

The Immunobiology of Tourette's Disorder, Pediatric Autoimmune Neuropsychiatric Disorders Associated with *Streptococcus*, and Related Disorders: A Way Forward

Tanya K. Murphy, M.D.,¹ Roger Kurlan, M.D.,² and James Leckman, M.D.³

Abstract

Obsessive-compulsive disorder (OCD) and related conditions including Tourette's disorder (TD) are chronic, relapsing disorders of unknown etiology associated with marked impairment and disability. Associated immune dysfunction has been reported and debated in the literature since the late 80s. The immunologic culprit receiving the most interest has been Group A *Streptococcus* (GAS), which began to receive attention as a potential cause of neuropsychiatric symptoms, following the investigation of the symptoms reported in Sydenham's chorea (SC) and rheumatic fever, such as motor tics, vocal tics, and both obsessive-compulsive and attention deficit/hyperactivity symptoms. Young children have been described as having a sudden onset of these neuropsychiatric symptoms temporally associated with GAS, but without supporting evidence of rheumatic fever. This presentation of OCD and tics has been termed pediatric autoimmune neuropsychiatric disorders associated with *Streptococcus* (PANDAS). Of note, SC, OCD, and TD often begin in early childhood and share common anatomic areas—the basal ganglia of the brain and the related cortical and thalamic sites—adding support to the possibility that these disorders might share a common immunologic and/or genetic vulnerability. Relevant manuscripts were identified through searches of the PsycINFO and MedLine databases using the following keywords: OCD, immune, PANDAS, Sydenham chorea, Tourette's disorder Group A *Streptococcus*. Articles were also identified through reference lists from research articles and other materials on childhood OCD, PANDAS, and TD between 1966 and December 2010. Considering the overlap of clinical and neuroanatomic findings among these disorders, this review explores evidence regarding the immunobiology as well as the relevant clinical and therapeutic aspects of TD, OCD, and PANDAS.

Introduction

OBSESSIVE-COMPULSIVE DISORDER (OCD) and related conditions including Tourette's disorder (TD) are prevalent disorders affecting as many as 0.3%–3% of the pediatric population (Karno et al. 1988; Khalifa and von Knorring 2003; Jin et al. 2005). They are chronic, relapsing disorders associated with marked impairment and disability. The etiologies of these disorders are unknown. Over the past several years, increasing evidence has pointed to immune-related causation in some cases of childhood-onset OCD, tic disorders, and other anxiety disorders such as separation anxiety. The most suggestive immunologic culprit implicated in the onset of these symptoms is Group A *Streptococcus* (GAS), and much of the work in this area arose from the investigation of Sydenham's chorea (SC) and rheumatic fever (RF). Of note, SC, OCD, and TD share common anatomic areas: the basal ganglia of the brain and the related cortical and thalamic sites. Some SC patients display motor and

vocal tics, obsessive-compulsive symptoms, and ADHD symptoms, adding support to the possibility that, at least in some instances, these disorders share a common etiology.

Pediatric Autoimmune Neuropsychiatric Disorders Associated with *Streptococcus*

Dr. Laurence Selling made one of the earliest reported cases of this potential correlation between the onset of tics and infectious disease in 1929 when he described three cases of tics associated with sinusitis (Selling 1929). Subsequently, psychoanalytic theories of TD prevailed (Kushner and Kiessling 1996). Just before the medicalization of TD in 1965, Langlois and Force described a 6-year-old child with TD and SC symptoms following several infectious illnesses that were successfully treated with antibiotics and neuroleptics (Langlois and Force 1965). They argued that Tourette was wrong to say TD was incurable and separate from SC but that

¹Department of Pediatrics and Psychiatry, University of South Florida, St Petersburg, Florida.

²Atlantic Neuroscience Institute, Overlook Hospital, Summit, New Jersey.

³Child Study Center, Yale University School of Medicine, New Haven, Connecticut.

TD should be viewed as a sequela to acute chorea. After a lag of ~20 years, the argument reappeared that, in at least some cases, tics and OCD are related to infectious processes. In the late 1980s, researchers noted that patients with SC often developed OCD symptoms; further inquiry revealed that patients with SC often had tics as well. Additional investigation found that some patients with GAS infections, but without the neurological findings of SC, also presented with OCD symptoms (Swedo and Leonard 1994; Allen et al. 1995). Similarly, around this same time, Louise Kiessling and colleagues reported on the association of tics during GAS outbreaks as seen in a developmental pediatric practice (Kiessling et al. 1993). The first case report (Allen et al. 1995) detailed four children who presented with sudden onset or worsening of OCD and/or tics following an infection (two viral, two GAS). In 1998, a group from the National Institute of Mental Health further characterized (in a 50 patient case series) an entity they called pediatric autoimmune neuropsychiatric disorders associated with *Streptococcus* (PANDAS). Careful reading of these case series suggests that GAS is the inciting trigger and that future exacerbations are activated not only by GAS infection but also by GAS exposure and viral illness as well.

After assimilating the presentation of these non-SC GAS-triggered neuropsychiatric disorders, researchers focused efforts on establishing definitive criteria of the phenotype (to minimize overlap with more typical OCD/tic presentations and the common childhood occurrence of GAS unrelated to neuropsychiatric presentation). Preliminary criteria for the diagnosis of PANDAS include (1) the existence of OCD or tic symptoms, (2) prepubertal onset, (3) symptoms occurring intermittently or following a sawtooth course, (4) temporal relationship of OCD/tic symptoms to GAS infection, and (5) presence of other neurological findings such as hyperactivity or choreiform movements. Since the initial description of this infection-triggered subtype, many studies have attempted to further elucidate the immune relationship and the potential pathophysiology that may be involved in PANDAS. Although there are several lines of evidence linking GAS infection and onset of some OCD/tic cases, establishing a true etiologic relationship has proven challenging.

What Does the Phenotype for PANDAS Look Like?

Traditionally, OCD has been seen as a chronic condition with symptoms that are relatively stable over time. Although this description accurately describes many patients with OCD, a subgroup of children and adolescents who have a dramatically different presentation has piqued the interest of many pediatric clinicians and researchers. Classically, the PANDAS presentation is foudroyant, that is, previously high-functioning and well-adjusted children show severe behavioral changes before their parents' eyes in a matter of 24–72 hours. In these cases, the OCD/tic symptoms may then diminish significantly or resolve completely over the course of 6–8 weeks. Sometimes, symptoms never reappear, whereas in others, subsequent episodic exacerbations may occur with either complete resolution between episodes, or a progressive worsening over time. In this sawtooth-progressive presentation, each subsequent episode may cause relatively more impairment, and the intervals between episodes, while still representing a relative improvement in symptoms, may diminish over time.

Behaviorally and developmentally, PANDAS (when compared with typical OCD) tends to be associated with greater prevalence and severity of separation anxiety, nightmares, personality changes, rage episodes, psychotic symptoms, and/or oppositional behaviors—all

of which can cause significant disruption to functioning (daily, social, and academic) (Swedo et al. 1998). A decline in handwriting and math skills may be observed, as well as the appearance of ADHD-like symptoms. In addition, PANDAS patients may begin bedwetting for the first time in their lives, and they may develop choreiform movements (albeit milder than those of SC) or other neurological soft signs (Swedo et al. 1998). Alternative presentations of neuropsychiatric symptoms have also reported to begin following GAS infections such as anorexia nervosa (Sokol 2000; Puxley et al. 2008), stuttering (Murphy, in submission), spasmodic torticollis or dysphonia (Murphy, unpublished manuscript), and ADHD (Swedo et al. 1998; Peterson et al. 2000).

Most commonly, these symptoms will be readily correlated with a strep infection that may follow or precede the onset of OCD/tic symptoms by a few days. Longer lag times of over 2 weeks are not often seen. If present, this may suggest that a subclinical strep infection occurred, making the correlation between the onset of infection and the initiation of OCD/tic symptoms difficult to confirm. Longer lag times have been well documented in RF, a disease that is clearly correlated with GAS infection, and even longer in SC. However, the GAS correlation, even in RF, is not always easy to delineate. For example, in one study, nearly two-thirds of cases occurred with minimal or no prior symptoms of pharyngitis (Ayoub 1992).

GAS in Causing Infections

GAS is a bacterium that has the capability of causing a wide range of infectious illnesses. These range from suppurative infections including pharyngitis, impetigo, necrotizing fasciitis, scarlet fever, and septicemia to nonsuppurative illnesses including RF, glomerulonephritis, and reactive arthritis. Strep throat infection is most commonly seen in children aged 5–15 years. In many cases of strep infections, symptoms are minimal and patients recover without ever making a visit to their physician. Typical symptoms in streptococcal pharyngitis include sore throat, fever, and swollen tonsils and lymph nodes. In younger children, strep may present with abdominal pain, nausea and vomiting, or perineal/vaginal erythema. The role of streptococcal skin infections, such as impetigo or folliculitis, in triggering neuropsychiatric symptoms has not been fully considered or explored, although an etiologic role has been theorized for RF (McDonald et al. 2006).

Strains of GAS have been changing over time. More recent strains have shown an increasing variety of mechanisms that allow the bacteria to avoid host defenses including antiphagocytic factors and capsule formation, which were lacking in earlier strains (Bisno et al. 2003). This increase in diversity among different strains of GAS as well as the incorporation of more effective virulence factors is responsible for the increasing incidence and severity of strep infections such as necrotizing fasciitis (Efstratiou 2000). On the other hand, other virulence factors may be responsible for an increase in incidence of strep infections that present with minimal symptoms of pharyngitis (Krause 2002). As an example, an increase in incidence of RF in the 1980s was frequently associated with no prior history of symptoms of pharyngitis (Ayoub 1992).

Linking GAS to OCD/Tics

The potential link between common childhood infections and lifelong neuropsychiatric disorders is among the most tantalizing and clinically relevant concepts in modern neuroscience (Table 1). The link may be most relevant in this group of disorders collectively described as PANDAS. Of concern, public awareness has

outpaced our scientific knowledge base, with multiple magazine and newspaper articles and Internet chat rooms calling this issue to the public’s attention. Compared with ~200 reports listed on Medline—many involving a single patient, and others reporting the same patients in different papers, with most of these reporting on subjects who do not meet the current PANDAS criteria—there are over 100,000 sites on the Internet where the possible *Streptococcus*–OCD–TD relationship is discussed. This gap between public interest in PANDAS and conclusive evidence supporting this link calls for increased scientific attention to the relationship between GAS and OCD/tics, particularly examining basic underlying cellular and immune mechanisms.

Administrative healthcare data

Perhaps the strongest evidence for GAS involvement in the onset of TD and OCD comes from a recent report by Mell et al. (2005). They conducted a case–control study of 144 children aged 4–13 years who received their first diagnosis of OCD, TD, or tic disorder between January 1992 and December 1999. Cases were matched to controls by birth date, sex, primary physician, and propensity to seek healthcare. Patients with OCD or tic disorder were more likely than controls to have had a streptococcal infection in the 3 months before onset date, and the risk of OCD or a tic disorder was higher among children with multiple streptococcal infections within 12 months. Indeed, having multiple infections with GAS within a

12-month period was associated with an increased risk of TD with an odds ratio of 13.6.

Although these findings were recently replicated in a U.S. national sample (Leslie et al. 2008), a separate study from the United Kingdom failed to support an association between streptococcal infection and postinfection recurrences of OCD and/or TD (Schrag et al. 2009). Limitations of the database, however, did not allow for determining a close temporal association of the streptococcal infection with the onset of OCD or tics. By making this association at 2 and 5 years, the detection of a temporal signal above the background GAS incidence in a typical pediatric population is mitigated. As well, the average age of OCD onset for study participants was 16 years of age, whereas most SC and PANDAS cases are thought to have a prepubertal onset (Swedo et al. 1998). To provide definitive evidence for or against the GAS link to neuropsychiatric symptoms, further studies should examine the relationship between GAS and postinfection recurrences of OCD and tics in a younger cohort, with data indicating clear temporal associations.

Serologic and prospective studies

One of the most contentious and challenging tasks is how best to definitively correlate the GAS infection with the onset of OCD/tic symptoms. A documented GAS infection coincident with onset of neuropsychiatric symptoms is not considered a strong enough evidence, as some children are streptococcal carriers. The gold

TABLE 1. CONTRIBUTIONS TOWARD ESTABLISHING AN IMMUNE AND INFECTION ASSOCIATION WITH OBSESSIVE-COMPULSIVE DISORDER AND TICS^a

	<i>Pros</i>	<i>Cons</i>	<i>Inconclusive</i>
Group A <i>Streptococcus</i> association	Kirvan et al. (2006), Mell et al. (2005), Muller et al. (2001), Murphy and Pichichero (2002), Swedo et al. (1998), Church et al. (2002), Murphy et al. (2007), Guerrero et al. (2003), Cardona and Orefici (2001)	Luo et al. (2004), Kurlan et al. (2008)	Perrin et al. (2004), Peterson et al. (2000)
ABGA	Church et al. (2003), Dale et al. (2005), Kiessling (1993), Martino et al. (2005), Pavone et al. (2004), Rizzo et al. (2006), Singer et al. (1998), Hoekstra et al. (2002)	Loiselle et al. (2004), Singer et al. (2005), Singer, Mink et al. (2005)	Morer et al. (2008), Murphy et al. (1997)
Immune treatment	Elia et al. (2005), Heubi and Shott (2003), Orvidas and Slattery (2001), Perlmutter et al. (1999), Selling (1929), Snider et al. (2005)	Hoekstra et al. (2004), Nicolson et al. (2000)	Garvey et al. (1999)
Immune markers	Black et al. (1998), Leckman et al. (2005), Monteleone et al. (1998), Morshed et al. (2001), Carpenter et al. (2002), Denys et al. (2004), Ravindran (1999), Mercadante et al. (2000), Kansy et al. (2006), Kawikova (2007), Roy et al. (1994)	Carpenter et al. (2002), Morer et al. (2005)	Luo et al. (2004)
D8/17	Murphy et al. (1997), Mittleman et al. (1997), Chapman et al. (1998), Hoekstra et al. (2002)	Inoff-Germain et al. (2003), Hamilton et al. (2003), Eisen et al. (2001)	Weisz et al. (2004), Murphy et al. (2001)
Animal studies	Hallett et al. (2000), Hoffman et al. (2004), Taylor et al. (2002).	Loiselle et al. (2004), Singer, Mink et al. (2005)	
Genetics	Lougee et al. (2000), Zai et al. (2004)	Huang et al. (2004)	
Non-Group A <i>Streptococcus</i> pathogens	Allen et al. (1995), Khanna et al. (1997), Budman et al. (1997), Muller et al. (2004), Muller (2001), Giulino et al. (2002), Singer et al. (2000)		

^aA comprehensive summary is not given because of limitations of space.

standard for identifying GAS relatedness would require either documentation of infection with a strep subtype that previously had not been present or, ideally, documentation of serial strep titers showing a temporal relationship between the onset of symptoms and the titer rise. An increase of 0.2 log or greater in strep titers following the onset of OCD/tic symptoms when compared with baseline levels would be considered a strong evidence for a correlation. Simply demonstrating the presence of elevated strep titers after the onset of OCD/tic symptoms is insufficient, as the presence of elevated titers is common in the 7–12 age group, even among children without symptoms of strep infections (Kaplan et al. 1998; Shet and Kaplan 2002). As many children who present with PANDAS are very young (ages 3–6 years), titer thresholds may need to be age adjusted because many laboratories use threshold values (e.g., an antistreptolysin O (ASO) of 200 IU/mL or DNase of 400 IU/mL or higher is needed to be considered elevated) (Renneberg et al. 1989).

In clinical settings, these lines of evidence are rarely obtained to definitively identify a case of PANDAS. It would be uncommon for a clinician to have baseline strep titers for a patient prior to or at the onset or exacerbation of OCD/tic symptoms. In addition, clinicians may be unlikely to subject patients to blood tests to determine strep titers within 6 weeks of onset of symptoms. Further, in clinical practice, strep cultures are generally not used to determine the presence of specific strains of GAS; rather, they are used to determine the presence or absence of a strep infection, which then guides treatment with an antibiotic. In one study of pediatricians, 79% reported that they would treat a presumed strep infection with antibiotics without a positive culture (Paluck et al. 2001). Many children presenting with a PANDAS-like presentation do not have this level of documentation to support GAS infection. Rigorous application of full diagnostic criteria for PANDAS is not always employed in the community setting, and the practice of unwarranted use of antibiotics in children without objective laboratory evidence of infection could increase antibiotic resistance in the pediatric population (Gabbay et al. 2008). It is this lack of a definitive diagnosis of GAS infection that lends to ambiguity and skepticism in establishing GAS relatedness to OCD/tic onset.

As in the clinical setting, establishing a correlation between GAS infection and OCD/tics in the research setting is also difficult. One retrospective study examined patients aged 5–17 years who developed tics. In this group, 53% were found to have an abrupt onset of symptoms, and of this subset, 21% were shown to have the onset within 6 weeks of infection (Singer et al. 2000). Another study examined strep titers in a group of 150 children at their initial evaluation for tics and showed that 38% with tics had elevated ASO titers compared with 2% in the control group (Cardona and Orefici 2001). Although those with a tic disorder did differentiate from the control group, suggesting a recent streptococcal infection, another possibility is that patients with persistently elevated titers may reflect a chronic immune response that then leaves patients more susceptible to exacerbations from other infections and stress (Read et al. 1986; Benatar et al. 1988). For example, in a study of 25 youth with OCD and/or tics with serial samples drawn every 6 weeks for an average of 16.5 months, patients with an episodic presentation in OCD/tic symptoms were more likely to have chronically elevated strep titers when compared with patients with a steadier or remitting course of symptoms (Murphy et al. 2004). In these subjects, chronic elevation of GAS titers could not be explained by frequent clinically apparent GAS infections. Similarly, Johnson et al. (2010) evaluated 160 participants to examine a possible association of GAS infections with the PANDAS syndrome throughout a 2-year

period (Johnson et al. 2010). Sequential samples more accurately define infection compared with single time-point cultures and single antibody titers.

For some patients with a PANDAS presentation, symptoms emerge only after repeated GAS infections over a relatively short time. The risk of developing tics appears to be increased in children who have had frequent GAS infections (Mell et al. 2005). Potential sequelae of frequent GAS infections are not limited to OCD/tic symptoms. In one study that followed 693 school age children with monthly strep cultures and behavioral observations, an increase in behavioral and motoric symptoms was seen especially in children who had repeated strep infections (Murphy et al. 2007). These findings suggest that a cumulative threshold of antibody is needed to trigger symptoms in some patients.

A major shortcoming of the PANDAS hypothesis has been the small number of prospective studies examining the temporal relationship between antecedent GAS infections and the onset or exacerbations of tic and OC symptoms (Luo et al. 2004; Murphy et al. 2004; Perrin et al. 2004; Kurlan et al. 2008; Lin et al. 2009; Leckman et al., in submission). Only two of these longitudinal studies prospectively identified PANDAS cases, using the published diagnostic criteria proposed by Swedo et al. (1998). Neither of these studies provides a strong support for the PANDAS hypothesis (Kurlan et al. 2008; Leckman et al., in submission). Kurlan et al. (2008) reported the results of a prospective, multicenter study of children who met stringent criteria for PANDAS ($n = 40$) and matched children with OCD or tic disorders ($n = 40$) who completed monthly throat cultures, 3-month blood antibody tests, and monthly phone or in-clinic evaluations for an average of 2 years (Kurlan et al. 2008). Although they did find a significantly higher rate of GAS infections as well as a higher rate of clinical exacerbations among the PANDAS cases, no more than 25% of the exacerbations in the PANDAS cases were temporally associated with a GAS infection. The more recent study by Leckman et al. (in submission) provides even less support for the PANDAS hypothesis because all the GAS-linked symptom exacerbations occurred in the non-PANDAS cases.

However, three possible limitations of these two studies warrant consideration. First, both studies informed primary healthcare providers of the results of throat cultures. As a result, the patients' primary clinicians were free, if they chose, to prescribe short-term antibiotics for symptomatic or asymptomatic patients with positive cultures. This practice could have potentially limited the number of exacerbations observed. Second, both the total number of clinical exacerbations and the total number of GAS infections were lower than that had been estimated, raising the possibility that the studies were underpowered. Third, the process by which the PANDAS cases were selected for these studies may have been flawed. Although the investigators in both studies prospectively identified PANDAS cases based on the published criteria, only a small minority of the clinical exacerbations recorded were consistent with the descriptions of PANDAS exacerbations in which the period of increased tic or OC symptom severity is associated with a sudden increase in the severity of psychiatric comorbidity, including emotional lability, intense anxiety, cognitive deficits, oppositional behaviors, motoric hyperactivity, and/or dysgraphia (Swedo et al. 1998). Although studies have linked antecedent GAS infections to symptom exacerbations, the majority occur without evidence of antecedent infection, suggesting that GAS infection may not be the only agent responsible for exacerbations (Kurlan et al. 2008), which has also been reported for SC (Berrios et al. 1985). The reasons for this discrepancy are not clear, but suggest that the

PANDAS cases identified by these studies may not be the same as the PANDAS cases studied by Swedo and colleagues.

A large proportion of current research into the pathophysiology of PANDAS has focused on exploring the role of alterations in the adaptive and innate immune function of affected youth. Genetic vulnerability to this type of immune response is likely as there has been some documentation of PANDAS in multiple siblings (Dranitzki and Steiner 2007); however, we have noted that this PANDAS presentation can be notably discordant in identical siblings. This described clinical presentation is likely the result of a gamut of gene–environment interactions involving patient-specific attributes such as immune vulnerability/resistance genes, the innate immune system, cellular immunity, familial risks, and environmental risks, as well as pathogen-specific attributes.

Studies examining the humoral response to tics, OCD, PANDAS, and SC

Currently, the predominating theory to explain the pathophysiology behind PANDAS is molecular mimicry whereby antibodies intended to target Group A Strep target brain proteins instead. Potential mechanisms by which these autoantibodies cause clinical manifestations in central nervous system (CNS) diseases include direct stimulation or blockade of receptors in the basal ganglia, or immune complexes promoting inflammation of these brain regions (Giedd et al. 1996, 2000). Antineuronal antibody binding to basal ganglia tissue was found in both patients with PANDAS (Pavone et al. 2004) and patients with ADHD (Sanchez-Carpintero et al. 2009), whereas in SC patients, increased antineuronal antibody binding to basal ganglia tissue correlates with symptom severity (Church et al. 2002; Husby et al. 1976; Kotby et al. 1998). More recently, monoclonal antibodies to *N*-acetyl-beta-D-glucosamine, the dominant epitope of GAS carbohydrate, and lysoganglioside GM1, a neuronal cell-surface molecule, have been cloned from children with SC (Kirvan et al. 2003, 2006). *In vitro*, these antibodies can induce increases in the activity of calcium/calmodulin-dependent protein kinase II (CaM kinase II), which in turn can lead to increases in dopamine production and release. CaM kinase II activation is a potential mechanism by which clinical symptoms ensue (Roberts-Lewis et al. 1986; Kantor et al. 1999). The anti-carbohydrate A antibody measures the immune response to *N*-acetyl-beta-D-glucosamine (Bloem et al. 1988). This antibody has shown interesting clinical relevance in studies of rheumatic heart disease and has been shown to fluctuate with OCD symptom changes (Murphy et al. 2004); however, brain cross reactivity of anti-carbohydrate A antibody from a nonclinical sample was not found (Sabharwal et al. 2006). In addition, antibodies directed against dopamine D1 and D2 receptors have also been detected in the serum of PANDAS cases (Cunningham and Perry 2008). The binding of autoantibodies to neuronal cell surface antigens may promote signal transduction, leading to the release of excitatory neurotransmitters, and may explain mechanistically the symptoms of SC and PANDAS. In contrast, not all studies conducted have shown that anti-brain antibodies correlate with clinical exacerbations in PANDAS and are a topic of continued debate (Morer et al. 2008; Singer et al. 2008; Gause et al. 2009).

Antibodies to basal ganglia are found in the sera of most TD, OCD, SC, and PANDAS subjects (Morshed et al. 2001; Pavone et al. 2004; Singer et al. 2004, 2005; Dale et al. 2005; Hoekstra et al. 2005; Kansy et al. 2006; Martino et al. 2007; Gause et al. 2009; Morris et al. 2009) and may extend beyond the basal ganglia to include the cerebellum and cerebral cortex (Bronze and Dale 1993).

One line of investigation has identified three putative autoantigens of 40, 45, and 60 kDa that were subsequently identified as glycolytic enzymes (aldolase C, neuron-specific and nonneuronal enolase, and pyruvate kinase M1) (Dale et al. 2006). Pyruvate kinase M1 was subsequently identified as an autoantigen in TD by an independent group of investigators, who found elevated anti-pyruvate kinase antibodies during streptococcal induced exacerbations of tics (Kansy et al. 2006). They also found that antibodies to pyruvate kinase reacted strongly with surface antigens of infectious strains of *Streptococcus*, and antibodies to streptococcal M proteins reacted with pyruvate kinase. However, increases in antibodies to aldolase C, enolase, and pyruvate kinase were not detected in serial serum specimens obtained during one of the prospective longitudinal studies described above (Kurlan et al. 2008; Singer et al. 2008). Methodological differences in the laboratory procedures and patient selection may account for some of the inconsistencies across studies (Martino et al. 2009).

A recently emerged separate line of evidence suggest that there may be a subgroup of TD patients who have an enhanced immune response to GAS. Specifically, Bombaci et al. (2009) tested the antibody response of tic patient sera to a representative panel of GAS antigens. More than 100 recombinant GAS proteins were placed on glass slides and probed against sera collected from children with chronic tic disorders but no overt pharyngitis or GAS infections. These results were compared with the findings from over 200 children with well-documented GAS pharyngitis as well as a smaller group of healthy control children without a history of tic disorder and no overt pharyngitis or GAS infections. A comparative analysis identified 25 antigens recognized by sera of all three groups and 21 antigens recognized by tic and pharyngitis sera, but poorly or not recognized by sera from children without tics. Remarkably, these antigens appeared to be, in quantitative terms, more immunogenic in tic patients than in pharyngitis patients. In addition, a third group of antigens appeared to be preferentially and specifically recognized by tic sera. These findings provide the first evidence that a subgroup of tic patient sera exhibit immunological profiles typical of individuals who elicited a broad, specific, and strong immune response against GAS. These preliminary findings need to be replicated with an adequate sample size that includes groups of children with pediatric onset OCD, subjects with well-characterized PANDAS, and age- and gender-matched healthy control subjects. Nevertheless, these data do provide a further indication that a subgroup of TD patients displays a pattern of enhanced immunological response to GAS antigens, which is consistent with the PANDAS hypothesis.

Finally, in a recent preliminary study, Kawikova et al. (2010) analyzed the plasma of 24 TD/OCD patients and 22 healthy age- and gender-matched controls by enzyme-linked immunosorbent assay (ELISA) for the levels of total and specific immunoglobulin G (IgG), IgM, and IgA against antigens previously identified in multiple sclerosis (myelin basic protein and myelin-associated glycoprotein), and SC (ganglioside-GM1, lysoganglioside, and tubulin). Total IgA was significantly decreased in TD/OCD patients compared with controls. Specific IgA against all antigens, except tubulin, were also decreased in the patients. The levels of total IgA and anti-myelin basic protein IgA were significantly lower in the PANDAS cases than in non-PANDAS cases or the healthy controls. If replicated in future studies, this relative IgA dysgammaglobulinemia could contribute to deviation of immune responses in TD/OCD patients by at least two mechanisms. First, inhibitory functions of IgA in plasma on immune responses may be reduced (Woolf and Kerr 2006), which could increase the vulnerability of TD/OCD

patients for developing autoimmune disorders (Jacob et al. 2008). Second, IgA secretion on mucosal surfaces could also be affected (Czerkinsky et al. 1987; Norhagen et al. 1989), and in this case, the very first steps of immune defense against mucosal pathogens would be affected. This could account for why a subgroup of TD/OCD patients appears to be more vulnerable to GAS and other upper respiratory tract infections.

Studies examining cellular responses in tics, OCD, and/or PANDAS

T and B lymphocytes play an important role in adaptive immunity, supporting cell-mediated and antibody-mediated immune responses. Among T lymphocytes, T-helper lymphocytes modulate both cell-mediated activity through macrophages and T-cytotoxic lymphocytes and antibody production by plasma cells. The adaptive immune system in turn also activates the innate effector mechanisms in an antigen-specific manner. In autoimmune disorders, the predominance of cell-mediated or humoral responses is a relevant consideration in both pathophysiology and therapeutics. Typically, autoimmune diseases result from the breakdown of immune tolerance processes, which suppress the activity of autoreactive T and B lymphocytes.

One mechanism of peripheral tolerance involves a subset of T lymphocytes called regulatory T cells (Tregs). Reduced numbers of Tregs are detected in autoimmune conditions including type 1 diabetes (Kukreja et al. 2002), lupus erythematosus (Crispin et al. 2003), rheumatoid arthritis (de Kleer et al. 2004), and multiple sclerosis (Matarese et al. 2005). Using flow cytometry techniques (Kawikova et al. 2007), lower numbers of Tregs were found in the peripheral blood of 37 children with TD and/or OCD compared with healthy children. The reduction of Tregs was most noticeable in TD patients with higher disease severity or during symptom exacerbations. This finding, if replicated, might be explained by a prolonged reaction to persisting foreign antigens, such as GAS, potentially leading to a compensatory loss. Alternatively, as suggested by Ferrari et al. (2008), who reported increased expression of the D5 dopamine receptor on peripheral blood cells of TD patients, activation of D5 dopamine receptors on Tregs reduces their immunosuppressive activity as well as their adhesive and migratory abilities (Kipnis et al. 2004; Ferrari et al. 2008).

Further support to increased peripheral immune activity comes from an exploratory study of lymphocyte surface markers. Specifically, Moller et al. (2008) reported significantly increased numbers of CD691 B lymphocytes and CD951 T-helper lymphocytes in 20 adults with TD, compared with healthy subjects. These results suggest increased B-cell activation and increased activation-induced apoptosis of T lymphocytes, respectively. An increased frequency of activated B lymphocytes is also supported by prior research pointing toward a higher density of immunoglobulin receptors on the surface of B cells in these patients (Hoekstra et al. 2004; Luo et al. 2004).

In summary, there are preliminary data suggesting alterations in cell-mediated immunity in a subgroup of patients with TD. In some cases, the findings have not been replicated. It is also possible that there are age or medication effects that have yet to be discovered, and it is unclear what degree of overlap is present between the subgroup of TD patients identified as having altered cell-mediated immunity and the PANDAS cases. Indeed, the number of Tregs reported in the study by Kawikova et al. (2007) was most pronounced in the non-PANDAS cases.

Specific effector molecules including cytokines differentially modulate the activity of innate and adaptive immune systems. A

number of early reports on serum and cerebrospinal fluid cytokine levels in OCD yielded discrepant results (Brambilla et al. 1997; Mittleman et al. 1997; Monteleone et al. 1998; Denys et al. 2004). Leckman et al. (2005) measured plasma levels of a broad array of cytokines in 46 pediatric TD patients and 31 healthy controls, reporting increased baseline levels of tumor necrosis factor- α (TNF- α) and interleukin-12 (IL-12). Of note, there was a 50%–60% rise of these two cytokines, plus a general increase of all the main cytokines explored, during periods of tic symptom exacerbation. However, these combined cytokine clinical fluctuations were more frequent in the non-PANDAS than in PANDAS cases. In contrast, Singer et al. (2008) found no association between clinical exacerbations (associated or not with GAS infection) and several effector molecules including both TNF- α and IL-12 (Singer et al. 2008).

Further support for the presence of pro-inflammatory mechanisms in TD is given by the observed increase in baseline plasma levels of neopterin, a soluble marker of T-cell activation by interferon gamma (IFN γ) (Luo et al. 2004; Hoekstra et al. 2007) and of two soluble adhesion molecules (vascular cell adhesion molecule-1 and E-selectin), which are involved in the recruitment of lymphocytes toward sites of inflammation (Martino et al. 2005). Nevertheless, measurement of effector molecules in the periphery provides little convincing support for the PANDAS hypothesis, particularly given the discrepant findings across studies and difficulties associated with measuring these molecules in a reliable fashion.

Immune gene expression profiling in peripheral blood cells and in the basal ganglia

A second line of evidence also indicates that immune mechanisms may play a role in the pathogenesis of a subgroup of TD cases. Specifically, microarray gene expression profiling of peripheral blood cells is helping the search for disease-specific gene expression fingerprints. In preliminary reports, a subgroup of TD patients overexpressed genes controlling the function of natural killer cells (Tang et al. 2005; Du et al. 2006; Lit et al. 2007). Most recently, Lit et al. (2007) studied the expression of many genes and found multiple pathways to be different between TD and controls within three discrete age groups (5–9, 10–12, and 13–16 years). Notably, across these age strata, expression of IFN response, viral processing, natural killer, and cytotoxic T-lymphocyte cell genes differed. Their findings suggest age-related IFN, innate immune, and protein degradation gene expression differences between a subgroup of TD cases and controls. Other preliminary data support dysregulation in cellular proinflammatory mechanisms. Gabbay et al. (2009) examined the potential role of cytokines in 32 children and adolescents with TD. Patients with comorbid OCD were found to have significantly elevated IL-12 plasma levels compared with controls, whereas IL-2 was significantly elevated in TD + OCD subgroup compared with the TD – OCD subgroup.

An examination of gene expression patterns in the putamen via a cDNA neuroarray comprising 1537 genes known to be related to neurological or neuropsychiatric disorders was conducted on three postmortem specimens from well-documented individuals with TD compared with four controls (Hong et al. 2004). Validation experiments were performed using reverse transcription-polymerase chain reaction and semiquantitative Western blot analyses. The IL-2 receptor beta gene was expressed at a much higher level in the TD brains. In a subsequent study, a postmortem evaluation of four adults with TD revealed significantly higher levels of monocyte chemotactic factor-1 (MCP-1), IL-2, IFN, and

protein tyrosine phosphatase receptor-N/islet associated antigen (PTPR-N/IA-2) in the basal ganglia of TD patients compared with controls. In addition, mRNA expression was elevated 6.5-fold for MCP-1, 2.3-fold for IL-2, and 16.1-fold for IA-2 when compared with controls. This examination showed first-time evidence for an increase in expression of two inflammatory markers directly in the basal ganglia, MCP-1 and IL-2. Replication of elevated expression of PTPR-N in TD patients could suggest that pathways involving this molecule may be relevant in TD pathogenesis (Morer et al. 2010).

In summary, there is evidence that a subgroup of TD cases may have increased levels of immune gene expression in the periphery and in the basal ganglia, which may play a role in TD pathogenesis. However, it is unclear if any of the patients with elevated immune gene expression are PANDAS cases. It is also clear that the family history of PANDAS cases, including those identified by Swedo and colleagues, is largely indistinguishable from that seen in TD or pediatric-onset OCD cases (Lougee et al. 2000).

Animal models

A variety of immune-based animal models have been developed to test the PANDAS hypothesis. An initial model in which sera from TD and OCD patients with high levels of antineural antibodies were microinfused into the dorsal lateral striatum initially appeared promising (Hallett et al. 2000; Taylor et al. 2002). However, a subsequent multisite study failed to demonstrate a significant difference in stereotypic behaviors induced by sera from neuropsychiatric patients containing either elevated or low concentrations of antineural antibodies (Singer et al. 2005). The results from this multisite study were similar to a third report that identified no significant differences for rodents infused in either the ventral or ventrolateral striatum with TD and PANDAS sera when compared with controls (Loiselle et al. 2004). This finding was consistent across all individual centers, as well as when analyzed as total mean values.

Independently, Hoffman et al. (2004) reported behavioral abnormalities reminiscent of those reported in PANDAS, and antibodies directed against *Streptococcus* M protein in peripheral blood and brain, in autoimmune disease-susceptible mice following immunization with GAS. More recently, the same group extended this model by examining whether peripheral anti-CNS antibodies are sufficient to reproduce the syndrome, and whether or not the effect is eliminated by depleting IgG before transfer into naive mice (Yaddanapudi et al. 2009). Their results demonstrated that the immunized animals showed stereotypic behaviors as well as deficits in motor coordination, learning/memory, and social interaction. They also demonstrated that humoral immunity is necessary and sufficient to induce the syndrome when naive mice are transfused with IgG from PANDAS mice. Consistent with this finding, depletion of IgG from donor sera eliminated the abnormal behaviors.

A new model of PANDAS pathogenesis

Published reports and emerging data provide evidence (1) that PANDAS cases are more vulnerable to GAS infections, (2) that cross-reactive antibodies can induce dopamine release as well as interact with dopamine D2 receptors, and (3) that there are powerful links between dopamine and the downstream immunological mechanisms involved in SC and PANDAS. Briefly, SC, pediatric-onset OCD, and TD have traditionally been viewed as hyperkinetic

disorders in which central dopamine systems play an important etiological role (Albin et al. 1989; Goodman et al. 1990). It is also well known that dopamine receptor–blocking agents are among the most effective and efficacious treatments of SC, TD, and tic-related forms of OCD (Axley 1972; Bloch et al. 2006; Scahill et al. 2006).

There is now evidence that dopamine can directly influence key immunological mechanisms that may be involved in SC and PANDAS (Kipnis et al. 2004; Besser et al. 2005). Specifically, it has been hypothesized that more frequent GAS infections lead to elevated levels of cross-reactive anti-GAS antibodies in the vulnerable children. When the permeability of blood–brain barrier is enhanced (Kim et al. 2006), these autoantibodies and lymphocytes may cross the blood–brain barrier. The cross-reactive antibodies may then activate CaM kinase II and increase dopamine release from nigrostriatal projection neurons. Locally, dopamine may then reach concentrations that inhibit suppressive functions of Tregs, further enhancing the activity of Th1 and B lymphocytes. These interactions may then establish an autoimmune inflammation within basal ganglia. At sites of chronic inflammation, antigen-specific as well as nonspecific triggers could further activate immune cells, causing release of various inflammatory mediators. This may further increase local dopamine release and clinically present in the form of tic, OC, and other neuropsychiatric symptoms. Some of the most exciting are recent data from Dr. Madeleine Cunningham's laboratory that cross-reactive antibodies found in PANDAS cases can directly interact, and likely activate, dopamine D2 receptors, but not dopamine D1 receptors (data presented at the 2008 9th International Congress of NeuroImmunology) (Cunningham and Perry 2008). If confirmed in future studies, this suggests that cross-reactive antibodies may act by directly interacting with D2 receptors in a fashion similar to what Diamond et al. (2006) have described in both systemic lupus erythematosus (SLE) and animal models of SLE. In the case of SLE, serum antibodies to one of the glutamine receptors (the *N*-methyl-D-aspartate receptors) are present, which can cause alterations in cognition and behavior following a breach in the blood–brain barrier. This has led some investigators to hypothesize that PANDAS, SC, and some cases of TD may be due to immunologically mediated increases in central dopamine levels and selective activation of central dopamine D2 receptors, which combine to produce the neuropsychiatric symptoms seen in these disorders, possibly even in the absence of inflammation.

In addition, an increase in the release of dopamine also could explain elevations in proinflammatory cytokines and deficits in Tregs. Specially, dopamine, acting directly via dopamine receptors, can increase significantly TNF- α secretion in resting normal human T cells and induce a fivefold elevation of the corresponding TNF- α mRNA (Besser et al. 2005). This again suggests that elevated levels of dopamine may contribute to PANDAS pathogenesis. Some TD patients have high levels of TNF- α , which are further increased during periods of symptom exacerbations (Leckman et al. 2005). An increase in TNF- α would increase the permeability of the blood–brain barrier and facilitate a CNS autoimmune response. In addition, dopamine, acting via dopamine D1 and D5 receptors, reduces the suppressive activity and the adhesive and migratory abilities of regulatory T cells (Kipnis et al. 2004). This suggests that elevated levels of dopamine may contribute to the PANDAS story. We have shown that some TD cases have reduced levels of regulatory T cells and show a further reduction during periods of symptom exacerbation (Kawikova et al. 2007). A reduction in Treg function would facilitate a CNS autoimmune response. We also note that caution is warranted with this interpretation because

relatively high levels of dopamine are needed to affect Tregs. This could mean that these effects would be more likely to occur in regions of the CNS where the dopamine innervations are the greatest rather than in the periphery. Finally, if PANDAS cases do suffer a relative dysgammaglobulinemia (Kawikova et al. 2010), this could account for their greater vulnerability to GAS infections.

Controversies in Establishing an Infectious Trigger

Alternative infectious precipitants

In 2004, a study by Perrin et al. (2004) showed that both viral and GAS infections can lead to acute behavioral changes. This study's primary aim was to assess for a delayed response to GAS after removing the acute behavioral group (those with concurrent behavioral changes and GAS infection at baseline) from the analysis. Our experience suggests that the relationship of GAS inducing behavioral changes more often occurs concurrently with evidence of the infection. Hoekstra et al. (2005) found tic exacerbations to occur after a cold but did not find a GAS association. A more recent study found that a large percentage (87.5%) of symptom exacerbations among PANDAS patients cannot be definitively attributed to GAS infections, although GAS-related exacerbations did occur in 7.5%–25% (Kurlan et al. 2008). The exacerbation rates (tics and/or OCD) were 0.56 per person-year for PANDAS case subjects and 0.28 per person-year for control subjects. A total of 43 definite or probable GAS infections were identified: 31 in PANDAS case subjects (in 22 subjects) and 12 in control subjects (in 9 subjects). The GAS (definite or probable) infection rates were 0.43 per person-year for PANDAS case subjects and 0.13 per person-year for control subjects. Moreover, reports of non-GAS triggered neuropsychiatric symptoms call into question the specificity of GAS in PANDAS-like presentations. Clearly not all symptom exacerbations are due solely to GAS and case reports support this possibility (Table 1), including the common cold, sinusitis, and *Mycoplasma pneumonia* (Hoekstra et al. 2005; Ercan et al. 2008; Leslie et al. 2008). Future prospective longitudinal studies are needed to confirm these findings and to clarify whether there is a common underlying immunological response that triggers symptom worsening.

The role of psychosocial stress

In some cases, OCD onset is preceded by stressful or traumatic events (Thomsen and Mikkelsen 1995) that have the potential to disrupt the psychoneuroimmune balance (Tait et al. 2008). Very little has been done to evaluate phenotypic differences in those presenting with PANDAS versus the typical childhood onset of tics and OCD. Significant overlap between the groups is likely. If true group differences exist, the etiology is still likely to be multifactorial with cumulative and varying contributions from hypothalamic-pituitary-adrenal (HPA) axis dysfunction and stress as well as from influences of genetics, nutrition, medication, and illness. Clinical observations as well as studies of TD and early-onset OCD have consistently suggested that these disorders are sensitive to psychosocial stress (Bornstein et al. 1990; Chappell et al. 1994; Charmandari et al. 2003; Hoekstra et al. 2004). For example, a number of reports documented an abnormal response to stress in TD patients (Chappell et al. 1996; Lin et al. 2007; Corbett et al. 2008). Recently, Lin et al. (2009) monitored 45 children with tic disorder and/or OCD and 41 matched healthy control subjects over a 2-year period for the level of psychosocial stress. Consecutive monthly ratings of tic, OC, and depressive symptom severity were

obtained. State-of-the-art structural equation modeling for unbalanced repeated measures was used to assess the temporal sequence of psychosocial stress measure changes with the severity of tic, OC, and depressive symptoms. Increases in tic and OC symptom severity did not occur after every new GAS infection. However, the structural equation model found that these newly diagnosed GAS infections were predictive of modest increases in future tic and OC symptom severity but did not predict future depressive symptom severity. In addition, the inclusion of new infections in the model greatly enhanced, by a factor of 3, the power of psychosocial stress in predicting future tic and OC symptom severity. These data suggest that a minority of children with TD and early-onset OCD were sensitive to antecedent GAS infections. These infections also enhanced the predictive power of current psychosocial stress on future tic and OC symptom severity.

Neurological and cardiac concerns

In addition to two case reports (Giedd et al. 1996; Tucker et al. 1996), Giedd et al. (2000) assessed selective basal ganglia involvement in a subgroup of 34 children with OCD and/or tics believed to be associated with GAS infections, compared with 82 healthy children. The average sizes of the caudate, putamen, and globus pallidus, but not of the thalamus or total cerebrum, were significantly greater in the PANDAS cases compared with controls and were similar in magnitude to those seen in children with SC. These findings are consistent with the hypothesis of an autoimmune response to streptococcal infection.

In PANDAS, studies have presented evidence that an overall worsening of neurological performance occurred with or followed OCD/tic symptoms (Swedo et al. 1998; Murphy et al. 2004). Choreiform movements that represented an overall worsening of neurological performance were noted to occur about 3 months following a tic exacerbation (Murphy et al. 2004). This type of lag is consistent with the finding that OCD symptoms precede the appearance of any motoric manifestation by days or weeks in patients with RF (Mercadante et al. 2000). The presence of neurological soft signs, such as choreiform movements and pronator sign/drift, are a frequently observed comorbidity among childhood onset OCD, tics, and ADHD; the significance of neurological soft signs in relationship to GAS infections has never been prospectively examined until recently (Murphy et al. 2007). In addition to choreiform movements, other subtle signs of neurological impairment have been reported to be associated with PANDAS (Swedo et al. 1998); however, neuropsychological dysfunction is commonly reported with OCD/tics (Kuelz et al. 2004; Bloch et al. 2006) and those with PANDAS may not have differentiating neuropsychological profile when compared with youth with typical (non-PANDAS) OCD and TD (Hirschtritt et al. 2009).

In addition, reports suggest that other non-SC neurological sequelae may be secondary to GAS. More recently, neurological sequelae including myoclonus (DiFazio et al. 1998), post-streptococcal basal ganglia encephalopathy (Dale et al. 2001), and restless legs syndrome (Matsuo et al. 2004) have been reported to be associated with GAS, suggesting that GAS may elicit a wide array of phenotypes that render varying degrees of overlap with RF. It is the absence of frank chorea and absence of carditis that differentiates PANDAS from SC. It is estimated that rheumatic carditis is found in 30%–64% of all SC patients, but data do not support a risk of developing rheumatic carditis for a child originally presenting with GAS-triggered OCD or tics (Snider et al. 2004). A milder spectrum of presentation may be possible as these children

may be at higher risk for clinically insignificant echocardiographic findings (Cardona et al. 2004; Segarra and Murphy 2008). Nonetheless, although not explicitly stated, the child should not meet criteria for RF as behavioral changes during the course of RF are well documented. Any child with a prominent presentation of chorea, cardiac findings, or arthritis would need further assessment to rule out RF.

Evaluation and Treatment

Evaluation

A recent examination of youth classified as PANDAS by their community physicians found that 61% did not strictly meet the NIH criteria for PANDAS (Gabbay et al. 2008). During the history gathering process, careful attention should be given to reports of repeated, frequent infections; evidence of GAS in a young child (e.g., unexplained abdominal pain accompanied by fever); scarlet fever; brief episodes of tics; OCD or compulsive urination, which remitted; and especially sudden onset of OCD or tics accompanying an infectious illness. In patients with abnormal neurological examination evidenced by muscle weakness, abnormal reflexes (slow return of patellar reflex, i.e., hung-up), or chorea, further workup is indicated. In patients with new-onset OCD or tics, or recent symptoms of exacerbation, a throat culture is a relatively benign procedure that will help rule out the possibility of symptoms being triggered by a subclinical GAS infection. Streptococcal titers obtained at symptom onset should be repeated to examine for a rise in titers after 4–6 weeks. In patients with onset exceeding 4 weeks prior, streptococcal titers add some support but do not provide definitive proof of a streptococcal trigger. However, elevated titers may not be seen in very young patients.

Antibiotics

Proof that antimicrobial prophylaxis significantly reduces recurrence and/or exacerbation of OC/tic symptoms would suggest a supportive role for infectious agents in the onset or worsening of these conditions. By examining the scant literature on using antibiotics to prevent SC recurrences, the complications in determining efficacy become apparent. Although prophylactic antibiotic therapy in patients with SC appears successful in the prevention of neuropsychiatric exacerbations (Gebremariam 1999), other investigators report that about a third will continue to have a recurrence (Terreri et al. 2002). Studies in which SC patients received monthly prophylactic injections of benzathine penicillin G showed that not all SC recurrences appear to be GAS triggered (Korn-Lubetzki et al. 2004) and that recurrences may occur after infections that are too mild or too brief to be easily detected (Berrios et al. 1985). These studies suggest that some improvement in the course occurs after prophylactic antibiotics, however, the sample sizes were small, all were open label, and most patients with SC take prophylactic antibiotics until their late teens. Consequently, data exist to compare overall neuropsychiatric severity of those receiving treatment with those who do not (Gebremariam 1999).

Although the PANDAS hypothesis remains unsettled, the current treatment for patients meeting the PANDAS criteria continues to be the standard of care practice for patients with OCD and/or TD. As a definitive association between GAS and OCD/tics has yet to be established, protocols for diagnosis and treatment of PANDAS are provisional. Studies have been criticized for flaws in design and small sample size (Kurlan and Kaplan 2004), and a clinical trial involving the use of prophylactic oral penicillin in treating apparent

episodes of PANDAS revealed no conclusive evidence that the antibiotic reduced clinical exacerbations (Garvey et al. 1999). An active comparative trial comparing penicillin and azithromycin (Snider et al. 2005) was also considered inconclusive by critics (Budman et al. 2005). In this study, 11 subjects were maintained on penicillin and 12 were maintained on azithromycin during the 12-month study. Subjects randomized to both drugs had a reduced number of streptococcal infections as well as a reduced number of neuropsychiatric exacerbations during the study year, with no side effects or reports of any adverse effects from the medications. The authors suggest that both antibiotics may be safe and effective in preventing GAS infection and in decreasing the number of neuropsychiatric exacerbations in these children, without any significant differences between groups. This study was limited, however, by the comparison of retrospective data for the baseline year with prospective data of the treatment year and by an active comparison. Anecdotal reports by patients receiving antibiotics (in clinical settings) suggest that some beta-lactam antibiotics are more effective than penicillin. Studies are needed, first, to establish antibiotic efficacy and, second, to determine which antibiotic is most efficacious in improving neuropsychiatric symptoms.

Another issue to be addressed is that antibiotics may serve an additional, nonantimicrobial role in the treatment of some disorders, although it has not yet been supported by clinical studies. Anecdotal reports of symptom improvement in PANDAS after 2–6 weeks of antibiotic treatment are intriguing and suggest other possible mechanisms besides prevention of GAS reinfection. One possible mechanism is that penicillin decreases antigenic load from undetected and asymptomatic intracellular GAS (Sela et al. 2000). Another possibility is via cytokine modulation. GAS is a potent inducer of $IFN\gamma$ and most proinflammatory cytokines (Miettinen et al. 1998). Penicillin perhaps serves a synergistic role in symptom improvement by specifically conjugating to $IFN\gamma$ and reducing $IFN\gamma$'s activity (Brooks et al. 2003, 2005). An interesting but not fully explored parallel is that selective serotonin reuptake inhibitors (SSRIs), currently the pharmacologic treatment of choice for OCD, have been found to exert anti-inflammatory effects through suppression of $IFN\gamma$ (Kubera et al. 2001). GAS infections have been reported to also lead to tryptophan degradation, which may influence serotonin function (Murr et al. 2001). Antibiotic therapy, theoretically, could allow for normalization of tryptophan levels. Moreover, penicillin may serve an additional, nonantimicrobial role in the treatment of some disorders (Rothstein et al. 2005), although it has not yet been supported by clinical studies. A recent screening of FDA-approved medications discovered that beta-lactam antibiotics such as ceftriaxone and penicillin promoted the expression of glutamate transporter GLT1 and demonstrated a neuroprotective role *in vivo* and *in vitro* when used in models of ischemic injury and motor neuron degeneration, both based in part on glutamate toxicity. These findings indicate that positive promoters of GT expression may have a unique role in neuroprotection in neurological disorders such as amyotrophic lateral sclerosis (Rothstein et al. 2005) and a potential role in glutamatergic therapies for OCD (Pittenger et al. 2006). PANDAS symptom improvement during antibiotic therapy is primarily expected to be secondary to antimicrobial effects, but the potential for multiple roles of penicillin (or other beta-lactam antibiotics) would open the door for other mechanisms in the PANDAS pathophysiology and treatment. The use of prophylactic antibiotics to treat PANDAS has become widespread in the community (Gabbay et al. 2008), although the evidence supporting their use is equivocal (Garvey et al. 1999; Budman et al. 2005; Snider et al. 2005). The safety and

efficacy of antibiotic therapy for patients meeting the PANDAS criteria needs to be determined in carefully designed trials. Until then, treatment continues to be the standard of care practices for patients with OCD and/or TD, such as medications (e.g., SSRIs) and therapies (e.g., cognitive behavioral therapy (CBT)) with evidence-based support. Nothing appears too unique about the neuropsychiatric presentation of PANDAS, which precludes using proven treatments. Those children with PANDAS may be more prone to adverse effects of medications (Murphy et al. 2006) but have also been shown to respond well to CBT (Storch et al. 2006). These children with new-onset OCD benefit by learning skills that will help to attenuate the severity of future exacerbations and minimize family accommodation.

Immunomodulatory treatments for PANDAS

A variety of immunomodulatory treatments have been studied in children with PANDAS. The results of a plasmapheresis or intravenous immunoglobulin (IVIG) trial in the treatment of children with PANDAS add additional support for an immune-mediated pathology of OCD and tics (Perlmutter et al. 1999). Specifically, Perlmutter et al. (1999) reported the results of a study in which children with acute exacerbations of OCD or tic disorders were randomly assigned treatment with plasma exchange (PE) (five single-volume exchanges over 2 weeks), IVIG (1 g/kg daily on 2 consecutive days), or placebo (saline solution given in the same manner as IVIG). Thirty children entered this study and 29 completed the trial. Ten received PE, 9 IVIG, and 10 received placebo. At 1 month, the IVIG and PE groups showed striking improvements in obsessive-compulsive symptoms, anxiety symptoms, and overall functioning. Treatment gains were maintained at 1 year, with 14 (82%) of 17 children “much” or “very much” improved over baseline (7 of 8 for PE, 7 of 9 for IVIG). This report was strongly criticized in an accompanying editorial (Singer 1999).

These possible treatment gains, however, appear to be specific to children who clearly meet the criteria for PANDAS, as plasma exchange in four children with severe chronic OCD did not result in significant improvements (Nicolson et al. 2000) and IVIG did not show efficacy for patients with tic disorders (Hoekstra et al. 2004). For these patients, it is possible that a previous immune-mediated process resulted in a chronic neurological state that is less responsive to immune therapies or that this group represented patients with nonimmune-mediated etiologies of their illness. As some youth presenting with PANDAS may spontaneously show remission, the use of IVIG or PE therapies needs to be carefully weighed for risks versus benefits. A larger-scale IVIG trial underway should inform on future recommendations for this treatment option. Thus far, there has not been a randomized double-blind study of corticosteroids to treat PANDAS. However, Garvey et al. (2005) reported the results of a randomized clinical trial for SC. In this study, clinical improvements appeared to be more rapid and robust in the IVIG and PE groups than in the prednisone group (mean chorea severity scores decreased by 72% in the intravenous immunoglobulin group, 50% in the PE group, and 29% in the prednisone group).

Improvement of symptoms of PANDAS with immune therapies such as plasmapheresis or IVIG would add additional support for an immune-mediated pathology of OCD and tics; however, inconclusive data support the use of immunomodulatory therapies at this time. Replication of these preliminary findings in properly controlled studies is needed before such treatments can be recommended.

Future Research Directions

There is a substantial, multifaceted scientific literature on PANDAS and the potential role of GAS infections in the pathobiology of TD and closely related disorders. The findings are many, but there is little consistency across studies. Given the overlapping clinical presentations of SC, TD, pediatric-onset OCD, and basal ganglia encephalopathy, it appears likely that some TD and pediatric-onset OCD cases are true PANDAS cases, but this has yet to be convincingly demonstrated, particularly in light of the equivocal or negative, prospective, longitudinal studies (Kurlan et al. 2008; Leckman et al., in submission). In our view, the diagnostic criteria and the assessment methodologies used to identify PANDAS need to be refined to focus on the broad range of psychopathology ostensibly associated with PANDAS. Specifically, in PANDAS, the period of increased tic or OC symptom worsening is also associated with a sudden increase in the severity of psychiatric comorbidity including emotional lability, intense anxiety, cognitive deficits, oppositional behaviors, frequent urination, motoric hyperactivity, and/or dysgraphia (Swedo et al. 1998; Murphy and Pichichero 2002). This is not adequately captured if the criteria for an exacerbation focus simply on the change in OC or tic symptoms.

Also given the substantial, but often contradictory, data concerning various immune markers, future studies should include as many of these putative biomarkers as possible. Volumetric brain imaging of the basal ganglia is also warranted. Finally, given the possibility that immune-modulatory treatments such as IVIG or PE may be efficacious, there is a clear need to replicate and extend the earlier study by Perlmutter et al. (1999). Ideally, such studies would also include the assessment of the biomarkers proposed as part of the novel model of PANDAS pathogenesis presented above.

Additional caveats are also in order. First, there is a distinct possibility that some forms of TD involve abnormalities of the immune system, which are not postinfectious byproducts of GAS infections. Therefore, the role of immunological factors in OCD and TD populations in general should be identified before stratifying into PANDAS versus non-PANDAS phenotypes. Previous studies have suggested that adult and pediatric patients with tics and/or OCD have evidence of variations in inflammatory markers, cytokines, antibodies, and white blood cells. Even some evidence to suggest the presence of GAS infection, together with relevant neuropsychiatric symptoms, is not sufficient to make a PANDAS diagnosis. For example, many youth with tic disorders have elevated GAS antibodies but never display the dramatic symptom course that is consistent with PANDAS. Clinicians who see these children typically do not need to direct tic or OCD diagnostic or therapeutic measures for GAS infections. That said, further studies are warranted, particularly in atypical cases in which there is clinical evidence of the abrupt onset or sudden worsening of other neuropsychiatric symptoms (personality change, psychosis, intense anxiety, loss of academic skills, dysgraphia, etc.) of an acute encephalopathy and in younger children, at the onset of illness.

Summary

An infectious association to the onset of pediatric neuropsychiatric symptoms would certainly help explain the enigmatic changes that can quickly occur in an otherwise healthy child. Because many infections can seemingly be insignificantly present, their pathology is often underestimated. Host and pathogen traits likewise have the potential to alter neuroendocrine and neu-

roimmune responses that collectively contribute to neuropsychiatric disease formation.

It is time for the National Institutes of Health, in combination with advocacy and professional organizations, to convene a panel of experts not to debate the current data, but to chart a way forward. For now we have only to offer our standard therapies in treating OCD and tics, but one day we may have evidence that also allows us to add antibiotics or other immune-specific treatments to our armamentarium.

Disclosures

Dr. Murphy has received research support from the National Institute of Mental Health, Forest Laboratories, Janssen Pharmaceuticals, Endo, Obsessive Compulsive Foundation, Tourette Syndrome Association, All Children's Hospital Research Foundation, Centers for Disease Control, and National Alliance for Research on Schizophrenia and Affective Disorders. Dr. Murphy is on the Medical Advisory Board for Tourette Syndrome Association. She receives textbook honorarium from Lawrence Erlbaum.

Dr. Kurlan has received research support from the NIH, Center for Disease Control, Neurologix, Kyowa, Boehringer-Ingelheim, and the Michael J. Fox Foundation.

James F. Leckman for the past 3 years receives the following funds: NIH (salary and research funding), Tourette Syndrome Association (research funding), Klingenstein Third Generation Foundation (medical student fellowship program), John Wiley and Sons (book royalties), McGraw Hill (book royalties), and Oxford University Press (book royalties).

References

- Albin RL, Young AB, Penney JB: The functional anatomy of basal ganglia disorders. *Trends Neurosci* 12:366–375, 1989.
- Allen AJ, Leonard HL, Swedo SE: Case study: A new infection-triggered, autoimmune subtype of pediatric OCD and Tourette's syndrome. *J Am Acad Child Adolesc Psychiatry* 34:307–311, 1995.
- Axley J: Rheumatic chorea controlled with haloperidol. *J Pediatr* 81:1216–1217, 1972.
- Ayoub EM: Resurgence of rheumatic fever in the United States. The changing picture of a preventable illness. *Postgrad Med* 92:133–136, 139–142, 1992.
- Benatar A, Beatty DW, Human DG: Immunological abnormalities in children with acute rheumatic carditis and acute post-streptococcal glomerulonephritis. *Int J Cardiol* 21:51–58, 1988.
- Berrios X, Quesney F, Morales A, Blazquez J, Bisno AL: Are all recurrences of "pure" Sydenham chorea true recurrences of acute rheumatic fever? *J Pediatr* 107:867–872, 1985.
- Besser MJ, Ganor Y, Levite M: Dopamine by itself activates either D2, D3 or D1/D5 dopaminergic receptors in normal human T-cells and triggers the selective secretion of either IL-10, TNFalpha or both. *J Neuroimmunol* 169:161–171, 2005.
- Bisno AL, Brito MO, Collins CM: Molecular basis of group A streptococcal virulence. *Lancet Infect Dis* 3:191–200, 2003.
- Bloch MH, Peterson BS, Scahill L, Otka J, Katsovich L, Zhang H, et al.: Adulthood outcome of tic and obsessive-compulsive symptom severity in children with Tourette syndrome. *Arch Pediatr Adolesc Med* 160:65–69, 2006.
- Bloem A, Zenke G, Eichmann K, Emmrich F: Human immune response to group A streptococcal carbohydrate (A-CHO). II. Antigen-independent stimulation of IgM anti-A-CHO production in purified B cells by a monoclonal anti-idiotypic antibody. *J Immunol* 140:277–282, 1988.
- Bombaci M, Grifantini R, Mora M, Reguzzi V, Petracca R, Meoni E, et al.: Protein array profiling of tic patient sera reveals a broad range and enhanced immune response against Group A *Streptococcus* antigens. *PLoS One* 4:e6332, 2009.
- Bornstein RA, Stefl ME, Hammond L: A survey of Tourette syndrome patients and their families: The 1987 Ohio Tourette Survey. *J Neuropsychiatry Clin Neurosci* 2:275–281, 1990.
- Brambilla F, Bellodi L, Perna G, Arancio C, Bertani A: Dopamine function in obsessive-compulsive disorder: Growth hormone response to apomorphine stimulation. *Biol Psychiatry* 42:889–897, 1997.
- Bronze MS, Dale JB: Epitopes of streptococcal M proteins that evoke antibodies that cross-react with human brain. *J Immunol* 151:2820–2828, 1993.
- Brooks BM, Hart CA, Coleman JW: Differential effects of beta-lactams on human IFN-gamma activity. *J Antimicrob Chemother* 56:1122–1125, 2005.
- Brooks BM, Thomas AL, Coleman JW: Benzylpenicillin differentially conjugates to IFN-gamma, TNF-alpha, IL-1beta, IL-4 and IL-13 but selectively reduces IFN-gamma activity. *Clin Exp Immunol* 131:268–274, 2003.
- Budman C, Coffey B, Dure L, Gilbert D, Juncos J, Kaplan E, et al.: Regarding antibiotic prophylaxis with azithromycin or penicillin for childhood-onset neuropsychiatric disorders. *Biol Psychiatry* 58:916–917, 2005.
- Cardona F, Orefici G: Group A streptococcal infections and tic disorders in an Italian pediatric population. *J Pediatr* 138:71–75, 2001.
- Cardona F, Romano A, Cundari G, Ventriglia F, Versacci P, Orefici G: Colour Doppler echocardiography in children with group A streptococcal infection related tic disorders. *Indian J Med Res* 119(Suppl):186–190, 2004.
- Chappell P, Leckman J, Goodman W, Bissette G, Pauls D, Anderson G, et al.: Elevated cerebrospinal fluid corticotropin-releasing factor in Tourette's syndrome: Comparison to obsessive compulsive disorder and normal controls. *Biol Psychiatry* 39:776–783, 1996.
- Chappell P, Riddle M, Anderson G, Scahill L, Hardin M, Walker D, et al.: Enhanced stress responsivity of Tourette syndrome patients undergoing lumbar puncture. *Biol Psychiatry* 36:35–43, 1994.
- Charmandari E, Kino T, Souvatzoglou E, Chrousos GP: Pediatric stress: hormonal mediators and human development. *Horm Res* 59:161–179, 2003.
- Church AJ, Cardoso F, Dale RC, Lees AJ, Thompson EJ, Giovannoni G: Anti-basal ganglia antibodies in acute and persistent Sydenham's chorea. *Neurology* 59:227–231, 2002.
- Corbett BA, Mendoza SP, Baym CL, Bunge SA, Levine S: Examining cortisol rhythmicity and responsivity to stress in children with Tourette syndrome. *Psychoneuroendocrinology* 33:810–820, 2008.
- Crispin JC, Martinez A, Alcocer-Varela J: Quantification of regulatory T cells in patients with systemic lupus erythematosus. *J Autoimmun* 21:273–276, 2003.
- Cunningham M, Perry H: Autoimmunity and behavior: Sydenham's Chorea and related disorders. Paper presented at the 9th International Congress of Neuroimmunology, Fort Worth, TX, 2008.
- Czerkinsky C, Prince SJ, Michalek SM, Jackson S, Russell MW, Moldoveanu Z, et al.: IgA antibody-producing cells in peripheral blood after antigen ingestion: Evidence for a common mucosal immune system in humans. *Proc Natl Acad Sci USA* 84:2449–2453, 1987.
- Dale RC, Candler PM, Church AJ, Wait R, Pocock JM, Giovannoni G: Neuronal surface glycolytic enzymes are autoantigen targets in post-streptococcal autoimmune CNS disease. *J Neuroimmunol* 172:187–197, 2006.
- Dale RC, Church AJ, Cardoso F, Goddard E, Cox TC, Chong WK, et al.: Poststreptococcal acute disseminated encephalomyelitis with

- basal ganglia involvement and auto-reactive antibasal ganglia antibodies. *Ann Neurol* 50:588–595, 2001.
- Dale RC, Heyman I, Giovannoni G, Church AW: Incidence of anti-brain antibodies in children with obsessive-compulsive disorder. *Br J Psychiatry* 187:314–319, 2005.
- de Kleer IM, Wedderburn LR, Taams LS, Patel A, Varsani H, Klein M, et al.: CD4+CD25 bright regulatory T cells actively regulate inflammation in the joints of patients with the remitting form of juvenile idiopathic arthritis. *J Immunol* 172:6435–6443, 2004.
- Denys D, Fluitman S, Kavelaars A, Heijnen C, Westenberg H: Decreased TNF-alpha and NK activity in obsessive-compulsive disorder. *Psychoneuroendocrinology* 29:945–952, 2004.
- Diamond A, Kenney C, Jankovic J: Effect of vagal nerve stimulation in a case of Tourette's syndrome and complex partial epilepsy. *Mov Disord* 21:1273–1275, 2006.
- DiFazio MP, Morales J, Davis R: Acute myoclonus secondary to group A beta-hemolytic *Streptococcus* infection: A PANDAS variant. *J Child Neurol* 13:516–518, 1998.
- Dranitzki Z, Steiner I: PANDAS in siblings: a common risk? *Eur J Neurol* 14:e4, 2007.
- Du X, Tang Y, Xu H, Lit L, Walker W, Ashwood P, et al.: Genomic profiles for human peripheral blood T cells, B cells, natural killer cells, monocytes, and polymorphonuclear cells: Comparisons to ischemic stroke, migraine, and Tourette syndrome. *Genomics* 87:693–703, 2006.
- Efstratiou A: Group A streptococci in the 1990s. *J Antimicrob Chemother*, 45(Suppl):3–12, 2000.
- Ercan TE, Ercan G, Severge B, Arpaouz M, Karasu G: Mycoplasma pneumoniae infection and obsessive-compulsive disease: a case report. *J Child Neurol* 23:338–340, 2008.
- Ferrari M, Termine C, Franciotta D, Castiglioni E, Pagani A, Lanzi G, et al.: Dopaminergic receptor D5 mRNA expression is increased in circulating lymphocytes of Tourette syndrome patients. *J Psychiatr Res* 43:24–29, 2008.
- Gabbay V, Coffey BJ, Babb JS, Meyer L, Wachtel C, Anam S, et al.: Pediatric autoimmune neuropsychiatric disorders associated with *Streptococcus*: Comparison of diagnosis and treatment in the community and at a specialty clinic. *Pediatrics* 122:273–278, 2008.
- Gabbay V, Coffey BJ, Guttman LE, Gottlieb L, Katz Y, Babb JS, et al.: A cytokine study in children and adolescents with Tourette's disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 33:967–971, 2009.
- Garvey MA, Perlmutter SJ, Allen AJ, Hamburger S, Lougee L, Leonard HL, et al.: A pilot study of penicillin prophylaxis for neuropsychiatric exacerbations triggered by streptococcal infections. *Biol Psychiatry* 45:1564–1571, 1999.
- Garvey MA, Snider LA, Leitman SF, Werden R, Swedo SE: Treatment of Sydenham's chorea with intravenous immunoglobulin, plasma exchange, or prednisone. *J Child Neurol* 20:424–429, 2005.
- Gause C, Morris C, Vernekar S, Pardo-Villamizar C, Grados MA, Singer HS: Antineuronal antibodies in OCD: Comparisons in children with OCD-only, OCD+chronic tics and OCD+PANDAS. *J Neuroimmunol* 214:118–124, 2009.
- Gebremariam A: Sydenham's chorea: Risk factors and the role of prophylactic benzathine penicillin G in preventing recurrence. *Ann Trop Paediatr* 19:161–165, 1999.
- Giedd JN, Rapoport JL, Garvey MA, Perlmutter S, Swedo SE: MRI assessment of children with obsessive-compulsive disorder or tics associated with streptococcal infection. *Am J Psychiatry* 157:281–283, 2000.
- Giedd JN, Rapoport JL, Leonard HL, Richter D, Swedo SE: Case study: Acute basal ganglia enlargement and obsessive-compulsive symptoms in an adolescent boy. *J Am Acad Child Adolesc Psychiatry* 35:913–915, 1996.
- Goodman WK, McDougle CJ, Price LH, Riddle MA, Pauls DL, Leckman JF: Beyond the serotonin hypothesis: A role for dopamine in some forms of obsessive compulsive disorder? *J Clin Psychiatry* 51(Suppl):36–43; discussion 55–38, 1990.
- Hallett JJ, Harling-Berg CJ, Knopf PM, Stopa EG, Kiessling LS: Antistriatal antibodies in Tourette syndrome cause neuronal dysfunction. *J Neuroimmunol* 111:195–202, 2000.
- Hirschtritt ME, Hammond CJ, Luckenbaugh D, Buhle J, Thurm AE, Casey BJ, et al.: Executive and attention functioning among children in the PANDAS subgroup. *Child Neuropsychol* 15:179–194, 2009.
- Hoekstra PJ, Anderson GM, Troost PW, Kallenberg CG, Minderaa RB: Plasma kynurenine and related measures in tic disorder patients. *Eur Child Adolesc Psychiatry* 16(Suppl 1):71–77, 2007.
- Hoekstra PJ, Manson WL, Steenhuis MP, Kallenberg CG, Minderaa RB: Association of common cold with exacerbations in pediatric but not adult patients with tic disorder: A prospective longitudinal study. *J Child Adolesc Psychopharmacol* 15:285–292, 2005.
- Hoekstra PJ, Minderaa RB, Kallenberg CG: Lack of effect of intravenous immunoglobulins on tics: A double-blind placebo-controlled study. *J Clin Psychiatry* 65:537–542, 2004.
- Hoffman KL, Hornig M, Yaddanapudi K, Jabado O, Lipkin WI: A murine model for neuropsychiatric disorders associated with group A beta-hemolytic streptococcal infection. *J Neurosci* 24:1780–1791, 2004.
- Hong JJ, Loiselle CR, Yoon DY, Lee O, Becker KG, Singer HS: Microarray analysis in Tourette syndrome postmortem putamen. *J Neurol Sci* 225:57–64, 2004.
- Husby G, van de Rijn I, Zabriskie JB, Abidin ZH, Williams RC: Antibodies reacting with cytoplasm of subthalamic and caudate nuclei neurons in chorea and acute rheumatic fever. *J Exp Med* 144:1094–1110, 1976.
- Jacob CM, Pastorino AC, Fahl K, Carneiro-Sampaio M, Monteiro RC: Autoimmunity in IgA deficiency: revisiting the role of IgA as a silent housekeeper. *J Clin Immunol* 28(Suppl 1):S56–S61, 2008.
- Jin R, Zheng RY, Huang WW, Xu HQ, Shao B, Chen H, et al.: Epidemiological survey of Tourette syndrome in children and adolescents in Wenzhou of P.R. China. *Eur J Epidemiol* 20:925–927, 2005.
- Johnson DR, Kurlan R, Leckman J, Kaplan EL: The human immune response to streptococcal extracellular antigens: Clinical, diagnostic, and potential pathogenetic implications. *Clin Infect Dis* 50:481–490, 2010.
- Kansy JW, Katsovich L, McIver KS, Pick J, Zabriskie JB, Lombroso PJ, et al.: Identification of pyruvate kinase as an antigen associated with Tourette syndrome. *J Neuroimmunol* 181:165–176, 2006.
- Kantor L, Hewlett GH, Gnegy ME: Enhanced amphetamine- and K⁺-mediated dopamine release in rat striatum after repeated amphetamine: differential requirements for Ca²⁺ and calmodulin-dependent phosphorylation and synaptic vesicles. *J Neurosci* 19:3801–3808, 1999.
- Kaplan EL, Rothermel CD, Johnson DR: Antistreptolysin O and Anti-Deoxyribonuclease B titers: Normal values for children ages 2 to 12 in the United States. *Pediatrics* 101:86–88, 1998.
- Karno M, Golding JM, Sorenson SB, Burnam MA: The epidemiology of obsessive-compulsive disorder in five US communities. *Arch Gen Psychiatry* 45:1094–1099, 1988.
- Kawikova I, Grady BP, Tobiasova Z, Zhang Y, Vojdani A, Katsovich L, et al.: Children with Tourette's syndrome may suffer immunoglobulin A dysgammaglobulinemia: Preliminary report. *Biol Psychiatry* 67:679–683, 2010.
- Kawikova I, Leckman JF, Kronig H, Katsovich L, Bessen DE, Ghebremichael M, et al.: Decreased numbers of regulatory T cells suggest impaired immune tolerance in children with tourette syndrome: a preliminary study. *Biol Psychiatry* 61:273–278, 2007.

- Khalifa N, von Knorring AL: Prevalence of tic disorders and Tourette syndrome in a Swedish school population. *Dev Med Child Neurol* 45:315–319, 2003.
- Kiessling LS, Marcotte AC, Culpepper L: Antineuronal antibodies in movement disorders. *Pediatrics* 92:39–43, 1993.
- Kim HS, Park H, Cho IY, Paik HD, Park E: Dietary supplementation of probiotic *Bacillus polyfermenticus*, Bispan strain, modulates natural killer cell and T cell subset populations and immunoglobulin G levels in human subjects. *J Med Food* 9:321–327, 2006.
- Kipnis J, Cardon M, Avidan H, Lewitus GM, Mordechay S, Rolls A, et al.: Dopamine, through the extracellular signal-regulated kinase pathway, downregulates CD4+CD25+ regulatory T-cell activity: Implications for neurodegeneration. *J Neurosci* 24:6133–6143, 2004.
- Kirvan CA, Swedo SE, Heuser JS, Cunningham MW: Mimicry and autoantibody-mediated neuronal cell signaling in Sydenham chorea. *Nat Med* 9:914–920, 2003.
- Kirvan CA, Swedo SE, Kurahara D, Cunningham MW: Streptococcal mimicry and antibody-mediated cell signaling in the pathogenesis of Sydenham's chorea. *Autoimmunity* 39:21–29, 2006.
- Korn-Lubetzki I, Brand A, Steiner I: Recurrence of Sydenham chorea: Implications for pathogenesis. *Arch Neurol* 61:1261–1264, 2004.
- Kotby AA, El Badawy N, El Sokkary S, Moawad H, El Shawarby M: Antineuronal antibodies in rheumatic chorea. *Clin Diagn Lab Immunol* 5:836–839, 1998.
- Krause RM: A half-century of streptococcal research: Then now. *Indian J Med Res* 115:215–241, 2002.
- Kubera N, Lin AH, Kenis G, Bosmans E, van Bockstaele D, Maes M: Anti-inflammatory effects of antidepressants through suppression of the interferon-gamma/interleukin-10 production ratio. *J Clin Psychopharmacol* 21:199–206, 2001.
- Kuelz AK, Hohagen F, Voderholzer U: Neuropsychological performance in obsessive-compulsive disorder: A critical review. *Biol Psychol* 65:185–236, 2004.
- Kukreja A, Cost G, Marker J, Zhang C, Sun Z, Lin-Su K, et al.: Multiple immuno-regulatory defects in type-1 diabetes. *J Clin Invest* 109:131–140, 2002.
- Kurlan R, Johnson D, Kaplan EL: Streptococcal infection and exacerbations of childhood tics and obsessive-compulsive symptoms: A prospective blinded cohort study. *Pediatrics* 121:1188–1197, 2008.
- Kurlan R, Kaplan EL: The pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS) etiology for tics and obsessive-compulsive symptoms: Hypothesis or entity? Practical considerations for the clinician. *Pediatrics* 113:883–886, 2004.
- Kushner HI, Kiessling LS: The controversy over the classification of Gilles de la Tourette's syndrome, 1800–1995. *Perspect Biol Med* 39:409–435, 1996.
- Langlois M, Force L: Nosologic and clinical revision of Gilles de la Tourette disease evoked by the action of certain neuroleptics on its course. *Rev Neurol* 113:641–645, 1965.
- Leckman JF, Katsovich L, Kawikova I, Lin H, Zhang H, Kronig H, et al.: Increased serum levels of interleukin-12 and tumor necrosis factor-alpha in Tourette's syndrome. *Biol Psychiatry* 57:667–673, 2005.
- Leslie DL, Kozma L, Martin A, Landeros A, Katsovich L, King RA, et al.: Neuropsychiatric disorders associated with streptococcal infection: A case-control study among privately insured children. *J Am Acad Child Adolesc Psychiatry* 47:1166–1172, 2008.
- Lin H, Katsovich L, Ghebremichael M, Findley DB, Grantz H, Lombroso PJ, et al.: Psychosocial stress predicts future symptom severities in children and adolescents with Tourette syndrome and/or obsessive-compulsive disorder. *J Child Psychol Psychiatry* 48:157–166, 2007.
- Lin H, Williams KA, Katsovich L, Findley DB, Grantz H, Lombroso PJ, et al.: Streptococcal upper respiratory tract infections and psychosocial stress predict future tic and obsessive-compulsive symptom severity in children and adolescents with Tourette syndrome and obsessive-compulsive disorder. *Biol Psychiatry* 67:684–691, 2009.
- Lit L, Gilbert DL, Walker W, Sharp FR: A subgroup of Tourette's patients overexpress specific natural killer cell genes in blood: A preliminary report. *Am J Med Genet B Neuropsychiatr Genet* 144B:958–963, 2007.
- Loiselle CR, Lee O, Moran TH, Singer HS: Striatal microinfusion of Tourette syndrome and PANDAS sera: Failure to induce behavioral changes. *Mov Disord* 19:390–396, 2004.
- Lougee L, Perlmuter SJ, Nicolson R, Garvey MA, Swedo SE: Psychiatric disorders in first-degree relatives of children with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS). *J Am Acad Child Adolesc Psychiatry* 39:1120–1126, 2000.
- Luo F, Leckman JF, Katsovich L, Findley D, Grantz H, Tucker DM, et al.: Prospective longitudinal study of children with tic disorders and/or obsessive-compulsive disorder: relationship of symptom exacerbations to newly acquired streptococcal infections. *Pediatrics* 113:e578–e585, 2004.
- Martino D, Church AJ, Dale RC, Giovannoni G: Antibasal ganglia antibodies and PANDAS. *Mov Disord* 20:116–117, 2005.
- Martino D, Defazio G, Church AJ, Dale RC, Giovannoni G, Robertson MM, et al.: Antineuronal antibody status and phenotype analysis in Tourette's syndrome. *Mov Disord* 22:1424–1429, 2007.
- Martino D, Defazio G, Giovannoni G: The PANDAS subgroup of tic disorders and childhood-onset obsessive-compulsive disorder. *J Psychosom Res* 67:547–557, 2009.
- Matarese G, Carrieri PB, La Cava A, Perna F, Sanna V, De Rosa V, et al.: Leptin increase in multiple sclerosis associates with reduced number of CD4(+)CD25+regulatory T cells. *Proc Natl Acad Sci USA* 102:5150–5155, 2005.
- Matsuo M, Tsuchiya K, Hamasaki Y, Singer HS: Restless legs syndrome: Association with streptococcal or mycoplasma infection. *Pediatr Neurol* 31:119–121, 2004.
- McDonald MI, Towers RJ, Andrews RM, Bengner N, Currie BJ, Carapetis JR: Low rates of streptococcal pharyngitis and high rates of pyoderma in Australian aboriginal communities where acute rheumatic fever is hyperendemic. *Clin Infect Dis* 43:683–689, 2006.
- Mell LK, Davis RL, Owens D: Association between streptococcal infection and obsessive-compulsive disorder, Tourette's syndrome, and tic disorder. *Pediatrics* 116:56–60, 2005.
- Mercadante MT, Busatto GF, Lombroso PJ, Prado L, Rossario-Campos MC, do Valle R, et al.: The psychiatric symptoms of rheumatic fever. *Am J Psychiatry* 157:2036–2038, 2000.
- Miettinen M, Matikainen S, Vuopio-Varkila J, Pirhonen J, Varkila K, Kurimoto M, et al.: Lactobacilli and streptococci induce interleukin-12 (IL-12), IL-18, and gamma interferon production in human peripheral blood mononuclear cells. *Infect Immun* 66:6058–6062, 1998.
- Mittleman BB, Castellanos FX, Jacobsen LK, Rapoport JL, Swedo SE, Shearer GM: Cerebrospinal fluid cytokines in pediatric neuropsychiatric disease. *J Immunol* 159:2994–2999, 1997.
- Moller JC, Tackenberg B, Heinzl-Gutenbrunner M, Burmester R, Oertel WH, Bandmann O, et al.: Immunophenotyping in Tourette syndrome—A pilot study. *Eur J Neurol* 15:749–753, 2008.
- Monteleone P, Catapano F, Fabrazzo M, Tortorella A, Maj M: Decreased blood levels of tumor necrosis factor-alpha in patients with obsessive-compulsive disorder. *Neuropsychobiology* 37:182–185, 1998.
- Morer A, Lazaro L, Sabater L, Massana J, Castro J, Graus F: Antineuronal antibodies in a group of children with obsessive-compulsive disorder and Tourette syndrome. *J Psychiatr Res* 42:64–68, 2008.

- Morer A, Wookjin C, Henegariu O, Bothwell ALM, Leckman JF, Kawikova I: Elevated expression of MCP-1, IL-2 and PTPR-N in basal ganglia of Tourette syndrome cases. *Brain Behav Immun* 2010 Mar 1 [Epub ahead of print].
- Morris CM, Pardo-Villamizar C, Gause CD, Singer HS: Serum autoantibodies measured by immunofluorescence confirm a failure to differentiate PANDAS and Tourette syndrome from controls. *J Neurol Sci* 276:45–48, 2009.
- Morshed SA, Parveen S, Leckman JF, Mercadante MT, Bittencourt Kiss MH, Miguel EC, et al.: Antibodies against neural, nuclear, cytoskeletal, and streptococcal epitopes in children and adults with Tourette's syndrome, Sydenham's chorea, and autoimmune disorders. *Biol Psychiatry* 50:566–577, 2001.
- Murphy ML, Pichichero ME: Prospective identification and treatment of children with pediatric autoimmune neuropsychiatric disorder associated with group A streptococcal infection (PANDAS). *Arch Pediatr Adolesc Med* 156:356–361, 2002.
- Murphy TK, Husted DS, Edge PJ: Preclinical/Clinical Evidence of Central Nervous System Infectious Etiology in PANDAS. In: *Advances in Neurology: Tourette Syndrome*, Vol. 99, edited by J.T. Walkup, J.W. Mink, P.J. Hollenbeck. Philadelphia: Lippincott Williams Wilkins, 148–158, 2006.
- Murphy TK, Sajid M, Soto O, Shapira N, Edge P, Yang M, et al.: Detecting pediatric autoimmune neuropsychiatric disorders associated with *Streptococcus* in children with obsessive-compulsive disorder and tics. *Biol Psychiatry* 55:61–68, 2004.
- Murphy TK, Snider LA, Mutch PJ, Harden E, Zaytoun A, Edge PJ, et al.: Relationship of movements and behaviors to Group A *Streptococcus* infections in elementary school children. *Biol Psychiatry* 61:279–284, 2007.
- Murr C, Gerlach D, Widner B, Dierich MP, Fuchs D: Neopterin production and tryptophan degradation in humans infected by *Streptococcus pyogenes*. *Med Microbiol Immunol (Berl)* 189:161–163, 2001.
- Nicolson R, Swedo SE, Lenane M, Bedwell J, Wudarsky M, Gochman P, et al.: An open trial of plasma exchange in childhood-onset obsessive-compulsive disorder without poststreptococcal exacerbations. *J Am Acad Child Adolesc Psychiatry* 39:1313–1315, 2000.
- Norhagen G, Engstrom PE, Hammarstrom L, Soder PO, Smith CI: Immunoglobulin levels in saliva in individuals with selective IgA deficiency: Compensatory IgM secretion and its correlation with HLA and susceptibility to infections. *J Clin Immunol* 9:279–286, 1989.
- Paluck E, Katzenstein D, Frankish CJ, Herbert CP, Milner R, Speert D, et al.: Prescribing practices and attitudes toward giving children antibiotics. *Can Fam Physician* 47:521–527, 2001.
- Pavone P, Bianchini R, Parano E, Incorpora G, Rizzo R, Mazzone L, et al.: Anti-brain antibodies in PANDAS versus uncomplicated streptococcal infection. *Pediatr Neurol* 30:107–110, 2004.
- Perlmutter SJ, Leitman SF, Garvey MA, Hamburger S, Feldman E, Leonard HL, et al.: Therapeutic plasma exchange and intravenous immunoglobulin for obsessive-compulsive disorder and tic disorders in childhood. *Lancet* 354:1153–1158, 1999.
- Perrin EM, Murphy ML, Casey JR, Pichichero ME, Runyan DK, Miller WC, et al.: Does group A beta-hemolytic streptococcal infection increase risk for behavioral and neuropsychiatric symptoms in children? *Arch Pediatr Adolesc Med* 158:848–856, 2004.
- Peterson BS, Leckman JF, Tucker D, Scahill L, Staib L, Zhang H, et al.: Preliminary findings of antistreptococcal antibody titers and basal ganglia volumes in tic, obsessive-compulsive, and attention deficit/hyperactivity disorders. *Arch Gen Psychiatry* 57:364–372, 2000.
- Pittenger C, Krystal JH, Coric V: Glutamate-modulating drugs as novel pharmacotherapeutic agents in the treatment of obsessive-compulsive disorder. *NeuroRx* 3:69–81, 2006.
- Puxley F, Midtsund M, Iosif A, Lask B: PANDAS anorexia nervosa—Endangered, extinct or nonexistent? *Int J Eat Disord* 41:15–21, 2008.
- Read SE, Reid HF, Fischetti VA, Poon-King T, Ramkissoon R, McDowell M, et al.: Serial studies on the cellular immune response to streptococcal antigens in acute and convalescent rheumatic fever patients in Trinidad. *J Clin Immunol* 6:433–441, 1986.
- Renneberg J, Soderstrom M, Prellner K, Forsgren A, Christensen P: Age-related variations in anti-streptococcal antibody levels. *Eur J Clin Microbiol Infect Dis* 8:792–795, 1989.
- Roberts-Lewis JM, Welsh MJ, Gnegy ME: Chronic amphetamine treatment increases striatal calmodulin in rats. *Brain Res* 384:383–386, 1986.
- Rothstein JD, Patel S, Regan MR, Haenggeli C, Huang YH, Bergles DE, et al.: Beta-lactam antibiotics offer neuroprotection by increasing glutamate transporter expression. *Nature* 433:73–77, 2005.
- Sabharwal H, Michon F, Nelson D, Dong W, Fuchs K, Manjarrez RC, et al.: Group A *Streptococcus* (GAS) carbohydrate as an immunogen for protection against GAS infection. *J Infect Dis* 193:129–135, 2006.
- Sanchez-Carpintero R, Albesa SA, Crespo N, Villoslada P, Narbona J: A preliminary study of the frequency of anti-basal ganglia antibodies and streptococcal infection in attention deficit/hyperactivity disorder. *J Neurol* 256:1103–1108, 2009.
- Scahill L, Erenberg G, Berlin CM Jr., Budman C, Coffey BJ, Jankovic J, et al.: Contemporary assessment and pharmacotherapy of Tourette syndrome. *NeuroRx* 3:192–206, 2006.
- Schrag A, Gilbert R, Giovannoni G, Robertson MM, Metcalfe C, Ben-Shlomo Y: Streptococcal infection, Tourette syndrome, and OCD: Is there a connection? *Neurology* 73:1256–1263, 2009.
- Segarra AR, Murphy TK: Cardiac involvement in children with PANDAS. *Journal of the American Academy of Child and Adolescent Psychiatry* 47:603–604, 2008.
- Sela S, Neeman R, Keller N, Barzilai A: Relationship between asymptomatic carriage of *Streptococcus pyogenes* and the ability of the strains to adhere to and be internalised by cultured epithelial cells. *J Med Microbiol* 49:499–502, 2000.
- Selling L: The role of infection in the etiology of tics. *Arch Neurol Psychiatry* 22:1163–1171, 1929.
- Shet A, Kaplan EL: Clinical use and interpretation of group A streptococcal antibody tests: a practical approach for the pediatrician or primary care physician. *Pediatr Infect Dis J* 21:420–426; quiz 427–430, 2002.
- Singer HS, Gause C, Morris C, Lopez P: Serial immune markers do not correlate with clinical exacerbations in pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections. *Pediatrics* 121:1198–1205, 2008.
- Singer HS, Giuliano JD, Zimmerman AM, Walkup JT: Infection: A stimulus for tic disorders. *Pediatr Neurol* 22:380–383, 2000.
- Singer HS, Hong JJ, Yoon DY, Williams PN: Serum autoantibodies do not differentiate PANDAS and Tourette syndrome from controls. *Neurology* 65:1701–1707, 2005.
- Singer HS, Loiselle CR, Lee O, Minzer K, Swedo S, Grus FH: Anti-basal ganglia antibodies in PANDAS. *Mov Disord* 19:406–415, 2004.
- Singer HS: PANDAS and immunomodulatory therapy. *Lancet* 354:1137–1138, 1999.
- Snider LA, Lougee L, Slattery M, Grant P, Swedo SE: Antibiotic prophylaxis with azithromycin or penicillin for childhood-onset neuropsychiatric disorders. *Biol Psychiatry* 57:788–792, 2005.
- Snider LA, Sachdev V, MaCkaronis JE, St. Peter M, Swedo SE: Echocardiographic findings in the PANDAS subgroup. *Pediatrics* 114:e748–e751, 2004.
- Sokol MS: Infection-triggered anorexia nervosa in children: Clinical description of four cases. *J Child Adolesc Psychopharmacol* 10:133–145, 2000.

- Storch EA, Murphy TK, Geffken GR, Mann G, Adkins J, Merlo LJ, et al.: Cognitive-behavioral therapy for PANDAS-related obsessive-compulsive disorder: Findings from a preliminary waitlist controlled open trial. *J Am Acad Child Adolesc Psychiatry* 45:1171–1178, 2006.
- Swedo SE, Leonard HL, Garvey M, Mittleman B, Allen AJ, Perlmutter S, et al.: Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: Clinical description of the first 50 cases. *Am J Psychiatry* 155:264–271, 1998.
- Swedo SE, Leonard HL: Childhood movement disorders and obsessive compulsive disorder. *J Clin Psychiatry* 55(Suppl):32–37, 1994.
- Tait AS, Butts CL, Sternberg EM: The role of glucocorticoids and progestins in inflammatory, autoimmune, and infectious disease. *J Leukoc Biol* 84:924–931, 2008.
- Tang Y, Gilbert DL, Glauser TA, Hershey AD, Sharp FR: Blood gene expression profiling of neurologic diseases: a pilot microarray study. *Arch Neurol* 62:210–215, 2005.
- Taylor JR, Morshed SA, Parveen S, Mercadante MT, Scahill L, Peterson BS, et al.: An animal model of Tourette's syndrome. *Am J Psychiatry* 159:657–660, 2002.
- Terrerri MT, Roja SC, Len CA, Faustino PC, Roberto AM, Hilario MO: Sydenham's chorea—Clinical and evolutive characteristics. *Sao Paulo Med J* 120:16–19, 2002.
- Thomsen PH, Mikkelsen HU: Course of obsessive-compulsive disorder in children and adolescents: a prospective follow-up study of 23 Danish cases. *J Am Acad Child Adolesc Psychiatry* 34:1432–1440, 1995.
- Tucker DM, Leckman JF, Scahill L, Wilf GE, LaCamera R, Cardona L, et al.: A putative poststreptococcal case of OCD with chronic tic disorder, not otherwise specified. *J Am Acad Child Adolesc Psychiatry* 35:1684–1691, 1996.
- Woof JM, Kerr MA: The function of immunoglobulin A in immunity. *J Pathol* 208:270–282, 2006.
- Yaddanapudi K, Hornig M, Serge R, De Miranda J, Baghban A, Villar G, et al.: Passive transfer of *Streptococcus*-induced antibodies reproduces behavioral disturbances in a mouse model of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection. *Mol Psychiatry* 15:712–726, 2009.

Address correspondence to:

Tanya K. Murphy, M.D.

Department of Pediatrics and Psychiatry

University of South Florida

800 6th St. South, Box 7523

St. Petersburg, FL 33701

E-mail: tmurphy@health.usf.edu

