In the past decade there has been renewed interest in psychiatric and movement disorders that develop in the context of streptococcal infection. There is increasing evidence that these disorders are autoimmune and are mediated by antibodies that bind and cause dysfunction within the central nervous system, specifically in the basal ganglia. The classical post-infectious autoimmune basal ganglia disorder is Sydenham’s chorea known for centuries to be associated with behavioural disturbance; however, recent studies have provided more systematic evidence of related psychopathology (Swedo et al., 1989). It now appears that a wide range of psychiatric and movement disorders can occur following streptococcal infection, in patients who do not meet diagnostic criteria for Sydenham’s chorea. The best described group have been given the acronym PANDAS (paediatric autoimmune neuropsychiatric disorders associated with streptococcal infection; Swedo et al., 1998). Children with PANDAS have tics and/or obsessive-compulsive disorder (OCD) temporally related to streptococcal infections. The accumulating data on the variability of post-streptococcal neurobehavioural syndromes, as well as new findings in relation to the cell and molecular biology of the neuroimmunological mechanisms, could help improve understanding of environmental factors involved in the pathogenesis of movement and psychiatric disorders. In this editorial we consider the hypothesis that group A beta-haemolytic streptococcus (GABHS) induces pathogenic autoantibodies reactive to components of the basal ganglia, and how improved understanding of this process can offer new lines of investigation into the causes of movement and behavioural disorders in children.

**CLINICAL FEATURES**

A wide range of psychopathology has been demonstrated in Sydenham’s chorea; emotional lability is characteristic, and OCD, attention deficit, depression and awkward behaviour are common associated features (Mercadante et al., 2000). A similar range of emotional and behavioural disturbance has been described in PANDAS, a newly characterised group of children who present shortly after GABHS pharyngitis, and show neuropsychiatric exacerbations after further infections. Although OCD and tics are the primary features of PANDAS, a wider range of emotional and behavioural symptoms have been described, including attention deficit, anxiety, oppositional defiant disorder and depression (Leonard & Swedo, 2001). Diagnostic criteria proposed for PANDAS include presence of OCD and/or tic disorder, prepubertal symptom onset, episodic course of symptom severity, association with GABHS infections and association with neurological abnormalities. A recent report of an adult patient with PANDAS suggests that these criteria could be too limiting (Bodner et al., 2001). PANDAS is often indistinguishable from Tourette syndrome, which prompted speculation that a subgroup of this condition could be secondary to streptococcal infections. This hypothesis has been supported by the high prevalence of positive GABHS serology in patients with tic disorders and Tourette syndrome compared with controls (Muller et al., 2000; Cardona & Oreifici, 2001). However, these findings have not been reproduced in other cohorts of established Tourette syndrome (Singer et al., 1998, 1999). The most impressive correlation between streptococcal infection and tic disorders has found in the study with the largest number of patients and the shortest duration of tic disorder (Cardona & Oreifici, 2001). When attempting to decide whether GABHS has a role in neuropsychiatric disorders, it is likely to be important to test patients at, or near, presentation. Once autoimmunity has been induced, exacerbations can be induced non-specifically by other stimuli such as vaccines or non-streptococcal infections, a phenomenon previously described in Sydenham’s chorea (Berrios et al., 1985).

More recently other post-streptococcal clinical phenotypes have been described, notably inflammatory autoimmune encephalitis associated with dystonia and emotional lability (Dale et al., 2001). Other groups have proposed that an attention-deficit hyperactivity disorder-like syndrome is the neuropsychiatric phenotype most strongly associated with streptococcal infection (Peterson et al., 2000).

In summary, reports to date suggest that the clinical phenotypes after GABHS infection include extrapyramidal movement (chorea, tics, dystonia) and psychiatric (OCD, attention deficit, anxiety, depression) disorders. The features can occur in combination or independently.

**PROPOSED DISEASE MECHANISM**

Previous investigation into post-streptococcal autoimmune disorders has focused on M proteins, the protein sequences expressed on streptococcal cell walls. The M protein amino acid sequences are highly variable, and only certain M protein serotypes have been associated with post-streptococcal autoimmunity. It is proposed that M protein amino acid sequences share homology with host basal ganglia antigens, and that autoimmune induction involves a process of molecular mimicry. Antibodies generated after certain GABHS infections may cross-react with basal ganglia proteins leading to central nervous system (CNS) dysfunction. Homology between amino acid sequences of streptococcal and basal ganglia antigens has been supported by the successful absorption of anti-brain antibodies by streptococcal antigens (Bronze & Dale, 1993; Dale et al., 2001). Lymphocytes and/or antibodies induced after streptococcal infection can cross the blood–brain barrier and, if a brain antigen is recognised, immune activation can occur. The dogma that the blood–brain barrier is an impervable wall has been dismissed in recent years, as it is clear that immune mediators are able to enter and leave the CNS under normal resting conditions (Archelos & Hartung, 2000). Support for this immune hypothesis includes the presence of serum antibodies that bind to basal ganglia proteins found in both Sydenham’s chorea (Husby et al., 1976) and PANDAS.
**IMPLICATIONS**

It is proposed that PANDAS and Sydenham’s chorea are immune-mediated basal ganglia disorders with consequent movement and psychiatric disorders. Some clinical phenotypes of PANDAS are similar to Tourette syndrome and OCD. Longitudinal studies are underway to determine whether a proportion of individuals with ‘idiopathic’ Tourette syndrome and OCD might have evidence of autoimmunity against basal ganglia. This important question clearly has broad implications for the understanding of causation, and perhaps for treatment. If an autoimmune aetiology can be proven confidently, immunotherapies could be indicated in common psychiatric disorders to induce autoimmune remission and therefore symptom remediation. In order to consider such treatments there must be clear clinical and laboratory diagnostic criteria. Positive streptococcal serology alone is inadequate for such a diagnosis, as GABHS is so prevalent in the paediatric community. The ultimate molecular goal would be to characterise the basal ganglia proteins involved in antibody binding, which could provide central clues to the neurotransmitter or second messenger systems involved, and even point towards novel drug targets for common movement and psychiatric disorders in children.

**DECLARATION OF INTEREST**

None.

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