Streptococcal infection, Tourette syndrome, and OCD

Is there a connection?

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ABSTRACT

Background: A causal relationship of common streptococcal infections and childhood neuropsychiatric disorders has been postulated.

Objective: To test the hypothesis of an increased rate of streptococcal infections preceding the onset of neuropsychiatric disorders.

Methods: Case-control study of a large primary care database comparing the rate of possible streptococcal infections in patients aged 2–25 years with obsessive-compulsive disorder (OCD), Tourette syndrome (TS), and tics with that in controls matched for age, gender, and practice (20 per case). We also examined the influence of sociodemographic factors.

Results: There was no overall increased risk of prior possible streptococcal infection in patients with a diagnosis of OCD, TS, or tics. Subgroup analysis showed that patients with OCD had a slightly higher risk than controls of having had possible streptococcal infections without prescription of antibiotics in the 2 years prior to the onset of OCD (odds ratio 2.59, 95% confidence interval 1.18, 5.69; $p = 0.02$). Cases with TS or tics were not more likely to come from more affluent or urban areas, but more cases lived in areas with a greater proportion of white population (p value for trend = 0.05).

Conclusions: The present study does not support a strong relationship between streptococcal infections and neuropsychiatric syndromes such as obsessive-compulsive disorder and Tourette syndrome. However, it is possible that a weak association (or a stronger association in a small susceptible subpopulation) was not detected due to nondifferential misclassification of exposure and limited statistical power. The data are consistent with previous reports of greater rates of diagnosis of Tourette syndrome or tics in white populations. *Neurology*® 2009;73:1256–1263

GLOSSARY

CI = confidence interval; **GP** = general practice; **OCD** = obsessive-compulsive disorder; **OR** = odds ratio; **PANDAS** = pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; **SI** = streptococcal infection; **TS** = Tourette syndrome.

Streptococcal infection (SI) can induce autoimmune neuropsychiatric disorders, the classic disorder being Sydenham chorea. In a number of small clinic-based studies, it has recently been shown that the phenotype of poststreptococcal neuropsychiatric disorders may be wider than just Sydenham chorea, perhaps also including tic disorders, obsessive-compulsive disorder (OCD), and other neuropsychiatric disorders with onset in childhood.^{1–5} It has been proposed that these neuropsychiatric disorders develop following SI by the process of molecular mimicry, whereby antibodies directed against bacterial antigens crossreact with brain targets. Anti-basal ganglia antibodies have been implicated in this process, though this is not a universal observation.^{6,7} A direct causal relationship with SI has therefore been postulated. Tic disorders and associated neuropsychiatric behavioral disorders are common and typically start in childhood. However, it is unknown how commonly Tourette syndrome (TS) or OCD occurs after SI, and whether these play an important role in the

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pathogenesis of these disorders at the population level. Careful epidemiologic studies are needed to assess the association between SI and these disorders.⁸⁻¹⁰ To date, only one epidemiologic study has been undertaken. This case-control study, in children aged 4–13 years, found that patients receiving their first diagnosis of TS, OCD, or tic disorder were over twice as likely (odds ratio [OR] 2.2) to have had prior SI in the 3 months before onset.¹¹ The risk was higher in those with multiple SIs within 12 months (OR 3.1). However, this study had a wide confidence interval (CI), with the lower estimate being consistent with merely a 5% relative increased odds. We therefore examined the association between throat infection among children and young adults and the onset of TS/OCD using a large primary care database. We hypothesized that throat infection among children and young adults is associated with the onset of TS/OCD.

METHODS Patients. Data were obtained from The Health Improvement Network (THIN, EPIC Database Research, London, UK). This is one of the world's largest computerized databases of anonymized longitudinal medical records from primary care. For this study, the extract included data from all practices for a cohort of patients in the age range 2 to 25 years during the period January 1, 1995–January 1, 2007. Patients had to be registered continuously from at least the age of 2 to ensure that there was no first diagnosis before registration (as patients cannot be traced between practices). Age 2 was chosen as it is very unlikely that a diagnosis of OCD, tics, or TS would have been made before this age. Missing day and month ($n = 12$) for date of birth were imputed at July 1, missing day only as the 15th ($n = 6$). The resulting data extract consisted of 678,862 patients with an average follow-up of 5.08 years, from 330 practices, who had general practitioner consultation data available since the age of 2 (children joining a practice after the age of 2 were dropped). This extract was used for a nested matched case-control study.

Case definition. We defined cases as patients who were diagnosed during the period January 1, 1997–January 1, 2007 with tics, TS, or OCD, identified using Medical READ codes, using code E272300 for TS ($n = 771$); codes E272000 ($n = 19$), E272200 ($n = 15$), E272100 ($n = 11$), E272z00 ($n = 6$), and F133.00 ($n = 4$) for tics; and code E203.00 ($n = 1,627$) for OCD (n is the number of episodes and not the number of children). Patients had to be registered with their practice for at least 2 years at their first incident episode to allow investigation of possible SI in the period preceding that episode. If medication for tics, OCD, or TS had been prescribed prior to the first episode, the case was dropped as an earlier first diagnosis was assumed ($n = 16$). Nine patients—6 with OCD and 3 with TS—had no recorded onset year and were dropped.

Matching. In order to maximize power, we aimed for 20 controls per case, matched to cases for general practice (GP) (thereby

controlling for diagnostic and referral differences between practices), sex, and year of birth.

Exposure definition. Cases were considered to be exposed to possible SI if they had presented to their doctor within 2 years prior to the date of the first incidence of tics, OCD, or TS with an illness potentially caused by SI. Medical READ codes were used to define exposure (see table e-1 on the *Neurology*[®] Web site at www.neurology.org). For controls, we used their case's date of onset of tics, OCD, or TS as a time marker. The time of the possible SI closest to symptom onset was used when there were subsequent infections. A series of planned subanalyses was undertaken using different definitions of exposure. First, we analyzed the risk of possible SIs within 5 years before the first incidence of OCD, TS, or tics since registration with the GP. Second, a subanalysis was done for those with a subsequent visit within 3 weeks as this may imply a more serious infection. Third, we stratified by whether patients were prescribed antibiotics for a possible SI, as such a prescription may indicate that the treating GP is more confident in the diagnosis of bacterial infection. We considered using more objective markers of SI but few patient records had supporting diagnostic evidence from throat swabs ($n = 67$) and ASO titers ($n = 6$) as better markers of SI. We also undertook a sensitivity analysis using a much more restricted range of exposure codes where SI was mentioned explicitly to reduce the risk of nondifferential misclassification (43ee.00, 65Q6.00, A34.00, A340.00, A340000, A340100, A340200, A340300, A340z00, A341.00, A341.11, A341.12, A34z.00, A3B0.00, A3BX100, A3BX600, Ayu3T00, H023.00, H023z00, H035.00, H035z00, H060700).

Confounding variables. For analytical purposes, we grouped age into a 4-level ordinal variable (2 to 4.99 years, 5 to 9.99 years, 10 to 14.99 years, and 15 to 25.99 years). Postcode indicators of area deprivation (Townsend quintiles), rurality (Rural and Urban Area Classification), and ethnicity, which are derived from the 2001 Census, were used. The Townsend index is a composite score based on the percentage of adults who are unemployed, do not own a car or home, and live in overcrowded conditions. Higher Townsend quintiles indicate greater area deprivation level. We classified rurality into urban, town/fringe, and village/isolated areas. We categorized the ethnicity variable into quintiles so that the highest quintile consisted of areas which had the largest proportion of white individuals.

Statistical methods. The data were analyzed using conditional logistic regression, to allow for the matching of cases and controls, with the case or control indicator as the outcome variable. We used a binary indicator of SI and ordinal measures of subsequent SI and of whether antibiotics were prescribed for SI as explanatory variables. SIs were considered limited to the 2-year period prior to onset of TS, OCD, or tic and, to account for a possible delayed onset reporting, limited to the 5-year period prior to onset. The possible confounding effects of Townsend quintile, rurality, and proportion of ethnicity were controlled for by inclusion as covariates in the regression models. All analyses were carried out for cases defined by symptom onset (retrospectively recorded; controls and cases $n = 4,774$) and defined by first consultation (controls and cases $n = 4,488$). Similar associations were seen in both sets of analyses and therefore those of symptom onset, which demonstrated stronger associations, are presented here. Analysis was carried out using Stata 10 MP (College Station, TX: StataCorp LP; 2007).

Standard protocol approvals, registrations, and patient consents. We received approval from the South East Research Ethics Committee, UK. Patients attending participating surger-

Table 1 Demographic and sociologic variables of cases with obsessive-compulsive disorder (OCD), Tourette syndrome (TS), and tics

	OCD				TS/tics			
	Cases, n (%)	Controls, n (%)	Odds ratio*	95% Confidence interval	Cases, n (%)	Controls, n (%)	Odds ratio*	95% Confidence interval
Total	129	2,211			126	2,308		
Gender								
Male	73 (56.6)	1,284 (58.1)			111 (88.1)	2,056 (89.1)		
Female	56 (43.4)	927 (41.9)			15 (11.9)	252 (10.9)		
Age group, y								
2-4	1 (0.8)	20 (0.9)			5 (4.0)	81 (3.5)		
5-10	21 (16.3)	399 (18.1)			71 (56.4)	1,375 (56.4)		
11-15	36 (27.9)	652 (29.5)			43 (34.1)	729 (31.6)		
16-25	71 (55.0)	1,140 (51.6)			7 (5.6)	123 (5.3)		
Townsend quintile†								
1‡	28 (23.5)	605 (29.1)	1		26 (21.3)	513 (23.0)	1	
2	17 (14.3)	398 (19.1)	0.89	(0.47, 1.67)	25 (20.5)	469 (21.1)	1.02	(0.57, 1.83)
3	33 (26.9)	435 (20.9)	1.67	(0.96, 2.91)	29 (23.8)	457 (20.5)	1.23	(0.68, 2.21)
4	30 (25.2)	396 (19.1)	1.88	(1.03, 3.41)	22 (18.0)	478 (21.5)	0.94	(0.51, 1.73)
5	12 (10.1)	245 (11.8)	1.07	(0.49, 2.36)	20 (16.4)	310 (13.9)	1.30	(0.67, 2.59)
p Value for trend				0.11				0.61
Rurality								
Urban‡	101 (88.6)	1,739 (87.2)	1		89 (80.2)	1,753 (85.6)	1	
Town/fringe	10 (8.8)	152 (7.6)	1.11	(0.41, 3.01)	17 (15.3)	194 (9.47)	2.06	(0.88, 4.81)
Village/isolated	3 (2.6)	103 (5.2)	0.28	(0.06, 1.26)	5 (4.5)	102 (4.98)	1.01	(0.34, 2.96)
p Value for trend				0.15				0.70
Ethnicity quintile§								
1‡	39 (34.2)	738 (37.0)	1		38 (34.2)	689 (33.6)	1	
2	29 (25.4)	443 (22.2)	1.48	(0.62, 3.52)	19 (17.1)	459 (22.4)	0.80	(0.32, 2.02)
3	24 (21.1)	535 (26.8)	0.99	(0.34, 2.87)	16 (14.4)	337 (16.45)	1.42	(0.47, 4.33)
4	14 (12.3)	170 (9.0)	2.20	(0.67, 7.24)	19 (17.1)	252 (12.3)	2.64	(0.82, 8.51)
5	8 (7.0)	99 (5.0)	2.90	(0.65, 13.0)	19 (17.1)	312 (15.2)	2.55	(0.71, 9.19)
p Value for trend				0.23				0.05

*Conditional logistic regression, matched on practice, sex, and year of birth.

†Higher quintiles indicate greater deprivation level.

‡Baseline category.

§Higher ethnicity quintiles indicate areas where the greatest proportion identified themselves as white.

ies were able to opt out of data collection, but individual consent was not obtained from patients as the primary care database data are anonymized.

RESULTS We identified 255 cases, 129 (51%) with a diagnosis of OCD, 108 (42%) of TS, and 18 (7%) of tics (table 1). As the number of cases with tics was small, we combined them with the TS group, resulting in a combined group of 126 cases (referred to as TS/tics for simplicity). These were matched to 4,519 controls (2,211 for OCD cases, 2,308 for TS/tics cases; table 2).

Table 1 presents the sociodemographic characteristics of cases and controls. As expected, cases and controls were comparable in terms of age and sex, 2 of the matching variables. There was a small majority

of males among the cases of OCD, and an expected, larger majority amongst cases of TS/tics. The OCD cases were older, with a median age at onset of 15.8 years, compared to a median age of 9.3 years in the TS/tics cases. There was no evidence that cases with either condition were more likely to come from more affluent areas or urban areas. There was some evidence that cases of TS/tics were more likely to live in areas where a higher proportion of the population was white (p for trend = 0.05; table 1). A similar association for cases of OCD was apparent, but supported by weaker evidence (table 1).

Twenty (15.5%) cases of OCD had been exposed to a possible SI in the 2 years prior to diagnosis (table

Table 2 Simple and multivariable models of streptococcal infection and obsessive-compulsive disorder

	No. (%)		Simple models*			Multivariable models*		
	Cases	Controls	Odds ratio	95% Confidence interval	p Value	Odds ratio	95% Confidence interval	p Value
Streptococcal infections <2 y before onset								
No†	109 (84.5)	1,877 (84.9)	1			1		
Yes	20 (15.5)	334 (15.1)	1.06	(0.64,1.75)		1.11	(0.67,1.88)	
p Value				0.83			0.69	
Consultations								
No streptococcal infection‡	109 (84.5)	1,877 (84.9)	1			1		
No subsequent consultation <3 wk	18 (14.0)	307 (13.9)	1.04	(0.61,1.75)	0.89	1.09	(0.63,1.88)	0.76
Subsequent consultation <3 wk	2 (1.55)	27 (1.22)	1.26	(0.30,5.38)	0.76	1.41	(0.32,6.18)	0.65
p Value for trend				0.78			0.63	
Antibiotics								
No streptococcal infection‡	109 (84.5)	1,877 (84.9)	1			1		
Streptococcal infection without antibiotic treatment	9 (6.98)	75 (3.39)	2.12	(1.00,4.48)	0.05	2.59	(1.18,5.69)	0.02
Streptococcal infection with antibiotic treatment	11 (8.53)	259 (11.7)	0.75	(0.39,1.43)	0.38	0.75	(0.38,1.48)	0.40
p Value for trend				0.71			0.79	
Streptococcal infections up to 5 y before onset								
No†	92 (71.3)	1,537 (70.3)	1			1		
Yes	37 (29.7)	648 (29.7)	0.96	(0.64,1.45)		1.03	(0.67,1.57)	
p Value				0.86			0.91	
Consultations								
No streptococcal infection‡	92 (71.3)	1,537 (70.3)	1			1		
No subsequent consultation <3 wk	34 (26.4)	608 (27.8)	0.95	(0.62,1.44)	0.79	1.00	(0.65,1.55)	0.99
Subsequent consultation <3 wk	3 (2.33)	40 (1.83)	1.27	(0.38,4.22)	0.70	1.44	(0.42,4.95)	0.56
p Value for trend				0.97			0.79	
Antibiotics								
No streptococcal infection‡	92 (71.3)	1,537 (70.3)	1			1		
Streptococcal infection without antibiotic treatment	11 (8.5)	126 (5.77)	1.44	(0.73,2.83)	0.30	1.71	(0.84,3.50)	0.14
Streptococcal infection with antibiotic treatment	26 (20.2)	522 (23.9)	0.84	(0.53,1.34)	0.48	0.88	(0.54,1.42)	0.59
p Value for trend				0.60			0.75	

*Conditional logistic regression, matched on practice, sex, and year of birth.

†Adjusted for ecologic measures of deprivation, rurality, and proportion of ethnic minority.

‡Baseline category.

2). There was a very similar rate of infection among the controls, and consequently no evidence of an association between OCD and SI ($p = 0.69$). There were very few instances of repeated consultation for a possible SI within 3 weeks of the first, with no apparent difference between cases of OCD and controls in exposure to these potentially more severe infection episodes. The expected association between possible SIs treated with antibiotics and OCD was not observed. Rather than antibiotic prescription distinguishing those exposure episodes where the treating GP was more confident of a bacterial cause, the data

were more consistent with the antibiotic preventing complications of infection. While numbers were small, OCD cases were more likely to have had a possible SI without antibiotic treatment compared to controls ($p = 0.02$). Repeating these analyses with exposure to possible SIs within 5 years prior to the diagnosis of OCD being considered gave very similar results (table 2).

Thirteen (10.3%) of the cases of TS/tics had been exposed to possible SI in the 2 years preceding diagnosis, with no evidence of a higher rate of infection in these cases compared to controls ($p = 0.15$; table

Table 3 Simple and multivariable models of streptococcal infection and Tourette syndrome/tics

	No. (%)		Simple models*			Multivariable models*		
	Cases	Controls	Odds ratio	95% Confidence interval	p Value	Odds ratio	95% Confidence interval	p Value
Streptococcal infections <2 y before onset								
No†	113 (89.7)	1,945 (84.3)	1			1		
Yes	13 (10.3)	363 (15.7)	0.60	(0.33, 1.10)		0.63	(0.34, 1.18)	
p Value				0.10			0.15	
Consultations								
No streptococcal infection‡	113 (89.7)	1,945 (84.3)	1			1		
No subsequent consultation <3 wk	13 (10.3)	331 (14.3)	0.67	(0.37, 1.21)	0.18	0.70	(0.37, 1.30)	0.26
Subsequent consultation <3 wk	0	32 (1.4)	/	/		/	/	
p Value for trend								
Antibiotics								
No streptococcal infection‡	113 (89.7)	1,945 (84.3)	1			1		
Streptococcal infection without antibiotic treatment	4 (3.17)	108 (4.68)	0.59	(0.21, 1.66)	0.32	0.68	(0.24, 1.91)	0.46
Streptococcal infection with antibiotic treatment	9 (7.14)	255 (11.1)	0.61	(0.30, 1.23)	0.17	0.62	(0.29, 1.30)	0.20
p Value for trend				0.12			0.16	
Streptococcal infections up to 5 y before onset								
No†	91 (72.2)	1,542 (69.2)	1			1		
Yes	35 (27.8)	686 (30.8)	0.86	(0.56, 1.32)		0.90	(0.58, 1.41)	
p Value				0.49			0.64	
Consultations								
No streptococcal infection‡	91 (72.2)	1,542 (69.2)	1			1		
No subsequent consultation <3 wk	33 (26.2)	636 (28.6)	0.88	(0.57, 1.35)	0.55	0.91	(0.58, 1.44)	0.70
Subsequent consultation <3 wk	2 (1.59)	50 (2.24)	0.67	(0.16, 2.83)	0.59	0.73	(0.17, 3.14)	0.67
p Value for trend				0.45			0.60	
Antibiotics								
No streptococcal infection‡	91 (72.2)	1,542 (69.2)	1			1		
Streptococcal infection without antibiotic treatment	6 (4.76)	190 (8.53)	0.51	(0.22, 1.20)	0.12	0.55	(0.23, 1.31)	0.18
Streptococcal infection with antibiotic treatment	29 (23.0)	496 (22.3)	1.01	(0.64, 1.58)	0.98	1.05	(0.65, 1.69)	0.85
p Value for trend				0.84			0.99	

*Conditional logistic regression, matched on practice, sex, and year of birth.

†Adjusted for ecologic measures of deprivation, rurality, and proportion of ethnic minority.

‡Baseline category.

3). None of the TS/tics cases had been exposed to a more serious infection, as indicated by a repeated consultation within 3 weeks of the first. No associations became apparent once the infections treated with antibiotics were separated from those that were not. Considering possible SIs within 5 years prior to the diagnosis of TS/tics also failed to support a positive association, though the upper CI was consistent with a modest increased risk. Analysis restricted to TS alone (rather than TS and tics combined) gave similar results. The sensitivity analysis using the restricted range of infections yielded similar results

(crude results for SI within 2 years for OCD were OR = 3.62, 95% CI 0.77, 17.0, $p = 0.10$, and within 5 years OR = 3.14, 95% CI 0.90, 11.0, $p = 0.07$). There were not enough data to calculate ORs for TS/tics using these time windows but with any lifetime exposure the OR was 0.92 (95% CI 0.19, 4.40, $p = 0.92$).

DISCUSSION This study could not confirm the association of neuropsychiatric disorders with SIs in a large community-based sample of children and young adults between 2 and 25 years. Cases with TS,

tics, or OCD were no more likely to have had possible SIs, as diagnosed clinically. The only association found was that cases with OCD were more likely to have had possible SIs not treated with antibiotics in the 2 years prior to diagnosis than controls. However, given the number of statistical comparisons and the opposite direction of this finding to prediction, this finding must be treated with caution as it may reflect a chance type I error.

In the previously reported population-based results from the United States,¹¹ cases were more than twice as likely than controls to have had a SI preceding OCD, TS, or tics. The results of the current study are based on a larger sample with 255 cases and almost 20 times as many controls, and hence had greater statistical power. The data on exposure were collected prospectively on a completely unselected and comprehensive sample of the general population, representative of the UK population (<http://www.epic-uk.org>),¹² and hence recall and selection bias could not operate. However, there are differences in study design that may have contributed to different outcomes in the 2 studies: the smaller population studied in the Mell et al.¹¹ article may have contributed to a type I error or, alternatively, methodologic issues in this study (see below) may have led to a type II error in this study. In particular, due to the low number of laboratory-confirmed cases, this study relied on clinical diagnosis as opposed to laboratory confirmation of SI and neuropsychiatric diagnoses relied on GP records. The crude incidence rates observed in our population were 4.0 for OCD and 3.6 for TS/tics per 100,000 person-years. This compares similarly to the rates from the Mell et al.¹¹ study, where 33 and 47 cases of OCD and TS were identified over an 8-year period from a population of around 75,000 children aged between 4 and 13 years (rates 5.5 and 7.8 per 100,000 person-years).¹¹ A previous birth cohort analysis from Denmark also ascertained 252 and 95 cases of OCD and TS from 127,782 children who were born either in 1990 or 1991 and followed up to December 2004. Assuming little loss to follow-up or censoring, this would result in 1,788,948 person-years of observation (over 14 years of follow-up) and an average annual incidence rate of 14.1 and 5.3 per 100,000 person-years for OCD and TS.¹³

Our analysis used wider time windows of exposure (2 years and 5 years) from the previous study (3 months and 1 year). We choose these longer gaps because of the inevitable delays among symptom onset, recognition of symptoms, health care seeking behavior, and general practitioner or specialist diagnosis.

We were also able to adjust for potential sociodemographic factors which may confound the risk of

SIs and neuropsychiatric disorder or its clinical diagnosis. The diagnosis of TS or tics was more frequent in areas with a large white population, suggesting either that the incidence of these disorders is lower in ethnic minority groups or that children from ethnic minorities are less likely to present to their doctor or be referred and diagnosed than white children, though our variable was ecologic rather than based on an individual measure of ethnicity. It is concordant with previous observations that white individuals have higher rates of TS as opposed to African black children and possibly children from the Far East.^{14,15}

There are several methodologic factors that need to be considered before accepting our negative findings as conclusive evidence of no causal association. 1) The outcome was based on GP records and hence the validity of diagnosis could not be confirmed. Most general practitioners are unlikely to make these diagnoses and would refer patients for a specialist diagnosis. A previous study using the same method for a diagnosis of autism found that 93% of diagnoses were confirmed.¹⁶ However, it is well-recognized from prevalence studies that screen-detected rates are far higher than those based on existing clinical diagnosis.¹⁷⁻²⁴ We are likely to have missed milder cases of disease, though if anything their inclusion would have further attenuated the results if we assume that the association with prior SI is stronger with more florid or severe cases. 2) The onset of TS, tics, or OCD relied on the retrospective date of onset. 3) The onset of TS, tics, and OCD is usually insidious and it is therefore difficult to establish the correct time of onset, and the relatively late age at onset suggests an earlier than reported age at onset. In both cases, our sensitivity analyses with wider time windows still failed to find any associations. 4) Diagnosis of SI was based on clinical impression, which is known to be have low accuracy (sensitivity between 39% and 87%),^{25,26} although use of guidelines improves this,²⁷ rather than streptococcal cultures or serology, which appeared to have been undertaken or recorded for a tiny minority of infection episodes. We used a fairly wide range of diagnostic codes, which would increase sensitivity, but at the expense of specificity, and hence it is possible that nondifferential misclassification would have attenuated any true association (false negative). We have looked at this in 2 different ways. The incidence of possible SIs in controls in this study (15%–16% over 2 years) was actually less than that reported in the Mell et al.¹¹ study (11%–16% over 1 year), which would be surprising if our false positive rate was higher than theirs. However, given differences in population demography, true population risk of infection, and dif-

ferent cultural and financial barriers in seeking a general practitioner diagnosis between the United Kingdom and United States, it is difficult to know how comparable these results are. Secondly, our repeated analysis using a much smaller and more specific set of codes where SI was explicitly mentioned still failed to find any association.

Only a prospective study with high diagnostic accuracy and laboratory confirmation of SI will be able to overcome these problems, but such a study would require a very large sample size and may be prohibitively expensive. However, a recent prospective study²⁸ examining the relationship between laboratory-confirmed β -hemolytic SIs and exacerbations of childhood tics and obsessive-compulsive symptoms in patients with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) and with chronic tic disorders or OCD found that only a minority of exacerbations in the PANDAS group and none in the other group were associated with these infections. While these cases were already diagnosed and an association with SI and onset of symptoms could therefore not be examined, the results argue against a strong causal relationship between group A SIs and clinical symptoms of tics or OCD at least in the majority of cases. As there is at present insufficient supportive evidence for a causal relationship between PANDAS and group A SIs, the American Heart Association²⁹ does not currently recommend routine laboratory testing for group A SI to diagnose, long-term antistreptococcal prophylaxis to prevent, or immunoregulatory therapy to treat exacerbations of this disorder.

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DISCLOSURE

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REFERENCES

- Muller N, Riedel M, Straube A, Gunther W, Wilske B. Increased anti-streptococcal antibodies in patients with Tourette's syndrome. *Psychiatry Res* 2000;94:43–49.
- Swedo SE, Leonard HL, Garvey M, et al. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: clinical description of the first 50 cases. *Am J Psychiatry* 1998;155:264–271.
- Dale RC, Heyman I, Surtees RA, et al. Dyskinesias and associated psychiatric disorders following streptococcal infections. *Arch Dis Child* 2004;89:604–610.
- Edwards MJ, Trikouli E, Martino D, et al. Anti-basal ganglia antibodies in patients with atypical dystonia and tics: a prospective study. *Neurology* 2004;63:156–158.
- Church AJ, Dale RC, Lees AJ, Giovannoni G, Robertson MM. Tourette's syndrome: a cross sectional study to examine the PANDAS hypothesis. *J Neurol Neurosurg Psychiatry* 2003;74:602–607.
- Singer HS, Hong JJ, Yoon DY, Williams PN. Serum auto-antibodies do not differentiate PANDAS and Tourette syndrome from controls. *Neurology* 2005;65:1701–1707.
- Rizzo R, Gulisano M, Pavone P, Fogliani F, Robertson MM. Increased antistreptococcal antibody titers and anti-basal ganglia antibodies in patients with Tourette syndrome: controlled cross-sectional study. *J Child Neurol* 2006;21:747–753.
- Kurlan R. Tourette's syndrome and 'PANDAS': will the relation bear out? Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection. *Neurology* 1998;50:1530–1534.
- Swedo SE, Leonard HL, Garvey M, et al. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: clinical description of the first 50 cases. *Am J Psychiatry* 1998;155:264–271.
- Garvey MA, Giedd J, Swedo SE. PANDAS: the search for environmental triggers of pediatric neuropsychiatric disorders: lessons from rheumatic fever. *J Child Neurol* 1998;13:413–423.
- 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.
- New medical research database launched. *Pharmaco Economics Outcome News* 2003;436.
- Atladottir HO, Parner ET, Schendel D, Dalsgaard S, Thomsen PH, Thorsen P. Time trends in reported diagnoses of childhood neuropsychiatric disorders: a Danish cohort study. *Arch Pediatr Adolesc Med* 2007;161:193–198.
- Robertson MM. The prevalence and epidemiology of Gilles de la Tourette syndrome: part 1: the epidemiological and prevalence studies. *J Psychosom Res* 2008;65:461–472.

15. Robertson MM. The prevalence and epidemiology of Gilles de la Tourette syndrome: part 2: tentative explanations for differing prevalence figures in GTS, including the possible effects of psychopathology, aetiology, cultural differences, and differing phenotypes. *J Psychosom Res* 2008; 65:473–486.
16. Fombonne E, Heavey L, Smeeth L, et al. Validation of the diagnosis of autism in general practitioner records. *BMC Public Health* 2004;4:5.
17. Robertson MM, Gourdie A. Familial Tourette's syndrome in a large British pedigree: associated psychopathology, severity, and potential for linkage analysis. *Br J Psychiatry* 1990;156:515–521.
18. Pappert EJ, Goetz CG, Louis ED, Blasucci L, Leurgans S. Objective assessments of longitudinal outcome in Gilles de la Tourette's syndrome. *Neurology* 2003;61:936–940.
19. Angst J, Gamma A, Endrass J, et al. Obsessive-compulsive severity spectrum in the community: prevalence, comorbidity, and course. *Eur Arch Psychiatry Clin Neurosci* 2004;254:156–164.
20. Mohammadi MR, Ghanizadeh A, Rahgozar M, et al. Prevalence of obsessive-compulsive disorder in Iran. *BMC Psychiatry* 2004;4:2.
21. Cilicilli AS, Telcioglu M, Askin R, Kaya N, Bodur S, Kucur R. Twelve-month prevalence of obsessive-compulsive disorder in Konya, Turkey. *Compr Psychiatry* 2004;45: 367–374.
22. McMahon WM, Carter AS, Fredine N, Pauls DL. Children at familial risk for Tourette's disorder: child and parent diagnoses. *Am J Med Genet B Neuropsychiatr Genet* 2003;121:105–111.
23. Kurlan R, McDermott MP, Deeley C, et al. Prevalence of tics in schoolchildren and association with placement in special education. *Neurology* 2001;57:1383–1388.
24. Lucas AR, Beard CM, Rajput AH, Kurland LT. Tourette syndrome in Rochester, Minnesota, 1968–1979. *Adv Neurol* 1982;35:267–269.
25. Ebell MH, Smith MA, Barry HC, Ives K, Carey M. The rational clinical examination: does this patient have strep throat? *JAMA* 2000;284:2912–2918.
26. Dobbs F. A scoring system for predicting group A streptococcal throat infection. *Br J Gen Pract* 1996;46:461–464.
27. McIsaac WJ, Kellner JD, Aufricht P, Vanjaka A, Low DE. Empirical validation of guidelines for the management of pharyngitis in children and adults. *JAMA* 2004;291:1587–1595.
28. Kurlan R, Johnson D, Kaplan EL. Streptococcal infection and exacerbations of childhood tics and obsessive-compulsive symptoms: a prospective blinded cohort study. *Pediatrics* 2008;121:1188–1197.
29. Gerber MA, Baltimore RS, Eaton CB, et al. Prevention of rheumatic fever and diagnosis and treatment of acute streptococcal pharyngitis: a scientific statement from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young, the Interdisciplinary Council on Functional Genomics and Translational Biology, and the Interdisciplinary Council on Quality of Care and Outcomes Research: endorsed by the American Academy of Pediatrics. *Circulation* 2009;119: 1541–1551.

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