Detection of antibodies to neuronal cell surface antigens has become an essential component of the diagnostic work-up of unexplained forms of encephalitis in association with epilepsy or movement disorders. One, now well-established, development is the finding of antibodies to N-methyl-D-aspartate receptors in a form of encephalopathy that often includes neuropsychiatric features and a variety of hyperkinetic and hypokinetic movements. This disorder was first described mainly in younger women and children, but subsequently also in men and less frequently in older patients of both sexes (reviewed in Dalmau et al., 2011 and Vincent et al., 2011), and responds to immunotherapies, although improvement can be slow. Another new entity is the disorder characterized by brief dystonic seizures, which often affect the face and arm (‘faciobrachial dystonic seizures’), associated with antibodies directed towards LGI1, a major component of the voltage-gated potassium channel complex (Irani et al., 2010, 2011). Patients with faciobrachial dystonic seizures usually, if not always, develop typical limbic encephalitis, but immunotherapies are highly effective in suppressing the seizures and may prevent the progression to cognitive involvement. Finally, although much less common, glycine receptor antibodies are now being detected in patients with syndromes encompassing excessive startle reactions, spasms, rigidity, phobias and autonomic and brainstem dysfunctions (reviewed in Vincent et al., 2011). As a result of the success in detecting each antibody in patients with these complex disorders, there is a growing acceptance that immune-mediated CNS diseases exist and are not uncommon; moreover, several reports suggest that early recognition and immunotherapies reduce hospitalization and improve long-term outcomes.

An area that has previously received much interest is the spectrum of diseases that encompass eponymously named conditions, such as Tourette’s syndrome and Sydenham’s chorea, paediatric autoimmune neuropsychiatric disorder associated with Streptococcus (PANDAS), and childhood forms of encephalitis lethargica. These disorders, though not always associated with a validated preceding infection, have, until now, largely defied elucidation by immunologists despite the strong circumstantial evidence that they should, at least in some cases, be autoimmune and probably involve pathogenic autoantibodies. In this issue of Brain, Dale and colleagues report antibodies to the dopamine-2 receptor (D2R) in children with autoimmune movement and psychiatric disorders. Russell Dale, now based in Sydney, and Fabriene Brillot have contributed significantly to the field of immune-mediated childhood disorders.

The authors studied a group of 17 children with ‘basal ganglia encephalitis’ taken from a larger cohort studied previously, including a subgroup of patients with encephalitis lethargica (Dale et al., 2004). The patients were defined by encephalopathy and movement disorders, commonly parkinsonism, dystonia or chorea. In 2004, autoantibodies against human ‘basal ganglia antigens’ were demonstrated in some of these patients, but the clinical relevance of such antibodies was not widely accepted, and it is notable that the method used, western blotting of soluble brain extracts, is not ideal for detecting membrane antigens that are likely to be the targets of pathogenic antibodies (as commented by Vincent, 2004); indeed, an intracellular enzyme was subsequently identified as a target antigen of these ‘anti-basal ganglia’ autoantibodies (Dale et al., 2006).

Things began to look more promising when, in collaboration with the Oxford Neuroimmunology Group, N-methyl-D-aspartate receptor antibodies were identified in 10 of the 20 patients with encephalitis lethargica (Dale et al., 2009). However, dopamine is of course the key neurotransmitter in the basal ganglia, and the dopamine receptor, D2R, is integrally linked to the control of movement and behaviour (Rice et al., 2011). Applying the currently established paradigm that antibodies with proven pathogenic potential bind to antigens that are involved in neurotransmission, such as receptors, ion channels or associated proteins (Vincent et al., 2011; Lancaster and Dalmau, 2012), the dopamine receptor was an appropriate candidate target for the remaining patients. Here, in a flow cytometry cell-based assay, 12 of the 17 children with basal ganglia encephalitis negative for N-methyl-D-aspartate receptor antibodies were found to have elevated IgG antibodies to the extracellular domain of D2R but not to D1R, D3R, D5R or dopamine transporter. These sera also bound to cultured striatal neurons and microtubule-associated protein 2-positive neurons in wild-type mouse striatum. Importantly, binding was much reduced in mice knocked out for the D2R and also after immunoadsorption of the sera with D2R-expressing cells, confirming with reasonable confidence the specificity for the D2R. The authors concluded that these patients have antibodies to the extracellular domain of the D2R.

The authors then proceeded to demonstrate antibodies to the D2R in a larger group of children with Sydenham’s chorea (10/30) or Tourette’s syndrome (4/44), but perhaps surprisingly not in...
PANDAS (0/22). Another group has recently reported both D1R and D2R antibodies in patients with Sydenham’s chorea and PANDAS (Brimberg et al., 2012), but their methods, using mainly ELISA and western blotting techniques, were not optimal for the detection of cell surface antigens, which may explain differences from the findings now reported.

As always, there are some cautionary issues. The number of positive patients (12/17 cases collected over 10 years) is small (at least for D2R antibodies in basal ganglia encephalitis/encephalitis lethargica), particularly considering that the patients have been accumulated by a paediatric neurologist with a long-standing interest in these putative immune-mediated movement disorders. Furthermore, in the current study, the rather weak binding to D2R (low signal-to-noise ratio) seen in the fluorescence assay in all positive patients and the low binding observed on D2R-expressing cells, raise some doubts about the levels and specificity of the antibodies.

Thus, the work needs confirmation in other laboratories, where a range of assays measuring the binding to different D2R isoforms expressed on the cell surface can be evaluated. Moreover, D2R antibody should be assessed in other paediatric and adult groups with movement and psychiatric disorders. Meanwhile, the search continues for the as yet unidentified antigenic targets in the remaining patients – either investigating further candidate antigens or involving a more generic search for conformational membrane antigens using strategies as previously described (Littleton et al., 2009) and successfully used by others (e.g. reviewed in Lancaster and Dalmau, 2012).

As we start to identify children with antibodies to the D2R, we will also have to optimize and the treatment of this. In this cohort, the authors suggest that children with D2R antibody-mediated encephalitis treated earlier with immunosuppression appear to have a better outcome, while acknowledging that two untreated patients recovered normally. As such, this observation is concordant with the other antibody-mediated encephalitides (Vincent et al., 2011). Optimal treatment in more chronic conditions such as Sydenham’s chorea and Tourette syndrome or in patients identified and treated later in the course of illness, however, can be challenging. Although the identification of potentially pathogenic antibodies will direct the clinician to the use of more immunotherapies, it is difficult to establish measures of improvement that do not rely too highly on neuropsychiatric and neurocognitive measures that do not always respond fully (or directly) to such treatments. As the mechanisms contributing to abnormal dopamine neurotransmission in these disorders begin to be unravelled, it may be possible to improve symptomatic treatments beyond or in addition to targeting the immune system.

Finally, the growing demand for antibody testing in children and adults with possible immune-mediated encephalopathies and the diversity of different targets are rapidly outstripping the number of research laboratories willing to perform so many different assays; development of highly sensitive and specific commercial assays for multiple antigen testing needs to keep pace with the growing demand. However, in the context of D2R, we first need confirmation of the utility of including it in the repertoire of antibodies that are now relevant to the diagnosis of adult and childhood autoimmune diseases.

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