

Review

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Autoimmunity and the basal ganglia: new insights into old diseases

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Summary

Sydenham's chorea (SC) occurs weeks or months after Group A streptococcal infection, and is characterized by involuntary, purposeless movements of the limbs, in addition to behavioural alteration. There is a body of evidence which suggests that SC is an immune-mediated brain disorder with regional localization to the basal ganglia. Recent reports have suggested that the spectrum of post-streptococcal CNS disease is broader than chorea alone, and includes other hyperkinetic movement disorders (tics, dystonia and myoclonus). In addition, there are high rates of behavioural sequelae, particularly emotional

disorders such as obsessive-compulsive disorder, anxiety and depression. These findings have led to the hypothesis that similar immune-mediated basal ganglia processes may be operating in common neuropsychiatric disease such as tic disorders, Tourette syndrome and obsessive-compulsive disorder. This review analyses the historical aspects of post-streptococcal CNS disease, and the recent immunological studies which have addressed the hypothesis that common neuropsychiatric disorders may be secondary to basal ganglia autoimmunity.

Introduction

The term 'basal ganglia' refers to a collection of nuclei lying in the centre of the brain, and include the caudate and putamen (also termed the striatum), globus pallidus, subthalamus and substantia nigra. The basal ganglia nuclei contain neurones that receive and modify information from the cerebral cortex. Dysfunction of the basal ganglia results in extrapyramidal movements (chorea, hemiballismus, dystonia, tics and parkinsonism). In addition to control of movements, the basal ganglia have an important role in control of behaviour and emotion. For example, there is accumulating evidence that the pathogenesis of obsessive-compulsive disorder is linked to caudate nucleus dysfunction, resulting in functional abnormalities in cortico-striatal circuits.¹

Sydenham's chorea (SC) was the first extrapyramidal movement disorder to be described. In 1686, Thomas Sydenham described a childhood syndrome characterized by sudden onset of rapid, involuntary and purposeless limb movements. In addition, he noted an alteration in behaviour and emotion. Initially, SC was thought to be a psychological response to stress or even hysteria. However by the 19th century, physicians noted a high incidence of 'rheumatism' in patients with chorea, and thereafter the association between rheumatic fever and SC was made.² At the beginning of the 20th century, streptococcal organisms were being isolated from patients with rheumatic fever and chorea, and subsequent epidemiological studies

confirmed the relationship between streptococcus, SC and rheumatic fever.³ However despite being recognized over 300 years ago, the disease remains enigmatic and poorly understood. During the second half of the 20th century, the incidence of SC significantly reduced in the West, although outbreaks of disease have been recorded in the US. Consequently, the majority of Western physicians would consider SC a historical disease, although it remains endemic in developing countries. In the 1980s, interest in SC was re-ignited by the re-emergence of sudden onset movement disorders and emotional disorders after streptococcal infections.⁴ However, unlike SC, the movement disorder phenotype was motor tics rather than chorea. As the clinical phenotype was similar to patients with 'idiopathic' tics and obsessive-compulsive disorder, this discovery renewed interest in Sydenham's chorea, which has become an autoimmune model for common movement and psychiatric disorders in children.⁵

I will review the clinical and pathological features of post-streptococcal CNS disease, and the recent studies attempting to identify whether basal ganglia autoimmunity may have a role in common movement and psychiatric conditions.

Although it would appear these syndromes occur predominantly in childhood, adult-onset disease has been described.⁶

Clinical features

Movement disorders (Table 1)

The best described of all movement disorders after beta haemolytic streptococcal infection remains chorea. Chorea is usually bilateral, although hemichorea does occur, albeit rarely. Perhaps it would not be surprising to learn that other movement disorders in addition to chorea may occur in post-streptococcal CNS disease. Indeed, basal ganglia disorders rarely conform to one extrapyramidal phenotype; for example in Huntington's disease,

tics, dystonia and parkinsonism may occur, although chorea remains the most characteristic phenomenon.^{7,8} Similarly, motor tics have been well recognized in the context of 'Sydenham's chorea'.⁹⁻¹¹

In the 1980s, an outbreak of Group A streptococcal tonsillitis in Rhode Island was associated with a 10-fold increase in the incidence of motor tics (without chorea);⁴ the concept of post-streptococcal tics was born. Subsequent identification of further patients led to the development of a new acronym: PANDAS (paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections).¹² In addition to tics, PANDAS patients had a high incidence of psychiatric disorders, particularly obsessive-compulsive disorder (OCD) (discussed later). The patients were clinically differentiated from 'idiopathic' tics and OCD by the temporal association with microbiologically-defined streptococcal throat infections. Furthermore, the patients often presented suddenly (rather than insidiously), and the mean age of onset of PANDAS patients was also younger than previously described tic and OCD cohorts.^{4,12} Given the high frequency of streptococcal infections in the community, two or more exacerbations associated with streptococcal infections were required for diagnosis of PANDAS.¹² However, the concept of PANDAS remained controversial,¹³ and a reliable biological marker has become necessary to improve diagnostic sensitivity and specificity (discussed later). Other than motor tics and chorea, other extrapyramidal movements have been described shortly after streptococcal pharyngitis, including dystonia and myoclonus.^{14,15} We have also described a patient with post-streptococcal paroxysmal dystonic choreoathetosis (PDC); this patient had episodes of chorea and dystonia lasting a few hours with intervening normal periods, suggesting that streptococcus is one of the causes of secondary PDC.¹⁶ An important question that arises is why some patients present with chorea, while other patients present with tics, dystonia or myoclonus. Demographics

Table 1 Summary of the clinical characteristics of post-streptococcal CNS syndromes

Phenotype	Extrapyramidal movement disorder	Characteristic psychiatric disorders	References
Sydenham's chorea	Chorea	OCD, anxiety, major depression, ADHD	11,33
PANDAS	Motor tics	OCD, anxiety, major depression, ADHD	12
Post-streptococcal dystonia/post-streptococcal ADEM	Dystonia	Emotional lability, OCD	14,25

PANDAS, paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; ADEM, acute disseminated encephalomyelitis; OCD, obsessive-compulsive disorder; ADHD, attention deficit hyperactivity disorder.

have demonstrated that cohorts of Sydenham's chorea are predominantly female, whereas post-streptococcal tic cohorts are predominantly male.^{12,17} This suggests a possible influence of sex on phenotypic expression. Relapses of SC during pregnancy (chorea gravidarum) further emphasize the potential importance of sex hormones on movement disorder expression.¹⁸ It is also possible that the extrapyramidal phenotype depends upon the specific basal ganglia region involved. It has been proposed that specific regions of the basal ganglia are associated with certain extrapyramidal phenotypes; for example, hemiballismus and parkinsonism are associated with the subthalamus and substantia nigra pathology, respectively, although this statement over-simplifies the pathophysiology of movement disorders.¹⁹

Psychiatric disorders

The high incidence of emotional factors in Sydenham's chorea has been recognized for over a century, and was initially referred to as a 'choreic temperament'. However, further evaluation of the psychiatric sequelae of Sydenham's chorea demonstrated emotional and disruptive behaviours were common accompaniments. A follow-up study showed high prevalence of emotional disorders (obsessive-compulsive disorder, anxiety, depression) and disruptive behaviours in 75% of patients.²⁰ More importantly, this study demonstrated that the behavioural consequences often remained for decades after the resolution of childhood chorea.²⁰ More recent examination of SC cohorts revealed a high incidence of obsessive-compulsive behaviours.²¹ These findings have come at a time when the pathogenesis of obsessive-compulsive disorder (OCD) has been linked to the basal ganglia (specifically caudate) and the cortico-striatal circuits.¹ Furthermore, the incidence of OCD appeared to be increasingly common in children who had relapses of SC.²² Subsequent analysis of cohorts of SC demonstrated that psychiatric comorbidity was not limited to OCD, but included other emotional disorders such as generalized anxiety, separation anxiety and major depression.¹¹ In addition, attention deficit hyperactivity disorder (ADHD) was significantly more prevalent compared to controls, suggesting that the spectrum of post-streptococcal psychiatric disorders is broader than previously thought.²³ There had been a number of reports of schizophrenia as an outcome of SC,²⁴ although recent literature and our experience have not repeated this observation.

The psychiatric morbidity of PANDAS is similar to (if not identical to), Sydenham's chorea. In the

acute stages, there is typically a rapid alteration in behaviours and emotional lability.¹² PANDAS was defined as post-streptococcal emergence of OCD and/or tics; however, analysis of 50 patients with PANDAS demonstrated a high incidence of other emotional disorders (major depression 36%, separation anxiety 20%), conduct disorders (oppositional defiant disorder 40%) and attention deficit hyperactivity disorder (40%).¹²

Other neurological features and outcome

The clinical outcomes would appear to be relatively specific to extrapyramidal movement and psychiatric disorders. Dysarthria and hypotonia are common accompaniments of chorea, and would be considered characteristic of SC.¹⁷ By contrast, dementia, seizures and visual impairments would be considered atypical. We have recently described 10 patients with a disseminated autoimmune encephalitis after streptococcal infections, where the clinical features were dystonia, encephalopathy and acute behavioural alteration, in association with inflammatory lesions predominantly of the basal ganglia.²⁵ Although the predominant features were dystonia and behavioural alteration, pyramidal tract signs were also common in these patients, suggesting dissemination of disease beyond the basal ganglia may occasionally occur in post-streptococcal CNS syndromes.

It is most physicians' impression that SC is a benign self-limiting disorder. However, persistence of chorea over 2 years has been observed in 50% of a recent Brazilian cohort.²⁶ When present, relapses of SC occur most commonly in the first year after onset, or during pregnancy (chorea gravidarum). It should be noted that persistent psychiatric sequelae are common, even after the apparent resolution of chorea.²⁰ By definition, PANDAS has a relapsing remitting course with temporal association with further infections.¹² Although streptococcal infections appear to be the initiators of disease, other infective triggers may be responsible for relapses.^{27,28} Although there are few longitudinal studies examining the natural history of disease, it is likely that the outcome of both SC and PANDAS is variable, varying from monophasic self-limiting disease, to a persistent relapsing remitting course for many decades (unpublished observation).

Pathogenesis

Pathology

As post-streptococcal CNS syndromes are rarely fatal, pathological examination has been limited to

a few post-mortem studies. By virtue of their fatal nature, it is possible that these post-mortem descriptions may represent the more severe end of the spectrum. It is also possible that some of the early reports may have mistakenly included cases of unrecognized genetic or neurodegenerative disorders such as Huntington's disease or metabolic disease.

The most consistent finding is of an encephalitis, with inflammatory changes predominantly of the basal ganglia and to a lesser extent the cortex.^{29,30} The caudate and putamen were usually the most severely involved basal ganglia regions.^{29,30} Perivascular infiltration by lymphocytes was characteristic in these descriptions. Neuronal degeneration was occasionally observed, although it was argued that neuronal death may be atypical given the excellent outcome in a proportion of patients with SC.²⁹ As previously mentioned, some studies have found conflicting findings; one case reported diffuse neuronal degeneration as the predominant feature.³¹

Imaging

Neuroimaging often provides insight into the localization of CNS disease, although is unlikely to provide detailed biological insight into pathogenesis. Imaging of the brain using conventional CT and MRI is commonly normal in post-streptococcal CNS disease.^{32,33} Occasionally, inflammatory changes have been described which are predominantly (but not exclusively) localized to the basal ganglia (Figure 1).^{14,25,34-37} Only rarely has enhancement after contrast been described, suggesting that disruption of the blood-brain barrier is not typical.³⁴ More sophisticated techniques, including volumetric studies, have shown that the caudate and putamen are specifically enlarged during the acute phase of Sydenham's chorea and PANDAS.^{23,32,38} Furthermore, anecdotal evidence has shown that basal ganglia size correlates with the disease course; a longitudinal case study demonstrated striatal enlargement during acute presentation with normalization during remission.³⁹ SPECT studies have shown hypermetabolism and increased glucose consumption in the basal ganglia.⁴⁰⁻⁴² Furthermore, a case report of proton spectroscopy has shown reduction of n-acetyl aspartate in the striatum, which was interpreted as indicative of neuronal dysfunction or loss.³⁵ Although the majority of imaging findings are reversible, occasionally irreversible striatal changes have been described suggesting permanent damage is possible.^{14,43,44} Although the majority of imaging studies have localized disease to the basal ganglia, imaging is rarely useful as a diagnostic tool alone, and is

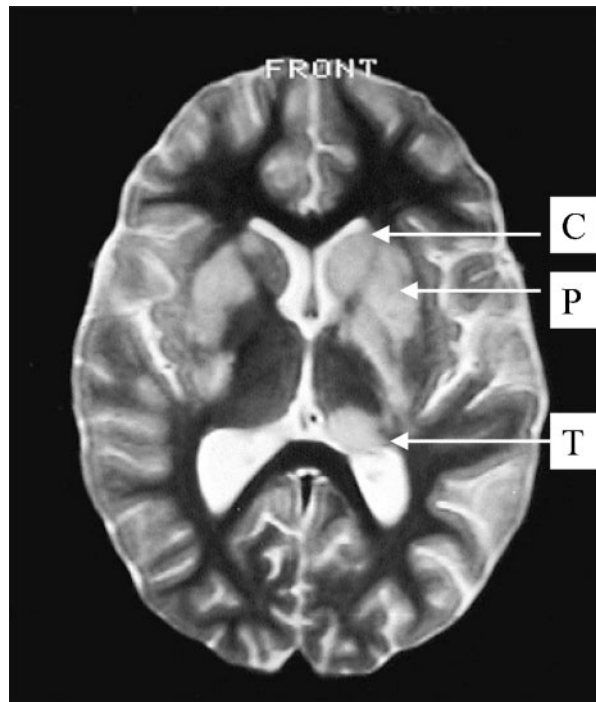


Figure 1. Post-streptococcal encephalitis presenting with dystonia and behavioural alteration. MRI brain T2 weighting, demonstrating inflammatory changes in bilateral caudate nuclei (C) bilateral putamen (P) and thalamus (T).

more commonly used to exclude other causes of movement disorders. The imaging studies also suggest that there is a spectrum of immune mediated brain pathology, ranging from mild swelling to gross irreversible inflammatory damage and cell death.

Anti-neuronal antibodies in post-streptococcal CNS syndromes

The immunopathogenesis of post-streptococcal CNS syndromes is incompletely understood. It is hypothesized that Group A streptococcal infection induces an immune response which cross-reacts with the brain. There is no evidence to suggest that streptococcal organisms directly enter the brain. The mediators of disease would therefore need to be immune components (or bacterial toxins) that are capable of entering the central nervous system and then mediating nervous tissue dysfunction or damage. Recent experiments have shown that activated lymphocytes or antibodies are capable of entering the CNS without disruption of the blood brain barrier.⁴⁵ If lymphocytes recognize antigens in the CNS, immune activation may occur with consequent neural dysfunction or damage.

Most of the investigation to date has focussed on anti-neuronal antibodies as the possible mediators

of disease. A functional antibody-mediated disease is considered more likely given the fact that a significant proportion of SC patients make a full recovery (in contrast to cytotoxic T-cell-mediated disease, where permanent damage would be anticipated). Experimental support for the antibody hypothesis was first demonstrated by Husby who described anti-neuronal antibodies using an immunofluorescent technique in 46% of Sydenham's chorea patients ($n=30$), compared to 14% of rheumatic fever (without chorea $n=50$), and only 1.8–4% of control subjects ($n=203$).⁴⁶ The antibodies demonstrated a cytoplasmic pattern of binding to caudate and subthalamus neurones, with occasional weaker staining in the cortex and medulla. Furthermore, Husby demonstrated a potential correlation between antibody reactivity and the clinical status, with antibody disappearance on chorea remission. In addition, the antibodies were removed by pre-incubating with a preparation of isolated caudate neurones, but not cerebral cortex or mouse liver, supporting antibody specificity to caudate neurones.⁴⁶ Two further studies have expanded upon these findings; both demonstrated antibodies reactive against basal ganglia neurones universally in acute SC (100%), although less commonly in the chronic or persistent stage;^{47–49} this phenomenon may be important when considering anti-neuronal antibodies as an autoimmune marker in cohorts of established neuropsychiatric disorders (discussed later). Although antibody assays using immunofluorescence were important in establishing a putative antibody hypothesis, Western immunoblotting studies by Church (using human basal ganglia as the autoantigen) have suggested that a conserved group of autoantigens are involved in auto-antibody binding.⁴⁷ The autoantigens have a molecular weights of 40, 45 and 60 kDa, and would appear to be restricted to, or enriched in, the basal ganglia.⁴⁷ A further small study also proposed that a 45 kDa was found in SC, although only during the acute stage.⁵⁰ Similar investigations in a PANDAS cohort found an increased incidence of anti-neuronal antibodies and positive streptococcal serology in patients with tics or choreiform movements.⁴ The immunofluorescence antibody binding pattern in these PANDAS patients was similar to SC. We have found similar anti-neuronal antibody findings in post-streptococcal autoimmune dystonia, and propose that the same auto-antigens are involved in all post-streptococcal CNS syndromes (chorea, tics, dystonia and autoimmune encephalitis).^{14,25,47} The identity of these antigens is currently unknown. The majority of studies have not found other auto-antibodies or anti-nuclear antibodies in SC or

PANDAS,⁴⁶ further suggesting that the immune response is relatively specific to basal ganglia antigens.

The presence of antibodies in serum does not necessarily infer pathogenicity. For example, antibodies could be produced as part of tissue damage. In order to demonstrate that a disorder is autoimmune, five criteria must be fulfilled:⁵¹ (i) presence of auto-antibodies; (ii) presence of antibodies in target tissue; (iii) induction of disease in animal model by passive transfer of antibody; (iv) induction of disease in animal model by auto-antigen immunisation; and (v) improvement of clinical symptoms after removal of antibodies with plasma exchange.

There are two published positive studies describing disease induction in rats after PANDAS antibody infusion into rat striatum.^{52,53} Both describe stereotypical movements in the rats infused with PANDAS antibody but not with control antibody infusion. However, another study, published in abstract form, has not reproduced this finding.⁵⁴

One controlled trial demonstrated benefit of plasma exchange and intravenous immunoglobulin in PANDAS compared to controls,⁵⁵ although the numbers in each group were small ($n=10$ in each group). No similar immunomodulatory studies exist in SC, where the literature is limited to small retrospective studies suggesting the benefits of corticosteroid treatments.⁵⁶ Therefore, although there is building evidence to support pathogenicity of the auto-antibodies (currently criteria 1,3 and 5 have been positively demonstrated), neither SC nor PANDAS can currently be considered as definite auto-antibody-mediated disorders.

The immune studies to date have almost completely focussed on anti-neuronal antibodies as the potential mediators of disease. However, alternative immune mechanisms are possible including cytotoxic T-lymphocyte attack, cytokine-mediated neuronal dysfunction and even superantigen-mediated immunity. A further unanswered question is why heart involvement (i.e. rheumatic carditis) seems to occur in SC, but not in PANDAS.

Streptococcus and brain epitope cross-reactivity

Although streptococcal organisms are the proposed mediators of SC and PANDAS, relatively little attention has focussed on why beta-haemolytic *Streptococcus* is capable of producing immune-mediated brain disease. The favoured hypothesis is that antibodies cross-react between streptococcal and brain epitopes (molecular mimicry). The surface M protein of Group A streptococci is considered

the major virulence factor. Immunization of rats with M6 streptococcal proteins has been shown to induce cross-reactive anti-brain antibodies. Furthermore, synthetic epitopes of M6 protein sequences were capable of inhibiting anti-brain antibodies from a patient with SC.⁵⁷ Husby's original experiments suggested that the antibodies against caudate neurones cross-reacted with epitopes of Group A streptococcal membranes.⁴⁶ It would also appear that the antibody cross-reactivity is specific to certain strains of streptococcus.^{25,46,57} However appealing, definitive evidence for the molecular mimicry phenomenon does not yet exist.

Genetics and disease predisposition

The majority of people who suffer streptococcal pharyngitis (most of us at some stage!) suffer no apparent complications, whereas a minority incur significant CNS sequelae. Patients with SC have a higher incidence of rheumatic fever (RhF) and SC in first-degree family members, compared to the general population.⁵⁸ This suggests that a genetic predisposition is important in addition to exposure to a virulent streptococcus organism. Likewise, the incidences of tics and OCD in first-degree relatives of children with PANDAS (39% and 26%, respectively) are significantly higher than in the general population, further supporting the importance of a genetic factor in disease evolution.⁵⁹

The mechanism of this genetic predisposition is not certain; classical HLA class I and II profiles in SC do not appear to predict a genetic vulnerability.⁶⁰ Instead, interest has focussed on a B-lymphocyte marker (D8/17) that is highly expressed in patients with rheumatic fever/SC compared to healthy controls and autoimmune controls (including post-streptococcal glomerulonephritis).^{61,62} This same marker is significantly more prevalent in PANDAS patients,⁶³ supporting immunological similarity between SC, rheumatic fever and PANDAS (Table 2).

Despite this intriguing finding, the function of this lymphocyte marker remains unknown.

Treatment

There are two potential treatment approaches to post-infectious autoimmune disorders: to prevent further exacerbating infections, or to modulate the autoimmune process. Antibiotic prophylaxis is an accepted treatment of RhF and SC, and should be continued throughout childhood.⁶⁴ It should be noted that large studies were required to establish a benefit of penicillin prophylaxis in SC. Initial attempts to replicate these findings in PANDAS using a double-blind placebo-controlled trial were unsuccessful, although this may have been due to a failure to achieve acceptable levels of prophylaxis.⁶⁵ A prospective study of antibiotic treatments for acute tonsillitis in PANDAS showed prompt improvements in obsessive-compulsive behaviours associated with antibiotic treatments, although this was an uncontrolled descriptive study.⁶⁶

The only placebo-controlled trial examining the benefit of immunomodulation (plasma exchange and intravenous immunoglobulin) demonstrated improvements in the patients treated with active agents compared to patients treated with sham (saline) infusions. Importantly, the treatment improvements were maintained at one year.⁵⁵ Interestingly, the same finding was not reproduced in OCD patients who did not have PANDAS, suggesting that the benefit of immune modulation is restricted to the PANDAS subgroup of neuropsychiatric disorders.⁶⁷ Currently, immune treatments should not be given routinely to SC or PANDAS patients until further controlled trials confirm their benefit. Carbamazepine and sodium valproate have been proposed to be useful symptomatic treatments of SC, and are probably preferable to haloperidol, which can cause unacceptable side-effects.⁶⁸

Table 2 SC, PANDAS and neuropsychiatric syndromes: percentage of B-cell lymphocytes expressing D8/17 on surface

Definition of positive	Patient group (n)	Patients positive	Controls (n)	Controls positive	Reference
> 12%	SC (n = 9)	89%	Healthy (n = 24)	17%	63
> 12%	PANDAS (n = 27)	85%	Healthy (n = 24)	17%	63
> 11.8%	RhF (n = 84)	99%	Healthy (n = 76)	14%	62
> 11.8%	TS/OCD (n = 31)	100%	Healthy (n = 21)	5%	74
95 th percentile of controls	Tic disorders (n = 33)	60.6%	Healthy (n = 20)	5%	75

All studies yielded statistically significant differences. TS, Tourette syndrome; OCD, obsessive-compulsive disorder; SC, Sydenham's chorea; PANDAS, paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; RhF, rheumatic fever.

Implications for 'idiopathic' neuropsychiatric syndromes

Tic disorders, Tourette syndrome and obsessive-compulsive disorder are considered to be variable phenotypic expressions of the same brain disorder. Although pathophysiology is considered to be related to dysfunction of cortico-striatal circuits, the exact pathology is unknown.¹ It is likely that a variety of processes can disrupt this circuit and result in these clinical phenotypes. The recognition of PANDAS has led to speculation that a subgroup of 'idiopathic' tic disorders, Tourette syndrome (TS) and OCD have a (post-streptococcal) immune mediated pathophysiology. Using the biological markers previously described in the context of SC and PANDAS, researchers have attempted to address this important question.

Elevated streptococcal serology was present in a cohort of German TS and Italian tic disorders, compared to age-matched controls.^{69,70} One American TS study demonstrated a similar association with streptococcal serology,⁴⁹ although two American TS studies found no such correlation.^{71,72}

Anti-neuronal antibody findings in TS have been generally supportive of the autoimmune hypothesis in TS; two studies have demonstrated the presence of anti-basal ganglia antibodies in TS compared to control groups, and have proposed that a striatal epitope of molecular weight 60 kDa is representative of TS antibody repertoires (similar to the findings by Church⁴⁷).^{71,73} Furthermore, the antigen is likely to be specific to (or enriched in) the caudate/putamen rather than globus pallidus or muscle.⁷³ Use of a neuron-like neuroblastoma cell line did not reproduce these findings,^{72,73} suggesting that human basal ganglia should be used as the antigenic substrate in future assays. However, a further study suggested that, although anti-neuronal antibodies are more prevalent in TS patients, the antibody reactivity was different to SC, and no common antibody reactivity could be recognized.⁴⁹ At present, it is difficult to know the exact proportion of TS who may have an autoimmune aetiology. Furthermore, due to the natural tendency for TS to wax and wane, longitudinal studies are required.

The D8/17 marker does not fluctuate with disease status, and therefore has potential benefits over anti-neuronal antibodies as markers of disease.⁶² Both studies measuring D8/17 in TS/tic/OCD cohorts have shown statistically elevated prevalence of this marker compared to control groups^{74,75} (Table 2).

Conclusion

The published findings strongly suggest that SC and PANDAS are immune-mediated brain disorders with selective involvement of the basal ganglia, although at present neither condition fulfils all the criteria for definite auto-antibody mediated disorders. Intriguing early data suggest a similar process may be occurring in a subgroup of tic disorders, Tourette's syndrome and obsessive-compulsive disorder. Therefore, further epidemiological and experimental studies are required to examine the extent of the relationship between streptococcus, autoimmunity and common neuropsychiatric disorders. A recent epidemiological community study of 1596 children reported 339 with a history of tics, often associated with co-morbid OCD and ADHD.⁷⁶ If the association with streptococcus is correct, collectively these disorders may prove to be the commonest form of autoimmune disease.

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