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Streptococcal upper respiratory tract infections and psychosocial stress predict future tic and obsessive-compulsive symptom severity in children and adolescents with Tourette syndrome and/or obsessive-compulsive disorder

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Abstract

Background: One goal of this prospective longitudinal study was to identify new group A beta hemolytic streptococcal (GABHS) infections in children and adolescents with Tourette syndrome (TS) and/or obsessive-compulsive disorder (OCD) compared to healthy control subjects. We then examined the power of GABHS infections and measures of psychosocial stress to predict future tic, obsessive-compulsive (OC), and depressive symptom severity.

Methods: Consecutive ratings of tic, OC and depressive symptom severity were obtained for 45 cases and 41 matched control subjects over a two-year period. Clinical raters were blinded to the results of laboratory tests. Laboratory personnel were blinded to case or control status and clinical ratings. Structural equation modeling for unbalanced repeated measures was used to assess the sequence of new GABHS infections and psychosocial stress and their impact on future symptom severity.

Results: Increases in tic and OC symptom severity did not occur after every new GABHS infection. However, the structural equation model found that these newly diagnosed infections were predictive of modest increases in future tic and OC symptom severity, but did not predict future depressive symptom severity. In addition, the inclusion of new infections in the model greatly enhanced, by a factor of three, the power of psychosocial stress in predicting future tic and OC symptom severity.

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Conclusions: Our data suggest that a minority of children with TS and early-onset OCD were sensitive to antecedent GABHS infections. These infections also enhanced the predictive power of current psychosocial stress on future tic and OC symptom severity.

Keywords

obsessive-compulsive disorder; Tourette's syndrome; tic; group A beta hemolytic streptococcal upper respiratory tract infections; PANDAS; ADHD; major depressive disorder (MDD); structural equation modeling

Tourette syndrome (TS) and pediatric onset obsessive-compulsive disorder (OCD) are etiologically related, chronic, familial neuropsychiatric disorders that affect as many as 0.3 - 3% of the pediatric population (1,2). They are chronic disorders that can be associated with impairment and disability.

The etiologies of these disorders are unknown. It has been hypothesized that some susceptible individuals develop these symptoms as a result of post-infectious autoimmune processes. Infections with group A beta hemolytic streptococci (GABHS) have been hypothesized to be responsible. Swedo et al. (3) have identified this subgroup with the acronym PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections). In addition to OCD, TS, and tic disorders (3-5), a specific link between attention deficit hyperactivity disorder (ADHD) and GABHS has been hypothesized, but not proven (3,5-7).

Many studies have emphasized the importance of psychosocial stress in mediating the progression of autoimmune diseases (8-11). Earlier cross-sectional and longitudinal studies of TS and early-onset OCD have consistently suggested that these disorders are sensitive to stress and show a heightened stress response (12-14). Psychosocial stress has also been shown to be an important factor in the onset and course of ADHD and Major Depressive Disorder (MDD) (15-17).

The goal of this blinded prospective longitudinal study was to examine *simultaneously* both the impact of newly diagnosed GABHS infections and of psychosocial stress in children and adolescents with TS and/or OCD. We had previously shown in this same cohort the impact of psychosocial stress on future tic, OC and depressive symptom severity (12). Our *a priori* hypothesis was that both new GABHS infections and psychosocial stress would influence future fluctuations in tic, OC, and depressive symptom severity. We applied a structural equation modeling framework with latent-time varying constructs to maximize our ability to examine this hypothesis.

Method

Subjects

The 86 subjects in this study were aged 7 to 17 years. Forty-five cases were recruited as well as 41 healthy controls. During a two-year study period, participants were monitored, on average, on a monthly basis (by telephone) and thrice-yearly in-person visits. All patients were followed at the Yale Child Study Center (April, 1999 to September, 2004) (18-20). Community controls were recruited from a list of 10,000 names purchased from a telemarketing company. Controls were group-matched for age, gender, socioeconomic status, and season of the year at entry into the study. Control subjects were selected *only if* there was no lifetime personal history, for the patient or any first-degree relative of a *DSM-IV* diagnosis of a chronic tic disorder, TS, OCD, or ADHD. No ethnic or racial groups were excluded. Information on past GABHS infections was *not* used in making decisions regarding participation.

Exclusion criteria for both groups included an IQ < 75; a serious medical or neurological illness; major sensory handicaps (blindness, deafness); head trauma resulting in loss of consciousness; current (past 6 months) psychiatric disorder that could interfere with participation, such as MDD; psychosis; or a pervasive developmental disorder.

The protocol was approved by IRBs at the Yale University and the central streptococcal laboratory at the University of Minnesota. All parents provided written informed consent after the study was described to them in detail. A separate assent form was used to ensure the informed participation of the child and adolescent subjects.

Clinical assessments

When a family entered the study, information concerning the patient was collected in a two-stage process (14,18-21). Initially the families in conjunction with experienced clinicians completed the Yale Global Tic Severity Scale (YGTSS) (22) and the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) (23) using both a self- and family-reports. Depression was assessed with the Children's Depression Rating Scale-Revised (CDRS-R) (24). Anxiety was measured with the Revised Children's Manifest Anxiety Scale (RCMAS) (25).

Comorbid psychiatric diagnoses, including ADHD, were made by three expert clinicians (JFL, RAK, and PJJ) after reviewing all available information including data from the Schedule for Affective Disorders and Schizophrenia for School-Age Children (26). The same diagnostic panel used the PANDAS criteria (3) to classify patients as possible, probable, definite PANDAS or non-PANDAS cases. These criteria require: the presence of OCD and/or a chronic tic disorder; an age at onset between 3 years and the beginning of puberty; a clinical course characterized by the abrupt onset of symptoms or by a pattern of dramatic recurrent symptom exacerbations and remissions; a temporal relationship between GABHS infections and the clinical course of illness; and neurologic abnormalities. Patients with PANDAS diagnoses of "probable" or "definite" were classified into the PANDAS group.

In addition, measurements of psychosocial stress were made using parent report (Parent Perceived Stress Scale, PSS-P) (27), youth self-report (Daily Life Stressors Scale, DLSS) (28), and a clinician-rated measure of long-term contextual threat (Yale Children's Global Stress Index, YCGSI) (19). Normal controls were also assessed for their stress level for comparison with the subjects who had been diagnosed with TS and/or OCD (12).

Longitudinal Evaluations

Tic and OC symptom severities were rated by an expert rater at the approximately monthly telephone contacts using the tic portion of the YGTSS and the CY-BOCS. Clinical raters were blinded to the results of laboratory tests. In-person visits occurred approximately every 4 months for additional monitoring of clinical severity and collection of biological specimens. The PSS-P ratings were made at each telephone and each in-person encounter while the DLSS and the clinician-rated YCGSI were obtained every 4 months. Data collected from this cohort of cases and controls concerning the effects of longitudinal psychosocial stress on future ratings of tic, OC, and depressive symptom severity using an identical analytic strategy has been previously reported (12).

As previously described in detail, tic and/or OC symptom exacerbations were identified by using a two-stage algorithm (18). If an exacerbation occurred, the patient was immediately re-evaluated and scheduled for two in-person visits when additional biological specimens were collected (an "exacerbation" visit was scheduled as soon as possible and "follow-up" visit was scheduled two months after the exacerbation visit). Most families completed their regularly

scheduled encounters. However, the number of encounters varied among the subjects from 4 to 26 (median = 24). However, some of the intervals were greater than one month. On eight occasions the interval was greater than 100 days. The mean time between consecutive staff-family encounters, across all patients, was 32.3 days (SD, 11.9).

Biological Specimens

Blood samples and throat cultures were obtained approximately every four months. As described (20), following centrifugation serum was stored in aliquots at -80°C . A total of 309 (cases) and 253 (controls) blood specimens were collected. Pharyngeal swabs were cultured on standard blood agar plates (20). Grouping of the streptococci was performed using a latex bead agglutination test (29). Throat cultures were obtained at 307 patient and 250 control subject visits.

Laboratory personnel were blinded to case or control status and clinical status. In addition, the results of the throat cultures were *not* shared with the participants' primary care clinicians. We informed the families before they enrolled and signed informed consents and assents that we were not in a position to share the culture results with their primary care clinicians because the laboratory performing the cultures (DEB) was not certified to report such results. If the family agreed to participate, we then told them directly that if they had any concern about a possible pharyngeal infection that they should contact their pediatrician immediately and follow their treatment recommendations. We also sent letters to each of the clinicians and had a pediatric nurse practitioner visit each of the practices. They were encouraged to follow whatever their standard procedures were and to treat the child with antibiotics, if indicated. We also shared with them the standard practice guidelines that were in place at that time (30).

GABHS infections

Serum obtained from each blood sample was assessed for anti-streptolysin O (ASO) and anti-deoxyribonuclease B (ADB) titers with standard methods (29,31,32). Table 1 presents the Definite and Possible criteria used to diagnose new GABHS infections based on titer changes and the culture results (33). Culture data from the enrollment visits which lacked the information required to determine whether new infection had occurred were not used in the analyses. Similarly, data from visits that occurred more than 100 days after a culture visit were not used in the analyses. As a result in the patient group, a total of 225 visits were available for evaluation. The mean time interval from a culture visit to the following rating encounter was 33.4 days (SD 13.8, range 4-99 days).

Medication status

Each subject's medication history was monitored at each encounter. Information was recorded according to the use of antibiotics as well as the class of psychotropic agents (adrenergic agonists, neuroleptics, serotonin reuptake inhibitors and other antidepressants, mood stabilizers, psychostimulants, benzodiazepines, and other agents). Baseline psychotropic medication status and changes in medication status, including the use of antibiotics (in separate models) were included in the structural equation modeling.

Statistical analysis

The baseline demographic and clinical data for cases and controls as well as PANDAS and non-PANDAS subjects were compared using either t-tests or Fisher Exact tests. A Poisson regression model was used to compare rates of infections in the affected subjects group, normal controls, and PANDAS and non-PANDAS subgroups. A similar model was used to examine the rate of exacerbations (across all cases and separately for the PANDAS and Non-PANDAS cases). To assess whether exacerbations were temporally associated with an antecedent GABHS

infection, we examined 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 (33). Next, we used a repeated measures analysis of variance to determine if there was any change in symptom ratings following a newly diagnosed GABHS infection.

Finally, a structural equation modeling framework was employed to explore the relationships between newly diagnosed GABHS infections, stress, severity of tic and OC symptoms, and depression. All the coefficients in a structural equation model are simultaneously estimated via maximum likelihood method with STATA add-on module GLLAMM (34) as it accommodates different measurement schedules among multiple longitudinal measures. First, we incorporated newly diagnosed GABHS infections as a binary variable into the longitudinal path models. The timing of the newly diagnosed GABHS infections (Definite or Possible) was based on the date of the second of two consecutive blood samples that met the criteria presented in Table 1. All Baseline data pertaining to GABHS infections were excluded. Separate runs were also performed comparing newly diagnosed GABHS infections defined by Definite criteria vs. Definite or Possible criteria.

As in our earlier study (12), a latent time-varying stress construct (SC) was modeled to represent the underlying true stress level manifested by the three available longitudinal stress measures: the YCGSI, the PSS-P and the DLSS. Time-lag effect was studied with mixed effect sub-models in a structural equation framework by using the nearest recorded past reading of a longitudinal measure as a covariate for a current reading. The effects of antecedent newly diagnosed GABHS infections and prior stress level on current tic, OC and depressive symptom severity were all explored. We also excluded all data points where the interval was greater than 100 days (N=8 events). The relationships between newly diagnosed GABHS infections, psychosocial stress and tic, OC and depressive symptom severity were studied via the sub-models within the structural equation modeling framework. Please see Lin et al. (12) for additional details. The correlations among different stress measures and among different time points of a same measure in a same subject were accommodated by the stress construct that could be affected by other covariates, including newly diagnosed GABHS infections, in the same model (34).

Results

Description of study cohort

Apart from gender, the cases and controls had similar demographic characteristics (Table S1 in Supplement 1). Eleven cases were given a presumptive diagnosis of PANDAS (probable or definite) based on their history (3). With the exception of gender the PANDAS cases were similar to non-PANDAS cases and unaffected controls with respect to mean age, ethnicity, parent education, and age of symptom onset (Table S2 in Supplement 1).

At baseline, cases had higher ratings of anxiety and depression as well as higher levels of psychosocial stress compared to the normal controls. PANDAS cases also had significantly higher baseline levels of anxiety, depression and psychosocial stress compared to the healthy controls group. No differences were noted comparing the PANDAS cases and non-PANDAS cases on any of these variables (Table S2 in Supplement 1).

GABHS infections

The PANDAS cases had the highest rate of Definite or Possible GABHS infections (0.40 per person per year) as compared to the non-PANDAS cases (0.34 per person/year) or the unaffected controls (0.35 per person/year) (Table 2; Table S3 in Supplement 1). The PANDAS

group was also at an increased risk for Definite GABHS infections when compared to the normal controls or non-PANDAS patients. However, none of these differences were statistically significant (Table 3).

Antibiotic treatment

Out of the 35 Definite and 21 Possible new GABHS infections, just five were treated with antibiotics. In the patient group, there were three treated infections out of 20 Definite and 10 Possible infections. In the control group, there were only two treated infections out of 15 Definite and 11 Possible newly diagnosed GABHS infections.

Relationship between newly diagnosed GABHS infections and tic and OC symptom exacerbations

First, we examined the rate of exacerbations (as a binary YES/NO) across all cases and separately for the PANDAS and Non-PANDAS cases. The number of exacerbations was higher among the PANDAS cases (0.64 per person per year) than among the Non-PANDAS cases (0.40 per person per year), but this difference was not significant. Next, we examined the number of “hits” (exacerbations that are temporally associated with either Definite or Definite plus Possible newly acquired GABHS infections) for all cases as well as for the PANDAS and Non-PANDAS groups separately. These results were not significant (Tables S4-S6 in Supplement 1).

Next, we examined whether or not a “Definite” or “Possible” new GABHS infection was associated with either no change or an improvement in their YGTSS and/or CYBOCS scores at their next encounter. There were 25 instances of a “Definite” or “Possible” new GABHS infection. Seventeen (68%) of these encounters were associated with either no change or an improvement in their YGTSS scores at their next encounter. A similar response was observed following the 200 visits identified as not having a Possible or Definite new infection 139/200 (70%). Although the percentage of culture visits associated with a “worsening” of tic symptoms was similar following new infection (32%) and no new infection (31%), the magnitude of the increase in YGTSS scores was significantly greater in the infection group (mean increase of 9.1 ± 6.0 versus 4.6 ± 3.3 ; ($F(1,17)=3.28$, $P=0.002$). A similar pattern was seen with regard to changes in OC symptom severity such that 17 of the 25 Possible and Definite new infections (68%) and 167 of 200 (84%) culture visits not representing new infections were followed by either no change or by improvements in OC symptoms. However, just the Definite plus Possible infections were modestly associated with an increase in OC symptom severity ($F(1,21)=6.28$, $P=0.02$).

Pathway analyses of the relationship between newly diagnosed GABHS infections, measures of psychosocial stress, and future ratings of symptom severity

Pathway analyses incorporating simultaneous modeling of all the variables revealed that within the patient group the prior occurrence of a Definite or Possible newly diagnosed GABHS infection ($P<.001$) and past levels of psychosocial stress (controlling for the effects of antecedent depression) were significantly ($P<.001$) associated with a future worsening of tic severity, as measured approximately one month later (Figure 1A). In the same model, increasing chronological age ($P<.001$) was associated with tic improvement. The inclusion of gender in the model was not associated with changes in future tic severity. Although the predictive power of Definite newly diagnosed GABHS infections was modest, the inclusion of this variable in the model increased the predictive power of the stress construct by a factor of almost three (from 0.13 to 0.37) (12). When that same model was run using both Definite and Possible newly diagnosed GABHS infections, the effect of stress and GABHS infections remained significant.

Pathway analyses also revealed that psychosocial stress and Definite plus Possible (but not Definite alone) newly diagnosed GABHS infections were significant predictors of future OC symptom severity (Figure 1B). Similar to the tic severity findings, the inclusion of Definite and Possible newly diagnosed GABHS infections greatly increased by a factor of more than three the power of psychosocial stress to predict future OC symptom severity (12). Current OCD severity was also a statistically significant predictor of future depressive symptoms.

Finally, together with depressive symptom severity, the Definite or Possible newly diagnosed GABHS infections greatly increased the current psychosocial stress level (Figure 1C). However, psychosocial stress, but not newly diagnosed GABHS infections (Definite or Possible criteria) were associated with a future worsening of depressive symptom severity.

Neither the severity of anxiety symptoms recorded over the course of the study, nor a diagnosis of ADHD at entry were statistically related to the severity of tics or OC symptoms recorded during the study period (data not shown). Likewise, when data concerning changes in a subject's antibiotic or medication status were included as a predictor, there was no influence on the relative significance of the directional findings depicted in Figures 1 A, B, C.

In an exploratory analysis, we also ran the model using just the data from the eleven PANDAS cases. The effect of Definite or Definite plus Possible newly diagnosed GABHS infections on future tic and OC symptom severity was even more significant in the 11 PANDAS cases than in all the patients (data not shown).

Discussion

During this blinded, prospective longitudinal study, periods of tic and OC symptom worsening were independently associated with antecedent newly diagnosed GABHS infections as well as higher levels of antecedent psychosocial stress. Compared to the earlier reports from the same sample (12), two novel findings appear. First, the impact of psychosocial stress is stronger when antecedent newly diagnosed GABHS infections are also considered in the model (Figure 1 A & B). Second, in this analysis using structural equation modeling, we found a significant, but modest, effect of newly diagnosed GABHS infections on future worsening of tic and OC symptom severity when all of the cases were evaluated. This was also the case when we examined just the 11 PANDAS cases. However, the number of putative PANDAS cases is too small to allow any firm conclusions.

A recently completed prospective longitudinal study that included 40 matched pairs, PANDAS cases vs. non-PANDAS TS/OCD cases found that many of the tic and OC symptom exacerbations were not associated with newly diagnosed GABHS infections and that most of the newly diagnosed GABHS infections did not lead to an exacerbation (33). However, the potential confounding effects of antibiotics were not reported. Indeed in that study, of 25 "Definite" new infections, 11 (44%) were treated and a similar rate was found for "Possible" new infections (31 infections of which 13 (42%) were treated). These rates are four times higher than in the present study.

Although the actual rates of newly diagnosed GABHS infections in this study were not significantly different across groups, our data add support to the suggestion that a subset of individuals with TS and/or OCD are at higher risk to develop GABHS infections relative to normal controls (4,5) or to non-PANDAS cases (33). Two studies using large administrative data bases have both reported that prior to (4,5) initial tic disorder or OCD onset (5), that a subset of patients were more likely to have a GABHS infection compared to controls.

However, the design of our study, specifically the timing of culture collection for determining the presence of streptococci and sera for determining an immune response at the time of

symptom exacerbations, has the potential to bias our findings in the direction of identifying a higher number of newly diagnosed GABHS infections in the patient group. This bias was not present in the recently completed prospective longitudinal study by Kurlan et al. who also found that the PANDAS group had a higher rate of Definite plus Probable GABHS infections than the non-PANDAS TS/OCD cases, 0.43 vs. 0.13 per person per year, respectively (33). The reasons underlying this increased risk require further study. It is possible that these cases are at increased risk for GABHS infections, but that this increased risk is unrelated to the etiology of their condition.

Another important limitation of this study concerns the way in which the timing of a newly diagnosed GABHS infection was estimated. Since we relied on the timing of the routine follow-up visits when blood and culture specimens were obtained to diagnose new infections, the actual infection might have occurred well before it was detected. More recent studies (33, Leckman personal communication) have involved more vigorous methods including routine visits every 3 months (rather than every 4 months), monthly throat cultures (rather than just collecting culture materials at the routine and exacerbation visits), as well as collecting more clinical data in order to estimate more accurately the actual point in time when the infection occurred. Although the timing of the consecutive staff-family encounters averaged 32 days, the interval on rare occasions was >100 days. These data points of >100 days were excluded from the longitudinal modeling. In the final data set, 84% of the staff-family encounters intervals were 45 days or less.

It has been postulated that GABHS infection must be the initial autoimmune response-inciting event for PANDAS cases but subsequent symptom exacerbations may be triggered by prior infections with other infectious agents (5); a number of other potential precipitating factors have been identified including the common cold (36) and *Mycoplasma pneumoniae* (37-39). Future prospective longitudinal studies are needed to confirm these findings and to clarify whether there is a common underlying immunological mechanism at work.

The immunological mechanisms than may underlie TS, OCD or PANDAS, if any, remain in doubt. Increased activation of immune responses has been suggested by changes in gene expression profiles of peripheral immune cells, relative frequency of lymphocyte subpopulations, and synthesis of immune effector molecules. Increased activity of cell-mediated mechanisms is suggested by the increased expression of genes controlling natural killer and cytotoxic T cells, increased plasma levels of some pro-inflammatory cytokines which correlate with disease severity, and increased synthesis of antineuronal antibodies (20,40-56). However, this remains a very controversial area of science as several of these findings have not been independently replicated (57-62). For example, a study using biological specimens from the earlier Kurlan et al. PANDAS study (33) failed to replicate earlier cytokine and antineuronal antibodies abnormalities in those patients where a newly diagnosed GABHS infection preceded an exacerbation (62). It is also clear that psychosocial stress could act in concert with immune dysregulation to mediate the progression of these disorders as it does in other infectious and autoimmune diseases (6-13).

Conclusion

Our study suggests that a minority of children with TS and early onset OCD are sensitive to antecedent GABHS infections leading to a slight worsening of their tic and OC symptoms. Psychosocial stress continues to be a more potent factor associated with future worsening of tic, OC and depressive symptoms. In addition to monitoring levels of psychosocial stress, it will be important for clinicians to be vigilant with regard to possible infections and other inflammatory processes that may compound the impact of psychosocial stressors. Although it is still controversial whether the current PANDAS criteria can be used to designate a unique

clinical entity, we believe that the clinical, epidemiological, and basic science observations supports further research into the potential role of the innate and adaptive immune systems in the pathogenesis of a subset of patients presenting with the sudden onset of tics and OCD symptoms (40). In addition there is evidence that suggests that there are crucial interactions between central and peripheral dopamine function and the innate and adaptive immune systems (40,63-66).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Pathway analyses of the relationships between longitudinally collected measures of newly diagnosed group A beta hemolytic streptococcal (GABHS) infections, psychosocial stress and tic, obsessive-compulsive and depressive symptom severity

Squares depict measured variables and circles represent latent variables. The standardized coefficients represent the size of the effects and the *P*-values in parentheses represent the significance of these effects as a result of the Wald test. An effect is deemed to be statistically significant if the *P*-value for the Wald test for each of the γ 's, α 's and β 's is smaller than 0.05 (see text). The standardized coefficients are the proportion of 1.0 standard deviation (SD) of the predicted variable that can be explained by 1.0 SD change in the predicting variable.

However, since GABHS infection is an event with a binary outcome for which analysis of SD is not appropriate, the GABHS coefficient was standardized only using the SD of the respective symptom severity measure. A solid line indicates a statistically significant positive relationship; a dashed line indicates a significant inverse relationship. The thickness of the line reflects its relative significance. An arrow indicates a predictive relationship, while a line without an arrow head indicates the relative contributions to the latent variable of psychosocial stress. The Stress Construct (SC) is the latent construct derived from the Yale Children's Global Stress Index (YCGSI), the Perceived Stress Scale–Parent (PSS-P) and the Daily Life Stress Scale (DLSS). The size of the coefficients associated the SC indicate the relative contributions of the PSS-P, DLSS, and YCGSI to the latent stress construct.

A. Future tic severity. Future tic improvement was associated with advancing chronological age. The standardized coefficient of 0.33 means that following an increase of 2.7 years of age (1 SD of all measures of age in the patient population), we observed a reduction of 33% of 1.0 SD of all the YGTSS scores ($.33 \times 9.0 \approx 3.0$). In addition, newly diagnosed GABHS infections (defined by either the Definite or the Definite plus Possible criteria) were associated with future worsening of tic severity. Due to the binary nature of the GABHS infection, the standardized coefficient of 0.41 (for Definite infections) means that the new infection associated with a 3.7 point increase of the YGTSS scores compared to the YGTSS score obtained approximately one month later ($.41 \times 9.0 \approx 3.7$). In addition, increases in past depressive symptoms (Children's Depression Rating Scale-Revised, CDRS-R_{T-1}) predict higher levels of current psychosocial stress, which in turn modestly, but significantly, predict increases in future tic severity (Yale Global Tic Severity Scale, YGTSS_{T+1}). Increases in current depressive symptoms (Children's Depression Rating Scale-Revised, CDRS-R_T) are also modestly, and independently, predictive of increases in future tic symptom severity (YGTSS_{T+1}). Prior tic symptom severity (YGTSS_{T-1}) does not affect current depressive symptom ratings; and past YGTSS scores also do not significantly affect current stress levels (data not shown). In the case of future tic severity, the DLSS has the strongest predictive. The inclusion of newly diagnosed GABHS infections greatly increased (by a factor of almost three) the effect size of psychosocial stress to predict future tic symptom severity, as the standardized coefficient increased from 0.13 to 0.37 (12).

B. Future obsessive-compulsive (OC) symptom severity. Future OC symptom worsening was associated with antecedent increases in SC and with Possible newly acquired GABHS infections, but not Definite, newly acquired GABHS infections. Increases Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) scores also predict future increases in depressive symptoms (CDRS-R_{T+1}). The degree of increase in OC symptom severity following Possible GABHS infections was less than that seen in predicting future tic severity. However, the inclusion of newly diagnosed GABHS infections greatly increased by a factor of more than three the power of psychosocial stress to predict future OC symptom severity as the standardized coefficient increased from 0.26 to 0.84 (12).

C. Future Depressive Symptom Severity. Antecedent increased in depressive symptom severity and with either Definite or Possible GABHS infections predict higher levels of psychosocial stress. Current levels of psychosocial stress, in turn, predicts future depressive symptom severity.

Table 1Criteria to Determine Possible and Definite Streptococcal Infections^{*}

Possible GABHS Infections	Definite GABHS Infections
<p>Either one of the following conditions (but not both) have to be met:</p> <p>1) A log₁₀ ASO OR ADB titer increase of 0.2</p> <p>OR</p> <p>2) A new isolation of GABHS without a corresponding rise in antibody titer.</p>	<p>Any of the following conditions have to be met:</p> <p>1) A rise in titer of 0.2 log in BOTH ASO and ADB antibodies</p> <p>OR</p> <p>2) A rise in titer of greater than 0.2 log in one or both antibodies</p> <p>OR</p> <p>3) Isolation of GABHS with a corresponding rise in an antibody titer of ≥ 0.2 log</p>

^{*} The timing of the new diagnosed infections was set at the point in time when the titer change was detected. ASO = anti-streptolysin O, ADB = anti-deoxyribonuclease B, GABHS = group A beta hemolytic streptococci.

Table 2

GABHS infections

Group	Period of observation (months)	Definite GABHS infections (infections per person per year)	Definite + possible GABHS infections (infections per person per year)
Controls	895	15 (0.20)	26 (0.35)
All Cases	1020.5	20 (0.24) [*]	30 (0.35) ^{**}
PANDAS cases	242	6 (0.30)	8 (0.40)
Non-PANDAS cases	778.5	14 (0.22)	22 (0.34)

GABHS = group A beta hemolytic streptococci; PANDAS = pediatric autoimmune disorders associated with streptococcal infections. No significant differences were observed comparing the rates of infections

^{*} In the longitudinal modeling only 19 instances could be used as in one instance the time interval between the visit at which a definite infection was detected and the following visit was greater than 100 days.

^{**} In the longitudinal modeling only 25 instances could be used as 4 possible infections were detected at the final visit of the study and for one definite infection the time interval between the visit at which the infection was detected and the following visit was greater than 100 days.

Table 3

Relative Risks for GABHS infections

	Relative Risk for Definite GABHS Infections	95% CI	Relative Risk for Definite + possible GABHS Infections	95% CI
All Cases/Controls	1.17	0.60, 2.28	1.01	0.60, 1.71
PANDAS/Controls	1.47	0.57, 3.8	1.13	0.51, 2.51
PANDAS/Non-PANDAS	1.38	0.53, 3.58	1.17	0.52, 2.62
Non-PANDAS/Controls	1.07	0.52, 2.22	0.97	0.55, 1.71

None of the Relative Risks above were statistically significant.

GABHS = group A beta hemolytic streptococci; PANDAS = pediatric autoimmune disorders associated with streptococcal infections. No significant differences were observed comparing the rates of infections