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Association Between Streptococcal Infection and Obsessive-Compulsive Disorder, Tourette's Syndrome, and Tic Disorder

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ABSTRACT. *Objective.* **Reports have suggested that streptococcal infection may be etiologically related to pediatric autoimmune neuropsychiatric disorders (PANDAS), but there are few good epidemiologic studies to support this theory. Using population-based data from a large West-Coast health maintenance organization, we assessed whether streptococcal infection was associated with increased risk for obsessive-compulsive disorder (OCD), Tourette's syndrome (TS), or tic disorder.**

Methods. **This is a case-control study of children 4 to 13 years old receiving their first diagnosis of OCD, TS, or tic disorder between January 1992 and December 1999 at Group Health Cooperative outpatient facilities. Cases were matched to controls by birth date, gender, primary physician, and propensity to seek health care.**

Results. **Patients with OCD, TS, or tic disorder were more likely than controls to have had prior streptococcal infection (OR: 2.22; 95% CI: 1.05, 4.69) in the 3 months before onset date. The risk was higher among children with multiple streptococcal infections within 12 months (OR: 3.10; 95% CI: 1.77, 8.96). Having multiple infections with group A β-hemolytic streptococcus within a 12-month period was associated with an increased risk for TS (OR: 13.6; 95% CI: 1.93, 51.0). These associations did not change appreciably when limited to cases with a clear date of onset of symptoms or with tighter matching on health care behavior.**

Conclusion. **These findings lend epidemiologic evidence that PANDAS may arise as a result of a postinfectious autoimmune phenomenon induced by childhood streptococcal infection.** *Pediatrics* **2005;116:56–60;** ***obsessive-compulsive disorder, Tourette's syndrome, tic, PANDAS.***

ABBREVIATIONS. GABHS, group A β-hemolytic streptococcus; OCD, obsessive-compulsive disorder; TS, Tourette's syndrome; PANDAS, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection; GHC, Group Health Cooperative; ICD-9, *International Classification of Diseases, Ninth Revision*; ADHD, attention-deficit/hyperactivity disorder; OR, odds ratio; CI, confidence interval.

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Recent evidence suggests that group A β-hemolytic streptococcal infection (GABHS) may increase the risk for obsessive-compulsive disorder (OCD), Tourette's syndrome (TS), or tic disorder. The prepubertal onset of OCD, TS, or tic disorder with symptom exacerbation after streptococcal infection has been termed PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection).[1] The possibility for a link has been described in patients with Sydenham's chorea, who frequently display obsessive-compulsive behavior.[2,3] In 1998, Swedo et al[1] described a group of 50 children in whom GABHS infection seemed to either trigger or exacerbate symptoms of such disorders. A number of other studies have also documented the onset or worsening of OCD, TS, and tics after streptococcal infection.[1–7]

Although important, these case-series reports do not provide particularly strong epidemiologic evidence for an etiologic relationship between streptococcal infection and OCD, TS, or tic disorder. Streptococcal infection is relatively common in childhood, and its occurrence among children with these disorders may represent little more than coincidental infection at the same rate found in the general population. Studies that look at the background rate of streptococcal infection and then compare this infection rate to that found among children with PANDAS would better assess the link between these neurologic disorders and streptococcal infection and would also help quantify the strength of this relationship.

Recognizing this, Kurlan et al,[8] Swedo et al,[1] and Garvey et al[9] have called for careful epidemiologic studies into the association between these disorders and streptococcal infection. We report here the findings of a population-based case-control study that assessed the risk among previously healthy children for development of OCD, TS, or tic disorder after streptococcal infection.

METHODS

Location

This study was performed at the Center for Health Studies at Group Health Cooperative (GHC), a large West-Coast health maintenance organization. GHC has >550 000 members, with ~75 000 enrolled children between 4 and 13 years of age. The demographics of its membership are similar in age, racial and ethnic make-up, and educational attainment as those in the surrounding area of King County, Washington, the largest county in Washington State.

GHC's automated databases routinely collect diagnostic data on hospitalizations, emergency-department visits, outpatient vis-

its, and pharmacy utilization for members seen at facilities both inside and outside of the GHC system. Diagnostic data for these visits are coded according to the *International Classification of Diseases, Ninth Revision* (ICD-9) system.[10] These databases have been used for a wide range of epidemiologic and health services research.[11]

Case Definition and Study Population

We defined potential cases as children or adolescents between 4 and 13 years old with a first diagnosis of OCD (ICD-9 code 300.3), unspecified or chronic tic disorder (ICD-9 codes 307.20 and 307.22, respectively), or TS (ICD-9 code 307.23), between January 1, 1992, and December 31, 1999, at any 1 of the GHC outpatient facilities. Medical records were examined for children when diagnoses (identified by the above-listed ICD-9 codes) were made by neurologists, psychiatrists, pediatricians, psychologists, or family medicine physicians.

We restricted the base population (from which cases and controls were selected) to GHC members continuously enrolled from 4 years of age. This particular enrollment restriction was made to increase the likelihood that the initial diagnosis of OCD, TS, or tic disorder in the automated databases represented the first medical diagnosis of this condition and was not a follow-up visit for a previously diagnosed condition (for example, in a GHC member who enrolled after the onset of illness). In addition, cases and controls were required to be continuously enrolled for at least 2 years before the symptom-onset date; this 2-year period constituted the "observation period."

To minimize potential interference of drug-induced tic exacerbations, we excluded children with attention-deficit/hyperactivity disorder (ADHD) from our analysis. Children were identified as having ADHD if they had at least 1 diagnosis with ICD-9 code 314 and ≥1 prescription for ADHD medication (methylphenidate, dextroamphetamine, mixed amphetamine salts, or pemoline) during the 2-year observation period.

Medical records of potential cases were reviewed to confirm case status and ascertain the onset date of first symptoms. Case status was confirmed if the diagnosis was made according to *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, diagnostic criteria, and reviewers recorded the date of onset of first symptoms as specified by the diagnosing physician. When the physician identified a range of dates between which the symptoms began, we imputed the onset date as the midpoint of the range. If the onset date was not stated, we imputed the onset date to be the date of the initial diagnosis.

To account for the uncertainty of exact onset of symptoms, in a subanalysis we performed analyses that excluded cases with imputed onset dates. The results from these analyses did not differ appreciably, and it is worth noting that any random misclassification of onset date would lend to a conservative bias to our findings and would serve primarily to minimize the strengths of the associations that were found.

For each case, we chose up to 5 controls who were enrolled at the time of the cases' onset date, matched by gender, age (±6 months), primary care physician, and propensity to seek health care. We matched on primary care physician to control for the diagnostic behavior of individual physicians and account for the possibility that some physicians might be more (or less) likely to diagnose streptococcal infection as well as OCD, TS, or tic disorder. To control for bias resulting from care-seeking behavior, we calculated the total number of outpatient visits made by cases and controls during the observation period before the date of diagnosis and matched cases and controls such that the absolute difference in the number of visits was <10.

Exposure

We assessed prior exposure to streptococcal infection using the automated laboratory databases to identify records of group A or B streptococcal infection of the throat occurring during the observation period. Throat cultures were inoculated on streptococcal-selective agar and incubated overnight. Typing was performed with pyrrolidonyl aminopeptidase or latex antigen testing.

Analysis

Because of the matching on physician as well as on health care–seeking behavior of the case and control, we used a conditional logistic-regression model to calculate the odds ratio (OR) as an approximation of the relative risk.[12] Statistical analyses were performed by using the Stata (Stata Corp, College Station, TX) *clogit* command.[13] Our models assessed the relationship between the number of prior streptococcal infections and new onset of OCD, TS, or tic disorder, adjusted for age, gender, physician, and care-seeking behavior. We performed 2 subanalyses in which we tested our results when (1) restricting cases to those with a specific onset date listed in the chart, as noted above (ie, the onset date was not imputed), and (2) restricting case-control matches to those for which the difference in total outpatient visits before diagnosis was ≤5.

RESULTS

We identified 318 potential cases of OCD, TS, or tic disorder at GHC occurring between 1992 and 1999; these included children with 1 of the relevant ICD-9 codes noted in the automated databases described above. We reviewed charts for 314 of these 318 children (4 charts were unavailable) and accepted 202 cases. The majority of exclusions were for children who had symptoms evaluated but for whom no specific diagnosis was made. If no diagnosis was made initially but was confirmed at a later visit, the case was accepted. Among the 202 accepted cases, the onset date for 21 cases preceded the beginning of our observation period, and for 37 cases we were unable to match controls, leaving 144 cases for our analyses (Table 1). Of these 144 cases, 106 were matched to 5 controls, 4 were matched to 4 controls, 10 were matched to 3 controls, 9 were matched to 2 controls, and 15 were matched to 1 control.

We first analyzed all 144 cases together and then separately by diagnosis: 33 with OCD (10 of these children also had TS or tic disorder in addition to OCD), 41 with TS, and 70 with tic disorder. Most (71%) of the affected children were male, which is consistent with the known male predominance in TS and early-onset OCD in boys (Table 1). Symptom onset was most common among children 4 to 6 years

TABLE 1. Case Demographics, *n* (%)

Total	144 (100)
Male	102 (71)
Female	42 (29)
Diagnosis	
OCD	33 (23)
With TS	6 (4)
With tic disorder, no TS	4 (3)
OCD only	23 (16)
Male	20 (61)
Female	13 (39)
TS, no OCD	41 (28)
With tic disorder	24 (17)
TS only	17 (12)
Male	35 (85)
Female	6 (15)
Tic disorder only	70 (49)
Male	47 (67)
Female	23 (33)
Age at diagnosis	
4–6 y	50 (35)
7–9 y	61 (42)
10–13 y	33 (23)
At at symptom onset	
0–3 y	6 (4)
4–6 y	61 (42)
7–9 y	51 (35)
10–13 y	27 (19)

of age (42%), whereas the most common age at the time of diagnosis was 7 to 9 years old.

Cases were more than twice as likely as controls to have had at least 1 streptococcal infection in the 3 months before disease onset (OR: 2.22; 95% confidence interval [CI]: 1.05, 4.69) and almost twice as likely to have had at least 1 streptococcal infection in the 12 months before onset (Table 2). When GABHS infection only was examined, cases were again more than twice as likely to have had infection in the 3 months before disease onset (OR: 2.50; 95% CI: 1.09, 5.70) (Table 3) and almost twice as likely as controls to have had GABHS in the 12 months before the onset date (OR: 1.81; 95% CI: 1.17, 3.43). When each condition was examined separately, the risk for tic disorder was significantly increased in the year after any streptococcal infection (OR: 2.81; 95% CI: 1.52, 5.19) (Table 2) or GABHS infection (OR: 2.06; 95% CI: 1.19, 5.14) (Table 3). The risk estimates were elevated, but nonsignificantly so, for both OCD and TS alone (Tables 2 and 3).

When we looked at the effect of multiple infections, few cases or controls (<1%) had >1 streptococcal infection in the 3 months before the onset date. However, cases were >3 times as likely to have had ≥2 streptococcal (OR: 3.10; 95% CI: 1.77, 8.96) or GABHS (3.46; 95% CI: 1.75, 11.1) infections in the year before disease onset. When examined for each disorder separately, having >1 GABHS infection in the 12 months before the onset date was 13-fold more common among cases with TS than controls (OR: 13.6; 95% CI: 1.93, 51.0). Cases with OCD and tic disorder were also more likely to have had multiple GABHS infections in the year before disease onset, but these associations were not statistically significant.

In the first subanalysis, we limited the analysis to the 75 cases with a clear onset date noted in the chart (and whose onset dates were therefore not estimated). In this analysis, the risk estimates for all conditions combined remained elevated and showed a statistically significant increase with single or multiple GABHS infections in the 12 months before onset of all diseases combined (OR: 2.44; 95% CI: 1.32, 4.52 for at least 1 GABHS infection; OR: 2.66; 95% CI: 1.82, 12.6 and for ≥2 GABHS infections). TS was associated with multiple GABHS infections in the 12 months before onset (OR: 5.33; 95% CI: 1.64, 17.3), and tic disorder was associated with any GABHS in the 12 months before onset (OR: 3.07; 95% CI: 1.40, 6.75).

In a second subanalysis, we used cases and controls with a difference of no more than 5 total outpatient visits in the 2 years before diagnosis. The risk among all diseases combined for infection in the 3 and 12 months before onset date did not change appreciably compared with the main analysis. Cases were >5 times more likely to have had multiple GABHS infections in the 12 months before disease onset (OR: 5.65; 95% CI: 1.81,17.6) and 70% more likely to have had at least 1 GABHS infection in the 3 months before disease onset (OR: 1.74; 95% CI: 0.76, 3.98).

DISCUSSION

Our findings lend support to an increasing body of evidence suggesting that neuropsychiatric or behavioral disorders such as OCD or TS may come about at least in part as a result of a postinfectious autoimmune phenomenon. In our study, streptococcal infection seemed to double the risk for a first diagnosis of OCD, TS, or tic disorder within the 3 months after infection, and multiple infections seemed to approximately triple the risk for a first diagnosis within 12 months' time.

The argument that these conditions are autoimmune in nature is supported by the findings of an increased prevalence of antibodies directed against

TABLE 2. Association of Streptococcal Infection (Strep) and Risk for Disease

	Cases, *n* (%)	Controls, *n* (%)	OR	95% CI
All cases				
Strep within 3 mo of onset				
Any	12 (8.3)	24 (3.9)	2.22	1.05, 4.69
Strep within 1 y of onset				
Any	32 (22)	78 (13)	1.91	1.20, 3.05
≥2	13 (9.0)	18 (2.9)	3.10	1.77, 8.96
OCD				
Strep within 3 mo of onset				
Any	2 (6.1)	3 (2.3)	2.66	0.54, 29.5
Strep within 1 y of onset				
Any	5 (15)	20 (16)	1.10	0.37, 3.26
≥2	1 (3.0)	4 (3.1)	1.21	0.12, 12.1
TS, no OCD				
Strep within 3 mo of onset				
Any	3 (7.3)	6 (3.3)	2.21	0.45, 8.89
Strep within 1 y of onset				
Any	6 (15)	20 (11)	1.20	0.44, 3.31
≥2	6 (15)	5 (2.8)	5.26	1.43, 19.3
Tic disorder only				
Strep within 3 mo of onset				
Any	7 (10)	15 (5.0)	2.03	0.77, 5.33
Strep within 1 y of onset				
Any	21 (30)	38 (13)	2.81	1.52, 5.19
≥2	6 (8.6)	9 (3.0)	3.16	1.01, 9.83

TABLE 3. Association of GABHS Infection and Risk for Disease

	Cases, *n* (%)	Controls, *n* (%)	OR	95% CI
All cases				
GABHS within 3 mo of onset				
Any	10 (6.9)	19 (3.1)	2.50	1.09, 5.70
GABHS within 1 y of onset				
Any	24 (17)	57 (9.4)	1.81	1.17, 3.43
≥2	10 (6.9)	12 (2.0)	3.46	1.75, 11.1
OCD				
GABHS within 3 mo of onset				
Any	2 (6.1)	2 (1.6)	3.81	0.70, 35.5
GABHS within 1 y of onset				
Any	4 (12)	17 (13)	0.99	0.31, 3.20
≥2	1 (3.0)	2 (1.6)	2.32	0.21, 25.6
TS, no OCD				
GABHS within 3 mo of onset				
Any	3 (7.3)	4 (2.2)	3.05	0.58, 16.2
GABHS within 1 y of onset				
Any	6 (15)	11 (6.0)	2.60	0.83, 8.12
≥2	6 (15)	2 (1.1)	13.6	1.93, 51.0
Tic disorder only				
GABHS within 3 mo of onset				
Any	5 (7.1)	13 (4.4)	1.87	0.62, 5.66
GABHS within 1 y of onset				
Any	14 (20)	29 (9.7)	2.06	1.19, 5.14
≥2	3 (4.3)	8 (2.7)	1.78	0.44, 7.18

the human caudate nucleus[14] and higher levels of antineuronal antibodies among patients with OCD and PANDAS.[15–17] Antineuronal antibodies are more frequent among children with tics or TS compared with controls, and patients with TS have higher levels of antibodies directed against the caudate and putamen.[18–20] Pathologic and imaging studies implicate basal ganglia dysfunction in these disorders,[21,22] and epitopes of streptococcal M protein, the major virulence factor of group A streptococci, have been shown to evoke antibodies that cross-react with the human brain.[23] Patients with TS have increased titers of antibodies against streptococcal M proteins; patients with TS and tic disorder have increased antistreptococcal antibodies compared with controls, as well.[7,24–26]

Although these data support the existence of PANDAS, the hypothesis that streptococcal infection directly leads to neurologic disorders in children is yet unproven.[27] A recent prospective study, for example, found no evidence that GABHS infections were associated with symptom exacerbations in children with TS or OCD.[28] Additional research is still needed to establish an etiologic relationship and identify the role, if any, for screening or targeted therapeutic interventions.[27]

Our study was unique in that it studied patients from a population-based health maintenance organization rather than using patients referred to a specialty clinic or research group. Additionally, by assessing children continuously enrolled from the age of 4 and doing extensive medical-record review to validate diagnoses and confirm case status, we were able to capture the first known diagnosis of OCD, TS, or tic disorder while also gathering unbiased information about the past history of streptococcal disease. Because we matched cases to controls within the same primary care practice and with the same care-seeking behavior, we were able to ensure that the relation found between streptococcal infection and OCD, TS, or tic disorder was not caused by differing diagnostic behavior of physicians or increased surveillance for streptococcal infections among specific individual physicians.

There are some limitations to our data. Our ability to confirm case status was limited to the information that was documented in the patient's medical record. Thus, we relied on the physician's diagnosis of OCD, TS, or tic disorder and did not have the ability to bring in children for standardized examinations by neurologists. Also, the symptom onset date we estimated from the chart likely differed by some amount from the true timing of disease onset, and thus we chose time windows to help account for the time lapsed before patients sought medical attention. Nevertheless, our best estimate of the onset date might have been subject to recall bias or reviewer measurement error. It is important to realize, however, that misclassification of outcome or exposure status in our study would likely have lent a conservative bias to the findings and an underestimate of the strength of the relationship between streptococcal infection and these disorders.

Another concern is that with greater public attention to the PANDAS hypothesis, providers may look more closely for evidence of streptococcal infection in children suspected of having neurologic disorders, which has the potential to bias retrospective analyses such as ours despite efforts to minimize this effect. In addition, neurologic disorders can be triggered by stress; hence, it is possible that the onset of TS, OCD, or tic disorders associated with streptococcal infection represent a nonspecific reaction to infection. The effects observed in our study, however, seem to be driven primarily by group A rather than group B streptococcal infection, suggesting a specific relationship between GABHS and these disorders.

When we examined various lags between strepto-

coccal infection and OCD, TS, and tic disorder, the association seemed strongest for streptococcal infection within the previous 3 months. Although this suggests that the disorders that are triggered by streptococcal infection occur relatively quickly after infection, it does not necessarily rule out a different or more prolonged interval in some cases.

Future epidemiologic studies should include an assessment of the interaction between genetics, streptococcal infection, and risk for PANDAS-like symptoms. Relatives of patients with PANDAS are more likely than those in the general population to have OCD and tic disorders,[29] suggesting that genetics play a pathogenic role in these disorders. Moreover, patients with PANDAS, rheumatic fever, and Sydenham's chorea are more likely than healthy controls to demonstrate D8/17 (a monoclonal antibody that identifies B-cell surface markers) positivity.[30–32] Finally, TS has also been shown to possess a major genetic component.[33–36] It may be that streptococcal infection serves as a trigger for symptoms in only a subset of certain subjects carrying a particular gene or set of genes. Although this would imply that infection is not a causal agent in all cases of TS, OCD, and tic order, it would also suggest that the risks of neurologic disorders caused by streptococcal infection are magnified greatly in the presence of a particular genetic make-up.

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