# Annotation: PANDAS: a model for human autoimmune disease

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**Background:** Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus infections (PANDAS) is a recently recognized syndrome in which pre-adolescent children have abrupt onsets of tics and/or obsessive-compulsive symptoms, a recurring and remitting course of illness temporally related to streptococcal infections, and associated neurologic findings including adventitious movements, hyperactivity and emotional lability. **Methods:** Inspired by observations of similar symptoms in children with Sydenham's chorea, a search was undertaken for clinical and laboratory evidence in support of the new syndrome. **Results:** Consistent and predictable clinical findings have been described in a large case series. Magnetic resonance imaging has supported the postulated pathobiology of the syndrome with evidence of inflammatory changes in basal ganglia. Antibasal ganglia antibodies have been found in some acute cases, mimicking streptococcal antigen epitopes. **Conclusions:** While PANDAS remains a controversial diagnostic concept, it has stimulated new research endeavors into the possible links between bacterial pathogens, autoimmune reactions, and neuropsychiatric symptoms. **Keywords:** PANDAS, Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus infections, Sydenham's chorea, streptococcal infection, autoimmunity, tics. **Abbreviations:** SC: Sydenham's chorea; EAE: experimental allergic encephalomyelitis; ARF: acute rheumatic fever; GAS: group-A beta-hemolytic *streptococcus pyogenes*; OCD: obsessive-compulsive disorder; ASO: antistreptolysin O; TS: Tourette's syndrome; ADHD: Attention-Deficit/Hyperactivity Disorder; IVIG: intravenous immunoglobulin.

Human beings have evolved in an environment sometimes threatening to their survival. Animals, bacteria, fungi, protozoa, viruses, and some as yet incompletely characterized 'life' forms (e.g., prions) have at times all attached themselves to human hosts and caused disease. Most of these until recently were, because unseen, largely unsuspected. That humanity survives is evidence of the effectiveness of its defenses. But the pathogens evolve as well, sometimes exploiting weaknesses in human immune systems. One of their techniques is mimicry of the molecular antigen epitopes that are recognized by human hosts as self (Cunningham & Fujinami, 2000).

It is postulated that by making use of molecular mimicry, pathogens can evade host immune defenses which are designed to distinguish between host and foreign antigens. The mimicry is not complete, so the host's immune system still mounts a defense against the invading organism. In the process, the 'look-alike' antigens provoke a loss of self-tolerance. The outcome may be autoimmune disease, in which the host immune system is now directed at self-antigen, resulting in damage to the tissues that display the antigen.

This annotation will review the evidence for autoimmune disorders, in the central nervous system in particular. It will review the contemporary evidence for the autoimmune etiology of Sydenham's chorea (SC), a disorder first described in the seventeenth century. And it will outline the clinical and laboratory support for a newly recognized autoimmune disease, which seems to have relationships to SC, including a common provocative agent, the streptococcus bacterium.

## PANDAS

Allen, Leonard, and Swedo (1995) published the earliest description of a newly recognized clinical phenomenon in which tics and Obsessive-Compulsive Disorder (OCD) seemed to be provoked by a preceding streptococcal infection. Subsequently, based on the first 50 cases thought to represent the subgroup, five inclusion criteria were defined (Swedo et al., 1998). (See Table 1.) The children in this sample had a very young age of onset of illness: 6.3 (SD = 2.7) years for tics and 7.4 (SD = 2.7) years for OCD. Additional neuropsychiatric comorbidities were common in these children and are worth noting. Twenty of these first 50 cases (40%) met DSM-IV (American Psychiatric Association, 1994) criteria for Attention-Deficit/Hyperactivity Disorder and/or Oppositional Defiant Disorder, 36% for Major Depressive Disorder, 28% for Overanxious Disorder, and 20% for Separation Anxiety Disorder. Six children (12%) had enuresis, sometimes episodic and correlated closely with periods of OCD/tic symptom worsening. In addition, choreiform movements (but not frank SC) were present in 25 of 26 of the children who were examined during an exacerbation. Exacerbations were also noted to be accompanied by emotional lability and

**Table 1** The five clinical criteria of the subgroup PANDAS

1. Presence of Obsessive-Compulsive Disorder and/or tic disorder (meeting DSMV-IV criteria)
2. Prepubertal symptom onset
3. Episodic course characterized by acute, severe onset and dramatic symptom exacerbations
4. Neurological abnormalities (e.g., choreiform movements) present during symptom exacerbations
5. Temporal relationship between GAS infections and symptom exacerbations

PANDAS: Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus infection; GAS: Group-A beta-hemolytic streptococcus; DSM-IV: *Diagnostic and Statistical Manual of Mental Disorders* (4th edn).

irritability, tactile/sensory defensiveness, motoric hyperactivity, and deterioration in handwriting.

Children meeting these clinical criteria have been identified in community-based studies, as well. In a prospective case series conducted over a three-year period, twelve children in a general pediatric practice presented with abrupt onset of OCD and met criteria for inclusion in the subgroup. Six of the twelve had positive culture or rapid antigen-detection assay positive for group-A beta-hemolytic streptococcus (GAS) at presentation of the OCD symptoms, and four others were positive within the month prior to onset. One patient had negative rapid antigen-detection assay at presentation, but an elevated ASO titer. The remaining child had undergone a tonsillectomy, because of recurrent GAS infections, in the month preceding the onset of OCD. In those children who did not have recurrence of their neuropsychiatric symptoms, complete resolution of OCD occurred in 5–21 days. Of course, all were treated appropriately for acute GAS infections (Murphy & Pichichero, 2002).

In another study, 83 consecutive patients referred with primary diagnosis of OCD to an academic child psychiatry clinic were evaluated retrospectively (by parent's and/or child's report) for upper respiratory symptoms coinciding with the onset of their neuropsychiatric symptoms. In this study, children and adolescents with a history of an upper respiratory infection were more likely to have experienced a sudden rather than an insidious onset of OCD symptoms and also to have a comorbid tic disorder (Giulino, Gammon, Sullivan, et al., 2002). The authors conclude that an upper respiratory infection coinciding with abrupt onset of OCD or tics should prompt clinicians to observe prospectively for inclusion in this newly recognized subgroup of childhood neuropsychiatric disorders.

From the earliest description, it has been postulated that the clinical phenomena were consequences of an autoimmune-mediated inflammatory process, most likely in basal ganglia, and most likely provoked by the streptococcus bacterium. The original authors (Swedo et al., 1998) gave the syndrome the acronym PANDAS, for Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus infection.

## Streptococcus-induced autoimmune disease

Group-A beta-hemolytic *Streptococcus pyogenes* is a bacterium responsible for numerous human maladies, and significant in the present context because of its ability to induce immune-mediated sequelae. Over the past 50 years it has been demonstrated that certain strains of the bacterium can provoke acute rheumatic fever (ARF), but only in susceptible hosts. Bacterial cell wall M protein has been completely characterized, and moieties of the protein have been found to mimic several cardiac proteins. But membrane proteins have also been implicated. Four peptides have been purified from membrane of throat-infectious strains of GAS, and the heart-reactive staining pattern of sera from ARF patients was abolished by preabsorption with these peptides. Additionally, cellular immune responses may play a role in the disease onset, and T cell autoreactivity may continue even after the bacterial mimic has been cleared (Visvanathan & Zabriskie, 2000).

There is also evidence for molecular mimicry and loss of self-tolerance in Sydenham's chorea (SC), the neurological manifestation of ARF. SC may occur as the solitary manifestation of ARF in up to 40% of cases (McMahon, Filloux, Ashworth, & Jensen, 2002) and as one symptom among others in much higher frequency (Bland & Jones, 1951). Onset may be delayed for several months after the precipitating GAS infection (Taranta & Stollerman, 1956; Taranta, 1959). In a study published in 1976, of 30 patients with SC, IgG antibody in 46.6% reacted preferentially with neuronal cytoplasm of human caudate and subthalamic nuclei (with only moderate to weak staining of cytoplasm in cortex or in nuclei of medulla). The presence of antineuronal antibodies correlated with the severity and duration of the chorea. Of greatest interest, the antineuronal antibody was absorbed out by GAS membrane (Husby, van de Rijn, Zabriskie, Abdin, & Williams, 1976). In a more recent study, cell wall M proteins from three rheumatogenic serotypes of GAS were used to evoke rabbit antibodies that then were found to cross-react with multiple human brain proteins. There was evidence of preference for basal ganglia proteins (Bronze & Dale, 1993). Additionally, M protein-specific brain protein antibodies were found in the plasma of a patient with SC. Among 11 patients with SC evaluated at the National Institute of Mental Health (NIMH), antineuronal antibodies directed against human caudate tissue were demonstrated in 10 (using Husby's techniques). Nine of 18 control subjects were positive (Swedo et al., 1993). Church and colleagues (2002) demonstrated that acute SC patients had significantly higher titers of anti-basal ganglia antibodies than patients with convalescent

SC, RF without SC, or healthy controls. In each of these studies, it is important to note that these are serum antibodies, and there is no documentation that the antibodies cross the blood–brain barrier. A recent study was unable, perhaps only because of sample limitations, to offer evidence of disruption of blood–brain barrier versus intrathecal presentation of anti-brain antigens in SC (Church et al., 2003).

A recently published study demonstrated GAS cross-reactive antibodies with biologic activity in both serum and cerebrospinal fluid samples from SC patients. Human hybridoma lines were derived from an SC patient and found to recognize the GAS surface carbohydrate N-acetyl-$\beta$-D-glucosamine, the major immunological epitope. The antibodies cross-reacted with central nervous system lysoganglioside. Binding of the antibody to neurons activated calcium/calmodulin dependent protein kinase II, postulated to affect neurotransmitter synthesis and release. Further, the cross-reactive monoclonal antibodies provoked *in vitro* neuronal cell signaling, as did sera from active SC subjects (Kirvan, Swedo, Heuser, & Cunningham, 2003). It is worth emphasizing that, in this case, neither the antigen nor the moiety which is mimicked is a protein.

Post-mortem studies (Ziegler, 1927; Greenfield & Wolfsohn, 1922) have been supported more recently by functional and structural brain imaging corroborating involvement of the basal ganglia in SC. In a structural neuroimaging study at the NIMH, 24 patients with SC were compared with 48 matched controls using cerebral magnetic resonance imaging (MRI). The SC group, when compared with the controls, showed increased volumes of caudate, putamen, and globus pallidus, but not of total cerebrum, prefrontal or midfrontal cortices, or of thalamus. These results suggest a relatively selective involvement of basal ganglia in SC (Giedd et al., 1995). It can be postulated that the pathogenesis of chorea is an immune complex phenomenon in which anti-streptococcal antibodies cross-react with basal ganglia tissue components (Husby et al., 1976; Moore, 1996; Swedo, 1994).

Not as completely characterized, but clearly relevant to the present discussion, are some less common neuropsychiatric syndromes reported to occur as sequelae of GAS. Ten children were seen in London, UK, between 1995 and 2000 with acute disseminated encephalomyelitis. Five of the children had dystonic extrapyramidal movement disorders, and 7 had a behavioral syndrome characterized by emotional lability, inappropriate laughter, echolalia and palilalia, inattention, separation anxiety, and confusion. Five had degrees of coma, 3 even requiring ventilatory assistance. None had ARF or SC. Anti-basal ganglia antibodies were significantly elevated compared to neurological and streptococcal controls. Fluorescent immunohistochemistry demonstrated specific binding to large striatal neurons. Antistreptococcal serologies (both ASO and anti-DNAse B) also were significantly elevated in the subjects. MRI showed hyperintense lesions on un-enhanced T2 scans. (T1 sequences were normal.) Eight of 10 children had lesions of basal ganglia, including caudate, putamen, and globus pallidus. Other deep gray structures, as well as supratentorial white matter, brainstem, cerebellum, and cord were involved in some cases (Dale et al., 2001). Although they were quite ill, 8 of the 10 children recovered completely – some after relapses – though one was left with chronic obsessive-compulsive symptoms. Infantile bilateral striatal necrosis, a disorder characterized by abnormal movements and basal ganglia abnormalities, has also been reported to occur subsequent to GAS infection (Dale et al., 2002).

## Neuropsychiatric symptomatology

Behavioral abnormalities and psychiatric symptoms are frequent among patients with SC. Symptoms include emotional lability in over 90% of cases, obsessions and compulsions in 60–80%, frequent hyperactivity and inattentiveness (with onset later than in typical childhood Attention-Deficit/Hyperactivity Disorder), Separation Anxiety Disorder, irritability, and age-regressed behaviors (Garvey & Swedo, 1997). These children typically have an abrupt onset of their symptoms. Nine of the 11 children in the NIH sample had acute onset of obsessive-compulsive symptomatology, and most had increased emotional lability, motoric hyperactivity, irritability, distractibility, and age-regressed behavior. The behavioral symptoms actually appeared days to weeks prior to the chorea. All had resolution of the psychiatric symptoms as their chorea waned, an average of seven months later (Swedo et al., 1993).

There is considerable symptom overlap among patients with SC and those with childhood onset Obsessive-Compulsive Disorder (Allen, Leonard, & Swedo 1995; Chapman, Pilkey, & Gibbons, 1958; Swedo et al., 1989). As many as three-fourths of SC patients have neuropsychiatric symptoms identical to those seen in OCD, namely contamination concerns, worry about harm to self or others, violent images, and checking, washing, and arranging rituals (Swedo, 1994; Swedo et al., 1989; Swedo et al., 1993). These OC symptoms have been reported to begin weeks prior to the onset of the movement disorder in SC, leading to speculation that in some cases OCD might occur as a sequela of GAS even in absence of chorea (Swedo, 1994). In a parallel series of investigations of pediatric patients with OCD, a number were observed to have a course characterized by abrupt symptom onset and a relapsing–remitting pattern of severity (Swedo et al., 1989). The exacerbations appeared to be triggered by infections, particularly with GAS (Allen, Leonard, & Swedo, 1995).

The lines of evidence for a post-streptococcal etiology of these neuropsychiatric symptoms continue to converge. For example, an association was documented between a community outbreak of GAS infections and a 10-fold rise in the number of children presenting with a new onset of tics (Kiessling, Marcotte, & Culpepper, 1993). In a group of Italian schoolchildren, exposure to GAS correlated with the onset of tics, and antistreptolysin O (ASO) titers correlated with severity of tics (Cardona & Orefici, 2001). In an 8-month longitudinal observational study of school-aged children in the United States, investigators found the incidence of motor tics (and problem behaviors) significantly higher during winter months when compared to springtime. GAS rates were not determined, but this time period overlaps with the seasonal prevalence of GAS infections in this age group, and the study provides indirect evidence of a temporal correlation between GAS infection and tics (Snider et al., 2002).

Antibodies against human caudate (as determined using Husby's technique) were found to be significantly higher in children with new onset movement disorders (including Tourette's syndrome, chronic motor or vocal tics, chorea, choreiform movements) than in children without those movement disorders. The children were in two samples, one of 50 and another of 33 subjects, referred to a neurodevelopmental clinic for Attention-Deficit/Hyperactivity Disorder (ADHD) or other disruptive behavior disorder, or learning disabilities (Kiessling et al., 1993). The same investigators found antibodies directed against the caudate and putamen to be significantly higher in a sample of children presenting with new onset OCD or obsessive-compulsive symptoms than in clinical controls without such symptoms (Kiessling, Marcotte, & Culpepper, 1994).

Antineuronal antibodies recognizing the putamen (but not the caudate or the globus pallidus) were significantly higher in 41 children meeting criteria for Tourette's syndrome (TS) than in 39 controls (Singer et al., 1998). TS patients were found to have significantly higher levels of total antineuronal and antinuclear antibodies than healthy controls in another study which examined these factors and antistreptococcal antibodies in children and adults with TS, SC, and other autoimmune disorders (Morshed et al., 2001). Markers for prior GAS infection were equivocal in this study, however.

A recent study, on the other hand, failed to find an association between antistreptococcal antibodies and diagnoses of Tourette's syndrome, ADHD, or OC symptoms or OCD in children (Loiselle, Wendlandt, Rohde, & Singer, 2003). But the authors point out that definition of elevated titers (and values expected at various ages) remains inconsistent from one laboratory to another. And point-in-time measurements may not be sufficient to demonstrate correlations because of interassay variability. To prove association definitively, samples should be analyzed in batches from longitudinal evaluations in which symptom changes can be correlated with rising and falling of titers.

## Animal models

Although research in autoimmune phenomena is advancing rapidly, this immune system response is still largely unexplained at the molecular level. There may be adaptive as well as, clearly at times, maladaptive significance. Animal models continue to offer fundamental information.

Experimental allergic encephalomyelitis (EAE) provided some of the earliest evidence for the phenomenon of microbial-induced autoimmunity. The clearest examples of EAE have been in rabbit models in which a viral protein, hepatitis B virus polymerase, mimics an 8- to 10-amino acid sequence on myelin basic protein. Peripheral injection of the viral peptide provoked in the rabbits the same perivascular infiltration in the central nervous system as that induced by inoculation of myelin basic protein or the encephalitogenic site of that protein (Oldstone, 2000). Specific cellular and humoral immune response occurred. In another laboratory, a five-amino acid residue was found to be the major epitope of myelin basic protein that binds to T-cell receptor and to major histocompatibility complex. An identical peptide from a papillomavirus induced EAE, while peptides differing by a single residue prevented EAE, apparently by modulating production of various cytokines (Oldstone, 2000).

Stereotypies and episodic utterances in rats have been proposed as an animal model of motor and vocal tics. Intrastriatal microinfusions of serum from TS patients have induced such behaviors in rats; post-infusion immunohistochemical analysis confirmed the presence of gamma globulin selectively bound to striatal neurons (Hallett, Harling-Berg, Knopf, Stopa, & Kiessling, 2000). Likewise, oral stereotypies were demonstrated in rats after bilateral infusions into the ventrolateral striatum with sera from patients with TS, and there were higher rates of stereotypies in the rats infused with the sera from patients with the highest levels of antineural antibodies (Taylor et al., 2002).

Autoimmunity has been postulated as the cause of at least some cases of a number of human diseases, including ankylosing spondylitis (*Klebsiella*), multiple sclerosis, Chagas' disease (*Trypanosoma cruzi*), Graves' disease, ulcerative colitis, systemic lupus erythematosis, diabetes mellitus, rheumatoid arthritis, and atherosclerosis. The pathogenesis of autoimmune cardiomyopathy and of myasthenia gravis varies, but a post-infectious model is proposed in some cases (group B coxsackieviruses and *Herpes simplex* virus, respectively). But the human disease with the best support for an autoimmune etiology remains ARF.

## The evidence for and against PANDAS

Three hundred years passed before Thomas Sydenham's clinical observations found their apparent support at the molecular level. It should take considerably less time to uncover the pathobiology of the possibly related autoimmune syndromes, PANDAS among them. Studies are ongoing to characterize the course and prognosis of the members of the PANDAS subgroup and to further refine the defining features. In addition, response to treatment and prevention of GAS infections may lend support to the etiology of the syndrome and to the validity of the descriptor. There are of course alternative points of view, and the validity of the subgroup has been questioned. (See below.)

If PANDAS follows the pattern of other post-infectious autoimmune disorders, it should be anticipated that the symptoms result from a unique combination of infective virulence and host susceptibility. It is well documented that, of the multiple serotypes of GAS, only a few strains lead to carditis (Cunningham, 2000). There is not yet evidence that this is the case for other post-streptococcal autoimmune disease, but it is expected: these sequelae are rare despite the fact that 15–20% of asymptomatic children have GAS positive throat cultures during outbreaks of pharyngitis in their schools (including asymptomatic infections, and carriers who do not form an immunological response to the GAS) (American Academy of Pediatrics, 2000).

The nature of the host susceptibility in post-GAS sequelae is also unknown, but presumed to involve genetic and developmental vulnerabilities. Family studies of rheumatic fever suggest it has an autosomal recessive inheritance with limited penetrance (Cunningham, 2000). In a study of 54 children with PANDAS, the rates of tic disorders and OCD were higher in first-degree relatives than the rates reported in the general population, and were similar to rates previously reported for tic disorders and for OCD (Lougee, Perlmutter, Nicolson, Garvey, & Swedo, 2000). A B-lymphocyte antigen identified by the monoclonal antibody labeled D8/17 appears in over 90% of rheumatic fever patients, but in less than 10% of healthy controls (Gibofsky, Khanna, Suh, & Zabriskie, 1991). There was preliminary evidence that the same marker might be over-expressed in patients with OCD and tic disorders (Murphy et al., 1997; Swedo et al., 1997). However, recent experience has shown declining sensitivity of the D8/17 marker (Hamilton, Garvey, & Swedo, 2003). Further, no association was found between D8/17 positivity and tics or OCD in a community-based sample (Inhoff-Germain et al., 2003). Of note, however, the overall rates of OCD and tics were lower than expected, and there were no cases of RF, suggesting the absence of immunogenic streptococcus in the community.

Certainly arguments *against* the autoimmune etiology of PANDAS must be considered (Singer & Loiselle, 2003). Cross-reactive antibodies are not universally present among patients with post-streptococcal tics or OCD. Further, the antibodies have been demonstrated in sera from healthy children without evidence of neuropsychiatric illness (Singer et al., 1998; Morshed et al., 2001). The episodic course of the children in the PANDAS groups may be temporally, though not causally, related to streptococcal infections. The GAS infections could be an 'incidental' finding, or the exacerbations might be nonspecific reactions to the stress of illness, rather than related to GAS-triggered autoimmunity (Findley et al., 2003). Given the frequency of GAS infections in this age group, temporal coincidence is also likely. For example, the neuropsychiatric symptoms could have a periodicity inherent in their pathobiology (Leckman, 2002), and the exacerbations might occur coincidentally with the GAS infections by random chance alone. And if a meaningful association were to be sought, it would require large epidemiological studies, since neuropsychiatric symptoms, particularly tics, and streptococcal infections are both very common in school-aged children.

One piece of evidence supporting the autoimmune hypothesis of the PANDAS subgroup is offered by the successful treatment of severely affected children with immunomodulatory interventions. After preliminary results indicated benefit from plasma exchange or intravenous immunoglobulin (IVIG) treatments in patients with SC (Garvey et al., 1996), a study was conducted using these treatments for children with PANDAS (Perlmutter et al., 1999). Twenty-nine subjects participated in a randomized double blind trial of plasma exchange, IVIG, or sham IVIG. Both active treatments were found to produce significantly greater improvements than placebo. The placebo group had little or no change in overall symptom severity. In the plasma exchange group, symptomatic improvement was seen as early as the end of the first week of treatment, and the improvement appeared to be more robust than with IVIG, especially in OCD symptomatology. Although the mechanism of action is incompletely understood, both treatments affect a number of components within the immune system, including clearance of cross-reactive antibodies (Kirvan et al., 2003). It is speculated that plasma exchange clears antigen-antibody complexes from blood, and that IVIG contains antibody that binds to and renders circulating antigens ineffective. The effectiveness of the immunomodulatory therapies lends further credibility to the putative pathogenesis.

In the study subjects, treatment gains were sustained. At one year follow-up, over 80% of patients who received active treatment remained much or very much improved, and symptoms were in the subclinical range of severity.

Ongoing long-term prospective studies at NIMH will follow-up with these patients and others in the PANDAS subgroup who received alternative therapies.

## Clinical implications

Based on evidence so far available, it is possible to draw some conclusions about the PANDAS subgroup and to make recommendations for treatment. It should be noted that the following are based on the authors' experiences and should not be presumed to represent an expert consensus.

1. The tics and obsessions and/or compulsions of the PANDAS subgroup respond to standard treatments in the same manner as do other cases of OCD and tics. Tics, when they are disruptive and embarrassing, are sometimes successfully treated with alpha adrenergic agonist medications. Occasionally, dopamine blocking drugs are used in refractory cases, but potentially serious side effects limit their use. Because tic disorders have a waxing and waning course, it may be prudent to adopt a watchful attitude to see if symptoms diminish without treatment. OCD is very effectively treated with the specific cognitive behavioral therapy called exposure and response prevention. Effectiveness of this therapy is largely dependent upon the training and skill of the therapist and upon the willingness and cooperation of patient (and often the family). Selective serotonin reuptake inhibiting medications also have documented effectiveness for the obsessions and compulsions of OCD, whether secondary to GAS or not. The best results are achieved with a combination of medications and cognitive behavioral therapy. The consultation of an experienced clinician is helpful both in identifying the illness and in obtaining advice about prognosis and treatments.

2. When standard treatments have failed, and when tics and/or obsessive-compulsive symptoms are severe and debilitating, consideration might be given to immunomodulatory interventions for children in the PANDAS subgroup. These treatments should be reserved for the most severely affected patients as neither plasma exchange nor IVIG is without risk. Plasma exchange in smaller children requires use of a central venous catheter, and this carries an inherent, albeit rare, risk of vascular perforation and infection. IVIG was for a time limited by the short supply of human immunoglobulin, a problem now apparently resolved. However, IVIG is a pooled blood product, and carries the risk of exposure to occult infectious agents. It must be kept in mind that these treatments are invasive interventions that require considerable expertise. In the United States, only a few research centers are providing IVIG or plasma exchange for the treatment of post-GAS neuropsychiatric symptoms. Further, it is important to note that these treatments are *not* indicated for non-PANDAS OCD or tic disorders. A trial of plasma exchange for five children and adolescents with chronic, treatment-refractory OCD found no benefit (Nicolson et al., 2000).

3. A child with abrupt onset of tics and/or OCD should be evaluated for GAS infection. Rapid streptococcal antigen-detection tests, if negative, should be backed up by the standard sheep's blood agar plate culture of the adequate throat swab, incubated for up to 48 hours before reporting on beta hemolysis. A negative test does not completely exclude GAS but is over 96% accurate when the throat swab is properly obtained. Positive cultures should prompt appropriate treatment for the acute infection. If the culture is negative and the onset of the PANDAS was at least 4 to 6 weeks prior, then ASO and anti-DNAse B could be obtained in attempt to document preceding GAS infection. Elevated titers are not an indication to treat with antibiotics, as they indicate a previous, rather than a current infection. There is no correlation between titer levels and symptom severity, as a child's symptoms may remit before the titers return to normal levels. Antistreptococcal titers often remain elevated for several months following an infection, and there is a great deal of interassay variability, making it difficult to use titers to follow clinical status.

4. Recurrence of symptoms should prompt re-evaluation for acute infection, as should sudden loss of response to medication for the tics or OCD.

5. At this time, there is insufficient support to justify the routine use of antibiotic prophylaxis. An ongoing study at the NIMH is evaluating whether or not prophylaxis is appropriate and effective for children who meet PANDAS criteria.

## The future

Research remains to be done in the explication of the etiopathogenesis of the PANDAS syndrome. Studies are under way to identify the specific antineuronal antigens and antibodies that characterize the members of the PANDAS subgroup. Then work can proceed to demonstrate mimicry between particular antigen epitopes of GAS (perhaps specific serotypes) and brain molecules displayed by vulnerable sites. It should then be possible to demonstrate: how presentation of self-antigen produces neuronal dysfunction; which tissue injuries correlate with which symptoms; why some individuals are vulnerable and others not; and whether anti-streptococcal vaccines could prevent the syndrome in vulnerable patients (or make it worse); and whether prompt treatment of GAS can prevent OCD/tics in some patients.

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