

Post-streptococcal autoimmune psychiatric and movement disorders in children

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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 neuro-behavioural 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 & Orefici, 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 & Orefici, 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 impenetrable 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

(Kiessling *et al*, 1993; Singer *et al*, 1998). New findings demonstrate that these antibodies bind specifically to basal ganglia proteins, and are universal in acute Sydenham's chorea and post-streptococcal dystonia (Dale *et al*, 2001; Church *et al*, 2002). Anti-basal ganglia antibodies are rarely found in children with uncomplicated streptococcal infection or in neurological controls, suggesting that this is both a sensitive and specific marker, and promises to be a useful diagnostic tool (Dale *et al*, 2001). However, not all investigators have shown such specific autoimmunity; one recent report found autoantibodies against a variety of neural components without any clear common antigen binding (Morshed *et al*, 2001).

A further question that arises is why the majority of people have an uncomplicated GABHS pharyngitis, whereas a minority induce an autoimmune response. Some evidence has arisen that post-streptococcal CNS disorders could be familial, suggesting a genetic predisposition (Lougee *et al*, 2000). Possible mechanisms underlying such a predisposition include aberrant lymphocyte handling. Intriguing support for this hypothesis comes from the high incidence of the B-lymphocyte marker D8/17 in patients with Sydenham's chorea and PANDAS (Hoekstra *et al*, 2001). However, the function of this marker is unknown, and as it is present in a significant proportion of the normal population, D8/17 should not be used as a diagnostic tool for those conditions.

EVIDENCE OF BASAL GANGLIA AUTOIMMUNITY

Structural imaging is normal in the majority of patients with Sydenham's chorea and PANDAS, although basal ganglia inflammatory lesions are common in post-streptococcal autoimmune dystonia (Dale *et al*, 2001). Giedd *et al* (2000) have demonstrated enlargement of the basal ganglia using volumetric techniques in patients with Sydenham's chorea and PANDAS, which resolves on symptom remission. Pathological studies of Sydenham's chorea and PANDAS are uncommon as these disorders are rarely fatal. The two documented pathological reports of Sydenham's chorea showed inflammatory changes primarily of the basal ganglia and cellular infiltrate by lymphocytes, in particular plasma cells, the primary role of

which is antibody production (Greenfield & Wolfsohn, 1922; Colony & Malamud, 1956). These reports might not represent the typical pathological features of post-streptococcal CNS disease.

For a neurological disorder to be recognised as autoimmune, five experimental features need to be proven: presence of autoantibody, immunoglobulins at target structure, response to plasma exchange, passive transfer of disease to animals, and disease induction with autoantigen (Archelos & Hartung, 2000). Myasthenia gravis is the only neurological disorder that fulfils all five criteria. Three of five criteria have been met in Sydenham's chorea/PANDAS to date, including amelioration of symptoms when antibody is removed; a recent controlled treatment trial in patients with PANDAS demonstrated symptom remediation with plasma exchange and intravenous immunoglobulin (Perlmutter *et al*, 1999). However, further randomised controlled trials in larger numbers of patients are required before such treatments can be recommended routinely. Another criterion involves induction of disease in an animal model; serum from children with PANDAS infused into rats induced tics in the animal, further evidence for a direct role of the antibody in pathogenicity (Hallett *et al*, 2000). All five criteria will need to be fulfilled before post-streptococcal CNS disorders can be considered autoimmune.

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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