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Pediatrics 2008;121;1188-1197
DOI: 10.1542/peds.2007-2657

ARTICLE

Streptococcal Infection and Exacerbations of Childhood Tics and Obsessive-Compulsive Symptoms: A Prospective Blinded Cohort Study

Roger Kurlan, MD[a], Dwight Johnson, BS[b], Edward L. Kaplan, MD[b], and the Tourette Syndrome Study Group

[a]Department of Neurology, University of Rochester School of Medicine, Rochester, New York; [b]World Health Organization Streptococcal Reference Laboratory, Department of Pediatrics, University of Minnesota School of Medicine, Minneapolis, Minnesota

The authors have indicated they have no financial relationships relevant to this article to disclose.

What's Known on This Subject

The PANDAS hypothesis suggests that streptococcal infection can induce exacerbations of tics and obsessive-compulsive symptoms by an autoimmune process. The hypothesis has never been tested in an appropriately prospective, controlled and blinded fashion.

What This Study Adds

Our prospective blinded cohort study showed that children meeting criteria for PANDAS have more clinical exacerbations, more streptococcal infections and more links between infection and exacerbation than matched controls. However, the results do not support PANDAS as being a unique clinical entity.

ABSTRACT

OBJECTIVE. If pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections is a unique clinical entity, we hypothesized that children meeting diagnostic criteria would have more clinical exacerbations temporally linked to bona fide group A β-hemolytic streptococcus infection than matched control subjects (chronic tic and/or obsessive-compulsive disorder with no known temporal relationship to group A β-hemolytic streptococcus infection).

PATIENTS AND METHODS. Subjects included 40 matched pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections case-control pairs who were prospectively evaluated with intensive laboratory testing for group A β-hemolytic streptococcus and clinical measures for an average of 2 years. Additional testing occurred at the time of any clinical exacerbations or illness. Laboratory personnel were blinded to case or control status and clinical (exacerbation or not) condition. Clinical raters were blinded to the results of laboratory tests.

RESULTS. The cases had a higher clinical exacerbation rate and a higher bona fide group A β-hemolytic streptococcus infection rate than the control group. Only 5 of 64 exacerbations were temporally associated (within 4 weeks) with a group A β-hemolytic streptococcus infection, and all occurred in cases. The number (5.0) was significantly higher than the number that would be expected by chance alone (1.6). Yet, ≥75% of the clinical exacerbations in cases had no observable temporal relationship to group A β-hemolytic streptococcus infection.

CONCLUSIONS. Patients who fit published criteria for pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections seem to represent a subgroup of those with chronic tic disorders and obsessive-compulsive disorder who may be vulnerable to group A β-hemolytic streptococcus infection as a precipitant of neuropsychiatric symptom exacerbations. Group A β-hemolytic streptococcus infection is not the only or even the most common antecedent event associated with exacerbations for these patients. Additional intensive studies are needed to determine whether there is clinical or scientific evidence to support separating out subgroups of tic disorder and/or obsessive-compulsive disorder patients based on specific symptom precipitants. *Pediatrics* 2008;121:1188–1197

www.pediatrics.org/cgi/doi/10.1542/peds.2007-2657

doi:10.1542/peds.2007-2657

Key Words
PANDAS, group A streptococcal infection, pharyngitis, tics, obsessive-compulsive disorder, neuropsychiatric symptoms

Abbreviations
GABHS—group A β-hemolytic streptococcus
PANDAS—pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections
OCD—obsessive-compulsive disorder
DSM-IV—*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*
ASO—antistreptolysin O
anti-DNase B—antideoxyribonuclease B
CY-BOCS—Children's Yale-Brown Obsessive-Compulsive Scale
YGTSS—Yale Global Tic Severity Scale
ADHD—attention-deficit/hyperactivity disorder
ASQ-P—Conners Abbreviated Symptom Questionnaire-Parent
CDI-SV—Child Depression Inventory-Short Version
MASC—Multidimensional Anxiety Scale for Children
TS—Tourette syndrome

Accepted for publication Nov 14, 2007

Address correspondence to Roger Kurlan, MD, University of Rochester School of Medicine, Mt Hope Professional Building, 1351 Mt Hope Ave, Suite 100, Rochester, NY 14620. E-mail: roger_kurlan@urmc.rochester.edu

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

SYDENHAM CHOREA, THE neurologic sequela associated with acute rheumatic fever, is hypothesized to represent an autoimmune-mediated response to group A β-hemolytic streptococcus (GABHS) infection.[1] In 1998, Swedo et al[2] suggested that immune-mediated central nervous system manifestations of GABHS infection may not be restricted to Sydenham chorea but may also include a spectrum of neurobehavioral disturbances that they termed pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS). It was hypothesized that GABHS infection can lead both to the onset of PANDAS and to clinical exacerbations over time. The authors described 50 patients meeting their proposed criteria for PANDAS. Although they indicated that tics and obsessive-compulsive disorder (OCD) are the characteristic neurobehavioral features of PANDAS, others have since suggested that the clinical spectrum might be more inclusive.[3–8]

Support for the PANDAS hypothesis has come from some studies reporting the presence of circulating antineuronal antibodies[9–12] and also from an increased prevalence of a B cell surface marker (D8/17), which has been reported to be associated with rheumatic fever[13] in patients with poststreptococcal neurobehavioral symptoms. Reported rapid clinical responses to antibiotics[14,15] and immune-modifying therapies, including corticosteroids,[16,17] intravenous immune globulin,[10,18] and plasma exchange,[9,18,19] have been presented to support the PANDAS hypothesis.

Potential problems with the PANDAS concept have been presented, including the possibility that clinical exacerbations after GABHS infection represent a nonspecific response to stress (which is known to occur in children with chronic tic disorders and OCD).[20–23] Moreover, many subjects meeting criteria for PANDAS have no detectable antineuronal antibodies, and brain autoantibody measures in some laboratories have not been able to differentiate between PANDAS case and control subjects.[24,25] Finally, prophylactic treatment with penicillin failed to prevent clinical exacerbations,[26] and treatment studies have not used critical design elements, such as appropriate blinding, control subjects, and randomization.[27,28]

Probably the biggest shortcoming of the PANDAS hypothesis has been the absence of accurate and intensive prospective data confirming a temporal relationship between antecedent GABHS infection and the onset or exacerbation of the clinical manifestations. This is a crucial issue, because GABHS infections occur very commonly in children, and any observed association with the clinical conditions could be based on chance alone, as has proven to be the case in other disorders sometimes suspected of having a streptococcal origin (eg, Kawasaki disease or Henoch purpura). Furthermore, data from attempts to document GABHS infection with single, isolated cultures or single antibody titers are invalid because they fail to differentiate new infections from the carrier state.[23] The lack of prospective and appropriately intensive laboratory and clinical assessments has greatly confounded the interpretation of previously published studies on the phenomenology, etiology, and treatment of PANDAS.

To accurately determine whether there is a specific temporal relationship between bona fide antecedent GABHS infection and exacerbation of symptoms in children meeting published diagnostic criteria for PANDAS,[2] we conducted an intensive, blinded clinical and laboratory prospective cohort study that included non-PANDAS control subjects. We hypothesized that, if PANDAS is a unique clinical entity, then children meeting diagnostic criteria would have more clinical exacerbations temporally linked to antecedent GABHS infections than the control subjects without PANDAS.

PATIENTS AND METHODS

Patients

A total of 40 matched case-control pairs were studied.

PANDAS Cases

Case subjects met all 5 of the published diagnostic criteria for PANDAS described by Swedo et al[2]: (1) the presence of OCD and/or a chronic tic disorder (Tourette disorder, chronic motor or vocal tic disorder), defined as meeting lifetime *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV), diagnostic criteria[29]; (2) age at onset between 3 years and the beginning of puberty; (3) clinical course characterized by the abrupt onset of symptoms or by a pattern of dramatic recurrent symptom exacerbations and remissions; (4) temporal relationship between GABHS infection and the clinical course of illness (onset and/or exacerbations) as reported by the subject or parent; and (5) neurologic abnormalities such as motoric hyperactivity, tics, or choreiform movements are present during a symptom exacerbation. For criterion 4 above, we used the criteria from Swedo et al[2] that a temporal relationship exists if antecedent GABHS infection occurs within 9 months of illness onset and/or within 4 weeks of clinical exacerbation. We required that a history of a temporal relationship for antecedent GABHS infection was present for ≥2 clinical events (onset plus 1 exacerbation or 2 exacerbations) and that laboratory evidence of an antecedent GABHS infection (positive throat culture and/or elevated antistreptolysin O [ASO] or antideoxyribonuclease B [anti-DNase B] titers) was present for ≥1 of the clinical events. In addition, we required the following for enrollment of case subjects: currently ≤16 years of age and informed consent provided by parent or guardian and assent provided by the subject. Exclusion criteria for PANDAS cases included the following: (1) possible Sydenham chorea; (2) presence of mental retardation, pervasive developmental disorder, or a secondary tic disorder other than PANDAS (eg, drug induced or neuroacanthocytosis); and (3) a psychiatric disorder other than OCD or tics as the primary focus of treatment.

Control Subjects

Inclusion criteria for control subjects were as follows: (1) presence of OCD and/or a chronic tic disorder by DSM-IV criteria[29]; (2) age at onset between 3 and 14 years; (3) currently ≤16 years of age; (4) on specific and focused questioning, the subject and/or parent do not report that the clinical course of illness (onset or exacerbations) is temporally related to GABHS infection; and (5) informed consent provided by parent or guardian and assent provided by the subject. The same exclusion criteria for PANDAS case subjects were also applied to control subjects. For both case and control subjects, if >1 sibling in the same family was eligible, only 1 child was enrolled.

Control subjects were individually matched to case subjects by age (within 2 years), geography (same enrolling site), and time of year (enrolled within 1 month of each other), because these are the primary factors influencing exposure to GABHS. If a member of a case-control pair dropped out of the study, he or she was replaced whenever possible within 2 months by another subject of the same type and matching characteristics. Data from the original subject and the replacement subject were treated as continual data from the same subject for purposes of analysis. All of the subjects were enrolled from among 9 clinical sites of the Tourette Syndrome Study Group (Appendix).

METHODS

At the initial visit, informed consent and/or assent were obtained. A systematic clinical interview and examination were performed to ensure that the subject satisfied all of the enrollment criteria. Information relevant to the classification of a subject as a case or control was reviewed by the principal investigator (Dr Kurlan) within 1 week to confirm that the classification was accurate. A fully structured psychiatric interview, the Diagnostic Interview Schedule for Children-DSM-IV version,[30] was used to verify that criteria for OCD or a chronic tic disorder were met. For eligible subjects, symptom severity was assessed with the following instruments: the Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) for OCD,[31] the Yale Global Tic Severity Scale (YGTSS) for tics,[32] the DSM-IV Attention-Deficit/Hyperactivity Disorder (ADHD) Rating Scale,[33] and the Child Global Assessment Scale for global functioning.[34] The parent or subject completed self-report rating scales for obsessive-compulsive symptoms (Leyton Obsessional Inventory-Child Version, Short Version),[35] tics (Tic Symptom Self-Report Scale), ADHD (Conners Abbreviated Symptom Questionnaire-Parent [ASQ-P]),[36] depression (Child Depression Inventory-Short Version [CDI-SV]),[37] and anxiety (Multidimensional Anxiety Scale for Children [MASC]).[38] The assessments for ADHD, depression, and anxiety symptoms were included to determine whether clinical exacerbations in association with GABHS infection are specific for tics and OCD or whether worsening is nonspecific and involves other childhood behavioral problems.

In addition, at the initial visit, a throat culture for GABHS and blood samples for ASO and anti-DNase B titers were obtained. All of the samples were sent by overnight courier to the World Health Organization Streptococcal Reference Laboratory at the University of Minnesota Department of Pediatrics. Throat culture processing, streptococcal serogrouping, T-protein agglutination characterization, opacity factor determination, M typing and/or *emm*-gene sequence typing, and ASO and anti-DNase B assays were performed in the streptococcus laboratory. The microbiologic and serologic methods have been described previously.[39] All of the β-hemolytic streptococci, not just group A, were grouped.

Each subject was systematically followed with clinical assessments and laboratory testing during a 24-month period. Near the end of the study, when it became apparent that the number of clinical exacerbations observed was less than the number expected, subjects completing the protocol were invited to extend the observation period by an additional few months. A throat culture for GABHS was obtained every 4 weeks. Blood was obtained for ASO and anti-DNase B titers routinely every 12 weeks. Rapid antigen detection tests were not used. A clinical evaluation visit occurred every 12 weeks and included CY-BOCS, YGTSS, DSV-IV ADHD Rating Scale, and the Child Global Assessment Scale. In addition, parents and/or subjects completed the self-report scales (Leyton Obsessional Inventory-Child Version, Short Version; Tic Symptom Self-Report Scale; ASQ-P; CDS-SV; and the MASC) every 4 weeks.

At the time of any clinical exacerbation of neuropsychiatric features, a clinical evaluation visit occurred within 3 days, a throat culture was obtained, and blood was obtained for ASO and anti-DNase B titers. Blood sampling for convalescent antibody titers was also performed 4 weeks later.

A clinical exacerbation was declared when the site clinical expert investigator determined that the subject experienced a clinically significant worsening of OCD or tics that lasted for $\geq$5 days and was not thought to be related to a reduction or discontinuation of prescribed medication. This operational definition of clinical exacerbation represented consensus criteria of our group of investigators (established after direct discussions) and was selected to reproduce clinical practice. To maintain reasonable consistency, the criteria for clinical exacerbation were reviewed at annual meetings of the research group during the study. The dates of onset of all of the clinical exacerbations were recorded. Information relevant to the determination that an exacerbation occurred was reviewed within 1 week by the principal investigator to confirm its occurrence. Whenever the subject or a household contact became ill with possible signs or symptoms of GABHS infection (operationally defined as fever, sore throat, or skin rash), the subject had a throat culture and blood sampling. Blood sampling for convalescent titers was repeated 4 weeks later. These clinical and laboratory assessments were in addition to the regularly scheduled clinical evaluations, cultures, and bleedings.

Throughout the study, laboratory personnel were unaware of subject diagnosis (PANDAS case or control) or clinical condition (exacerbation or not), and clinical raters were blinded to laboratory results. Each subject's primary care physician received laboratory results by facsimile directly from the streptococcal laboratory and made the decision about instituting appropriate therapy, which was also not revealed to the clinical raters.

During the study, subjects were allowed to take their usual medications for OCD, tics, or other conditions. Such treatment could be modified by the site investigator according to standard clinical practice. No immune-modifying or prophylactic and/or active antibiotic therapy specifically directed at PANDAS was permitted.

Each GABHS infection was classified as "definite," "probable," or "possible" based on whether a new M/*emm* type of the organism was recovered, whether a 0.2 log rise (significant rise[39]) in ASO and/or anti-DNase B titer was associated, and whether the subject had accompanying clinical symptoms of streptococcal pharyngitis (fever, sore throat, pharyngeal erythema, or exudates). Infections classified as definite were positive for

TABLE 1 **GABHS Infection Classifications**

Variable	Throat Culture Yielded GABHS	Titer Rise	Symptoms	Classification
1	+	+	+	Definite
2	+	+	−	Probable
3	+	−	+	Probable
4	−	+	+	Probable
5	+	−	−	Possible
6	−	+	−	Possible

TABLE 2 **Non-GABHS Infection Classifications**

Variable	Symptoms of Pharyngitis	GABHS Culture	Antibody Titer Rise	Throat Culture Yielded Nongroup A Strep
1	+	−	−	+
2	+	−	−	−
3	−	−	−	−

all 3 of the criteria, those classified as probable had 2 positive criteria, and those classified as possible had at least culture or serologic evidence of GABHS infection. The classification scheme for GABHS infection is shown in Table 1. A plus sign in the culture column indicates that GABHS was recovered during the episode in question (and the strain was of a heterologous M/*emm* type). Any culture positive for nongroup A streptococci (negative for GABHS) and a temporally associated antibody rise was not classified as a possible or probable GABHS infection. The 3 subcategories of probable infection as shown in Table 1 were not analyzed separately. Any potential effect of antibiotic therapy was not considered in this classification scheme. Illness and/or infections with no evident relationship to GABHS were classified into the following groups: (1) symptoms of pharyngitis with positive throat culture for a nongroup A streptococcus; (2) symptoms of pharyngitis with negative throat culture and no significant rise in antibody titers; and (3) symptoms of illness other than pharyngitis (eg, gastroenteritis or fever alone), negative culture, and no rise in antibody titer (Table 2).

It was of primary interest to identify exacerbations that were temporally associated with an antecedent GABHS infection. Various time windows were used to define a temporal association, the 1 of primary interest being the interval of 0 to 4 weeks; this window means that an exacerbation was considered to be temporally associated with an infection if the infection occurred within 4 weeks before the exacerbation. Other time windows were examined, with the widest being −4 to 8 weeks; this window means that an exacerbation was considered to be temporally associated with an infection if the infection occurred any time between 8 weeks before and 4 weeks after the exacerbation.

The duration of follow-up for each subject was divided into 2 periods: infection periods and noninfection periods. The infection period was based on the duration of the time window (see above). For example, if the time window was −4 to 8 weeks, the total duration of time that a subject spent in an infection period was the sum of the 12-week time windows over all of the infections. These windows were appropriately truncated if they overlapped or if they fell outside of the time window of the subject's participation in the study.

Under the null hypothesis of no temporal association between infections and exacerbations, exacerbations were expected to be randomly distributed between the infection periods and the noninfection periods. For each subject, the expected number of "hits" (exacerbations that are temporally associated with documented GABHS infections) under the null hypothesis was calculated as the number of exacerbations experienced by the subject multiplied by the proportion of time that the subject spent in an infection period. This quantity was summed across subjects in each group of subjects (PANDAS or control) to obtain the total number of "hits" that would be expected by chance alone.

The results are reported in terms of the observed number of "hits" in each group along with a 95% confidence interval for the true mean number of hits (given the fixed number of person-years of follow-up in this study) based on the assumption that the number of hits follows a Poisson distribution. If the lower confidence boundary was higher than the expected number of hits under the null hypothesis, then the observed number of hits was significantly higher than the number of hits expected by chance alone, using a 2-tailed significance level of 5%.

These analyses were performed using various definitions of the time window used to define an exacerbation that is temporally associated with an infection and various definitions of what constitutes a GABHS infection. The primary definition of a GABHS infection was 1 that was considered to be probable or definite according to the criteria in Table 1. These analyses were performed only for the PANDAS group, because no hits linked to GABHS infection were observed in the control group. Similar analyses were performed for illnesses and/or infections unrelated to GABHS for both the PANDAS and control groups.

Baseline characteristics of the PANDAS case and control subjects were compared using either *t* tests or Fisher's exact tests, as appropriate. The rates of infections and exacerbations were compared between the 2 groups using Poisson regression models that included case-control status as the independent variable of interest and duration of follow-up as an offset term. The model parameters were estimated using generalized estimating equations to account for the within-pair correlation. Exacerbation severity, as measured by the changes in YGTSS scores and the CY-BOCS total score between the "exacerbation visit" and the immediately preceding visit, was compared between case and control subjects using an analysis of covariance model that allowed for multiple exacerbations in the same subject. This model included case-control status as the factor of interest and the score at the visit immediately preceding the exacerbation as a covariate. A compound symmetry correlation structure was assumed to account for multiple exacerbations that may have occurred in the same subject.

RESULTS

Forty case-control pairs were enrolled between February 2002 and March 2003. Sixteen subjects (10 case subjects and 6 control subjects) withdrew at some point before completing the full protocol; the reasons for withdrawal (moved to new location, intensity of the protocol, frequent blood draws, noncompliance, or lost to follow-up) did not differ substantially between the 2 groups. During the study, 4 case and 3 control subjects were replaced. The baseline demographic and clinical characteristics of the originally enrolled case and control subjects are summarized in Table 3. The groups were comparable with the exceptions that PANDAS case subjects seemed to more often have a psychiatric diagnosis other than tic disorder or OCD. Also, PANDAS case subjects more frequently ($P = .03$) reported a positive family history of rheumatic fever. We did not make efforts beyond the historical information provided to confirm the reported family history of rheumatic fever.

The duration of follow-up was 1.94 ± 0.51 (mean ± SD) years for PANDAS case subjects and 2.08 ± 0.33 years for control subjects (counting withdrawn case subjects and their replacements as single subjects). The percentage of subjects followed for ≥2 years was 87.5% (35 of 40) for PANDAS case subjects and 92.5% (37 of 40) for control subjects. The mean number of throat cultures collected was similar for PANDAS case subjects (24.3 ± 6.8; range: 4–34) and control subjects (24.3 ± 5.4; range: 7–35), as was the mean number of sera collected for antibody testing (PANDAS: 13.9 ± 5.3; range: 1–25; control subjects: 12.7 ± 4.0; range: 4–26). As examples in support of the importance of intensive and prospective laboratory monitoring in this study, 1 subject had 23 GABHS recoveries from 25 throat cultures (all type M/*emm*-77) and another had 24 recoveries (all type M/*emm*-2) from 24 cultures.[40] At the time of initial contact, for both of these subjects, ASO and anti-DNase B titers were in the "elevated" range, and during the 25 month period of observation, both titers did not increase and remained static or even decreased. Neither subject had symptoms of pharyngitis, and neither was treated with an antibiotic at any time during the period of observation. It is clear that, in these cases likely representing the GABHS carrier state, any single positive culture or elevated antibody titer might be misinterpreted as evidence of new infection, which clearly was not the case. This, again, emphasizes the advantage of intensive observations.

As shown in Table 4, a total of 65 clinical exacerbations occurred during the study, 40 in PANDAS case subjects (in 21 subjects) and 25 in control subjects (in 14 subjects). The types of exacerbations were as follows: tics alone, $n = 26$; OCD alone, $n = 7$; ADHD alone, $n = 1$; tics and OCD, $n = 18$; tics and ADHD, $n = 5$; and tics, and OCD and ADHD, $n = 8$. Only 1 exacerbation did not involve tics or OCD, and this occurred in a control subject. 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 GABHS infections were identified, 31 in PANDAS case subjects (in 22 subjects) and 12 in control subjects (in 9 subjects). The GABHS (definite or probable) infection rates were 0.43 per person-year for PANDAS case subjects and 0.13 per person-year for control subjects.

As shown in Table 5, PANDAS case subjects had a higher risk for clinical exacerbation of tics or OCD than control subjects, but this did not reach statistical signif-

TABLE 3 Baseline Demographic and Clinical Characteristics of the Subjects

Variable	PANDAS Cases ($N = 40$)	Controls ($N = 40$)
Male gender, %	70.0	70.0
Age (mean ± SD)	11.0 ± 1.9	11.4 ± 1.7
Race, %		
White	95.0	87.5
Hispanic	2.5	0.0
Other	2.5	12.5
Clinical diagnosis		
TS, %	75.0	87.5
Chronic motor tic disorder	7.5	2.5
Chronic vocal tic disorder	2.5	0.0
Tic disorder NOS	10.0	2.5
OCD	52.5	40.0
Other psychiatric diagnoses, %		
ADHD	31.6	23.7
Separation anxiety	25.6	12.8
Specific phobia	28.2	15.4
Major depression	12.8	7.7
Positive family history, %		
Tics	45.0	47.4
OCD	52.5	42.1
ADHD	42.5	47.4
Anxiety disorder	55.0	52.6
Mood disorder	37.5	29.0
Rheumatic fever	22.5	5.3[a]
YGTSS scores (mean ± SD)		
Motor	9.8 ± 5.8	10.0 ± 5.2
Vocal	5.6 ± 5.7	5.6 ± 4.7
Total tic	15.6 ± 9.8	15.6 ± 8.5
Overall impairment	13.2 ± 13.8	11.1 ± 10.3
Total	29.1 ± 21.8	26.7 ± 17.1
Other ratings		
CY-BOCS	11.3 ± 9.0	6.9 ± 7.3[b]
ADHD	19.9 ± 13.0	19.1 ± 13.4
ASQ-Parent	6.7 ± 6.1	4.8 ± 5.0
CDI-SV	12.6 ± 2.5	12.0 ± 3.1
MASC	49.3 ± 16.3	47.3 ± 19.0
CGAS-Investigator	72.7 ± 16.5	73.5 ± 15.5
Medications used[c]		
α-Agonist	26	28
Antipsychotic	11	11
SSRI	18	26
Stimulant	13	12
Atomoxetine	11	9
Minor tranquilizer	5	8
Mood stabilizer	4	8
Baclofen	2	1
Pergolide	2	1

SSRI indicates selective serotonin reuptake inhibitor; CGAS, Children's Global Assessment Scale; NOS, not otherwise specified.

[a] $P = .03$.

[b] $P = .02$.

[c] Number of subjects taking each medication is shown. Many subjects were taking >1 medication.

TABLE 4 Numbers and Rates of Clinical Exacerbations and GABHS Infections

Variable	PANDAS Case Subjects	Control Subjects
No. of clinical exacerbations		
Tics or OCD	40	24
ADHD or other symptoms	18	2
Any	40	25
Exacerbation rates (per person-year)		
Tics or OCD	0.56	0.28
ADHD or other symptoms	0.24	0.02
Any	0.56	0.29
Number of GABHS infections		
Definite	8	5
Definite + probable	31	12
Definite + probable + possible	37	19
Culture positive for GABHS	36	16
Number of other infections and/or illnesses		
Culture positive, not group A	11	9
Pharyngitis symptoms with negative culture and no antibody rise	40	28
Non-GAS viral and/or bacterial infection	22	22
Infection rates (per person-year)		
Definite	0.10	0.06
Definite + probable	0.43	0.13
Definite + probable + possible	0.50	0.25
Culture positive for GABHS	0.49	0.21
Culture positive, not group A	0.23	0.10
Pharyngitis symptoms with negative culture and no antibody titer rise	0.47	0.33
Non-GABHS viral/bacterial infection	0.30	0.27

GAS indicates group A streptococcus.

TABLE 5 Relative Risks (PANDAS Cases and/or Controls) for Exacerbations and Infections

Variable	RR	95% CI	*P*
Clinical exacerbations			
Tics or OCD	1.78	0.96–3.30	.07
GABHS infections			
Definite	1.71	0.58–5.05	.33
Definite + probable	2.76	1.44–5.30	.002
Definite + probable + possible	2.08	1.17–3.70	.01
Culture positive for GABHS	2.40	1.30–4.45	.005
Non-GABHS infections and/or illnesses			
Pharyngitis symptoms, culture positive, not group A	1.31	0.41–4.12	.65
Pharyngitis symptoms, negative culture, no antibody titer rise	1.53	0.92–2.52	.10
Other non-GABHS viral and/or bacterial infection	1.07	0.63–1.80	.80

RR indicates relative risk; CI, confidence interval.

icance (relative risk: 1.78; $P = .07$). PANDAS case subjects were also at increased risk for GABHS infection when compared with control subjects. This was only statistically significant for infections classified as definite or probable or definite or probable or possible (Table 5). PANDAS case subjects did not have a significantly higher incidence of symptoms consistent with a non-GABHS infection (Table 5).

For our primary analysis, 4 weeks was the selected time window between GABHS infection and clinical exacerbation to define a hit (exacerbation temporally associated with an antecedent GABHS infection), because this is the time period originally described for PANDAS.[2] With this time interval and considering definite or probable GABHS infections, only 5 hits were observed out of the 64 clinical exacerbations of tics and/or OCD. All of the hits occurred in PANDAS subjects. The number of hits expected by chance alone fell slightly outside of the 95% confidence interval for the true mean number of hits, suggesting that, in PANDAS case subjects, exacerbations were significantly associated with antecedent infection (4 weeks after an infection). Similar results (but only 3 hits) were seen when considering only GABHS infections classified as definite. No hits were observed in control subjects for GABHS infections, although the expected number of hits was extremely small (0.03 for definite GABHS infections and 0.13 for definite or probable GABHS infections) given the relatively low number of exacerbations of tics and/or OCD[24] and GABHS infections (5 definite and 12 definite or probable) observed in this group.

We also analyzed other definitions of GABHS infection and other time windows, including up to 8 weeks after an infection and a 2- to 4-week period before the identified infection to account for the possibility that the infection might have been present before our culture and blood sampling times (Table 6). Although latencies of up to several months have been reported between GABHS infection and the onset of Sydenham chorea, our study focused on clinical exacerbations of PANDAS and not onset of the condition, and latencies >8 weeks

TABLE 6 Observed and Expected Number of Hits (PANDAS Case Subjects)

Infection Classification	Observed No. of Hits	95% CI	Expected No. of Hits
Definite GABHS infections, time window, wk			
−2 to 4	3	0.62–8.77	0.88
−2 to 6	4	1.09–10.24	1.17
−2 to 8	4	1.09–10.24	1.46
−4 to 4	4	1.09–10.24	1.15
−4 to 6	5	1.62–11.67	1.44[a]
−4 to 8	5	1.62–11.67	1.73
0 to 4	3	0.62–8.77	0.58[a]
0 to 6	4	1.09–10.24	0.88[a]
0 to 8	4	1.09–10.24	1.17
Definite or probable GABHS infections, time window, wk			
−2 to 4	8	3.45–15.76	2.42[a]
−2 to 6	9	4.12–17.08	3.16[a]
−2 to 8	9	4.12–17.08	3.91[a]
−4 to 4	9	4.12–17.08	3.22[a]
−4 to 6	10	4.80–18.39	3.96[a]
−4 to 8	10	4.80–18.39	4.62[a]
0 to 4	5	1.62–11.67	1.60[a]
0 to 6	6	2.20–13.06	2.34
0 to 8	6	2.20–13.06	3.09

CI indicates confidence interval.
[a] $P \leq .05$.

would be unlikely to have etiologic significance. The results might have differed if such long latencies were assessed. The assessment of these other combinations of time intervals and infection classifications revealed a general trend suggesting that exacerbations of tics and/or OCD were temporally associated with GABHS infections in PANDAS case subjects. However, based on all of these analytic strategies, we found that 75.0% to 92.5% of exacerbations in PANDAS case subjects occurred with no observed evidence of a temporal relationship to GABHS infection.

When considering non-GABHS illnesses and/or infections, no hits were observed for any time window analyzed for the PANDAS subjects. This included group G streptococci (acquired by 4 subjects during the study), which can cause pharyngitis and are known to have acquired some group A characteristics, such as M-like surface proteins. Although control subjects experienced no hits for GABHS infections, some temporal associations with clinical exacerbations were observed for non-GABHS illnesses and/or infections in this group. Those reaching statistical significance at the nominal 5% level are shown in Table 7. There was no predominance of any specific M/*emm* among the episodes leading to hits.

The severity of the exacerbations of tics and/or OCD is described for PANDAS case and control subjects in Table 8. There were significant mean increases in the YGTSS total tic and total scores in PANDAS subjects at the time of exacerbation; the magnitudes of the mean increases were slightly less for control subjects, but the differences between case and control subjects were not statistically significant. Similar results were seen when the exacerbations were restricted to those involving tics and those involving OCD. The lack of statistical significance for some of these results, particularly in control subjects, needs to be interpreted in light of the small numbers of exacerbations observed and the correspondingly wide confidence intervals, as shown in Table 8.

TABLE 7 Observed and Expected Number of Hits (Control Subjects): Non-GABHS Infections

Infection Classification	Observed No. of Hits	95% CI	Expected No. of Hits
Pharyngitis symptoms, negative culture, no antibody titer rise, time window, wk			
−2 to 6	4	1.09–10.24	1.01[a]
−4 to 4	4	1.09–10.24	0.98[a]
−4 to 6	5	1.62–11.67	1.24[a]
−4 to 8	5	1.62–11.67	1.50[a]
No pharyngitis symptoms, negative culture, no antibody titer rise, time window, wk			
−2 to 4	5	1.62–11.67	1.60[a]
−2 to 6	6	2.20–13.06	2.15[a]
−4 to 4	6	2.20–13.06	2.11[a]
−4 to 6	7	2.81–14.42	2.65[a]

Only time windows with results statistically significant at the nominal 5% level are shown. CI indicates confidence interval.
[a] $P \leq .05$.

DISCUSSION

In this prospective, blinded, case-control study of children who met published diagnostic criteria for PANDAS, the large majority of clinical exacerbations could not be linked to antecedent bona fide GABHS infection. Although the rate of exacerbations temporally linked to GABHS infections exceeded that expected by chance alone, the increase was marginal. The small number of exacerbations linked to GABHS in the PANDAS group did not seem to be clinically distinct from the majority of exacerbations that were not linked to the infection. Our study clearly demonstrated that single or infrequent cultures or serum collections are inadequate and misleading when determining whether a bone fide GABHS infection has occurred. This has been a weakness of several previous reports where intensive prospective observations have not been made.

It is important to note that our study did not address a potential association between GABHS infection and onset of symptoms, an important aspect of the PANDAS hypothesis, but we only addressed subsequent clinical exacerbations. Perrin et al[41] prospectively followed 814 children presenting with sore throat in a community pediatric practice and found no evidence that those culture positive for GABHS were more likely to develop tics or OCD during the subsequent 3 months. In this study, however, all of the patients newly diagnosed with GABHS were treated with antibiotics, leaving the possibility that such prompt treatment might have reduced the risk of developing neuropsychiatric symptoms.

Our study results must be interpreted with caution, because the number of clinical exacerbations and the number of GABHS infections observed were smaller than originally anticipated, particularly in control subjects. Based on published descriptions of the observed course of PANDAS case subjects by Swedo et al,[26] we expected 3 exacerbations per person-year but observed only 0.56 per person-year, and we expected 0.85 GABHS infections (definite or probable) per person-year but observed only 0.43 per person-year.

It is surprising that our study, which included longer, more frequent, and more intense clinical and laboratory monitoring than any other published study of PANDAS, identified an unexpectedly small number of exacerbations and GABHS infections, but these results have important implications. First, although meeting published diagnostic criteria of Swedo et al,[2] our PANDAS case subjects seem clinically different. The course of our cohort was more benign than described,[2,15,26] characterized by a rate of only 1.12 exacerbations of symptoms in 2 years and exacerbation severity not substantially greater than that in the control subjects. This observation indicates that, at least during our ~2-year observation period, PANDAS case subjects treated with standard therapies for their tics, OCD, or behavioral symptoms generally did very well clinically. Prophylactic antibiotic or immune-modifying therapies were not allowed for our PANDAS subjects, and it is unclear how such treatments aimed at a postinfectious autoimmune mechanism[14–19] could substantially impact what seems to be an already seemingly benign course with standard symp-

TABLE 8 **Severity of Tics and/or OCD Exacerbations in PANDAS Case and Control Subjects**

Variable	PANDAS Case Subjects			Control Subjects			PANDAS − Control Difference		
	Mean Change	95% CI	*P*	Mean Change	95% CI	*P*	Mean Change	95% CI	*P*
YGTSS									
Total score	11.0	(4.2 to 17.9)	.003	6.8	(−0.9 to 14.5)	.08	4.2	(−6.1 to 14.5)	.41
Total tic score	4.8	(1.5 to 8.1)	.006	2.2	(−1.6 to 6.0)	.25	2.6	(−2.4 to 7.7)	.30
CY-BOCS	1.6	(−0.4 to 3.6)	.11	1.0	(−1.1 to 3.1)	.34	0.6	(−2.2 to 3.5)	.66

Mean change indicates the mean change in score between the "exacerbation visit" and the immediately preceding visit, adjusted for the score at the immediately preceding visit using an analysis of covariance model (see text for details); CI, confidence interval.

tomatic therapy. Of interest, our observed rate of exacerbations (0.56 per person-year) was similar to the rate in the "treatment year" reported by Snider et al[15] (0.5 per person-year for those treated with penicillin and 0.9 for those treated with azithromycin) to support the efficacy of prophylactic antibiotics for PANDAS. Our study indicates that these low rates of exacerbation can be seen in patients meeting criteria for PANDAS in the absence of prophylactic antibiotics. Contrary to the impression conveyed in the original descriptions of PANDAS,[2] only a small minority (7.5%–25%) of the clinical exacerbations in our case subjects had credible evidence of being associated with GABHS infection, which makes the rationale for prophylactic antibiotic therapy even less appealing.

Up to now, most clinicians have regarded stimuli that might exacerbate Tourette syndrome (TS) and/or OCD symptoms as nonspecific, pointing to the notion that virtually any type of stress might precipitate tics. This is 1 of the reasons that led to questioning of the PANDAS hypothesis, because it was unclear whether GABHS infection was a truly unique and specific precipitant.[20–23] Indeed, a recent prospective longitudinal study has documented that increases in psychosocial stress are predictive of future symptom severities in children with TS and/or OCD.[42]

Our findings did reveal some important differences between subjects classified as having PANDAS and the control subjects, however. PANDAS case subjects had more clinical exacerbations, more GABHS infections, a higher percentage of a positive family history of rheumatic fever, and were the only subjects to demonstrate any exacerbations with a temporal link to antecedent GABHS infection. Control subjects, but not patients with PANDAS, experienced some clinical exacerbations temporally linked to non-GABHS infections.

These findings suggest to us a refined conceptualization of the clinical entity of TS and/or OCD, incorporating a heterogeneity of potential precipitants for exacerbations that might differ in type and sensitivity from patient to patient. Within this viewpoint, PANDAS would represent a subgroup of patients with TS and/or OCD whose symptoms are vulnerable to GABHS infection, although not exclusively. A community-based case-control study found that children presenting with tics or OCD were more likely than control subjects to have had a GABHS infection in the previous 3 months, and the risk was higher in those with multiple infections.[43] That retrospective study may also have identified a subgroup of patients with TS and/or OCD whose symptoms are sometimes linked to GABHS infection. Perhaps these patients have an inherited susceptibility to infection with this organism (as suggested by the higher number of infections seen in our subjects with PANDAS) or a disturbed immune response to GABHS (as suggested by the more frequent family history of rheumatic fever that we observed). The more frequent report of family members with rheumatic fever by subjects with PANDAS could, on the other hand, be because of recall bias in individuals focused on GABHS infection as a possible cause of their symptoms.

It is possible that there are other patient subgroups that may be susceptible to other precipitating factors, such as other types of infections or emotional stress. In support of this possibility is the temporal association between clinical exacerbations and non-GABHS acquisition that we identified in some of our control subjects. Also, a recent study identified the common cold as a precipitant of clinical exacerbations in children with tics.[44]

It is questionable whether there is any heuristic value in separating out TS and/or OCD subgroups based on their typical precipitants (as has been done for PANDAS), but this might be reasonable if there are identified differences in neurobiologic mechanisms or therapeutic responses. The more frequent psychopathology in our group with PANDAS suggests that certain brain regions might have special vulnerability to GABHS-related mechanisms if they are indeed distinct. Further studies of genetic background, circulating antineuronal antibodies, cytokines, and other immune factors may be helpful in ultimately determining whether a GABHS-related TS and/or OCD subgroup has unique pathogenetic mechanisms. Our findings suggest that the subgroup of patients with TS and/or OCD whose symptoms are sometimes related to GABHS infection (ie, those meeting criteria for PANDAS) has a fairly benign clinical course when treated with standard therapies for their symptoms. Well-designed controlled clinical trials can determine whether antibiotic or immune-modifying therapies add any therapeutic or prophylactic value.

CONCLUSIONS

The overall findings from our study suggest that children with PANDAS represent a subgroup of patients with TS or OCD who may be susceptible to GABHS infection as a precipitant of their symptoms. The more frequent family history of rheumatic fever reported by the subjects with PANDAS suggests that they may have a genetic vulnerability to GABHS infection in general or infection with certain strains of GABHS that might induce autoimmune manifestations, but more study of this possibility is needed to document any importance. It is likely that there may be other TS and/or OCD subgroups with precipitants other than GABHS. Further research on disease mechanisms and therapy are needed to determine whether separating out subgroups based on clinical precipitants has clinical or scientific merit. Based on the uniqueness of our observations, it is clear that careful prospective and intensive clinical and laboratory assessments are critical for such future studies.

APPENDIX. MEMBERS OF THE TOURETTE SYNDROME STUDY GROUP

Principal Investigator
Roger Kurlan, MD (University of Rochester)

Coprincipal Investigator
Caroline M. Tanner, MD (Stanford University)

Chief Biostatistician
Michael P. McDermott, PhD (University of Rochester)

Project Managers
Nancy Pearson, RN, MS; Elisabeth A. de Blieck, MPA, CCRC (University of Rochester)

Clinical Trials Coordination Center Director
Karl Kieburtz, MD (University of Rochester)

Advisory Committee
Judah Denburg, MD (McMaster University); Benjamin Lahey, PhD (University of Chicago); James F. Leckman, MD (Yale University); David Oakes, PhD (University of Rochester); John Walkup, MD (Johns Hopkins)

Site Investigators
Donald Gilbert, MD; Tara Lipps, RN, MSN, CNP (Cincinnati Childrens Hospital); Barbara Coffey, MD, MS; Daniel Geller, MD; Loren Gianini; Fé Vivas (Harvard University/McLean Hospital); Robert King, MD; James F. Leckman, MD; Heidi Grantz, MSW; Eileen Hanrahan, RN, MS, PNP; Barbara Peterson-Cremer; Susan Quatrano (Yale University); Leon Dure, MD; Jane Lane, RN, BSN; Donna Pendley, LPN (University of Alabama); Barbara Coffey, MD; Rachel Goldman Shechter; Lauren Santucci (New York University); Harvey Singer, MD; Dana Bridges, MS, CFNP (Johns Hopkins); Cathy L. Budman, MD; Denise Petrizzi, MS, PNP; Kristan Baker; Jennifer Newman, MA (North Shore-Long Island Jewish Health System); Peter G. Como, PhD; Cheryl Deeley, MS, RNc (University of Rochester); Bradley Schlaggar, MD, PhD; Angie Wernle, RN (Washington University); Thomas Lowe, MD; Sharane Darlington; Carol Lindemann, RN, MS, NP (University of California San Francisco)

ACKNOWLEDGMENTS
This work was supported by National Institutes of Health (National Institute of Neurological Disorders and Stroke) research grant 1RO1 NS42240. The Tourette Syndrome Association (Bayside, NY) provided support for the Streptococcal Reference Laboratory. Special thanks to Karen Lundon for logistic support and to Cheryl Kunde for technical assistance.

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