antibodies have been recognised, such as anti-Hu, -Ma2, -CV2/CRMP5,[17] and no doubt more will be identified, with their related syndromes, in the future.

Other psychiatric disorders

Alzheimer's disease is reported to be associated with inflammatory brain changes that have been attributed to autoimmunity, and specific serum autoantibodies have recently been proposed as diagnostic biomarkers.[18] Claims of response to treatment with COX-1 inhibiting non-steroidal anti-inflammatory drugs have also been made. Autism spectrum disorder is reported to be associated with increased serum anti-nuclear antibodies, and autoimmune physical disease is reported to occur in almost 50% of families of individuals with autism.[19]

Conclusion

With the introduction of new immunological techniques and the expansion of immuno-neuropsychiatric research in the past decade, evidence is accumulating, in many cases suggestive rather than conclusive, that at least a subset of psychiatric disorders has an autoimmune basis. Psychiatrists would be well-advised to keep abreast of this rapidly developing subject, not least for its therapeutic potential.

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100 words

The therapeutic alliance

Simon Heyland

Psychotherapists may depend on it, but all psychiatrists use it in forming and maintaining healthy relationships with patients. To some degree the alliance relies on 'adult' qualities in the patient such as willingness to cooperate and ability to tolerate treatment. It is also partly contingent on the patient's transference patterns manifest as a need for love or attention. But we have a part to play too: jointly formulating and agreeing the goals and the tasks of treatment, and maintaining an appropriate bond which will support this work. Occasionally this bond may just hinge on our ability to acknowledge our mistakes.

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