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Neuropsychiatric Disorders Associated with Streptococcal Infection: A Case-Control Study among Privately Insured Children

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Abstract

Objective—To assess whether antecedent streptococcal infection(s) increase the risk of subsequent diagnosis of obsessive-compulsive disorder (OCD), Tourette's syndrome (TS), other tic disorders, attention deficit hyperactivity disorder (ADHD) or major depressive disorder (MDD) in a national sample of privately insured children.

Method—Using health insurance claims data, we compared the prior-year occurrence of streptococcal infection in children aged 4–13 years with OCD, TS or tic disorder newly diagnosed between January 1998 and December 2004 to that of a cohort of matched controls. Conditional logistic regression models were used to determine the association of prior streptococcal sore throat or scarlet fever with a diagnosis of OCD, TS, or tic disorder. We repeated the analyses for two other infectious diseases (otitis media and sinusitis) and one non-infectious condition (migraine). We also investigated the potential specificity of this association by performing similar analyses focused on newly diagnosed attention deficit hyperactivity disorder (ADHD) and newly diagnosed major depressive disorder (MDD).

Results—Subjects with newly diagnosed OCD, TS, or tic disorder were more likely than controls to have had a diagnosis of streptococcal infection in the previous year (OR: 1.54, 95% CI: 1.29, 2.15). Prior streptococcal infection was also associated with incident diagnoses of ADHD (OR: 1.20, 95% CI: 1.06, 1.35) and MDD (OR=1.63, 95% CI: 1.12, 2.30).

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Conclusions—These findings provide epidemiologic evidence that some pediatric onset neuropsychiatric disorders, including OCD, tic disorders, ADHD and MDD, may be temporally related to prior streptococcal infections. Whether this is the result of a non-specific stress response or secondary to an activation of the immune system remains to be determined.

Keywords

obsessive-compulsive disorder; Tourette's syndrome; tic; PANDAS; ADHD

Introduction

Previous studies have suggested a link between Group A beta hemolytic streptococcal (GABHS) infections and the onset or worsening pediatric obsessive-compulsive disorder (OCD), Tourette's syndrome (TS) and tic disorder. However, most of these studies have involved small samples or case reports. The prepubertal onset of OCD, TS, or tic disorder with abrupt symptom exacerbation after streptococcal infection has been termed PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection).¹ The possibility of such a link is based in part on the observation that patients with Sydenham's chorea frequently display de novo tics and obsessive-compulsive symptoms.^{2, 3} The only large-scale study to address this issue was conducted by Mell and colleagues,⁴ who identified 144 cases of new-onset OCD, TS or tic disorder along with 609 matched controls who were enrolled in a large health maintenance organization in the Seattle, Washington area. They found that patients with new-onset OCD, TS or tic disorder were significantly more likely to have prior streptococcal infections diagnosed in the year before illness onset. Their findings were even more robust when they limited their analysis to just those cases with a positive culture of GABHS, as recorded in the medical record.

The objective of the present study was to replicate the results of Mell et al. using a larger, more nationally representative sample. Next, we examined the number of streptococcal infections recorded after the incident diagnosis of tic disorder, TS or OCD to establish if these individuals were at greater risk to develop subsequent streptococcal infections. Third, we sought to examine whether the association with prior streptococcal infections was specific, or if subjects with newly diagnosed tic, TS, or OCD also had a higher number of antecedent otitis media or sinusitis infections. Finally, to test the specificity of new-onset tic, TS, or OCD disorders as sequelae of streptococcal infection, we performed a comparable association analysis for two additional groups of children: those diagnosed for the first time with attention deficit hyperactivity disorder (ADHD) or major depressive disorder (MDD).

Method

Sources of data

Data for the study came from Thompson Healthcare's MarketScan® database for the years 1998 through 2004. This database contains private healthcare claims collected nationally from approximately 60 different private companies who self-insure their employees and their dependents. The database contains information on all inpatient and outpatient claims, including diagnostic information coded according to the International Classification of Diseases, Ninth Revision. This database has been used for a wide range of child mental health epidemiologic and health services research, including by our group.^{5–9}

Sample – Cases

Cases were defined as being between 4 and 13 years of age with a new primary diagnosis of obsessive-compulsive disorder (303.3x), tic disorder (307.20 or 307.22) or Tourette's

syndrome (307.23) made at least two years after their initial enrollment or first healthcare claim. Cases were further restricted to those individuals who were continuously enrolled since the age of 4 and who had no diagnosis of ADHD (314.xx) in the two years prior to the initial diagnosis of interest.

To evaluate the specificity of any findings, two groups of cases were also selected. The first contrast group was composed of cases with a newly made diagnosis of ADHD. Potential cases were defined as being between 4 and 13 years of age with a primary diagnosis of ADHD (314.xx). Cases were further restricted to those individuals who were continuously enrolled since the age of 4 and who did not have a diagnosis of OCD, tic disorder or TS. The rationale for this exclusion was to minimize the potentially confounding impact of ADHD comorbidity on these analyses.

A second contrast group was composed of cases with a newly made diagnosis of MDD. Potential cases were defined as being between 4 and 13 years of age and with a primary diagnosis of MDD (296.2x – 296.3x). Cases were further restricted to those individuals who were continuously enrolled since the age of 4 and who did not have a diagnosis of OCD, tic disorder or TS. The rationale for this exclusion was to minimize the potential confounding impact of MDD comorbidity on these analyses.

Sample – Controls

Up to five controls were matched to each case based on date of enrollment, birth year, sex, and three-digit zip code. Ten matches were initially selected per case, but in order to control for the bias of propensity to seek healthcare, we excluded those controls that, when compared to their matched case, had a difference of 10 or more outpatient visits during the two years prior to the diagnosis (reference) date. A separate group of controls were matched to each ADHD case and each MDD case based on date of enrollment, birth year, and sex using identical procedures.

Data Analysis

Using the administrative claims data, subjects' clinical records were examined, and diagnoses of streptococcal sore throat or scarlet fever (034.0x) were identified. Multiple diagnoses made within 8 weeks of each other were counted as a single episode to control for multiple visits for the same infection. The number of streptococcal infections was separately compared across cases and controls during one year and three month periods before the reference date.

Conditional logistic regression models were used to calculate the odds ratios (OR) and 95% confidence intervals (CI) associated with having any infection within three months or one year of the diagnosis date.

In keeping with the study's case-control design, two infectious status conditions served as outcome variables (i.e. one or more infection within three or twelve months preceding diagnosis), and six psychiatric diagnoses as predictor variables (i.e. TS, tics, OCD, ADHD, MDD, and all diagnoses combined). Additional models were similarly fitted, but using migraine, sinusitis, and otitis media as dependent variables. In the case of migraine, and due to small cell sizes, one of the models was collapsed by combining tics and TS into a single predictive category.

In order to address the question of the cases' subsequent susceptibility to streptococcal infections, we divided the cases and controls based on whether they had had at least one infection in the year prior to their initial diagnosis of OCD, tic disorder or TS. We then computed the number of streptococcal infections as well as the number of outpatient visits that occurred after the reference date for each group.

Results

OCD, TS and tic disorder cases vs. controls

We identified 742 cases of newly diagnosed OCD, TS and tic disorder in our sample, along with 3,647 controls. The diagnostic, age and gender breakdown of the cases and controls is presented in Table 1. The majority of cases were diagnosed with tic disorder (64.6%), with fewer cases diagnosed with OCD (24.9%) or TS (10.5%). The average age and percent of females were comparable across the cases and controls.

Table 2 shows the results of the conditional logistic models testing the association of a new diagnosis of OCD, TS or tic disorder with prior streptococcal infection. Prior streptococcal infection within 1 year of onset was associated with increased likelihood of a new diagnosis of OCD, TS or tic disorder (OR: 1.54; CI: 1.29, 2.15). When examined by individual diagnosis, this association was statistically significant for OCD (OR: 1.76; CI: 1.11, 2.81) and tic disorder (OR: 1.66; CI: 1.20, 2.31), but not for TS (OR: 1.22; CI: 0.56, 2.64). There were no statistically significant associations of streptococcal infection within 3 months prior to onset and risk of disease, either across all cases or by individual disorder.

Cases with antecedent streptococcal infection in the year prior to the onset of OCD, tic disorder or TS ($N = 108$) were three times more likely than the cases without a prior streptococcal infection ($N=634$) to have an additional diagnosis of either streptococcal sore throat or scarlet fever (0.46 ± 0.91 vs. 0.15 ± 0.50 , $t = -3.52$, $p < 0.001$). These diagnoses occurred in the context of a comparable number of subsequent outpatient visits (27.5 ± 33.5 vs. 24.3 ± 39.1 , $t = -0.89$, NS). Controls with an antecedent streptococcal infection in the year prior to the reference date were also more likely than controls without a prior streptococcal infection to have an additional diagnosis of streptococcal sore throat or scarlet fever, but there were no significant differences between cases and controls either among those with prior streptococcal infections or those without in terms of likelihood of subsequent diagnosis of streptococcal sore throat or scarlet fever.

Table 3 shows the results of the conditional logistic models testing the association of prior otitis media, sinusitis or migraine with a new diagnosis of OCD, TS or tic disorder. There were no significant associations of a new diagnosis of OCD, TS or tic disorder with otitis media or sinusitis, although there was an association for sinusitis with all cases (OR: 1.40; CI: 1.01, 1.95). There were no significant associations of prior streptococcal infection within 3 months of onset with risk of disease for any of these conditions (data not shown).

ADHD cases vs. controls

We also identified 3,650 cases of newly diagnosed ADHD along with 18,114 controls. The age and gender breakdown of the cases and controls are also included in Table 1. As expected from the matching procedure used to select controls, the average age and percent female were comparable between cases and controls.

The results of the conditional logistic models testing the association of prior streptococcal infections with a diagnosis of ADHD are presented in Table 4. Subjects with a diagnosis of ADHD were significantly more likely to have a streptococcal infection within the past year (OR: 1.2; CI: 1.06, 1.35), but not within the past 3 months.

MDD cases vs. controls

Finally, we identified 342 cases of newly diagnosed MDD along with 1,710 controls. As also shown in Table 1, average age and proportion of females were very similar across cases and controls.

The results of the conditional logistic models testing the association between a diagnosis of MDD and prior streptococcal infections are included in Table 4. Subjects with a diagnosis of MDD were significantly more likely to have a streptococcal infection within the previous year (OR: 1.63; CI: 1.12, 2.30), but not within the past 3 months.

Discussion

The association between streptococcal infections and a variety of neuropsychiatric disorders, including tic disorders, OCD, ADHD and MDD, adds to a substantial body of science linking somatic illness and psychiatric morbidity in both adults and children.¹⁰ In the case of OCD, TS, tic disorders and ADHD, a specific link with GABHS has been hypothesized.^{1–4, 11} Although in the case of MDD the link appears to be more general, and perhaps related to a class of medical disorders associated with immune activation;¹² there is at least one case study where the link between GABHS and MDD has been suggested.¹³

Tic Disorders and OCD

We note that this is the first independent, partial replication of the results reported by Mell et al.⁴ using a five times larger and more nationally representative sample. Mell and colleagues⁴ found a comparable odds ratio of 1.91 (CI: 1.20, 3.05) to that reported here (OR: 1.54; CI: 1.29, 2.15). Consistent with earlier reports (see Luo et al.¹⁴ and Kurlan R, Kaplan EL, McDermott MP, and The Tourette's Syndrome Study Group, "Streptococcal infection and exacerbations of childhood tics and obsessive-compulsive symptoms: A prospective blinded cohort study," submitted for publication) it appears that some individuals with OCD, tic disorder or TS may be more susceptible to streptococcal infections, with the putative PANDAS cases being diagnosed three times more frequently with streptococcal sore throat than the remainder of the cases in the years following their initial diagnosis, although the risk was not significantly elevated relative to controls. These findings may also lend limited support to an increasing body of evidence suggesting that some subgroup of early onset neuropsychiatric disorders such as OCD or TS may come about, at least in part, as a result of post-infectious phenomena. If such a subgroup exists, however, our data suggest that it forms only a small proportion of new-onset cases of tic disorders or OCD.

Our report has several notable methodological weaknesses compared to Mell et al.'s study. First, we were unable to match by provider in order to control for the diagnostic predilections of individual physicians and account for the possibility that some physicians might be more (or less) likely to diagnose streptococcal infections as well as OCD, TS, or a tic disorder. Second, the Mell et al. report confirmed case status and date of onset of first symptoms by record review of DSM-IV criteria and accepted only 202 of the 318 (64%) potential cases of OCD, TS, or tic disorder. They also confirmed prior exposure to streptococcal infection using the results of laboratory databases to identify records of group A or B streptococcal infection of the throat. For example, when Mell and colleagues limited their analyses to just the cases with positive GABHS throat cultures, their results were more robust, with an odds ratio of 13.6 (CI: 1.93, 51.0) for the new onset of TS following two or more confirmed GABHS infections in the year prior to the initial diagnosis. These findings may have contributed to finding a weaker association with OCD, tic disorders and TS in this study than is actually the case.

We found no increased occurrence of otitis media or migraine prior to the initial diagnoses of OCD, tic disorders and TS, but did observe an increased prior occurrence of sinusitis (all cases: OR: 1.40; CI: 1.01, 1.95). Although we hesitate to read much into this finding, we cannot discount the possibility that it may reflect an increased susceptibility to some, but not all, infectious diseases in children with these neuropsychiatric disorders, and/or the possibility that infection with agents other than GABHS may predispose to this class of disorders. If so, this observation again raises the question of the specificity of the relationship between GABHS

infections and these disorders. One possible candidate is the common cold.¹⁵ Recently, Hoekstra et al.¹⁶ reported a strong association between the self-report of a common cold and tic symptom exacerbation 4 weeks later in a group of 20 children, aged 7–15 (OR:4.69, $p=0.001$). In addition, viral infections associated with the common cold are the most frequent cause of acute sinusitis.¹⁷ Future studies are needed to examine the relationship between the common cold, sinusitis and other common infectious pediatric diseases and the development of ADHD and MDD, among other conditions.

ADHD

It also appears that some children are at greater risk to have had one or more streptococcal infections prior to their initial diagnosis of ADHD. Although ADHD is frequently comorbid with TS and other tic disorders, as well as with early-onset OCD,¹⁸ we excluded individuals with comorbid ADHD from the OCD, TS and tic disorder cases included in this study. Similarly, we excluded from the ADHD set of cases individuals with comorbid OCD, TS and tic disorder diagnoses.

Major Depressive Disorder

The finding of an increased risk of antecedent streptococcal infection before the first onset of MDD may open a new link between depression and immunological activity.^{10, 12} In response to a GABHS infection, innate immune cells produce pro-inflammatory cytokines that may act on the brain to cause stress, anxiety, and sickness behavior. The resulting inflammation and the psychological effects might partially account for the increased prevalence of MDD observed in this sample. One strength of the present study is that it examines the children with diagnostic claims data prior to the diagnosis of any specific neuropsychiatric disorders; hence the rates of diagnosed prior infection are largely unbiased by the children's subsequent diagnostic status with respect to these disorders.

Even if these results are confirmed, the underlying mechanisms for these associations are not entirely clear. For example, GABHS infections may increase the level of stress, which could further predispose a vulnerable child to one or more of these conditions.^{19–23} It is also possible that features of the neuropsychiatric disorder sufficiently precede the diagnosis being made so that the sequelae of the neuropsychiatric disorder itself may affect the vulnerability to develop an infectious disease because of associated health-relevant behaviors. Bidirectional processes may also play a role.

Alternatively, common host vulnerabilities or environmental risks may account for these associations. It is also possible, given the widespread publicity given to the PANDAS hypothesis, that parents and health care providers were more vigilant for possible streptococcal infection on the part of the of children with diagnosed tic, TS, or OCD as opposed to increased host susceptibility. It is unlikely, however, that this could account for the increased risk for MDD.

The results of this study are further qualified by the limitations of the administrative data used in this study, rather than from systematically obtained clinical data, especially around diagnostic classification. This is a shortcoming inherent to studies that rely on secondary analyses to secure large sample sizes. Perhaps the largest limitation and potential threat to the study's validity has to do with the fundamental impossibility of detecting causal relationship within the context of such a case-control study.

Future epidemiologic studies should include an assessment of the interaction among genetic factors, psychosocial stress, streptococcal and other infections, vaccinations, and risk for developing a broad range of neuropsychiatric disorders. Relatives of patients with PANDAS

are more likely than those in the general population to have OCD and tic disorders,²⁴ suggesting that specific host susceptibility factors may play a pathogenic role in these disorders. Genetic factors have been repeatedly implicated in the development of TS and OCD as well as ADHD and pediatric-onset MDD.^{25–27} It may be that infection (inflammation and sickness behavior) can serve as a trigger for symptoms in only a subset of genetically susceptible individuals. It is likely that the etiology and genetics of these disorders are complex, such that antecedent infections are a causal agent in only a subset of cases. As noted above, psychosocial stress clearly is associated with worsening of tic and obsessive-compulsive,²² as well as depressive symptoms.²¹ It is possible that psychosocial stressors also contribute in a bidirectional fashion to the initiation of these disorders; perhaps through an interaction leading to greater host susceptibility to GABHS infections as well as to other, but not all, infectious diseases.

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Table 1

Characteristics of the cases and their matched controls, stratified by diagnosis.

Variable	Cases	Matched Controls
OCD, TS, Tic Disorder Group		
N	742	3,647
Diagnosis, N (%)		
OCD	185 (24.9)	–
TS	78 (10.5)	–
Tic disorder	479 (64.6)	–
Female, N (%)	234 (31.5)	1,183 (32.4)
Age in years, mean $\pm$ SD	6.6 $\pm$ 1.5	6.4 $\pm$ 2.3
ADHD Group		
N	3,650	18,114
Female, N (%)	928 (25.4)	5,030 (27.8)
Age in years, mean $\pm$ SD	7.8 $\pm$ 1.5	7.8 $\pm$ 1.7
MDD Group		
N	342	1,710
Female, N (%)	115 (33.6%)	579 (33.9%)
Age in years, mean $\pm$ SD	7.6 $\pm$ 1.7	6.6 $\pm$ 1.9

Note: OCD = Obsessive-compulsive disorder; TS = Tourette's syndrome; ADHD = attention-deficit hyperactivity disorder; MDD = major depressive disorder.

Table 2

Association of streptococcal sore throat or scarlet fever (Strep) and odds of being diagnosed with obsessive-compulsive disorder (OCD), Tourette's syndrome (TS), or another tic disorder.

	Cases, <i>N</i> (%)	Controls, <i>N</i> (%)	OR	95% CI
All Cases				
Strep within 3 mo of onset	28 (3.8)	103 (2.8)	1.36	0.89, 2.10
Strep within 1 yr of onset	108 (14.6)	331 (9.1)	1.54	1.29, 2.15
OCD				
Strep within 3 mo of onset	10 (5.4)	27 (3.0)	1.95	0.90, 4.22
Strep within 1 yr of onset	32 (17.3)	93 (10.3)	1.76	1.11, 2.81
TS				
Strep within 3 mo of onset	1 (1.3)	17 (4.5)	0.26	0.03, 2.07
Strep within 1 yr of onset	10 (12.8)	40 (10.5)	1.22	0.56, 2.64
Tic disorder				
Strep within 3 mo of onset	17 (3.6)	59 (2.5)	1.43	0.83, 2.47
Strep within 1 yr of onset	66 (13.8)	198 (8.4)	1.66	1.20, 2.31

Note: OR = Odds ratio, 95% CI = 95% confidence interval. Confidence intervals that exclude the null value are marked in bold.

Table 3

Association of select pediatric disorders and the odds of being diagnosed with obsessive-compulsive disorder (OCD), Tourette's syndrome (TS), or another tic disorder during the preceding year.

	Cases, <i>N</i> (%)	Controls, <i>N</i> (%)	OR	95% CI
Otitis Media				
All Cases	165 (22.2)	699 (19.2)	1.23	0.98, 1.52
OCD	43 (23.2)	148 (16.4)	1.48	0.96, 2.30
TS	18 (23.1)	68 (17.9)	1.26	0.61, 2.62
Tic disorder	104 (21.7)	483 (20.4)	1.14	0.87, 1.49
Sinusitis				
All Cases	49 (6.6)	177 (4.9)	1.40	1.01, 1.95
OCD	14 (7.8)	41 (4.6)	1.72	0.92, 3.24
TS	4 (5.1)	24 (6.3)	0.83	0.28, 2.44
Tic disorder	31 (6.5)	112 (4.7)	1.41	0.93, 2.14
Migraine				
All Cases	8 (1.1)	21 (0.6)	1.90	0.83, 4.32
OCD	3 (1.6)	5 (0.6)	2.92	0.70, 12.2
TS or Tic disorder	5 (0.9)	16 (0.6)	1.56	0.57, 4.32

OR = Odds ratio, 95% CI = 95% confidence interval. Confidence intervals that exclude the null value are marked in bold.

Table 4

Association of streptococcal sore throat or scarlet fever (Strep) and the odds of being diagnosed with attention deficit hyperactivity (ADHD) or major depressive disorder (MDD).

	Cases, <i>n</i> (%)	Controls, <i>n</i> (%)	OR	95% CI
ADHD				
Strep within 3 mo of onset	123 (3.4)	539 (3.0)	1.14	0.93, 1.39
Strep within 1 yr of onset	449 (12.3)	1,902 (10.5)	1.20	1.06, 1.35
MDD				
Strep within 3 mo of onset	15 (4.4)	327 (2.6)	1.46	0.84, 2.55
Strep within 1 yr of onset	41 (12.0)	301 (7.0)	1.63	1.12, 2.30

Note: OR = Odds ratio, 95% CI = 95% confidence interval. Confidence intervals that exclude the null value are marked in bold.