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**The Pediatric Autoimmune Neuropsychiatric Disorders Associated With
Streptococcal Infection (PANDAS) Subgroup: Separating Fact From Fiction**

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COMMENTARIES

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The Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infection (PANDAS) Subgroup: Separating Fact From Fiction

ABBREVIATIONS. OCD, obsessive-compulsive disorder; PANDAS, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection; NIMH, National Institute of Mental Health.

Over a century ago, Sir William Osler wrote, "To carefully observe the phenomena of life in all its phases . . . to call to aid the science of experimentation, to cultivate the reasoning faculty, so as to be able to know the true from the false—these are our methods."¹

These were also the methods that led to the discovery of poststreptococcal obsessive-compulsive disorder (OCD) and tic disorders and a decade of observations and research resulting in the description of a novel cohort of patients, the pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS) subgroup.^{2,3} In this issue of *Pediatrics*, Kurlan and Kaplan raise questions about the veracity of these data.⁴ To respond, we will provide a brief literature review and clarification of the guidelines for management of a patient in the PANDAS subgroup.

The discovery of the PANDAS subgroup was the result of 2 parallel lines of clinical research conducted at the National Institute of Mental Health (NIMH): studies of children with OCD and investigations of children with Sydenham's chorea, the neurologic manifestation of rheumatic fever. Systematic observations of children with OCD revealed that, although the majority of children had a gradual onset of symptoms over several weeks to months, a subgroup of the patients experienced an explosive "overnight" onset of obsessions and compulsions followed by a relapsing-remitting symptom course.⁵ Closer observation revealed that the neuropsychiatric symptom relapses frequently occurred after episodes of streptococcal pharyngitis or scarlet fever. These findings in OCD closely paralleled those from

a series of investigations of Sydenham's chorea.⁶ In those studies, 65% to 100% of children with Sydenham's chorea were noted to have obsessive-compulsive symptoms, typically presenting 2 to 4 weeks before the onset of the adventitious movements and peaking in severity simultaneously with the chorea.^{6,7} Longitudinal observations of the OCD subgroup and the patients with Sydenham's chorea clearly demonstrated a temporal association between streptococcal infections and obsessive-compulsive symptoms. This relationship was not only observed consistently among patients presenting to the NIMH but also noted by several independent groups.⁸⁻¹¹ The nature of the association was unknown, and the observations could not elucidate whether the streptococcal infections played an etiologic role, but these issues would be addressed through subsequent scientific experimentation.

The title of the article by Kurlan and Kaplan⁴ provides a provocative starting point for discussion of the scientific hypotheses that derive from the clinical observations of the PANDAS subgroup. However, the authors subsequently blur the distinction between clinical observation and scientific investigation, leading them to dismiss the well-documented observations that neuropsychiatric symptoms are associated with streptococcal infections in the PANDAS subgroup because the etiology of PANDAS "remains a yet-unproven hypothesis."⁴ The authors thus recommend against obtaining throat cultures or serial titers in patients with abrupt-onset OCD and tics "until more definitive scientific proof is forthcoming." We strongly disagree with this recommendation. The continued threat of rheumatic fever mandates the detection and appropriate treatment of streptococcal infections, including asymptomatic infections, the leading cause of rheumatic carditis in the United States.¹² If one argues that OCD and tics are a manifestation of streptococcal infection for children in the PANDAS subgroup, then the infections aren't really "silent" or "asymptomatic." In either case, a conservative treatment course would include administration of antibiotics for culture-proven streptococcal infections. In addition, Murphy and Pichichero¹¹ have documented that prompt treatment of streptococcal infections is associated with a rapid diminution of obsessive-compulsive symptom severity for some children in the PANDAS subgroup. Thus, the potential benefits of appropriate diagnosis and treatment of an occult streptococcal infection far outweigh the modest cost of obtaining a throat swab and culture. Of course, when throat cultures are obtained, there is a risk of falsely identifying a "carrier" as an asymptomatic infection, but this risk is small. Systematic studies typically report the frequency of

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carriers to be <5% to 10%.¹³ Thus, the vast majority of positive throat cultures represent true streptococcal infections, for which antibiotics administration is the accepted standard of care.

CLINICAL CRITERIA

Kurlan and Kaplan contend that the 5 criteria defining the PANDAS subgroup are not “particularly useful in distinguishing patients suspected of PANDAS from children with more typical cases of TS [Tourette’s syndrome] or OCD.”⁴ In actuality, the criteria have been used successfully by a variety of clinical groups to define cohorts of patients with common clinical characteristics and a predictable clinical course.^{3,9–11,14} This had been the original purpose of describing the PANDAS subgroup: to enable investigators to identify a clinically homogeneous group of patients for inclusion in research studies at the NIMH and elsewhere. Subsequent investigations have demonstrated that the criteria have clinical utility as well, in that they define a distinct cohort of patients who are uniquely responsive to novel therapeutic interventions and prevention strategies. The following is a clarification of the criteria.

The Presence of a Tic Disorder and/or OCD

The symptom characteristics and severity required for diagnosis are defined in the *Diagnostic and Statistical Manual of Mental Disorders*.¹⁵ The neuropsychiatric symptoms of the PANDAS subgroup were intentionally limited to tics and obsessive-compulsive symptoms because of our interest in establishing a homogeneous patient cohort for research studies. Subsequent interest in the PANDAS subgroup has sparked a number of authors to speculate that the criteria should be expanded to include other related disorders such as attention-deficit/hyperactivity disorder¹⁶ and anorexia.¹⁷ However, such a change requires systematic evidence documenting that the association between streptococcal infections and symptom onset in these disorders is not merely a chance finding; to date, such systematic studies have not been done.

Prepubertal Age at Onset, Usually Between 3 and 12 Years of Age

This criterion was based on historical data demonstrating that rheumatic fever and other poststreptococcal sequelae are uncommon before the age of 3 years and after the age of 12 years.¹⁸ Fischetti¹⁹ provides a possible explanation for the rarity of postpubertal sequelae of streptococcal infections and demonstrated the presence of serum antibodies conferring protection against streptococcal infections in 98% of healthy 12-year-old controls, making it unlikely that poststreptococcal neuropsychiatric symptoms would have their initial presentation after this age. Thus, we set the age range for the PANDAS subgroup at a point that had biological relevance and would include 98% of the cases.

Abrupt Symptom Onset and/or Episodic Course of Symptom Severity

Prospective longitudinal investigations have demonstrated that this criterion is the most useful in identifying children in the PANDAS subgroup.^{2,3,9–11} Contrary to the concerns expressed by Kurlan and Kaplan,⁴ the abrupt onset of tics in the PANDAS subgroup is clearly different from the typical onset of an isolated, intermittent, simple motor or vocal tic, because children in the PANDAS subgroup experience the simultaneous onset of several different motor and vocal tics of such intensity and frequency that emergency treatment is often sought.¹⁴ PANDAS-related OCD is also easily distinguished from non-PANDAS OCD, because the latter patients have a slow, gradual symptom onset, whereas children in the PANDAS subgroup have an overnight “explosion” of obsessive-compulsive symptoms, reaching maximal, clinically significant impairment in 24 to 48 hours.^{3,20}

The episodic, relapsing-remitting course of the PANDAS subgroup is distinctly different from the undulating, waxing-waning course seen in other patients with OCD or tic disorders.^{20,21} When the symptoms of a child in the PANDAS subgroup are graphed against time, a “saw-toothed” pattern emerges, in which periods of symptom quiescence are interrupted abruptly by severe symptom exacerbations; these relapses typically take several weeks to months to resolve. Prospective, longitudinal evaluation of these patients allows for documentation of the relationship between the symptom exacerbations and streptococcal infections: throat cultures obtained at the beginning of a symptom relapse will be positive, and titers obtained at baseline and 4 to 6 weeks later will demonstrate a clinically significant rise.

Temporal Association Between Symptom Exacerbations and Streptococcal Infections

Although it was postulated initially that there could be a significant time lag between the inciting streptococcal infection and the presentation of the neuropsychiatric sequelae (such as that seen in Sydenham’s chorea),⁶ clinical observations of the PANDAS subgroup revealed that the window is actually much narrower. Exacerbations of neuropsychiatric symptoms begin within 7 to 14 days after the streptococcal infection and usually occur simultaneously (ie, a throat culture obtained because of the recent onset of OCD and/or tics is positive).^{3,11,20,21}

One caveat in evaluating the relationship between streptococcal infections and neuropsychiatric symptoms is that the disorders are so common that co-occurrence can be a random coincidence rather than a clinically significant finding. OCD occurs in 1% to 2% of school-aged children, and transient motor tics occur in as many as 10% to 25% of early elementary students.^{22,23} Furthermore, during regional streptococcal epidemics, the majority of children will be infected at least once during the outbreak.¹³ Thus, as discussed in our original report,³ a single positive throat culture or elevated antistreptococcal antibody titer is not sufficient to determine that a child’s neu-

ropsychiatric symptoms are associated with streptococcal infections.^{3,20} Instead, the determination that a child fits the PANDAS profile is made through prospective evaluation and documentation of the presence of streptococcal infections in conjunction with at least 2 episodes of neuropsychiatric symptoms, as well as demonstrating negative throat culture or stable titers during times of neuropsychiatric symptom remission.³ A child who has multiple symptom exacerbations without evidence of streptococcal infection would not be considered part of the PANDAS subgroup, nor would a child who has numerous streptococcal infections without subsequent symptom exacerbations.

Presence of Neurologic Abnormalities During Periods of Symptom Exacerbation

Neurologic examination of acutely ill children in the PANDAS subgroup reveals that 95% have choreiform movements.³ These fine piano-playing movements of the fingers are not easily confused with the writhing adventitious movements of Sydenham's chorea.²⁴ Choreiform movements are not present at rest and must be elicited through stressed postures, whereas choreatic movements are present continuously and increase with unrelated voluntary movements. In addition, choreiform movements are an isolated finding, whereas the choreatic movements of Sydenham's chorea are accompanied by a failure to sustain tetanic contractions (milk-maid's grip, snake-like tongue) and muscle weakness.^{6,18} Choreiform movements and chorea may share a common pathophysiology (related to dysfunction of the basal ganglia), but the clinical manifestations are quite distinct, and children in the PANDAS subgroup do not represent missed cases of Sydenham's chorea. In fact, rheumatic fever, including Sydenham's chorea, is a strict exclusionary criterion for the PANDAS subgroup.³

SCIENTIFIC HYPOTHESES

Clinical observations of the PANDAS subgroup led to a number of scientific hypotheses including the postulate that the tics and OCD represent sequelae of group A streptococcal infections. This eti-

ologic hypothesis involves a series of factors including pathologic strains of group A streptococcal bacteria, host susceptibility (genetic, developmental, or other), and abnormal immune responsivity (Fig 1). The working model of pathogenesis not only provides a framework for understanding the etiology of OCD and tic disorders but also allows for the development of novel intervention and prevention strategies. A recent review provides a detailed description of the model as well as ongoing research efforts directed at understanding the pathologic mechanisms involved in the PANDAS subgroup.²⁵

CLINICAL RECOMMENDATIONS

These guidelines are drawn from our clinical and research experience as well as the practice parameters of the American Academy of Child and Adolescent Psychiatry.²⁶

1. Laboratory testing: Children with an abrupt onset or exacerbation of OCD or tic disorder should have a throat culture obtained. If the symptoms have been present for >1 week, serial antistreptococcal titers may be indicated to document a preceding streptococcal infection. (Titers should be timed to catch the rise at 4–6 weeks.)
2. Use of antibiotics: Antibiotics are indicated only for the treatment of acute streptococcal infections as diagnosed by a positive throat culture or rapid streptococcal test. Clinical trials are underway to determine whether prophylactic antibiotics will be useful in the management of children in the PANDAS subgroup, but at present, they are not indicated. In the only placebo-controlled trial reported to date, penicillin administration failed to prevent streptococcal infections (14 of 35 infections occurred during the penicillin phase of the crossover trial), and thus there were no between-group differences in neuropsychiatric symptom severity.²⁷
3. Management of neuropsychiatric symptoms: Children in the PANDAS subgroup respond to treatment with standard pharmacologic and behavioral therapies. Obsessive-compulsive symptoms are treated best with a combination of medication

Model of Pathogenesis for PANDAS

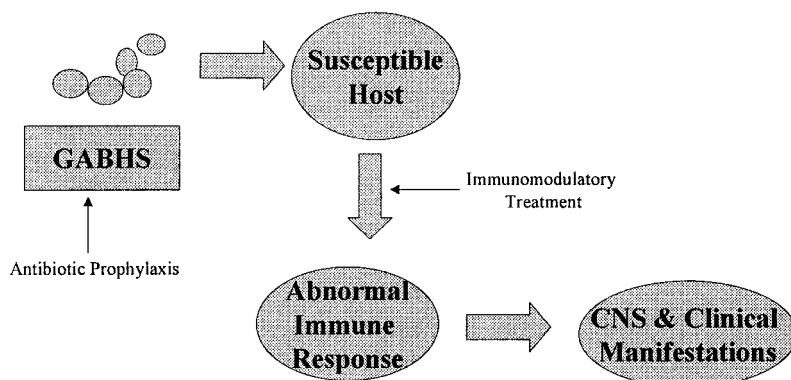


Fig 1. Model of pathogenesis for PANDAS.

(typically, a serotonin reuptake-blocking drug) and cognitive-behavior therapy, and motor and vocal tics respond to a variety of pharmacologic agents.

4. Immunomodulatory therapies: A randomized, placebo-controlled trial of intravenous immunoglobulin and therapeutic plasma exchange demonstrated significant and persistent improvements for a group of 29 severely affected children meeting criteria for the PANDAS subgroup.²⁸ The specificity of their response was demonstrated through a subsequent open-label trial of plasma exchange, which failed to produce benefits among children not meeting the PANDAS criteria.²⁹ After the publication of these reports, the American Society for Apheresis ranked therapeutic plasma exchange for poststreptococcal OCD and tic disorders "acceptable as second-line therapy or as an adjunct to primary therapy based on controlled trials."³⁰ Thus, immunomodulatory therapy may be a consideration for acutely and severely affected children in the PANDAS subgroup. Clinicians considering such an intervention are invited to contact the PANDAS research group at the NIMH for consultation.

CONCLUSIONS

The PANDAS subgroup is both a clinical entity and the subject of scientific experimentation. Systematic, longitudinal observations have demonstrated that the PANDAS subgroup has a distinct clinical presentation and an identifiable course of symptoms and that, for these children, there is a clear relationship between streptococcal infections and neuropsychiatric symptom exacerbations. Additional research is required to determine the nature of that relationship as well as to determine the etiopathogenesis of the poststreptococcal obsessive-compulsive symptoms and tics. Additional studies are required also to determine the role of immunomodulatory therapies and antibiotics prophylaxis for this group of patients. Meanwhile, it is time to end the debate about the existence of the PANDAS subgroup and begin to "call to aid the science of experimentation . . . so as to be able to know the true from the false."

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Navigating the Recent Articles on Girls' Puberty in *Pediatrics*: What Do We Know and Where Do We Go from Here?

ABBREVIATIONS. PROS, Pediatric Research in Office Settings; NHANES, National Health and Nutrition Examination Survey; NHES, National Health Examination Survey.

After the publication of the Pediatric Research in Office Settings (PROS) study on the age of onset of pubertal characteristics and menses in US girls in 1997,¹ a spate of related articles have appeared on emerging questions and controversies over recent pubertal data and the implications of these findings for clinical practice. The purpose of this commentary is to 1) summarize the consistencies and contradictions among some of these newer communications, 2) address misconceptions and misinterpretations of the PROS data, and 3) identify legitimate points of disagreement and areas for additional investigation.

A survey of just some of the recent articles demonstrates the scope of additional research both in our country and abroad.²⁻¹⁷ The 1997 PROS study, a convenience sample of 17 077 white and black girls seen in pediatric practices across the United States and Puerto Rico used the Tanner method¹⁸ to describe the ages of onset of breast development, pubic hair growth, and menarche. It found that the mean ages for these characteristics varied significantly between white and black girls (with black girls being at younger ages), the median age of menarche for black girls had dropped over the past several decades, and the ages for the onset of development seemed to be earlier than previous US studies as well as Marshall and Tanner's classic 1969 study.¹⁸ The PROS study pointed out that the prevalence of secondary sexual

characteristics in girls <8 years old was substantially higher than what had been believed previously and "that more appropriate standards for defining delayed and precocious puberty may need to be developed, that the timing of sex education in the schools may need revision, and that the etiology and effects require further study." The authors stated, "The findings of this study need to be confirmed in other research including a nationally representative sample such as HANES [Health and Nutrition Examination Survey]."¹ After the PROS study, Kaplowitz et al², using its data, provided additional analyses and new recommendations calling for the age for referral for precocious puberty to be lowered.

Between October 2002 and April 2003, *Pediatrics* alone has published 10 articles on puberty markers or issues.¹⁹⁻²⁸ Several of these articles beg for comment, in particular the articles that propose changes in practice or present interpretations of findings that contradict those of other recent articles. Six of the articles have been based wholly or in part on the most recent National Health and Nutrition Examination Survey (NHANES) data, and some present overlapping results or conflicting conclusions.^{20,21,23-25,28}

The October 2002 article by Wu et al²⁰ analyzed data from the NHANES to report on ethnic differences in secondary sexual characteristics and menarche. The authors presented mean ages of onset for breast and pubic hair growth and for menses by race and ethnicity as well as odds ratios of having attained pubertal milestones among the 3 racial/ethnic groups studied in the NHANES. Tables 1 and 2 compare these results with those of the PROS study¹ and the analyses of the NHANES data for average ages of onset of breast and pubic hair growth and menses by Sun et al²⁴ and Chumlea et al²⁵, respectively. Age at menarche was estimated by Wu et al by both the status quo method as well as an estimate based on the self-reported age using a failure time model, both under the assumption of a normal distribution of the event (Table 2). Their mean ages for menarche differ slightly from those of the Chumlea et al analysis (see below) of the NHANES data published in January 2003 because of different statistical methods. Wu et al concluded that black girls enter puberty earliest, followed by Hispanic and then white girls. Numerous studies, including the 1997 PROS study, have found earlier puberty among black girls. The Wu et al analysis provides the important additional information that racial and ethnic differences among the NHANES populations are independent of select social and economic factors.

In the same issue of *Pediatrics*, the article by Freedman et al²² looked at the relation of age at menarche to race, time period, and anthropometric dimensions by using the Louisiana population followed in the Bogalusa Heart Study. Their assessment of secular trends in menarcheal age between 1973 and 1994 found that the mean menarcheal age decreased by 9.5 months for black girls and 2 months for white girls over the 20-year time period. As in other studies, they also found that black girls matured earlier than white girls.

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