Pediatric autoimmune neuropsychiatric disorders associated with streptococci (PANDAS): update
Stanford T. Shulmana,b

Introduction
The term Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococci, commonly referred to as ‘PANDAS’, has been used for a group of neuropsychiatric disorders that are proposed to have an autoimmune basis and to be related to infection with group A beta-hemolytic streptococci (GAS) [1]. These neuropsychiatric disorders are obsessive–compulsive disorder (OCD) and tic disorder or Tourette’s syndrome.

One neurologic disease is unequivocally linked to GAS infection, Sydenham chorea. The most prominent English physician of the 17th Century, Thomas Sydenham (1624–1689), described both chorea minor (now termed Sydenham chorea) and the polyarthritis of acute rheumatism (now acute rheumatic fever), but curiously he never linked these two entities. By 1850, however, there was wide acceptance for the association of chorea with acute rheumatism [2]. When the Jones criteria for the diagnosis of acute rheumatic fever (ARF) were proposed in 1944 by T. Duckett Jones, chorea was included as a major manifestation [3,4], and it remains as such in the most recent revision of the Jones criteria [5]. The inclusion of chorea as an important component of ARF is strongly supported by its occurrence in patients who have other features of ARF, particularly migratory polyarthritis and/or classic acute rheumatic carditis or chronic rheumatic heart disease. In contrast to other forms of ARF, in patients with ‘pure’ chorea, lacking arthritis or carditis or other major criteria, the relation of the illness to recent GAS infection is often difficult to establish because the latent period between the inciting GAS infection and the onset of chorea is as long as 6 months, in contrast to the 2–4-week latency for arthritis and carditis. As a result, serologic evidence of recent GAS infection (such as elevated antistreptolysin O or anti-DNAse B titers) is often lacking in ‘pure’ chorea [5].

Purpose of review
To review recent developments related to the proposed entity Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococci (so-called ‘PANDAS’).

Recent findings
The relationship between obsessive–compulsive disorder (OCD) or tics/Tourette’s syndrome in childhood to antecedent group A streptococci (GAS) is unclear. One recent prospective cohort study found that more than 85% of clinical exacerbations in OCD/tic behavior in patients who met criteria for PANDAS had no relationship to GAS infection. Another study found no correlation between clinical exacerbations and changes in a variety of markers of brain autoimmunity, the proposed pathogenesis of PANDAS. A third recent study concluded that, compared with specialty clinic diagnoses, patients diagnosed with tics or Tourette’s by physicians in the community were significantly more likely to be diagnosed with PANDAS without meeting the proposed criteria, most lacked supporting laboratory evidence of GAS infection, and they were more likely to be treated with unjustified short-term to chronic antibiotic and/or immunomodulatory therapy.

Summary
Despite continued research in the field, the relationship between GAS and specific neuropsychiatric disorders (PANDAS) remains elusive. It is possible that GAS infection may be but one of the many stressors that can exacerbate tic/Tourette’s or OCD in a subset of such patients.

Keywords
group A streptococci, obsessive–compulsive disorder, PANDAS, tic disorder, Tourette’s syndrome

Curr Opin Pediatr 21:127–130
© 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins
1040-8703
Swedo et al. [1] proposed that Sydenham chorea, OCD, and Tourette’s syndrome are related disorders with an autoimmune basis related to cross-reactive immune responses involving GAS and brain epitopes, and they coined the acronym PANDAS for the OCD and Tourette’s syndrome components. Kirvan and Cunningham and their co-workers [6,7] have published data from elegant studies that confirm that antibodies in sera of acute chorea patients react with the surface of neuronal cells by recognizing lysoganglioside, which cross-reacts with the GAS epitope N-acetylgalcosamine, and that this interaction signals the induction of calcium calmodulin-dependent protein kinase II, which in turn leads to increased tyrosine hydrolase activity and enhanced dopamine release. The autoimmune link between GAS and OCT/Tourette’s syndrome, however, has remained more tenuous [8–10]. This is in part related to the quite high background rates of both GAS infections and neuropsychiatric behaviors (especially tic disorder) in the prepubertal population that coincides with the age distribution of PANDAS. In addition, the presumed autoimmune basis of PANDAS has been challenged by some investigations [11,12]. In this review, several recent publications that attempt to shed light on these issues are discussed.

**PANDAS: diagnostic criteria**

The diagnostic criteria for PANDAS that were proposed by Swedo et al. in 1998 include the following: OCD and/or chronic tic disorder (Tourette’s, chronic motor, or vocal tic disorder) that meets the DSM-IV diagnostic criteria; age at onset between 3 years and the onset of puberty; clinical course with an abrupt onset of symptoms and/or a pattern of dramatic recurrent exacerbations and remissions; temporal relation between GAS infection and onset and/or exacerbations of clinical symptoms; and neurologic abnormalities such as motoric hyperactivity, tics, or choreiform activity during an exacerbation [1].

**Relation of exacerbations to streptococcal infection**

Kurlan et al. [13**] recently reported a prospective blinded cohort multicentered study of 40 matched pairs, comprised of children who met the diagnostic criteria for PANDAS and controls who had chronic tic disorder and/or OCD without an apparent temporal relation to GAS infections. The goal of the investigators was to assess whether there is a specific temporal relationship between bona-fide antecedent GAS infection and exacerbation of neuropsychiatric symptoms. These patients were evaluated prospectively with fairly intensive testing for GAS by culture and serologic testing as well as clinical evaluations over a 25-month observation period, with additional testing at times of clinical exacerbations or illness. Clinical evaluators and laboratory personnel were blinded to which group a specific patient belonged to. The mean duration of follow-up was 1.94 ± 0.51 years for the PANDAS case patients and 2.08 ± 0.33 years for the control patients.

During this study, there were 40 clinical exacerbations of OCD and/or tics among 21 PANDAS patients and 24 exacerbations among 13 controls, for rates of 0.56 and 0.28 exacerbations per person-year, respectively. The relative risk (RR) for exacerbations was 1.78 [95% confidence interval (CI) = 0.96–3.30, \(P = 0.07\)]. There were 31 definite or probable GAS infections identified in 22 PANDAS patients and 12 such infections among nine control patients, for rates of 0.43 and 0.13 per person-year, respectively (RR = 2.76, 95% CI = 1.44–5.30, \(P = 0.002\)). There was no significant difference between the groups with respect to non-GAS infections or other illness during the study period. Most importantly, only five of the total of 64 exacerbations were temporally associated (within 4 weeks) with a GAS infection; all five occurred in PANDAS cases and none in the controls. Although this exceeded the number expected by chance, only 5/40 (12.5%) clinical exacerbations in PANDAS patients and 0/24 among controls had a temporal relation to GAS infection. Thus, 35/40 (87.5%) exacerbations among the PANDAS patients had no relation to GAS. A reasonable conclusion from these data is that patients who fit the PANDAS criteria appear to represent a subgroup of children with chronic tic disorder and/or OCD who experience some GAS-associated exacerbations, but that in this group GAS infections are not the sole or even the most common antecedent of exacerbations, accounting for only five of the 40 exacerbations that were observed in a group of 40 patients over 2 years. The authors also conclude that their findings do not support PANDAS as a unique clinical entity. Although the data are not presented, the authors also state that there was no predominance of a specific *emm* type of GAS among those that were recovered and were temporally associated with a clinical exacerbation.

Overall, these data from the most careful prospective study performed to date provide little or no support for a role for prophylactic antistreptococcal antibiotics in patients suspected to have PANDAS, as only 5/40 (12.5%) of exacerbations over about 80 person-years of observation were possibly associated with a preceding GAS infection. From these numbers, an average of 0.06 exacerbations per patient-year might be preventable by continuous anti-GAS prophylaxis; thus, treatment for about 16–17 patient-years would be required to prevent one exacerbation. The authors also note that the exacerbations that were observed were rather mild in severity.

**Relation of clinical exacerbations to autoimmune markers**

Because of the proposed autoimmune pathogenesis of PANDAS, another recent study, by Singer et al. [14**], sought evidence of a correlation between clinical exacer-
bations of PANDAS and a change in autoimmune markers. These investigators studied serum antibodies to human caudate, putamen, and prefrontal cortex by ELISA and western immunoblotting, IgM and IgG antibodies to lysoganglioside G_{M1} and G_{M1} ganglioside by ELISA; they used a competitive inhibition ELISA antibody assay using N-acetyl-β-D-glucosamine and lysoganglioside G_{M1}, and they also assessed serum levels of multiple cytokines and chemokines. Serial serum samples from 12 children diagnosed with PANDAS were studied, including for each child two sera obtained before an exacerbation, two sera during, and two sera after the exacerbation. In six of the 12 children the exacerbation had been associated with a documented GAS infection, and in the other six there was no such association. These investigators found no correlation between clinical exacerbations and any of the autoimmune markers that they studied, and also no difference in these markers among those whose clinical exacerbations were and were not associated with GAS.

These findings appear to supplement others that also have challenged a role of autoimmunity in PANDAS, including reports showing a lack of auto-antibody specificity in cross-sectional studies [11], concerns about the previously published plasma exchange and intravenous immunoglobulin (IVIG) treatment study in PANDAS [15], and the failure of PANDAS sera microinfused into rodent striatum to produce changes in animal behavior [16]. The authors’ conclusion that their findings raise ‘serious concerns about the viability of autoimmunity as a pathophysiological mechanism in this disorder’ appears justified.

**PANDAS: diagnostic and therapeutic inaccuracies**

A third recent study in *Pediatrics* [17] examined whether PANDAS was diagnosed appropriately by community physicians (on the basis of the criteria proposed by Swedo *et al.* [1]) and assessed whether there has been unwarranted use of antibiotic therapy for children with tics and obsessive-compulsive symptoms without identification of an infectious relationship. Gabbay *et al.* [17] performed a retrospective cross-sectional observational study of 176 children and adolescents who were evaluated at the Institute for Tourette and Tic Disorders at the New York University Child Study Center. Thirty-one (17.6%) of the 176 participants had been diagnosed with PANDAS by community physicians. The investigators found that 19 of these 31 (61.3%) failed to meet the criteria of Swedo *et al.*, many of whom had no laboratory documentation of GAS infection or only a single elevated antistreptolysin O titer, which does not reflect an acute infection. After testing at the specialty clinic, only 12 of the 31 diagnoses of PANDAS were considered appropriate, and seven of the 145 other children who had not been diagnosed with PANDAS were thought at the specialty clinic to meet criteria for that diagnosis, for a total of 19. Thus, there was substantial overdiagnosis as well as underdiagnosis of this disorder by the community physicians.

Of the 31 participants diagnosed in the community, 27 (87%) had been treated with antibiotics for periods of 1 week to long-term prophylaxis for up to 4 years; antibiotics included penicillins, macrolides/azalides, erythromycin/sulfasoxazole, clindamycin, and cefadroxil. The large majority (22/27, 82%) of those who had been treated with antibiotics lacked laboratory evidence of an infection, and 12 of the 22 who were treated received long-term prophylaxis for up to 4 years. Additionally, two of the 31 (7%) community-diagnosed patients had been treated with steroids and IVIG for tics. Equally distressing is that only 19/31 (63%) of the community-diagnosed PANDAS patients had received conventional psychopharmacologic treatment for tics (an α-adrenergic agonist or neuroleptic agent) or for OCD (a selective serotonin uptake reuptake inhibitor).

These observations highlight several important current issues: PANDAS is frequently diagnosed by community physicians in patients who do not meet the proposed criteria for diagnosis; unwarranted use of antibiotics, often for prolonged periods of time and often without any laboratory evidence of GAS infection, is common among community physicians; some patients are receiving unproven immunomodulatory therapies that may have potentially serious adverse effects; and many tic/OCD patients are not receiving the recommended conventional therapy for these conditions.

**Conclusion**

In the more than a decade since Swedo *et al.* proposed the relationship between GAS infection and the neuropsychiatric conditions OCD and Tourette’s/tic disorder, much controversy has ensued. It is clear that PANDAS is overdiagnosed, but it is not clear that it represents a unique subset of the larger universe of prepubertal patients with these neuropsychiatric features. That there is an OCD/tic disorder patient group with an autoimmune pathogenesis specific to GAS infection has not been proved and seems increasingly unlikely. It also appears much more likely that many childhood stressors have the potential to induce exacerbations of OCD and/or Tourette’s/tic disorder and that GAS contributes to this to a relatively minor degree. Additional studies over the next decade should provide more definitive answers to this important issue. Unless more convincing data supportive of a direct link to GAS emerge, the use of long-term prophylaxis (as currently used to prevent recurrent ARF) should be discouraged, and potentially harmful and unproved therapies such as plasma exchange, IVIG, or immunosuppression should be avoided.
References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest
•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).


This is a landmark clinical study that found that only a small proportion of ‘PANDAS’ exacerbations are temporally related to streptococcal infection.


This is a surprising new study that challenges the concept that ‘PANDAS’ has an autoimmune pathogenesis.


This important study highlights that inaccurate diagnosis and therapy of ‘PANDAS’ are rampant in the community.