

CT General Assembly
Insurance & Real Estate Committee Public Hearing

Testimony in Support of **SB 206, AAC Health Insurance Coverage for Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal Infections.**

By Lynn Johnson
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Just a little over a year ago, my 12 year old daughter, Lauren ran up and down the streets of her neighborhood "trick-or-treating" with her friends-laughing and smiling!

Who could have predicted her life would be forever be altered when she woke up the next morning. As my daughter sat on the floor of our living room, happily trading her candy with her friends, there were unknown changes occurring in her body and brain. As Lauren slept that night, her condition would manifest into a little known disease we now call PANDAS/PANS. Lauren awoke the next day literally sneezing 25,000x a day! A violent vocal tic that left her home bound and completely non-functional. Her life had been forever altered overnight.

Over the next few weeks; dozens of doctors would be unsuccessful in trying to help Lauren. Her story quickly gained the local, national and even worldwide media attention. Soon after, she would be correctly diagnosed with this autoimmune disorder and get the help she desperately needs. To our surprise we quickly learned that Lauren is not alone. She doesn't suffer from some "rare disorder" but from a rarely known disorder that is rarely, correctly diagnosed. The IVIG (intravenous immunoglobulin) treatment she desperately needed was scheduled to take place within a few weeks.

On the eve of the day my daughter received that IVIG treatment; I sat in a small cafe with Lauren's wonderful, caring, brilliant immunologist, Dr. Denis Bouboulis and made a commitment to create an organization where families, physician's and other healthcare providers could come together to find hope and healing. The morning after, my daughter woke up symptom free, no more sneezing tic. It was completely gone. Her treatment was a complete success.

Since we began the PANDAS Resource Network, just 22 short months ago, our community is now over 4000 families strong. Our families come from every corner of the country and many parts of the world.

My daughters story and Nicole Terry's story is just a small glimpse inside view of a ballooning epidemic called PANS.

As Thousands of children with PANDAS are still suffering. They go from doctor to doctor looking for answers, they are misdiagnosed, therefore unsuccessfully treated.

If and when they finally find the correct diagnosis of PANS/PANDAS they travel across the country to get treatment from the less than a dozen physicians who understand how to effectively treat this disorder. The physical emotional and financial impact these families endure is indescribable.

The numbers of children affected by this devastating disorder is shocking. NIH Senior Investigator, Dr. Susan Swedo, (who discovered PANDAS) estimates that 5% of the pediatric population suffers from PANDAS; yet, most are undiagnosed or misdiagnosed. I guarantee you as you sit here and listen to my testimony there is someone very close to you that suffers from this disorder; they just don't know it yet.

Over the past few years, physicians and researchers have discovered that there are many common childhood illnesses that cause PANDAS; hence there is a new acronym in place; PANS (Pediatric Acute Neuropsychiatric Disorder) .We also learned that among our family members, almost 50% of PANDAS families have more than one child affected by PANDAS and/or have a combination of these infections that can lead to PANDAS, such as Strep, Mycoplasma Pneumoniae and Lyme. Again, these children suffer for years un-diagnosed therefore untreated.

What further compounds PANDAS/PANS is that even when a parent successfully finds a correct diagnosis, even if they travel far to treatment their child needs, it is often denied by insurance companies on the basis that there is not enough research to support the medically necessity, yet.

Like my daughter and others; I wonder how many children will become severely disabled in their prime of life because of physician ignorance to correctly diagnose and insurance denials for effective treatment.

I entreat this panel to step up to the challenge to help these families in despair.

Studies show that our PANDAS children are profoundly ill. Yet only 1 randomized clinical trial that has shown that IVIG treatment IS in fact effective, has been done to date and a duplicate study is currently underway.

What should we do in the face of this uncertainty? When science is uncertain, who decides what to do? Do patients get treated or are they abandoned and told to wait for research that, in the case of PANDAS, may be years in the making? To illustrate the point, I'd like to use the example of an upper GI (gastro-intestinal) bleed. Suppose there are two treatment options, but there is insufficient evidence to support either one? Still, the patient with an upper GI bleed must be treated. To do otherwise, might risk death or serious disability for the patient. Such is the case with PANDAS/PANS.

Faced with the challenging task of diagnosing and choosing treatment options for disorders and disease in the light of our world of constant change with new

research. In a world where there are medical breakthroughs and new answers on a continuing basis. Dr.'s are making these decisions with their patients based on the knowledge they have knowing the situation on a personal, intimate level. These physician are not "self-proclaimed" specialists but highly respected doctors who are willing to dedicate their life to continuous research and education so they can best meet the need of this growing epidemic.

I hope you will find by my testimony today and the many pieces of information & stories I have provided, useful. Some of these stories are success stories post treatment. Some are desperate pleas for help and frustration from families who still struggle to find hope and healing.

Our PANDAS families are the pioneers in understanding this disorder and our goal is that our children's children will not have to face the same challenges and obstacles to receive accurate diagnosis and obtain effective treatment. I humbly ask the General Assembly today, how can we leave these children suffering?

Respectfully Submitted,

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PANDAS/PANS Information for physician's/other healthcare providers

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Sydenham Chorea (SC) and Rheumatic Fever (RF), OCD and related conditions including Tourette's disorder (TD) affect 0.3-3% of children. These conditions share a common anatomic area of the brain: the basal ganglia and the cortical and thalamic sites.

Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus □ A history of reported cases of these illnesses with streptococcus (GAS) infections goes back to 1929 and have been debated as incurable by some and curable by a few others for several decades. In the late 1980's the argument reappeared with various studies including Dr. Sue Swedo's work in 1994 (Swedo □ and Leonard 1994; Allen et al, 1995).

Preliminary criteria to diagnose PANDAS included 1) existence of OCD or tic, 2) prepubertal onset, 3) symptoms occurring intermittently or following a sawtooth course, 4) relationship of OCD/Tic symptoms to GAS infection, 5) presence of neurological findings such as hyperactivity or choreiform movements.

What does the Phenotype for PANDAS Look Like? PANDAS versus OCD tends to be associated with greater prevalence of the following:

- separation anxiety
- nightmares
- personality change
- rage episodes
- psychotic symptoms
- oppositional behaviors
- deterioration in handwriting and math skills
- ADHD-like symptoms
- choreiform movements milder than Sydenham's Chorea
- neurological soft signs
- anorexia nervosa
- spasmodic torticollis (neck movements) or dysphonia (vocal quality)

Classically PANDAS presentation is with previously high-functioning and well-adjusted children having a severe behavioral change within 24-72 hours. The symptoms may diminish within 6 to 8 weeks. Sometimes they may never reappear. For others, episodic exacerbations may occur sometimes with resolution but other times with more impairment and severity with each exacerbation.

Typically PANDAS has been thought to occur within a few days of a GAS infection. If longer time elapse than this there may be subclinical strep. Longer lag times of several months are well documented with RF and SC cases.

GAS (Group A Strep) Infections

GAS is capable of a wide range of illnesses. Strains of strep have been changing. Most recent strains have developed ways of avoiding the immune system defenses, i.e., new strains have a capsule formation (Bismo et al 2003). There is an increased incidence and severity of strep and perhaps the bacteria is more virulent with the strains that present with minimal symptoms of pharyngitis (Krause 2002).

Link between GAS and OCD/ Tics

There is a gap between public awareness of this illness (100,000 sites or links via the Internet) and scientific knowledge and conclusive evidence. Administrative Healthcare Data

The strongest evidence for GAS involvement in the onset of TD and OCD comes from....(Mell et al 2005). They conducted a case control of 144 children. Patients with OCD or tic disorder were more likely than controls to have had strep in the 3 months before onset date. Further studies should examine this relationship further.

Serologic and Prospective Studies

A discussion of the complexity of difficulty in correctly documenting GAS infections. A GAS infection is not considered to be strong enough evidence (by some) because many children may be strep carriers.

Many parents site the NIMH website information on PANDAS is flawed because the current NIMH guidelines for PANDAS ask that a baseline of strep titers be known of the PANDAS child before administering antibiotics. Finding the baseline is very near impossible for most patients because:

- Most clinicians will not give the blood test (titer levels of ASO and D-nase) and then re-administer the blood test 6 to 8 weeks later when there is often a rise in titer levels. Many PANDAS children do not get the level of documentation needed by the current NIMH guidelines.
- For some patients with PANDAS symptoms emerge only after repeated GAS infections over a short period of time. The risk of developing tics appears to increase with children that have frequent GAS infections (Mell et al 2005). A study following 693 children showed an increase in behavioral and motoric symptoms with repeated strep infections (Murphy et al 2007).
- It suggests a cumulative threshold of antibody is needed to trigger symptoms in some patients.
- PANDAS is likely a gamut of genetic issues, immune vulnerability/resistance genes, immune system, cellular immunity, familial risk histories, environmental risks, and strep serotype pathogens.

Studies Examining the Humoral Response to tics, OCD, PANDAS, and SC

1) The predominating theory to explain the pathophysiology behind PANDAS is molecular mimicry. Antibodies from the child intended to target GAS instead target brain proteins. Potentially the antibodies affect the Central Nervous System (CNS) by way of direct stimulation OR blocking of receptors in the basal ganglia. □ 2) Anti-neuronal (misbehaving) antibodies were found in one study to bind to the basal ganglia tissue in both PANDAS, ADHD and SC patients. □ 3) Anti-neuronal antibodies directed against the D1 and D2 brain receptors have also been detected in PANDAS blood serum (Cunningham and Perry 2008). □ 4) The binding of these anti-neuronal antibodies to strep and then neuronal cells may promote signal transduction (confusion!) which leads to exciting of neurotransmitters, and may explain... the symptoms of SC and PANDAS. □ 5) Some of these misbehaving auto-antibodies to basal ganglia are found in the blood sera of most TD, OCD, SC, and PANDAS subjects. □ 6) A recent study suggests that there may be a subgroup of TD patients who have an enhanced immune response to GAS which is consistent with the PANDAS hypothesis. □ 7) Finally, in a recent preliminary study (Kawikova et al 2010) – the plasma of 24 TD/OCD patients immunoglobulin levels were analyzed for IgG, IgM, IgA against antigens previously identified in multiple sclerosis and SC. The total IgA in the 24 patients was significantly decreased in the patients. This may be considered IgA dysgammaglobulinemia which may contribute to poor immune responses due to 1) the IgA in plasma may reduce beneficial immune responses and 2) IgA protective secretions could also be affected.

Studies Examining Cellular Responses in tics, OCD, and/or PANDAS

Typically autoimmune diseases result from the breakdown of the immune process which suppress the T-cell and B-cell activity. □ 1) Reduced numbers of T-regulatory (Tregs) cells are detected in autoimmune illnesses. Lower Tregs were found in the blood of 37 children with TD and/or OCD (Kawikova 2007). The reduction was even greater in TD children who were experiencing higher symptom severity. □ 2) Also, increased B-cell activation has been found that also increases T-cell lymphocytes. □ 3) Increased inflammatory mechanisms have been found in TD plasma.

Immune Gene Expression Profiling in Peripheral Blood Cells and in the Basal Ganglia

There is evidence of a genetic component in TD patients. It is unclear if any of these patients are actually PANDAS cases. However, it is clear that family history of PANDAS cases is largely indistinguishable from that seen in TD or pediatric-onset OCD cases (Lougee et al 2000).

Research on TD

There is evidence that indicates immune mechanisms may play a role in TD. In a preliminary report a subgroup of TD patients expressed genes that overreacted in the control of natural killer cells and other immune markers. Also, preliminary data support dysregulation in several cell inflammatory mechanisms which are directly linked to the basal ganglia.

Animal Models

Immune based animal models have mixed results. However, (Hoffman et al 2004) reported behavioral abnormalities that were PANDAS-like, in mice that were autoimmune compromised and then injected

with GAS.

Also, (Yaddanapudi et al 2009) – extended this model to examining the peripheral anti-Central Nervous System antibodies. Their results demonstrated that the strep injected mice had deficits in motor coordination, learning/memory, and social interaction. Depleting the infected IgG (immunoglobulin) from the mice than eliminated the abnormal behaviors.

A New Model of PANDAS Pathogenesis

Emerging data indicate: 1) PANDAS cases are more vulnerable to GAS infections; 2) Cross-reactive antibodies can induce dopamine release and interact with D2 brain receptors; and 3) There are powerful links to dopamine in SC and PANDAS.

1) Some of the most exciting recent data comes from Dr. Madeline Cunningham's laboratory that demonstrates that cross-reactive antibodies (misbehaving) found in PANDAS cases can directly interact, and likely activate the dopamine D2 receptor (Cunningham and Perry 2008). If confirmed in future studies, this suggests that various receptors are altering the blood brain barrier and altering cognition and behavior as has been found in prior work by (Diamond et al 2006).

Furthermore if there is an:

2) Increase in dopamine there is an elevation in inflammatory cells and lowering of positive T-regulatory (Treg) activity. (Kawikova et al 2007) has shown that TD cases do have lower Treg cells during exacerbations. This would then increase the likelihood of a negative Central Nervous System response.

3) Finally, if PANDAS cases do suffer a relative dysgammaglobulinemia (Kawikova et al 2010) this could account for their greater vulnerability to GAS infections.

Please note: Dysgammaglobulinemia is diagnosed by an immunologist who looks at the total IgG in a child and a several other factors – lymphocytes, cytokines, etc. If this is diagnosed a child gets IVIG. Usually the symptoms are failure to thrive and very low IgG level to name a few—at a very young age. PANDAS kids may be borderline to this actual diagnosis but it explains to many of us parents — -why IVIG has worked.

The Role of Psychosocial Stress

In some cases, OCD onset is preceded by a stressful or traumatic event. Clinical observations in TD and early-onset OCD cases consistently suggest these children are sensitive to psychosocial stress.

Increases in tics and OCD did not occur with every new GAS infection. But where there were further GAS infections – the symptom severity increased.

Neurological and Cardiac Concerns

The average areas of brain size of 34 children with possible PANDAS were significantly greater in the: caudate, putamen and globus pallidus (but not the thalamus or total cerebrum). These findings are consistent with the hypothesis of an autoimmune response to strep infections.

Only recently has it been noticed that there is a worsening of Neurological function following the onset of OCD or tics in PANDAS children. Neurological soft signs, i.e., choreiform movements, pronator drift (weakness in extension of limbs) (Murphy et al 2000). In Rheumatic Fever, similar neurological symptoms occur many days or weeks after the infection (up to 4 months) (Mercadante et al 2000).

In addition, reports suggest other neurological signs not of an SC origin: myoclonus (sudden jerking), restless leg syndrome. IT IS THE ABSENCE OF FRANK CHOREA and CARDITIS that differentiates PANDAS from SC. IF THERE IS PROMINENT PRESENTATION OF: Chorea, Cardiac findings, or Arthritis – further assessment is needed to rule out Rheumatic Fever.

Evaluation and Treatment

Instructions to Physicians

A recent review of children diagnosed with PANDAS did not meet the NIH criteria (Gabby et al 2008).

During history intake the following questions should be asked of patient: Have there been repeat and frequent infections (not just strep; evidence of GAS infection (in young child it could manifest as abdominal pain and fever), scarlet fever; brief episodes of tics, OCD or compulsive urination which remitted; especially sudden onset of tics or OCD accompanying an illness?

If there are abnormal neurological symptoms – further examine the child.

At onset: AT LEAST conduct a throat culture that will rule out subclinical GAS infections. Do a blood draw and get the titer level and repeat 4 to 6 weeks after the onset as they will rise at this time. If the onset exceeds 4 weeks from an illness the titers may or may not be raised – but this doesn't rule out PANDAS.

Antibiotics There is scant research on the efficacy of antibiotics for the illness of Sydenham Chorea (SC). However, prophylactic antibiotics seem to successfully stop or reduce the physical and neuropsychiatric symptoms of SC. In SC the antibiotics are taken until late teens. If prophylaxis antibiotics significantly reduce recurrence and/or exacerbation of OCD/tic symptoms this supports the role for infectious agents in the onset or worsening of these conditions.

To date small studies have looked at the use of: penicillin, azithromycin, beta-lactin antibiotics may be superior to penicillin – the studies indicate these antibiotics can be safe and effective.

Further studies need to be done on the efficacy of each type of antibiotic in the improvement of neuropsychiatric symptoms.

The antibiotics may be acting in a non-antimicrobial manner. Anecdotal reports (from parents to physicians) of improvement of PANDAS after 2 to 6 weeks of antibiotics are intriguing and suggest mechanisms besides prevention of GAS. Further studies need to be done to look at why this has worked for many children.

Why sustained antibiotics may work:

- 1) It lessens the load antigens from undetected or intracellular GAS;
- 2) Penicillin may reduce inflammatory cytokines;
- 3) Repeated GAS infections lead to tryptophan degradation which then inhibits serotonin (mood lability issues ensue if this occurs);
- 4) Glutamate transporters (GT) may be at work in neurological symptoms and antibiotics like ceftriaxone and penicillin may improve PANDAS symptoms (Rothstein et al 2005).

Widespread use of antibiotics for PANDAS needs to be further studied. There has been some adverse affects of PANDAS children using SSRI's (Murphy et al 2006) – but CBT can be helpful to teach coping mechanisms.

IMMUNOMODULATING TREATMENTS FOR PANDAS

The IVIG study of 30 children by (Perlmutter et al 1999) showed that 82% maintain very much improved from PANDAS symptoms. This study was very criticized. Where there is not a clear PANDAS onset – phoresus or IVIG has not been helpful. A LARGER IVIG study is underway to investigate these findings.

There has not been a study using prednisone use for PANDAS. However, in a study looking at SC (Garvey et al 2005) – it was helpful but not as effective as phoresus or IVIG.

FUTURE RESEARCH DIRECTIVES

There are many studies looking at PANDAS but little consistency across studies. The onset and exacerbation criteria for studies must go beyond the reviewing the change OCD and tic symptom alone.

Assessment methodologies must be refined to classify PANDAS versus need to be uniform. (Swedo et al, 1998, Murphy and Pichichero, 2002) outlined the following at onset of PANDAS: sudden increase in severity of psychiatric comorbidity including emotional lability, intense anxiety, cognitive deficits, oppositional behaviors, frequent urination, motoric hyperactivity, and/or dysgraphia .

Studies need to include: immune markers, volumetric brain imaging of the basal ganglia, IVIG and Phoresus studies.

Some caveats need to be looked at:

- It is possible that some forms of TD may involve immune abnormalities that are not byproducts of reaction to GAS infections.
- The role immunological factors of children with OCD and TD in general should be identified.
- Elevated GAS titers in children with sudden onset of OCD or Tic symptoms only (without PANDAS criteria being met) does not mean that the eradication of the GAS infection will stop the OCD or TIC symptoms.

Further studies should also be done of children who do not present with abrupt onset of PANDAS like symptoms but are atypical – meaning they gradually do present with neuropsychiatric symptoms (personality change, psychosis, intense anxiety, loss of academic skills, dysgraphia, etc.).

Research Information (click on the [blue hyperlinks](#) to open research paper(s))

Here you will find chronology and the short summary of each paper in case starting with early insights by Husby in 1976 and then the recent work on passive transfer in 2009. If you click on the [underlined words](#), you'll be taken to the relevant papers. □ □ **Discovery of anti-neural antibodies with GABHS**

In 1976, [Husby](#) found that antibodies to GABHS bonded with neuronal tissue in the caudate nucleus (basal ganglia).

- He noted that this binding was found for strep of emm-type 6, 11, and 12.
- He also noted that the reaction did not occur in rabbit brains but only human neural tissue.
- 46% of sera from 30 children with rheumatic chorea showed IgG antibody reacting with neuronal cytoplasm of human caudate and subthalamic nuclei.
- The antibody was also detected in 14% of 50 children with active rheumatic carditis. 203 controls showed no such antibody response.

In 1977-1979, Husby found these antibodies were pronounced in [Huntington's Chorea](#) and in [Sydenham Chorea](#) □ □ [ARF and the D8/17 marker](#) □ □ In 1989 [Swedo](#) published her study looking at 70 children with OCD over a ten year period where she noted the incredible similarity in symptoms. □ □ By 1993, [Bronze and Dale](#) published their findings that neural tissue had cross reactivity with antibodies to the M protein from strep emm-type 6. This was essentially a rediscovery of Husby but with the further isolation that the antibodies were to the M protein. □ □ In 1994, Swedo published a fascinating paper entitled "[Speculations on antineuronal antibody-mediated neuropsychiatric disorders of childhood](#)" where she proposed the hypothesis that neurological abnormalities of childhood may be caused by antineuronal antibodies resulting from a GABHS infection. This seemed to combine Husby's and Bronze and Dale's theories together. □ □ In 1995, [Swedo and Allen](#) found 4 children who exhibited sudden onset OCD symptoms coincident with infections. Two of the children had exacerbations coincident with GABHS infections and two with viral infections. Treatment with plasmapheresis, IVIG and prednisone were all found effective. They called this treatable subset of OCD, **PITAND** (pediatric infection-triggered auto-immune neuropsychiatric disorder). □ □ In 1997, [Swedo](#) found that the D8/17 marker from [Khanna \(1989\) work on Acute Rheumatic Fever](#) seemed to correlate and support the theory of a distinct genetic pre-disposition for OCD and chorea. She labeled this distinct OCD subgroup **PANDAS** – in case you wondered where the term came in. □ □ **IVIG and Plasmapheresis** □ □ In 1998, [Swedo](#) published the landmark paper entitled "Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: clinical description of the first 50 cases." In which they separated and defined a clinical subgroup of OCD patients. □ □ Challenges to the definition came out almost immediately, most notably from Singer and [Kurlan](#) who had been studying Tourettes Syndrome and did not think that the definition properly separated the group from children with TS. This has essentially been the argument for the last decade. Singer/Kurlan testing TS kids and Swedo testing the PANDAS subgroup of OCD kids. □ In 1999, [Perlmutter and Swedo](#) conducted a blinded placebo controlled study that demonstrated that IVIG and Plasmapheresis reduced symptoms by some 45 and 50% respectively for the PANDAS subgroup. A later study by [Nicolson](#) showed no improvement for OCD and TS patients who did not fit the PANDAS subgroup (i.e., no post-streptococcal exacerbations). □ □ **Discovery of new antibodies (24.3.1)** □ □

In 2003, [Kirvan and Swedo](#) published the landmark Nature paper entitled "Mimicry and auto-antibody-

mediated neuronal cell signaling in Sydenham chorea” which pulled together all the above papers into a finding that there were three distinct antibodies that cross-reacted with Lysogangliosides in the brain. In addition, they found one of these antibodies caused significant CaM Kinase II activation in sera. □□ During this time, Dale, Church and others were making similar observations regarding anti-basal ganglia-antibodies (ABGA). However, not all thought the research sufficient. Kurlan, Kaplan and Singer wrote many articles questioning whether the subgroup was sufficiently distinct. They were consistently unable to repeat Swedo's experiments and questioned therefore whether the diagnostic criteria was strong enough and whether causality was actually shown. Unfortunately, most of their studies were on kids with chronic tics and controlled OCD -- It is questionable whether they had any PANDAS subgroup in their proported PANDAS kids. □□ **Clarifying the presentation differences of PANDAS (sudden onset, episodic course)** □□

In 2004, Swedo responded to Kurlan and Kaplan's comments explaining the different presentation of PANDAS from traditional OCD in that PANDAS presented with sudden onset and distinct episodes unlike the Tourettes presentation from Kurlan. □□

In 2006, Kirvan and Cunningham published their finding that children from the Swedo studies were distinct from Tourettes and traditional OCD/ADHD patients in that the Sydenham Chorea and PANDAS children had elevated CaM Kinase II activation in their sera. □□ In 2007, Kirvan further showed that Tubulin is a target of the anti-neural antibodies in patients with sydenham chorea. □□ **Confusing TS subjects with PANDAS OCD subgroup** □□

Despite all of this, in June of 2008, Kurlan and Singer published that their 2 year longitudinal study did not find any of the findings of Swedo or Kirvan. However, it appears that Kurlan was studying Tourettes children (i.e., individuals with relatively stable OCD symptoms) and Singer used rabbit brains for testing for cross-reactivity (despite Husby's paper in 1977). Based on the very minor changes to OCD levels over the 2 year period, it certainly doesn't look like Kurlan had any PANDAS kids in his group. □□ **Creation of a mouse model of PANDAS (EAE) and passive transfer**

In August of 2009 Yaddanapudi showed behavioral abnormalities in a set of mice after inoculation with GABHS. These mice were especially bred to have high T-cell rates and be prone to blood-brain barrier disruption. Yaddanapudi showed that IgG transferred from inoculated mice to non-inoculated mice transferred the behavioral abnormalities. This is known as **passive transference** and a key finding for proving auto-antibody effects.

Explanation of how the Blood-brain barrier is crossed

In November 2009, Bartholomäus et al. unlocked a key part of explaining how the blood-brain-barrier can be breached. Using mice similar to Yaddanapudi (i.e., bred to have high T-cell rates and prone to blood-brain barrier disruption), they were able to watch individual T-cells cross the blood-brain-barrier. Once across, the T-cells produced inflammation recruiting other T-cells to the site of the breach. This could explain how antibodies in the blood stream cross the blood-brain barrier which has been the missing element since Husby's initial findings over three decades ago.

Research/References:

[Swedo1997] S Swedo et al, "Identification of Children With Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections by a Marker Associated With Rheumatic Fever", Am J Psychiatry 154:1, January 1997 <http://ajp.psychiatryonline.org/cgi/reprint/154/1/110.pdf> □□ [Kirvan2006] Kirvan CA, Swedo SE, Kurahara D, Cunningham MW, "Streptococcal mimicry and antibody-mediated cell

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IVIg immune inhibitory activity: APC is key

Beng H. Chong and James J. H. Chong

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● ● ● IMMUNOBIOLOGY

Comment on Aubin et al, page 1727

IVIg immune inhibitory activity: APC is key

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In this issue of *Blood*, Aubin and colleagues show that IVIg interacted with FcγRs on APCs, resulting in reduced antigen presentation and inhibition of antigen-specific T-cell response.¹ This finding suggests a key role for APCs in IVIg action.

Recent evidence suggests that an essential step in the immunopathology of autoimmune disease (AD) involves antigen-presenting cells (APCs) presenting antigen to antigen-specific CD4⁺ T helper cells,² which, in turn, induce antigen-specific B cells to produce autoantibodies (see figure). Costimulatory molecules including

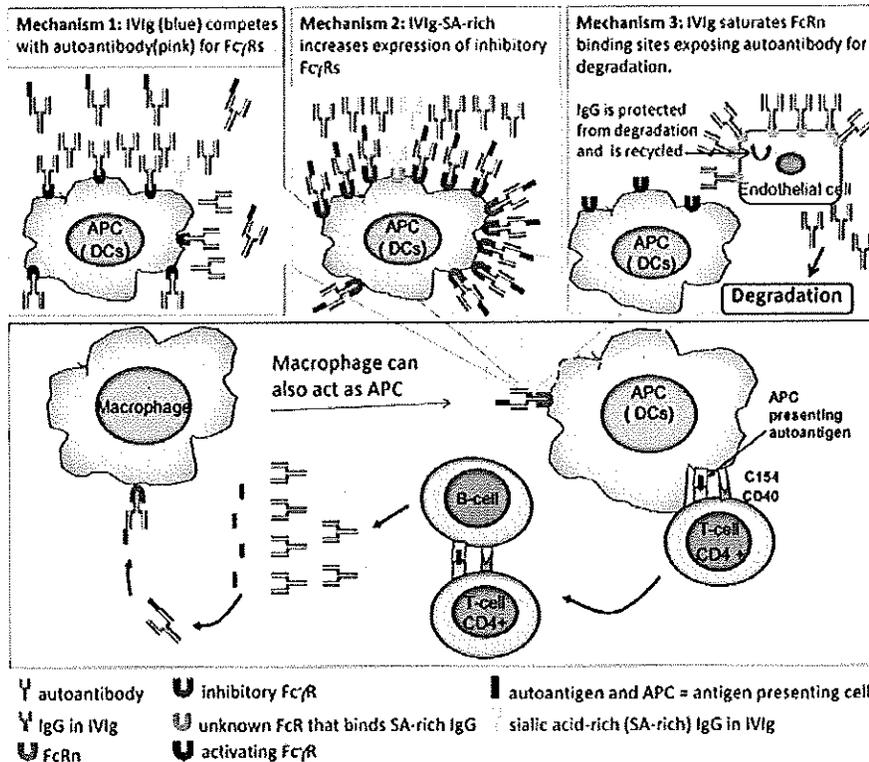
CD40 and CD154 play an important role in these cellular interactions, which perpetuate the disease. Autoantibodies bind autoantigens to form immune complexes (ICs) that are taken up by APCs via Fcγ receptors (FcγRs) for antigen processing and presentation, thus maintaining the pathogenic loop.^{3,4}

Intravenous immunoglobulin (IVIg) has been used to treat AD for more than 2 decades. The precise mechanism(s) of action is still unclear.⁵ In this issue of *Blood*, Aubin and colleagues¹ provide evidence suggesting that IVIg acts at the level of APC even though they found that IVIg inhibited antigen-specific T-cell and B-cell response. Mice immunized with ovalbumin (OVA) in the presence of IVIg generated reduced numbers of antigen-specific T cells compared with mice immunized with OVA in the absence of IVIg. IVIg treatment during OVA immunization significantly reduced OVA-specific antibody production. These suppressive activities of IVIg were not the result of decreased APC surface expression of MHCII and CD80/CD86 costimulatory molecules, as previously postulated, but were the consequence of IVIg interfering with IC binding to activating FcγRs expressed on APC.

Three mechanisms have been proposed for the immune suppressive action of IVIg⁶ (see figure) in which pathogenic IgG/IC and FcγRs on APC are believed have a role.

Mechanism 1: IVIg competes with IC for activating FcγRs. In this mechanism, high-dose IVIg competes with IC for activating FcγRs on APC surface.⁶ Data of Aubin et al¹ would favor this mechanism. First, these investigators showed that 2.4G2, FcγRIII-specific monoclonal antibody blocked OVA-IC binding to bone marrow dendritic cells (BM-DCs), used as APC in this study. Second, they found that intact IV IgG inhibited antigen-specific T-cell response but its F(ab') fragments did not.

Third, BM-DCs from γ chain-deficient mice (lacking FcγRs) failed to activate CD4⁺ T cells in the presence of IC. Altogether, their results suggest that IVIg via its Fc domain competes with IC for binding to activating FcγRs expressed on APCs, consequently reduces APC antigen presentation, and inhibits CD4⁺ T-cell activation and other downstream immune responses. One reservation in interpreting these data is that monomeric IgG in



A model for the immunopathology of autoimmune disease. Some aspects such as the role of cytotoxic T cells and regulatory T cells are not included. Proposed mechanisms whereby IVIg interferes with immune complex-APC interaction are shown in the top 3 panels.

IVIg binds activating FcγRs (FcγRIII and VI) with low affinity,⁵ and it would seem surprising that IVIg would be able to compete with IC for binding to these Fc receptors.

Mechanism 2: IVIg induces expression of inhibitory FcγRs. Kaneko and colleagues⁷ showed recently that 1% to 2% of IgG in IVIg has sialic acid at the Asn297-linked glycan, and IVIg enriched in Fc-sialylated IgGs has increased immune inhibitory activity. These investigators proposed a mechanism of action for IVIg in which Fc-sialylated IgGs bind to a unique receptor (still to be identified) on macrophages/APCs and up-regulate expression of inhibitory FcγRs such as FcγRIIB. Up-regulation of inhibitory FcγRs dilutes out the effects of activating FcγRs. They also argued that as Fc-sialylated IgGs are present only in small quantities in IVIg, this explains the high dose of IVIg required for immune inhibitory effect. In contrast, Aubin et al¹ observe that IVIg inhibited antigen presentation to the same degree with BM-DC (APC) from FcγRIIB^{-/-} and FcγRIIB^{+/+} (wild-type) mice, suggesting that the immune inhibitory effect of IVIg is FcγRIIB-independent.

Mechanism 3: IVIg saturates FcRn binding; FcRn binds pathogenic or non-pathogenic IgGs and protects them from catabolism. The third mechanism postulates that high doses of IVIg saturate the available FcRn binding sites and expose pathogenic autoantibodies, not bound to FcRn, to catabolic removal, thus reducing the amount of circulating autoantibodies. Consistent with this mechanism, Li et al showed that IVIg-treated wild-type mice, but not neonate FcRn-deficient mice, were protected from developing bullous skin disease when the animals were infused with antibodies from patients with pemphigus vulgaris.⁸ Mechanism 3, however, is not yet widely accepted because there is some evidence against FcRn having a role in IVIg action.⁵

An important drawback in the study of Aubin et al¹ is that they did not use an autoimmune disorder animal model and their findings may not necessarily represent the effects of IVIg in AD. Further studies are required, particularly studies using an autoimmune experimental system. Nevertheless, the findings in this study are helpful in providing insights into the mechanism(s) of IVIg action. If subsequently confirmed by further studies, the knowledge gained may inform development of effective novel therapies for AD,¹ such as de-

veloping antibodies, peptides, or small molecules that block IC binding to activating FcγRs on APCs.

Conflict-of-interest disclosure: B.H.C. has consulted for Commonwealth Serum Laboratory. J.J.H.C. declares no competing financial interests. ■

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● ● ● PLATELETS & THROMBOPOIESIS

Comment on Lubenow et al, page 1797

HIT: more than just heparin

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In this issue of *Blood*, Lubenow and colleagues provide the first strong evidence that there is much more besides heparin in triggering the adverse drug reaction, HIT.¹

To date, research has focused on identifying whether differences in heparin composition influence the risk of immunization against platelet factor 4/heparin (PF4/heparin) complexes, the target of the immune response that characterizes heparin-induced thrombocytopenia (HIT). And, indeed, longer-chain and more sulfated heparins are more likely to trigger immunization and clinically evident HIT.²

As with any drug reaction, however, only a minority of patients who receive the offending drug are affected. Usually, this is attributed to poorly defined "idiosyncratic" (patient-specific) factors. But in the case of HIT, the perception has grown that there must be additional nondrug, but also nonidiosyncratic, factors that influence immunization risk. The evidence behind this concept has been mostly indirect. For example, surgical patients appear to be more likely to develop HIT than medical patients.³ This is very different from an "idiosyncratic" reason where Mr X has an inherently higher risk of HIT than Mr Y. Rather, both Mr X and Mr Y would have a higher risk of HIT if they received heparin in the context of surgery, rather than if they received heparin as medical patients.

Now, Lubenow et al provide direct evidence that nondrug factors do indeed strongly influence anti-PF4/heparin immunization and HIT risk. They performed a randomized controlled trial comparing 2 types of heparin—unfractionated heparin (UFH) and a low-molecular-weight heparin (LMWH) preparation (certoparin)—administered for thromboprophylaxis after trauma. Patients were classified as "major" and "minor" trauma and were systematically evaluated for immunization (various tests for anti-PF4/heparin antibodies) and for HIT (thrombocytopenia and/or thrombosis bearing a temporal relationship to formation of platelet-activating antibodies). In their study, major trauma referred primarily to fractures of the pelvis, femur, tibia, fibula, or humerus; minor trauma to almost everything else (usually, distal upper-extremity, shoulder, and distal lower-extremity fractures).

The table summarizes the frequency of anti-PF4/heparin antibody immunization, as per a combination of immunoassays, categorized by severity of trauma (major, minor) and for type of heparin (UFH, LMWH). The corresponding data for clinical HIT are also shown.

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

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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 etiological 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 leads 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 antibrain 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 (Woof 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 (Morier 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 pneumoniae* (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

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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 (Terrerri 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 γ and most proinflammatory cytokines (Miettinen et al. 1998). Penicillin perhaps serves a synergistic role in symptom improvement by specifically conjugating to IFN γ and reducing IFN γ '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 γ (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-

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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.

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