

## Clinical Factors Associated with Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections

Tanya K. Murphy, MD, Eric A. Storch, PhD, Adam B. Lewin, PhD, Paula J. Edge, BS, and Wayne K. Goodman, MD

**Objective** To explore associated clinical factors in children with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS).

**Study design** Children with tics, obsessive-compulsive disorder, or both (n = 109) were examined with personal and family history, diagnostic interview, physical examination, medical record review, and measurement of baseline levels of streptococcal antibodies.

**Results** Significant group differences were found on several variables, such that children in whom PANDAS (versus without PANDAS) were more likely to have had dramatic onset, definite remissions, remission of neuropsychiatric symptoms during antibiotic therapy, a history of tonsillectomies/adenoidectomies, evidence of group A streptococcal infection, and clumsiness.

**Conclusion** The identification of clinical features associated with PANDAS should assist in delineating risks for this subtype of obsessive-compulsive disorder/tics. (*J Pediatr* 2011; ■:■-■).

The term PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections) refers to a disorder in children who manifest symptoms of obsessive-compulsive disorder (OCD), tic disorders, or both associated with a distinctive course, a temporal association with group A streptococcal (GAS) infection, and evidence of concurrent neurologic abnormalities (ie, severe hyperactivity, fine motor skill loss [handwriting deterioration], or adventitious movements such as choreiform movements).<sup>1</sup> The distinctive course is defined by prepubertal onset of symptoms, episodic symptom severity, and a range of other psychiatric symptoms (eg, irritability, frequent mood changes, separation anxiety, hyperactivity, late-onset attention problems, personality change, oppositional behaviors), sleep disturbances, and deterioration in math skills and handwriting.<sup>2,3</sup>

Distinguishing PANDAS from other presentations of OCD or tics and, occasionally, from Sydenham chorea (SC) confounds researchers and clinicians, making it difficult to establish practical treatment protocols. Currently, careful delineation of the neuropsychiatric course offers the best framework with which to study the proposed GAS association. A core feature of PANDAS has been a dramatic onset and a fluctuating course, with course characteristics (eg, episodic, sawtooth, remitting, progressing, chronic) likely varying with age of onset, illness duration, pattern of co-morbidity, and the patient's sex. Although both tic and OCD have the potential to manifest a chronic and disabling course, only tic disorder nosology acknowledges the potential for an episodic course. Perhaps less recognized, OCD often has an episodic course,<sup>4</sup> with some individuals spontaneously remitting.<sup>5</sup> Whether children with a PANDAS subtype typically will go on to remission or progress to a more chronic course of illness is not known. The symptom course that is characteristic of PANDAS may not differ from the typical course of OCD and tics early in the illness.

With the exception of children with an explosive onset of OCD/tics occurring simultaneously with GAS, the timing and the type of GAS association to make a definitive argument for PANDAS has not been well defined. The main issue is the differentiation of a true inciting GAS infection, whether clinical or subclinical, from GAS carrier states. Even further uncertainty exists on how much importance to ascribe to GAS exposure from close contacts. How synchronous the temporal association between GAS infection (or exposure) and symptom-onset has thus far been undefined. It has been proposed that neuropsychiatric

From the Department of Pediatrics, University of South Florida, St. Petersburg, FL (T.M., E.S., A.L.); Department of Psychiatry, University of Florida, Gainesville, FL (P.E.); and Department of Psychiatry, Mount Sinai School of Medicine, New York, NY (W.G.)

Supported by National Institute of Mental Health (R01 MH063914 and K23 MH01739). T.M. received research funding from National Institutes of Health/National Institute of Mental Health, Center for Disease Control, Tourette Syndrome Association, Otsuka Pharmaceuticals, Forest Pharmaceuticals, and Ortho-McNeill Janssen Pharmaceuticals. E.S. receives funding from National Institutes of Health/National Institute of Mental Health, National Institutes of Health/National Institute of Child Health and Human Development, The Brain and Behavior Research Fund, Otsuka Pharmaceuticals, Foundation for Prader-Willi Research, Tourette Syndrome Association, All Children's Hospital Research Foundation, and Ortho-McNeill Janssen Pharmaceuticals. A.L. receives funding from NARSAD, the International Obsessive-Compulsive Disorder Foundation, the University of South Florida Research Council, Otsuka Pharmaceuticals, and the Joseph Drown Foundation. The other authors declare no conflicts of interest.

0022-3476/\$ - see front matter. Copyright © 2011 Mosby Inc. All rights reserved. 10.1016/j.jpeds.2011.07.012

anti-A <sub>CHO</sub>	Anti-group A streptococcal carbohydrate antigen
anti-DNaseB	Anti-deoxyribonuclease B
ASO	Antistreptolysin O
GAS	Group A streptococcal
OCD	Obsessive-compulsive disorder
PANDAS	Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections
SC	Sydenham chorea

symptom-onset that occurs 1 to 6 months after GAS infection could be a chance association.<sup>6</sup> However, in cases of pure SC (no evidence of carditis), an infection triggered etiology generally is presumed by the presence of GAS antibody elevations that can be observed after a lag between the suspected inciting infection and the onset of symptoms. GAS antibody elevations observed within weeks of the onset of OCD or tics is not enough in the current state of the field to establish a diagnosis of PANDAS.

Unfortunately, PANDAS criteria and associated clinical features that may serve to differentiate PANDAS from OCD/tics disorders without PANDAS are not well established. The purpose of this study was to examine which core features of PANDAS (eg, OCD/tic symptom course, GAS infection history, neurologic symptoms, and immune history) provide the most meaningful differentiation between subjects with and without a PANDAS classification and which additional clinical factors best exemplify the PANDAS presentation to advance the understanding of risks related to disease onset.

## Methods

A total of 109 patients with childhood-onset OCD, tics, or both, ages 4 to 17 years, were asked to participate in the study. The study inclusion criterion was meeting the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria for OCD, a tic disorder, or both. Recruitment was weighted to enrolling children with history of any infection-related symptom flare-ups or history of dramatic onset of either OCD or tics, although children not meeting these criteria also were included. Age of symptom-onset was determined by using all available information, including pediatrician records, reports from parents and teachers, and self-reports from the child. Patients with a psychotic disorder, significant medical illness, or non-tic neurologic disorder at baseline were excluded from the study. Patients on stable doses of psychotropic medication for their condition were not excluded.

### Measures

The Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime<sup>7</sup> is a structured clinical interview to assess the presence of *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* diagnoses in children. The Children's Yale-Brown Obsessive Compulsive Scale<sup>8</sup> is a clinician-rated, semi-structured interview that assesses the severity of OCD symptoms; strong psychometric properties have been demonstrated. The Yale Global Tic Severity Scale<sup>9</sup> is a clinician-rated, semi-structured interview that assesses tic severity; strong psychometric properties have been documented.

A filmed neurologic examination was conducted to record any adventitious facial and limb movements, spooning or extension of arms, or other movements based on both the neurologic examination of soft signs<sup>10</sup> and the choreiform

movement assessment.<sup>11</sup> Videotapes were scored by an experienced rater (P.E.) blinded to subjects' clinical and serologic status. In the choreiform segment, subjects were assessed with arms/hands outstretched in pronated and supinated positions (20 seconds each), then rated for severity of distal (fingers and wrist) and proximal (arms, elbows, and shoulders) choreiform (quick, jerky) movements. Movements were scored with Touwen 0 to 3 scale: 0 = no movement visible during the 20 seconds; 1 = 2 to 5 isolated twitches; 2 = 6 to 10 twitches; 3 = continuous twitching.<sup>11</sup>

The Immune-Related OCD/TS Evaluation, an evaluation tool devised by the first author, was completed by the physician with the parent of each subject. The use of this instrument with patients assumes a diagnosis of OCD or tics. The Immune-Related OCD/TS Evaluation elicited information germane to the diagnosis of immunologic conditions, infections, rheumatic fever, SC, and other movement disorders. Detailed descriptions about the course of neuropsychiatric symptoms were obtained as were examination of the presence of PANDAS operational criteria developed by Swedo,<sup>3</sup> age of onset of symptoms, symptom characteristics, and parental impression of symptom course. This instrument also screened for family history of autoimmune illnesses, recent stresses, and effect of medications on illness course.

### Study Procedures

This study was approved by the institution's human subjects review board. Study procedures were explained, the informed consent was reviewed, and parents/subjects were given the opportunity to ask questions. Before participation, parents gave written consent, and subjects gave oral assent, and when age-appropriate ( $\geq 7$  years), written assent. After participation, subjects participated in the baseline assessment with the measures aforementioned. All assessments were conducted either by the first author or by a trained clinician with experience in pediatric OCD and tic disorders. Ratings were based on patient and parent response, clinician judgment, and behavioral observation.

### Case Assignment

Participant diagnostic information, symptoms, and family history of autoimmune disorders were obtained through clinical interview, medical records, baseline laboratory tests including streptococcal antibodies, and psychological ratings. Specific areas of interest were: participant diagnosis of immunologic conditions, infections, rheumatic fever, SC and other movement disorders; course of neuropsychiatric symptoms; age of symptom-onset; details about co-morbid presentations; extent of GAS infection and exposure, other infectious triggers; recent stresses; and presence of PANDAS operational criteria as developed by Swedo et al.<sup>3</sup> For each participant, the first author assigned a classification of either "PANDAS" or "without PANDAS" (course and GAS relatedness not consistent with PANDAS) on the basis of putative criteria described by Swedo et al. To establish inter-rater reliability of the case-ness rating, the third author independently assessed a subsample of 25 cases. Assessment consisted of a review of all available data. Overall, inter-rater reliability was high (intraclass

correlation coefficient = 0.86). These data were designed to assimilate an impression of PANDAS at an initial presentation during a clinical assessment by the child's pediatrician or psychiatrist without any prospective observation.

### Streptococcal Antibodies

Three antibody assays, antistreptolysin O, anti-deoxyribonuclease B, and anti-A carbohydrate (anti-A<sub>CHO</sub>), were collected in 99 of the 109 children. The use of 3 antibodies reduces the false-negative rate of a single test from 20% to approximately 5% to 10%. All streptococcal antibody tests were performed in the University of Florida's streptococcal antibody laboratory. To minimize assay variability and to maximize the ability to detect individual's changes with time, the full complement of samples from the same patient was assayed in the same run. The Sure-View ASO test kit (Fister Scientific, Pittsburgh, Pennsylvania)<sup>12</sup> was used. Reagents used, technique, reading, and interpretation of the anti-deoxyribonuclease B (anti-DNaseB) and anti-A<sub>CHO</sub> assays have been described previously.<sup>13</sup>

Earlier studies have established that a significant antibody rise can be detected approximately 2 weeks after an acute streptococcal infection (ie, pharyngitis) and that the antibody response typically peaks 3 to 4 weeks after that infection.<sup>14</sup> A child was classified as having elevated titers when any one of the 3 levels obtained at the baseline visit was higher than the set threshold. Thresholds used were  $\geq 200$  for antistreptolysin O (ASO),  $\geq 240$  for the anti-DNaseB, and  $\geq 2.76$  for the anti-A<sub>CHO</sub> antibody levels. These levels were not age adjusted and may have resulted in some false-negative results for children in the preschool range.<sup>15</sup>

### Analytic Design

Descriptive statistics were calculated for study variables. Group differences (in PANDAS caseness) were examined

with  $\chi^2$  test; risk ratios were calculated to report likelihood of subjects with PANDAS to present with a particular criterion. No statistical correction for multiple tests was used.

## Results

A total of 109 patients (66.6% males) were asked to participate in the study. Average age was  $9.2 \pm 2.4$  years; average age of onset of disorder was  $5.7 \pm 2.5$  years. Demographic data are presented in **Table I**. Of the 109 subjects, 41 were classified as having PANDAS (28 male; mean age at evaluation, 8.63 years; SD, 2.1). Subjects without PANDAS ( $n = 68$ ) had a mean age of 9.36 years (SD, 2.3) and 38 were male. Subjects in the PANDAS group were statistically more likely to: (1) have had definite remissions in neuropsychiatric symptoms; (2) have dramatic onset of symptoms; (3) have definite remissions; (4) show remissions of neuropsychiatric symptoms during antibiotic therapy; (5) have elevated streptococcal titers; (6) have episodes of fever/sore throat at onset/flare up; (7) show positive GAS culture results with symptom onset/flare up; and (8) present with clumsiness. Risk ratios and inferential statistics are presented in **Table II**. Duration of illness was shorter in subjects classified as having PANDAS. No notable group differences were found in affective instability, episodic psychotic symptoms, OCD, tic disorder, or separation anxiety. Although not statistically significant, 61% of subjects with PANDAS had attention-deficit hyperactivity disorder versus 46% of subjects without PANDAS. An elevation of one or more streptococcal titers was found in all the subjects with PANDAS (by case definition), especially ASO antibody (**Table III**). With stringent criteria for GAS association (documented GAS culture or rising

**Table I.** Subject demographics by group classification

	PANDAS			Without PANDAS		
	Total (%)	M (%)	F (%)	Total (%)	M (%)	F (%)
Subjects enrolled	41	28 (68)	13 (32)	68	38 (56)	30 (44)
Ethnicity						
Hispanic	2 (5)	2 (7)	0	5 (7)	4 (10)	1 (3)
Asian	0	0	0	3 (4)	3 (8)	0
African American	1 (2)	1 (4)	0	0	0	0
Caucasian	38 (93)	25 (89)	13 (100)	60 (88)	31 (82)	29 (97)
Diagnosis						
OCD, no tics ( $n = 22$ )	8 (20)	5 (18)	3 (23)	14 (21)	4 (11)	10 (33)
Tic, no OCD ( $n = 19$ )	5 (12)	3 (11)	2 (15)	14 (21)	10 (26)	4 (13)
OCD+tic ( $n = 68$ )	28 (68)	20 (71)	8 (62)	40 (59)	24 (63)	16 (53)
ADHD ( $n = 56$ )	25 (61)	18 (64)	7 (54)	31 (46)	20 (53)	11 (37)
Affective instability	24 (59)	15 (54)	9 (69)	42 (62)	24 (63)	18 (60)
Psychotic symptoms	5 (12)	4 (14)	1 (8)	6 (9)	3 (8)	3 (10)
Separation anxiety	12 (29)	8 (29)	4 (31)	15 (22)	7 (18)	8 (27)
Duration of illness, years*	2.8	2.8	2.7	3.9	3.8	4.0
Age at onset, years	5.9	5.8	6.1	5.6	5.8	5.5
Ratings						
CYBOCS	21.8 $\pm$ 7.3	21.2 $\pm$ 7.6	22.8 $\pm$ 6.7	20.6 $\pm$ 9.6	19.9 $\pm$ 10.1	21.3 $\pm$ 8.9
YGTSS	21.7 $\pm$ 9.9	19.56 $\pm$ 9.7	21.2 $\pm$ 10.8	17.2 $\pm$ 9.9	18.2 $\pm$ 10.3	15.5 $\pm$ 9.2

ADHD, attention-deficit hyperactivity disorder; CYBOCS, Children's Yale-Brown Obsessive Compulsive Scale; YGTSS, Yale Global Tic Severity Scale.

\*Duration of illness was significantly shorter for those youth meeting PANDAS caseness versus youth who did not ( $t(107) = -2.27, P < .025$ ).

**Table II.** Frequency of symptom item adherence by cases with PANDAS

	Total (n = 109)		PANDAS (n = 41)		Without PANDAS (n = 68)		PANDAS vs. without PANDAS	
	n	%	n	%	n	%	$\chi^2$	Risk ratio
<b>Diagnosis/course</b>								
Definite prepubertal symptoms	103	94.5	40	97.6	63	92.6	—*	1.05
Male sex	66	60.6	28	68.3	38	55.9	1.65	1.22
OCD only	22	20.2	8	19.5	14	20.6	.02	.95
Tic disorders only	19	17.4	5	12.2	14	20.6	1.25	.59
OCD and tic disorder	68	62.4	28	68.3	40	58.8	.98	1.16
Definite remissions	68	62.4	31	75.6	37	54.4	4.90 <sup>†</sup>	1.39
Dramatic onset	62	56.9	29	70.7	33	48.5	5.14 <sup>†</sup>	1.46
Dramatic flare-ups	73	67.0	29	70.7	44	64.7	.42	1.09
Onset new and significant but not dramatic	28	25.7	11	26.8	17	25.0	.04	1.07
Dramatic onset + definite remissions	40	36.7	21	51.2	18	26.5	6.82 <sup>†</sup>	1.94
<b>Infection related</b>								
Rising ASO/DNaseB/A <sub>CHO</sub> titers	7	6.4	5	12.2	2	2.9	—*	4.15
Elevated ASO/DNaseB/A <sub>CHO</sub> titers (of 99 with baseline data)	77	77.8	39	100	38	63	18.4 <sup>‡</sup>	1.58
Remission of neuropsychiatric symptoms during antibiotic therapy	17	15.6	12	29.3	5	7.4	9.33 <sup>§</sup>	3.98
GAS exposure via a family member	13	11.9	2	4.9	11	16.2	—*	.30
Fever and/or clinical sore throat without GAS confirmed	23	21.1	5	12.2	18	26.5	3.3	.46
Positive GAS culture	59	54.1	32	78.0	27	39.7	15.14 <sup>‡</sup>	1.96
Rising titers or positive GAS culture	62	56.9	34	82.9	28	41.2	18.2 <sup>‡</sup>	2.01
Frequent GAS infections before 7 years of age	53	48.6	23	56.1	30	44.1	1.47	1.27
History of tonsillectomies/adenoidectomies	34	31.2	19	46.3	15	22.1	7.03 <sup>§</sup>	2.10
<b>Neurologic</b>								
Compulsive/frequent urination	34	31.2	17	41.5	17	25.0	3.23	1.66
Handwriting deterioration	24	22.0	12	29.3	12	17.6	2.01	1.66
Choreiform	81	74.3	32	78.0	49	72.1	.48	1.08
Enuresis	27	24.8	10	24.4	17	25.0	.01	.98
Clumsiness	17	15.6	10	24.4	7	10.3	3.86 <sup>†</sup>	2.37
Deterioration in school performance	20	18.3	10	24.4	10	14.7	1.60	1.66
Motor overflow/pronator drift	69	63.3	30	73.2	39	57.4	2.75	1.28
<b>Sum</b>								
Rising titers or + GAS culture + dramatic onset	38	34.9	26	63.4	12	17.6	21.4 <sup>‡</sup>	3.46
Rising titers or + GAS culture + definite remissions	44	40.3	25	61.0	19	27.9	11.6 <sup>¶</sup>	2.18
Rising titers or + GAS culture + dramatic onset + definite remissions	26	23.9	19	46.3**	7	10.3	18.3 <sup>‡</sup>	4.50

\* $\chi^2$  could not be determined, because at least one expected cell frequency was <5 (Fisher exact probability test indicated  $P > .05$ ).

<sup>†</sup> $P < .05$ .

<sup>‡</sup> $P < .0001$ .

<sup>§</sup> $P < .01$ .

<sup>¶</sup> $P < .001$ .

\*\*Percentages are based on available data. A number of cases were missing titer information necessary to categorize as rising/not rising, and (to a lesser degree) as high/not high.

antibodies) at onset or flare up with course features that included dramatic onset and definite remissions, 46% of the PANDAS group met this requirement versus 10% in the without PANDAS group. The remaining 54% of subjects with PANDAS had dramatic onset with GAS (n = 15), GAS exposure (n = 2), or fever (n = 5). Documentation of rise in ASO and anti-DNaseB

antibodies between time of onset to 4 to 8 weeks later was found in only a minority of subjects (on the basis of previously obtained clinical studies before baseline assessment).

## Discussion

This study was conducted to determine the strength of core and associated clinical factors with PANDAS cases. Although limitations of the study included the subjective assessment of raters on the basis of original features of PANDAS and the accuracy of recall of symptoms and onset by parents, significant study strengths include the use of objective laboratory values and extensive review of factual medical records. As defined by the putative PANDAS criteria and supported by the clinician's impression of PANDAS caseness, GAS correlation, dramatic onset, and definite remission were strong predictors. Although nearly all of our subjects were prepubertal at symptom onset, those having a shorter duration of illness were more often associated with a PANDAS presentation. One possibility is that patients examined earlier in their course of illness have

**Table III.** Titer assessments by groups

	PANDAS (n = 39)*		Without PANDAS (n = 60)*		$\chi^2$	P value
	n (%)	n (%)	n (%)	n (%)		
Elevated ASO	23 (59)	22 (37)	4.7	.03		
Elevated anti-DNaseB	19 (49)	24 (40)	.73	.39		
Elevated anti-A <sub>CHO</sub>	14 (36)	15 (25)	1.4	.24		
No elevations	0 (0)	22 (37)	40.1	<.0001		
1 titer elevations	16 (41)	16 (27)	2.2	.13		
1 titer elevations	21 (54)	19 (32)	4.8	.03		
3 titer elevations	2 (5)	3 (5)	†	.66		

\*On the basis of collected samples at baseline visit.

<sup>†</sup> $\chi^2$  could not be determined, because at least one expected cell frequency was <5 (Fisher exact probability test indicated  $P > .05$ ).

a higher reporting of GAS association and are more likely to have an episodic course with more definitive remissions. Whether this observation is related to the etiology of onset or is a clinical coincidence will need further investigation.

We did not find specificity for some characteristics thought to distinguish PANDAS, namely dramatic flare-ups and choreiform movements. Another observation that was more specific to the PANDAS group was remission or partial remission of symptoms while taking antibiotics. The design of the two published studies has precluded drawing a definitive conclusion on the efficacy of antibiotic use for PANDAS.<sup>16-19</sup> The safety, efficacy, dosing, and duration of antibiotic use for purported cases of PANDAS needs further study before recommendation.

At least one streptococcal antibody level was elevated in most patients regardless of group assignment. Although many of the patients were recruited in this study because they had some features of PANDAS (ie, flare-ups, frequent streptococcal infections, etc.), this finding is not surprising. ASO antibody level was the only antibody significantly associated with cases versus non-cases (59% versus 37%, respectively;  $P = .03$ ). Streptococcal antibody tests provide evidence only for an antecedent streptococcal infection. Elevations in these antibodies are not diagnostic of PANDAS, but require careful consideration of the clinical history and examination. In some cases, particularly for very young children, limited earlier exposures to GAS might affect likelihood of surpassing the threshold for elevated antibody levels. Other factors such as hyperlipidemia, treatment with antibiotics, and the individual's ability to mount a strong immune response, are other potential reasons for variations in antibody levels. Frequent exposure, reinfection,<sup>20</sup> or stronger than typical immune responses<sup>21</sup> to GAS are likely reasons for sustained titers or the slower rate of decline in some of these children and may contribute to a fluctuating course.<sup>5</sup>

An increased rate of OCD and Tourette syndrome in first-degree family members of patients with PANDAS<sup>22</sup> has been reported. In the case series of 54 patients with PANDAS, 39% had family history of tics and 23% had family history of OCD (when subclinical OCD cases were included) in 100 first-degree relatives. Currently, the prevalence of immune disorders in family members has not been examined in the PANDAS subtype of OCD or tics despite some clinical evidence of a linkage.<sup>1,23</sup> Family members of our subjects had a substantial prevalence of autoimmune disease compared with the general population.<sup>24</sup>

We found a high association between PANDAS cases and rate of tonsillectomies and adenoidectomies. This finding may suggest that pre-existing infections such as otitis and pharyngitis were related to risk of the development of neuropsychiatric symptoms<sup>25,26</sup> or that removal of this lymphoid tissue increased immunologic risks<sup>27,28</sup> that may be associated with increased risk of OCD/tics.<sup>5</sup> Although symptomatic GAS infections have been shown to decrease after tonsillectomy,<sup>29</sup> the role of non-carrier state subclinical infections has not been documented. Recent research has shown that children with hypertrophy of adenoids and tonsils exhibit

both local and general changes in immunologic parameters.<sup>27</sup> Both humoral (immunoglobulin A, G, M levels) and cellular (CD3+, CD4+, CD8+ lymphocyte counts) immune factors decreased significantly postoperatively, but 6 months postoperatively, findings are normal. The effect of a transient, immune modulation associated with surgical removal of the tonsils, adenoids, or both on the development of autoimmune sequelae has not been studied.

Approximately one-half our subjects had multiple streptococcal infections before the age of 7 years (49% of group overall, 56% of those with PANDAS). Recent studies<sup>3,10,30</sup> suggest risk associated with repeat GAS infections in children who have neuropsychiatric symptoms. For example, a history of multiple GAS infections within a 12-month period was associated with increased risk for Tourette syndrome (OR = 13.6).<sup>26</sup> Another source found a number of earlier GAS infections to be positively related to severity of course and incidence of relapse.<sup>3</sup> A school study examining motoric signs and behavior while obtaining monthly GAS cultures on 693 schoolchildren found that those with repeated GAS infections during the 8-month study had more frequent neuropsychiatric findings.<sup>25</sup> In our study, we were specifically interested in children with frequent GAS infections at an early age. Vulnerability to neuropsychiatric sequelae may occur when a cumulative threshold effect of repeat infections is reached in a young child. Although the development of rheumatic fever is rare in children <5 years old, the effect of early GAS infections on future immune response to GAS and neuropsychiatric vulnerability is unknown. Neuroimmune reactions may be non-specific to the type of infectious trigger and caused by an inherent, broader immunologic risk. Reasons for GAS recurrence are likely complex and numerous.<sup>31</sup> Most of the recurrences of GAS are relapses (ie, infection by the same streptococcal strain rather than new infections caused by a different strain).<sup>20</sup>

Currently, the exact prevalence of the PANDAS subtype remains unknown<sup>32</sup> because most studies of PANDAS have been based on targeted recruitment, leading to difficulties in identification of base-rates and probabilities for encountering the disorder. For example, although all our subjects had OCD, tics, or both, our study selected for subjects who met two or more PANDAS criteria (ie, prepubertal onset, fluctuating course, dramatic onset, GAS association). Most subjects were prepubertal and many had a fluctuating course, but a minority met more stringent criteria for PANDAS requiring dramatic onset and clearly identifiable association with GAS. Despite our attempt from the outset to enrich the sample with PANDAS, only 38% were assigned the PANDAS classification. This study advances the literature by validating a set of largely objective criteria compared with clinician impression. Defining risks and associated features will have a major impact on determining the etiology of this pediatric disorder and evaluating treatments. ■

*We thank Muhammad W. Sajid, MD, for his assistance in the confirmation of diagnoses, physical examinations, and inter-rater assessments, P. Jane Mutch, PhD, for ratings and institutional review*

board administration, and Mark Yang, MD, (posthumously) for his contribution in statistical design and support.

Submitted for publication Jul 29, 2010; last revision received May 24, 2011; accepted Jul 11, 2011.

Reprint requests: Tanya K. Murphy, MD, Professor & Rothman Endowed Chair, Department of Pediatrics, University of South Florida, 800 6th St, South, Box 7523, St. Petersburg, FL 33701. E-mail: [tmurphy@health.usf.edu](mailto:tmurphy@health.usf.edu)

## References

- Swedo SE, Garvey M, Snider L, Hamilton C, Leonard HL. The PANDAS subgroup: recognition and treatment. *CNS Spectr* 2001;6:419-22. 25-6.
- 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;156:356-61.
- Swedo SE, Leonard HL, Garvey M, Mittleman B, Allen AJ, Perlmutter S, et al. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: clinical description of the first 50 cases. *Am J Psychiatry* 1998;155:264-71.
- Perugi G, Akiskal HS, Gemignani A, Pfanner C, Presta S, Milanfranchi A, et al. Episodic course in obsessive-compulsive disorder. *Eur Arch Psychiatry Clin Neurosci* 1998;248:240-4.
- Murphy TK, Sajid M, Soto O, Shapira N, Edge P, Yang M, et al. Detecting pediatric autoimmune neuropsychiatric disorders associated with streptococcus in children with obsessive-compulsive disorder and tics. *Biol Psychiatry* 2004;55:61-8.
- Kurlan R, Kaplan EL. The pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS) etiology for tics and obsessive-compulsive symptoms: hypothesis or entity? Practical considerations for the clinician. *Pediatrics* 2004;113:883-6.
- Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, et al. Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry* 1997;36:980-8.
- Schall L, Riddle MA, McSwiggin-Hardin M, Ort SI, King RA, Goodman WK, et al. Children's Yale-Brown Obsessive Compulsive Scale: reliability and validity. *J Am Acad Child Adolesc Psychiatry* 1997;36:844-52.
- Leckman JF, Riddle MA, Hardin MT, Ort SI, Swartz KL, Stevenson J, et al. The Yale Global Tic Severity Scale: initial testing of a clinician-rated scale of tic severity. *J Am Acad Child Adolesc Psychiatry* 1989;28:566-73.
- Vitiello B, Ricciuti AJ, Stoff DM, Behar D, Denckla MB. Reliability of subtle (soft) neurological signs in children. *J Am Acad Child Adolesc Psychiatry* 1989;28:749-53.
- Touwen B. Examination of the child with minor neurological dysfunction. In: *Clinics in developmental medicine*. London: Heinemann; 1979. p. 53.
- Klein GC, Baker CN, Moody MD. Comparison of antistreptolysin O latex screening test with the antistreptolysin O hemolytic test. *Appl Microbiol* 1970;19:60-1.
- Ayoub EM, Harden E. Immune response to streptococcal antigens: diagnostic methods. In: Rose NR, Hamilton RG, Detrick B, eds. *Manual of clinical laboratory immunology*. 6 ed. Washington, DC: American Society of Microbiology; 2002. p. 409-17.
- Ayoub EM, Kaplan E. Host-parasite interaction in the pathogenesis of rheumatic fever. *J Rheumatol Suppl* 1991;30:6-13.
- Kaplan EL, Rothermel CD, Johnson DR. Antistreptolysin O and anti-deoxyribonuclease B titers: normal values for children ages 2 to 12 in the United States. *Pediatrics* 1998;101(1 Pt 1):86-8.
- Garvey MA, Perlmutter SJ, Allen AJ, Hamburger S, Lougee L, Leonard HL, et al. A pilot study of penicillin prophylaxis for neuropsychiatric exacerbations triggered by streptococcal infections. *Biol Psychiatry* 1999;45:1564-71.
- Budman C, Coffey B, Dure L, Gilbert D, Juncos J, Kaplan E, et al. Regarding "antibiotic prophylaxis with azithromycin or penicillin for childhood-onset neuropsychiatric disorders." *Biol Psychiatry* 2005;58:916-7.
- Gilbert D, Gerber AA. Regarding "antibiotic prophylaxis with azithromycin or penicillin for childhood-onset neuropsychiatric disorders." *Biol Psychiatry* 2005;58:916.
- Snider LA, Lougee L, Slattery M, Grant P, Swedo SE. Antibiotic prophylaxis with azithromycin or penicillin for childhood-onset neuropsychiatric disorders. *Biol Psychiatry* 2005;57:788-92.
- Lee LH, Ayoub E, Pichichero ME. Fewer symptoms occur in same-serotype recurrent streptococcal tonsillopharyngitis. *Arch Otolaryngol Head Neck Surg* 2000;126:1359-62.
- Bombaci M, Grifantini R, Mora M, Reguzzi V, Petracca R, Meoni E, et al. Protein array profiling of tic patient sera reveals a broad range and enhanced immune response against group A streptococcus antigens. *PLoS One* 2009;4:e6332.
- Lougee L, Perlmutter SJ, Nicolson R, Garvey MA, Swedo SE. Psychiatric disorders in first-degree relatives of children with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS). *J Am Acad Child Adolesc Psychiatry* 2000;39:1120-6.
- Hilario MO, Len CA, Roja SC, Terreri MT, Almeida G, Andrade LE. Frequency of antinuclear antibodies in healthy children and adolescents. *Clin Pediatr (Phila)* 2004;43:637-42.
- Murphy TK, Storch EA, Turner A, Reid JM, Tan J, Lewin AB. Maternal history of autoimmune disease in children presenting with tics and/or obsessive-compulsive disorder. *J Neuroimmunol* 2010;229:243-7.
- Murphy TK, Snider LA, Mutch PJ, Harden E, Zaytoun A, Edge PJ, et al. Relationship of movements and behaviors to group A streptococcus infections in elementary school children. *Biol Psychiatry* 2007;61:279-84.
- Mell LK, Davis RL, Owens D. Association between streptococcal infection and obsessive-compulsive disorder, Tourette's syndrome, and tic disorder. *Pediatrics* 2005;116:56-60.
- Zielnik-Jurkiewicz B, Jurkiewicz D. Implication of immunological abnormalities after adenotonsillectomy. *Int J Pediatr Otorhinolaryngol* 2002;64:127-32.
- van den Akker EH, Sanders EA, van Staaik BK, Rijkers GT, Rovers MM, Hoes AW, et al. Long-term effects of pediatric adenotonsillectomy on serum immunoglobulin levels: results of a randomized controlled trial. *Ann Allergy Asthma Immunol* 2006;97:251-6.
- 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.
- Storch EA, Murphy TK, Geffken GR, Soto O, Sajid M, Allen P, et al. Psychometric evaluation of the Children's Yale-Brown Obsessive-Compulsive Scale. *Psychiatry Res* 2004;129:91-8.
- Holm SE. Treatment of recurrent tonsillopharyngitis. *J Antimicrob Chemother* 2000;45(Suppl):31-5.
- March JS. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS): implications for clinical practice. *Arch Pediatr Adolesc Med* 2004;158:927-9.