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PANDAS: A Model for Autoimmune Neuropsychiatric Disorders.

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Focus Points

• Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) represents a newly recognized subgroup of pediatric obsessive-compulsive disorder (OCD) and tics.

• There is increasing evidence that the symptoms in the PANDAS subgroup have an autoimmune etiology analogous to that of Sydenham's chorea, namely inflammation of basal ganglia secondary to molecular mimicry by antigen epitopes of the streptococcus in vulnerable individuals.

• Children in the subgroup are typically prepubertal, have an abrupt onset of symptoms, have a remitting and recurring course of illness associated temporally with group-A b-hemolytic streptococcus infections, and have associated neurologic symptoms including movement disorders and hyperactivity.

• Treatment of children in the PANDAS subgroup can be quite successful, using standard-of-care interventions for OCD and tics; for the most severely affected children, heroic treatment with immunomodulatory interventions may also be successful during acute stages.

Abstract

Inspired by clinical observations and supported by systematic investigations, a subgroup of childhood obsessive-compulsive disorder (OCD) has recently been recognized; this subgroup is known as pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS). Children in this group have an abrupt,

prepubertal onset of tics and/or OCD, associated neurological abnormalities (eg, adventitious movements or motoric hyperactivity), and a relapsing and remitting course in which symptom exacerbations are triggered by group-A β-hemolytic streptococcus (GAS) infections. The etiology of the tics and OCD in this subgroup is unknown but is postulated to be similar to that of Sydenham's chorea. That is, in a susceptible host, certain GAS strains incite production of antibodies, which cross-react with cellular components in basal ganglia causing inflammation and resulting in neuropsychiatric symptoms. Appropriate diagnosis can facilitate treatment and possibly offer prognostic and preventive advantages.

Introduction

Sir William Osler[1] may have been the first to write of the observed association between obsessive-compulsive disorder (OCD) symptoms and Sydenham's chorea (SC) when he described "bizarre" and "perseverative" behaviors in children with "chorea minor" in 1894. More recent clinical reports have noted the association between SC and OCD in children with rheumatic chorea and in adult psychiatric patients with a history of SC.[2-4] Studies conducted at the National Institute of Mental Health (NIMH) have demonstrated that OCD symptoms were more common in children with SC than among children with rheumatic carditis[5] and that obsessions and compulsions affected >70% of children in the weeks near the onset of their chorea.[6,7] Recently, in São Paulo, Brazil, where rheumatic fever (RF) and SC have been endemic, it has been observed that approximately two thirds of children during their initial episode of SC also demonstrate OCD symptoms. Furthermore, the frequency of OCD increases with repeated episodes of chorea, so that 100% of children are affected after three or more recurrences of SC.[8] In children with SC, the OCD symptoms are indistinguishable from those among children with primary OCD and include contamination fears, anxiety about harm to self or others, doubting, concerns with symmetry, and other common obsessions, as well as compulsive cleaning, checking, ordering, arranging, and hoarding.

Given these clinical observations, it was perhaps inevitable that postinfectious OCD symptoms might be proposed to occur even in the absence of acute chorea.[5,6] Longitudinal observations[9,10] of a large cohort of pediatric patients with OCD provided support for this postulate, as a subgroup of the patients was noted to have an acute onset of symptoms, an episodic course characterized by periods of complete symptom remission interrupted by abrupt and dramatic symptom exacerbations, and a close temporal relationship between relapses and preceding group-A β-hemolytic streptococcus (GAS) infections (either scarlet fever or streptococcal pharyngitis).[11,12] The subgroup was given the acronym PANDAS, to refer to their shared clinical and presumed etiopathogenic features: pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections.[12]

This article outlines two case studies of PANDAS children and subsequently describes the clinical features of the proposed subgroup of childhood OCD (and tic) disorders, reviews the evidence for its autoimmune etiology, and outlines treatment strategies for children in whom the pathology is suspected. The clinician should take away from this article an increased awareness of the entity, a facility in searching for diagnostic support for it, and a strategy for treatment and perhaps for prevention.

Case Studies

The cases described below represent composites; though they are seemingly extreme, they would be quite recognizable to families whose lives have been turned upside-down by the disorder. The following cases should be used as guides in the clinical identification of children in the PANDAS subgroup and should be examined in conjunction with the remaining sections of this article.

Case 1: Harry

Bright, verbal, compliant, and attractive, Harry was thriving in first grade. After a 48-hour "virus" in which vomiting was more prominent than sore throat, the 6-year-old returned to school, apparently in his usual state of health. (He had not seen a physician, and only later did his family learn that streptococcal pharyngitis had been documented in a classmate.) But the following Saturday morning he came from his bedroom tearful because he had nothing "clean" to wear. By the end of the day, the household was near chaos, trying to comply with Harry's new and inflexible rules regarding contamination. Anyone entering his room had to remove shoes and walk only in areas outlined by him with tape on the carpet. Soon only his mother could enter at all, and finally not even she. No clothing was uncontaminated and he spent the day wrapped in a sheet. He cried frequently and without provocation and frequently screamed at family members for minor infractions, behaviors which were quite out of character for him.

Harry was noted to be motorically activated, fidgeting in his chair at the dinner table for a few minutes before jumping up to pace about the room. He had urinary frequency, new onset of nocturnal enuresis, and even an episode of daytime enuresis. The contamination fears, irritability, and hyperactivity continued for several weeks. It was a month before he could return to school, and even then the teachers were surprised by the changes in him. He was inattentive, restless, irritable, and tearful. His handwriting had become virtually illegible. On the playground, this previously developing athlete was clumsy and uncoordinated.

Case 2: Hermione

Another composite child, described here, is prototypical of the less severely affected patient. Always an intense and sensitive child, Hermione had an abrupt onset of symptoms 10 days after a mild streptococcal sore throat. Subsequently, the 8-year-old girl began to constantly ask for reassurance that she had not done or said something hurtful. Within 2 days of onset, the symptom was consuming all of the family's energy. After consultation with a child and adolescent psychiatrist, Hermione was referred to a skilled cognitive-behavioral therapist. Working with the family, and with the child's enthusiastic compliance, the therapist was able to bring the symptom quickly under control, and therapy was terminated. But 6 weeks later the symptom recurred worse than previously and quite abruptly. Hermione had a sore throat but no fever, and hardly seemed sick. But she had begun clearing her throat loudly and with annoying frequency, and she was brought to the pediatrician for that reason. A throat culture revealed GAS, which was treated with a 10-day course of amoxicillin. Cognitive-behavioral therapy was resumed. Once again, the symptom abated quickly and did not recur. The throat clearing disappeared more slowly. (The therapist advised the family to make no further comments about it to Hermione.) The psychiatrist carefully educated the family about OCD symptoms and advised them to take the child to her pediatrician at once if any OCD symptoms appeared, even in absence of typical strep throat symptoms.

Clinical Features of PANDAS

Inclusionary criteria for the PANDAS subgroup were published in 1998[12] and remain the working definition. They include presence of tic disorder and/or OCD, prepubertal age of onset, usually 3–12 years of age, abrupt onset of symptoms, a relapsing-remitting episodic course, temporal association between symptom exacerbations and GAS infections, and neurologic abnormalities present during exacerbations.

As noted, obsessions and compulsions in the PANDAS subgroup are not distinguishable from those in unselected children with OCD, nor are the tics in any way unique. On the other hand, the average age of onset in the subgroup is approximately 3 years younger than that previously reported for childhood-onset OCD[10,13] and 2 years younger than the average age of onset for tic disorders.[14] As is typical of childhood tics and OCD in general, children in the PANDAS subgroup do not seem to be evenly divided between boys and girls. Rather, boys outnumber girls by almost three to one in older children, and nearly five to one among children <8 years of age.[12]

The PANDAS subgroup becomes most distinguishable through prospective observation of its unique clinical course. Onset of symptoms, including tics and/or obsessions and compulstions, is often dramatically abrupt, even overnight in some cases. Symptoms may remain at peak severity for several weeks or longer, and then gradually subside, often disappearing completely. Children often return to their normal baseline until a subsequent GAS infection precipitates an exacerbation of symptoms. This remitting-recurring course is in striking contrast to the gradual onset and persistent symptoms usually seen in childhood-onset OCD[9,10] and differs considerably from the typical waxing and waning course of childhood tic disorders.[14]

Interestingly, the PANDAS subgroup shares clinical features with SC in addition to OCD symptoms. Since the time of Osler, clinicians have noted emotional lability, inattentiveness, separation anxiety, and motoric hyperactivity in SC? patients,[1,7] all of which are common in PANDAS children as well.[12] Additional findings in the PANDAS subgroup include urinary frequency and nocturnal and daytime enuresis,[12,15] deterioration in handwriting,[16] and choreiform movements of hands and fingers. These latter adventitious movements may well be related to the apparent difficulties with handwriting and can be elicited during structured examinations, such as the Physical and Neurological Exam for Subtle Signs,[17] which searches for soft neurological signs.

Etiopathogenesis

Both the choreiform movements and the OCD symptoms are thought to be due to dysfunction in corticostriato-thalamocortical circuitry.[18] In SC, both structural and functional neuroimaging studies[19-21] have confirmed pathology of basal ganglia, specifically caudate, putamen, and globus pallidus. Autopsy studies[22,23] have also suggested primary basal ganglia involvement. A volumetric magnetic resonance imaging study[24] of 34 children who met criteria for the PANDAS subgroup also documented enlargement of these structures, and in one case,[25] normalization of caudate size following immunomodulatory treatment of the acute illness was observed.

The etiopathogenesis of symptoms in both SC and PANDAS children may well be triggered by “molecular mimicry” of the GAS (in which the shape or sequence of molecules provokes immune response that also targets self-molecules), which may cause loss of self-tolerance. SC occurs in 10% to 30% of acute RF cases[26] several months after the precipitating GAS infection,[27,28] and may be the only manifestation of acute RF.[26] The evidence for an autoimmune mechanism in SC is considerable: in a study published in 1976,[29] nearly 50% of SC patients demonstrated an antibody reacting preferentially with neuronal cytoplasm of human caudate and subthalamic nuclei; the antineuronal antibody was absorbed out by GAS membrane. Presence of antineuronal antibodies correlated with the severity and duration of the chorea. Few control sera or sera from other disease states were positive. In a more recent study,[30] cell-wall M-proteins from three serotypes of GAS known to provoke RF were used to evoke rabbit antibodies that then were found to cross-react with multiple human brain proteins. There was evidence of preference for basal ganglia proteins. Additionally, M-protein–specific antibrain antibodies were found in the plasma of a patient with SC.

In patients with SC evaluated at the NIMH,[7] antineuronal antibodies directed against human caudate tissue were demonstrated in 10 of 11 subjects. Out of 18 control subjects, 9 were positive. Nine of the subjects had throat cultures positive for GAS at the time of diagnosis of their SC. In another study,[31] acute SC patients had significantly higher titers of antibasal ganglia antibodies than were found in the sera of patients with convalescent SC, RF without SC, or healthy controls.

The most specific molecular biological description of the autoimmune phenomena in SC was published only recently.[26] Human hybridoma lines derived from an SC patient were found to recognize the major GAS surface carbohydrate *N*-acetyl-d-glucosamine, and to attach to human basal ganglia tissue sections. The antibodies cross-reacted with central nervous system lysoganglioside. Binding of the antibody to neurons activated calcium/calmodulin dependent protein kinase II, postulated to affect neurotransmitter synthesis and release. Moreover, the cross-reactive monoclonal antibodies provoked *in vitro* neuronal cell signaling, as did sera from active, but not convalescent, SC subjects.

Further Evidence of Autoimmunity

There is also support for a postinfectious etiology for tic disorders. As an example, an association was documented between a community outbreak of GAS infections and a 10-fold rise in the number of children presenting with a new onset of tics.[32] Additionally, in a group of Italian schoolchildren, exposure to GAS, as documented by antistreptolysin-O titers, correlated with the onset of tics; antistreptolysin-O titers also correlated with severity of tics.[33]

In an 8-month longitudinal study[34] of school-aged children in the United States, investigators found the incidence of motor tics (and problem behaviors) significantly higher during the winter months compared to the spring months. GAS rates were not determined, but this time period overlaps with the seasonal prevalence of GAS infections in this age group, and the study provides indirect evidence of a temporal correlation between GAS infection and tics.

Antibodies against human caudate were found to be significantly higher in children with new-onset movement disorders (including Tourette's syndrome [TS], chronic motor or vocal tics, chorea, and choreiform movements) than in children without those movement disorders.[32] The children with movement disorders were also more likely to have evidence of preceding streptococcal infection. Antineuronal antibodies recognizing the putamen were significantly higher in 41 children meeting criteria for TS than in 39 controls.[35] In this study,[35] there was not a clear association with preceding streptococcal infection. TS patients were found to have significantly higher levels of total antineuronal and antinuclear antibodies than healthy controls in another study, which examined these factors and antistreptococcal antibodies in children and adults with TS, SC, and other autoimmune disorders.[36] However, markers for prior GAS infection were equivocal in that investigation, in that the correlation did not appear as strong among the child patients.

Animal models have provided partial support for the proposed autoimmune mechanism of tic disorders. Intrastriatal microinfusions of γ-globulins from TS patients have induced stereotypies and episodic utterances in rats, thought to be analogous to tic-like behaviors in humans.[37] Postinfusion immunohistochemical analysis confirmed the presence of γ-globulin selectively bound to striatal neurons. Likewise, oral stereotypies were demonstrated in rats after bilateral infusions into the ventrolateral striatum of sera from patients with TS, and there were higher rates of stereotypies in the rats infused with the sera from patients with the highest levels of antineuronal antibodies.[38]

The Autoimmune in PANDAS

Antibodies directed against the caudate and putamen were found to be significantly higher in a sample of children presenting with new-onset OCD or OCD symptoms than in clinical controls without such symptoms.[39] Considering the studies of tics and OCD as a single unit provides support for an autoimmune etiology of some childhood-onset OCD and tic disorders. The etiology of the neuropsychiatric symptoms in the PANDAS subgroup is postulated to be analogous to that of SC: a rheumatogenic strain of GAS infects a susceptible host and induces an abnormal immune response, with inflammatory reaction and possibly disruption of putative blood-brain barrier; there may be spontaneous resolution and then subsequent exacerbation when challenged by antigen or even by nonspecific factors.

The Role of Streptococcal Infections

Evidence for the etiologic role of GAS infections in RF remains circumstantial, though it is also nearly overwhelming. Epidemiologic investigations have demonstrated the close temporal relationship between epidemics of scarlet fever and subsequent outbreaks of RF. Recrudescence of RF is prevented by penicillin prophylaxis. Ongoing studies at the NIMH and elsewhere are attempting to apply a similar associative strategy to demonstrate a causal relationship between GAS infections and the OCD and tic symptoms of the PANDAS subgroup. Prospective longitudinal assessments have been effective in some cases in demonstrating the difference between a child with standard OCD and a child who falls into

the PANDAS subgroup.

Of course, the frequency of occurrence of both disorders—OCD/tics and GAS pharyngitis—is such that co-occurrence could be random yet relatively frequent. OCD occurs in 1% to 2% of school-age children, and transient motor tics occur in as many as 10% to 25% of early elementary school students.[34,40] During school outbreaks of streptococcal pharyngitis, 15% to 50% of children will be found with subclinical infection or carrier status (based on positive throat cultures).[41] The determination, therefore, that a child meets the PANDAS criteria must be made through prospective evaluation and documentation of the presence of GAS infections in temporal association with at least two episodes of abrupt onset of neuropsychiatric symptoms (tics and/or OCD), as well as through demonstration of negative throat culture or stable titers during times of neuropsychiatric symptom remission. A child who has multiple symptom exacerbations without evidence of streptococcal infections would not be considered a member of the PANDAS subgroup, nor would a child who has numerous streptococcal infections without subsequent symptom exacerbations.

Alternative Viewpoints

Arguments against an autoimmune etiology of PANDAS must be considered.[42] Cross-reactive antibodies are not universally present among patients with poststreptococcal tics or OCD. Furthermore, the antibodies have been demonstrated in sera from healthy children without evidence of neuropsychiatric illness. The episodic course of the children in the PANDAS groups may be temporally, yet not causally, related to GAS infections. The infections could be an incidental finding or the exacerbations might be nonspecific reactions to the stress of illness, rather than related to GAS-triggered autoimmunity.[43] Moreover, the neuropsychiatric symptoms could have a periodicity inherent in their pathobiology,[44] and the exacerbations might occur with the GAS infections coincidentally and randomly, as was noted above.

Treatment

The strongest support for the autoimmune hypothesis of the etiology of the PANDAS subgroup may be offered by the successful treatment of severely affected children with immunomodulatory interventions. In a randomized, placebo-controlled trial[45] conducted at the NIMH, both intravenous immunoglobulin (IVIG) and plasma-exchange transfusions produced significant improvements in children with tics and/or OCD meeting PANDAS criteria. OCD symptoms were reduced by 45% to 58% at 1 month posttreatment with IVIG or plasma exchange respectively, while placebo (sham IVIG) administration had no effect on OCD symptom severity. Tic symptoms were also improved, with a 49% decrease in the TS Unified Rating Scale. Moreover, follow-up 1 year later revealed that 14 of 17 children (82%) who had received plasma exchange or IVIG were “much” or “very much” improved from baseline. The effectiveness of these immunomodulatory therapies suggests that circulating immune factors play a role in the pathophysiology of the symptoms. However, both treatments have a broad spectrum of potential mechanisms of action, from clearance of circulating antibodies and cytokines, to activation of subpopulations of T-cells and B-cells. Thus, the specific mechanism of therapeutic effect remains speculative.

IVIG and plasma exchange are not so widely available, and both treatments have attendant risks to be considered in the risk-benefit calculation. Immunoglobulin, a pooled human blood product, had been in short supply recently; when it is available, it carries a risk of transmitting occult infectious agents. In addition, administration of IVIG is accompanied by a variety of adverse effects, including fever and headache. Plasma exchange sometimes requires placement of a central venous line in a child of small stature, with attendant risks of bleeding and infection.

Less Intensive Measures

Whereas immunomodulatory treatments may be indicated for a severely-impaired child, standard OCD treatments and GAS prophylaxis are the mainstays of treatment of most children in the PANDAS subgroup. Cognitive-behavioral therapy (CBT), for one, has documented effectiveness in childhood OCD,[46] and there is anecdotal evidence of its utility in the OCD symptoms of the PANDAS subgroup. The treatment requires an emotionally ready and developmentally capable child, but the family must also be ready and able to participate in the treatment, since childhood OCD often enlists family members in perpetuating and reinforcing its cognitions and behaviors. Although the treatments have been manualized,[47] the therapist should be experienced and skillful in implementing them. Capable therapists are more widely available than in the recent past and may be found through referral by child/adolescent psychiatrists, through the Web site of the Obesessive-Compulsive Foundation,[48] or through the Web site of the Association for the Advancement of Behavior Therapy.[49] It is often helpful, as well, to suggest reading materials intended for families[50-52] at the beginning of interventions. Both the child and the family may need help to appreciate that what may appear to be bizarre and even frightening ideas and behaviors are actually the result of a neurobiological disruption, readily treatable now and in future recurrences.

At least in the case of the PANDAS subgroup, those possible recurrences might well be preventable. Following the model of RF, antibiotic prophylaxis could prove to be useful. That intervention remains the subject of studies ongoing at NIMH. In the meantime, given the possible link between GAS and PANDAS, antibiotics are clearly safe and appropriate to treat proven infections quickly and adequately. It is standard to treat GAS pharyngitis with a 10-day course of penicillin or erythromycin.

In the case of a child with PANDAS, having a low threshold of GAS suspicion seems in order. Given that GAS pharyngitis is often minimally symptomatic, if the child has an abrupt recurrence of tics, OCD, or other neurologic symptoms, a rapid strep test should be obtained, backed up by a 48-hour throat culture if the rapid test is negative. Previously effective interventions for the OCD symptoms should be reinstituted in any case. It can be hoped that prompt treatment of the infection will minimize the severity and duration of all symptoms, and there is some support for that proposition.[15]

There have been two recent reports of children whose apparent PANDAS symptoms resolved after tonsillectomy.[53,54] In both reports, pairs of siblings, one with tics and one with OCD, had sustained improvements after surgery terminated their recurrent GAS tonsillar infections. On the other hand, unreported clinical experience at the NIMH includes children whose PANDAS had begun only after tonsillectomy. Thus, the NIMH was unable, based on available evidence, to offer advice about the utility of tonsillectomy for poststreptococcal neuropsychiatric disorders. Of course, there are other clear indications for surgery, including recurrent bouts of streptococcal pharyngitis, tonsillar abscess, obstructive sleep apnea, and others.[55,56]

Whereas childhood OCD at one time was thought to have a poor prognosis,[9,57] more recent studies demonstrate that ≥50% of children actually do well, while a significant percentage learn to manage their illness with success.[13,57,58] It seems safe to assume children in the PANDAS subgroup will do as well, and they may in fact do considerably better, since some exacerbations may be preventable. This postulate is the subject of ongoing investigation at the NIMH.

Not yet mentioned, but part of the treatment armamentarium for OCD, are the serotonin reuptake inhibitors. At least three (clomipramine, sertraline, and fluvoxamine) have secured Food and Drug Administration indications for childhood OCD and should be considered for a child who has significant symptoms and is unable or unwilling to participate in CBT, or for whom that approach has been ineffective. Medications can also be helpful as adjunctive measures to behavioral therapies, especially early in the course of the illness to provide symptomatic relief. On occasion, a neuroleptic may be indicated on a temporary basis if the child's distress is overwhelming or if the obsessions seem delusional; at such a point, the consultation of an experienced child and adolescent psychiatrist is invaluable.

Tics are sometimes the primary symptom of the PANDAS subgroup[12] and can be as severe and disabling as OCD symptoms. If indicated, the standard pharmacologic treatments of childhood tic disorders (α-agonists and sometimes neuroleptics) may be appropriate.

Conclusion

There is clinical and mounting laboratory evidence supporting the existence of a subgroup of childhood OCD and tics, called PANDAS, which has a postulated autoimmune etiology analogous to that of SC. Antigenic epitopes, probably from bacterial cell membranes, mimic human central nervous system molecules, and the autoimmune phenomena that follow result in a myriad of symptoms. There are safe and effective treatments for the most troubling symptoms of the disorder, and these should be available in most communities where child mental health specialists practice. The symptoms respond to standard therapies, but the recognition that symptoms may have a poststreptococcal etiology should lead to evaluation and treatment of streptococcal infections in the acute stages of the illness. *PP*

References

1. Osler W. *On Chorea and Choreiform Affections*. London, UK: H.K. Lewis; 1894:33-35.

2. Chapman AH, Pilkey L, Gibbons MJ. A psychosomatic study of eight children with Sydenham's chorea. *Pediatrics*. 1958;21(4):582-595.

3. Freeman JM, Aron AM, Collard JE, MacKay MC. The emotional correlates of Sydenham's chorea. *Pediatrics*. 1965;35:42-49.

4. Grimshaw L. Obsessional disorder and neurological illness. *J Neurol Neurosurg Psychiatry*. 1964;27:229-231.

5. Swedo SE, Rapoport JL, Cheslow DL, et al. High prevalence of obsessive-compulsive symptoms in patients with Sydenham's chorea. *Am J Psychiatry*. 1989;146(2):246-249.

6. Swedo SE. Sydenham's chorea. A model for childhood autoimmune neuropsychiatric disorders. *JAMA*. 1994;272 (22):1788-1791.

7. Swedo SE, Leonard HL, Schapiro MB, et al. Sydenham's chorea: physical and psychological symptoms of St. Vitus dance. *Pediatrics*. 1993;91(4):706-713.

8. Asbahr FR, Ramos RT, Negrao AB, Gentil V. Case series: increased vulnerability to obsessive-compulsive symptoms with repeated episodes of Sydenham chorea. *J Am Acad Child Adolesc Psychiatry*. 1999;38(12):1522-1525.

9. Leonard HL, Swedo SE, Lenane MC, et al. A 2- to 7-year follow-up study of 54 obsessive-compulsive children and adolescents. *Arch Gen Psychiatry*. 1993;50(6):429-439.

10. Swedo SE, Rapoport JL, Leonard H, Lenane M, Cheslow D. Obsessive-compulsive disorder in children and adolescents: clinical phenomenology of 70 consecutive cases. *Arch Gen Psychiatry*. 1989;46(4):335-341.

11. Allen AJ, Leonard HL, Swedo SE. Case study: a new infection-triggered autoimmune subtype of pediatric OCD and Tourette's syndrome. *J Am Acad Child Adolesc Psychiatry*. 1995;34(3):307-311.

12. Swedo SE, Leonard HL, Garvey M, et al. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: a clinical description of the first 50 cases. *Am J Psychiatry*. 1998;155(2):264-271.

13. Thomsen PH, Mikkelsen HU. Course of obsessive-compulsive disorder in children and adolescents: a prospective follow-up study of 23 Danish cases. *J Am Acad Child Adolesc Psychiatry*. 1995;34(11):1440.

14. Leckman JF, Peterson BS, Pauls DL, Cohen DJ. Tic disorders. *Psychiatr Clin North Am*. 1997;20(4):839-861.

15. Murphy ML, Pichichero ME. Prospective identification and treatment of children with pediatric autoimmune

neuropsychiatric disorder associated with group A streptococcal infection (PANDAS). *Arch Pediatr Adolesc Med*. 2002;156(4):356-361.

16. Perlmutter SJ, Garvey MA, Castellanos X, et al. A case of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections. *Am J Psychiatry*. 1998;155(11):1592-1598.

17. Denckla MB. Revised Neurological Examination for Subtle Signs (1985). *Psychopharmacol Bull*. 1985;21(4):773-793.

18. Snider LA, Swedo SE. Pediatric obsessive-compulsive disorder. *JAMA*. 2000;284(24):3104-3106.

19. Goldman S, Amrom D, Szliwowski HB, et al. Reversible striatal hypermetabolism in a case of Sydenham's chorea. *Mov Disord*. 1993;8(3):355-358.

20. Weindl A, Kuwert T, Leenders KL, et al. Increased stiatal glucose consumption in Sydenham's chorea. *Mov Disord*. 1993;8(4):437-444.

21. Giedd JN, Rapoport JL, Kruesi MJ, et al. Sydenham's chorea: magnetic resonanace imaging of the basal ganglia. *Neurology*. 1995;45(12):2199-2202.

22. Greenfield JG, Wolfsohn JM. The pathology of Sydenham's chorea. *Lancet*. 1922;2:603-606.

23. Ziegler L. The neuropathological findings in a case of acute Sydenham's chorea. *J Nerv Ment Dis*. 1927;65:273-281.

24. Giedd JN, Rapoport JL, Garvey MA, Perlmutter S, Swedo SE. MRI assessment of children with obsessive-compulsive disorder or tics associated with streptococcal infection. *Am J Psychiatry*. 2003;157(2):281-283.

25. Giedd JN, Rapoport JL, Leonard HL, Richter D, Swedo SE. Case study: acute basal ganglia enlargement and obsessive-compulsive symptoms in an adolescent boy. *J Am Acad Child Adolesc Psychiatry*. 1996;35(7):913-915.

26. Kirvan CA, Swedo SE, Heuser JS, Cunningham MW. Mimicry and autoantibody-mediated neuronal cell signaling in Sydenham chorea. *Nat Med*. 2003;9(7):914-920.

27. Taranta A, Stollerman GH. The relationship of Sydenham's chorea to infections with group A streptococci. *Am J Med*. 1956;20(2):170-175.

28. Taranta A. Relation of isolated recurrences of Sydenham's chorea to preceding streptococcal infections. *N Engl J Med*. 1959;260(24):1204-1210.

29. Husby G, van de Rijn I, Zabriskie JB, Abdin ZH, Williams RC Jr. Antibodies reacting with cytoplasm of subthalamic and caudate nuclei neurons in chorea and acute rheumatic fever. *J Exp Med*. 1976;144:1094-1110.

30. Bronze MS, Dale JB. Epitopes of streptococcal M proteins that evoke antibodies that cross-react with human brain. *J Immunol*. 1993;151(5):2820-2828.

31. Church AJ, Cardoso F, Dale RC, Lees AJ, Thompson EJ, Giovannoni G. Anti-basal ganglia antibodies in acute and persistent Sydenham's chorea. *Neurology*. 2002;59(2):227-231.

32. Kiessling LS, Marcotte AC, Culpepper L. Antineuronal antibodies in movement disorders. *Pediatrics*. 1993;92 (1):39-43.

33. Cardona F, Orefici G. Group A streptococcal infections and tic disorders in an Italian pediatric population. *J Pediatr*. 2001;138(1):71-75.

34. Snider LA, Seligman LD, Ketchen BR, et al. Tic and problem behaviors in school children: prevalence,

characterization and associations. *Pediatrics*. 2002;110(2 pt 1):331-336.

35. Singer HS, Giuliano JD, Hansen BH, et al. Antibodies against human putamen in children with Tourette syndrome. *Neurology*. 1998;50(6):1618-1624.

36. Morshed SA, Parveen S, Leckman JF, et al. Antibodies against neural, nuclear, cytoskeletal, and streptococcal epitopes in children and adults with Tourette's syndrome, Sydenham's chorea, and autoimmune disorders. *Biol Psychitry*. 2001;50(8):566-577.

37. Hallett JJ, Harling-Berg CJ, Knopf PM, Stopa EG, Kiessling LS. Anti-striatal antibodies in Tourette syndrome cause neuronal dysfunction. *J Neuroimmunol*. 2000;111(1-2):195-202.

38. Taylor JR, Morshed SA, Parveen S, et al. An animal model of Tourette's syndrome. *Am J Psychiatry*. 2002;159 (4):657-660.

39. Kiessling LS, Marcotte AC, Culpepper L. Antineuronal antibodies: tics and obsessive-compulsive symptoms. *J Dev Behav Pediatr*. 1994;15(6):421-425.

40. Flament MF, Whitaker A, Rapoport JL, et al. Obsessive compulsive disorder in adolescence: an epidemiological study. *J Am Acad Child Adolesc Psychiatry*. 1988;27(6):764-771.

41. American Academy of Pediatrics. Group A streptococcal infections. In: Pickering LK, ed. *Red Book: 2003 Report of the Committee on Infectious Diseases*. 26th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2003:573-584.

42. Singer HS, Loiselle C. PANDAS: a Commentary. *J Psychosom Res*. 2003;55(1):31-39.

43. Findley DB, Leckman JF, Katsovich L, et al. Development of the Yale Children's Global Stress Index (YCGSI) and its application in children and adolescents ith Tourette's syndrome and obsessive-compulsive disorder. *J Am Acad Child Adolesc Psychiatry*. 2003;42(4):450-457.

44. Leckman JF. Tourette's syndrome. *Lancet*. 2002;360(9345):1577-1586.

45. Perlmutter SJ, Leitman SF, Garvey MA, et al. Therapeutic plasma exchange and intravenous immunoglobulin for obsessive-compulsive disorder and tic disorders in childhood. *Lancet*. 1999;354(9185):1153-1158.

46. March JS. Cognitive-behavioral psychotherapy for children and adolescents with OCD: a review and recommendations for treatment. *J Am Acad Child Adolesc Psychiatry*. 2003;34(1):7-18.

47. March JS, Mulle K, Herbel B. Behavioral psychotherapy for children and adolescents with obsessive-compulsive disorder: an open trial of a new protocol-driven treatment package. *J Am Acad Child Adolesc Psychiatry*. 1994;33 (3):333-341.

48. Obsessive-Compulsive Foundation Web site. Available at: www.ocfoundation.org. Accessed February 24, 2004.

49. Association for the Advancement of Behavior Therapy Web site. Available at: www.aabt.org. Accessed February 24, 2004.

50. Swedo SA, Leonard HL. *Is It "Just a Phase"?* New York, NY: Golden Books; 1998.

51. March JS, Mulle K. *OCD in Children and Adolescents: A Cognitive-Behavioral Treatment Manual*. New York, NY: Guilford Press; 1998.

52. Chansky TE. *Freeing Your Child from Obsessive-Compulsive Disorder: A Powerful, Practical Program for Parents of Children and Adolescents*. New York, NY: Three Rivers Press; 2001.

53. Heubi C, Shott SR. PANDAS: pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections—an uncommon, but important indication for tonsillectomy. *Int J Pediatr Otorhinolaryngol*. 2003;67(8):837-840.

54. Orvidas LJ, Slattery MJ. Pediatric autoimmune neuropsychiatric disorders and streptococcal infections: role of otolaryngologist. *Laryngoscope*. 2001;111(9):1515-1519.

55. Paradise JL, Bluestone CD, Colborn DK, Bernard BS, Rockette HE, Kurs-Lasky M. Tonsillectomy and adenotonsillectomy for recurrent throat infection in moderately affected children. *Pediatrics*. 2002;110(1 pt 1):7-15.

56. Darrow DH, Siemens C. Indications for tonsillectomy and adenoidectomy. *Laryngoscope*. 2002;112(8 pt 2):6-10.

57. Peterson BS, Pine DS, Cohen P, Brook JS. Prospective, longitudinal study of tic, obsessive-compulsive, and attention-deficit/hyperactivity disorders in an epidemiological sample. *J Am Acad Child Adolesc Psychiatry*. 2001;40 (6):685-695.

58. Wewetzer C, Jans T, Muller B, et al. Long-term outcome and prognosis of obsessive-compulsive disorder with onset in childhood or
adolescence. *Eur Child Adolesc Psychiatry*. 2001;10(1):37-46.