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Group A Streptococcal Infections Are Associated With Increased Risk of Pediatric Neuropsychiatric Disorders: A Taiwanese Population-Based Cohort Study

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ABSTRACT

Objective: This study evaluated the association between group A streptococcal (GAS) infections and the risks of developing tic disorders, obsessive-compulsive disorder (OCD), and attention-deficit/hyperactivity disorder (ADHD).

Methods: We conducted a follow-up cohort study in 2014 using Taiwan's National Health Insurance Research Database. The study cohort consisted of patients younger than 18 years with newly diagnosed GAS infection (*ICD-9-CM* codes 034 [streptococcal sore throat and scarlet fever] and 482.31 [pneumonia due to Streptococcus, group A]) from 2001 to 2010. All patients having GAS infection codes between 1996 and 2000 were excluded. We assessed the patients' risks of developing tic disorders, OCD, and ADHD (*ICD-9-CM* codes 300.3 [obsessive-compulsive disorders], 301.4 [obsessive-compulsive personality disorder], 307.2 [tic disorder, unspecified], and 314 [attention deficit disorder]) and compared these risks with those of a control cohort. The primary outcomes of this study were the overall neuropsychiatric disorder occurrence and the occurrence of separate subtypes.

Results: We examined 2,596 patients and 25,960 controls. The incidence of neuropsychiatric disorders in the GAS infection cohort (60.42 per 10,000 person-years) was significantly higher than that in the comparison cohort (49.32 per 10,000 person-years) (hazard ratio [HR] = 1.22; 95% CI, 1.00–1.49). The largest increased risk was for tic disorders (HR = 1.63; 95% CI, 1.02–2.62). Patients hospitalized for GAS infection had a 1.96-fold higher risk of neuropsychiatric disorders than did people without GAS infection (HR = 1.96; 95% CI, 1.23–3.12), and there was no difference in risk between outpatients with GAS infection and people without GAS infection (HR = 1.14; 95% CI, 0.92–1.41). Patients with moderate or high frequencies of GAS infection–related clinic visits had much higher risks of developing a neuropsychiatric disorder and, specifically, tic disorders and ADHD (all *P* values for trend < .05). These risks were not increased in patients with a low frequency of clinic visits.

Conclusions: Our results confirmed an association between previous group A streptococcal infection and neuropsychiatric disorders.

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In 1994, Swedo[1] reported the first case of a girl with rheumatic chorea and obsessive-compulsive disorder (OCD). In 1995, Allen et al[2] described 4 patients in whom OCD or Tourette syndrome manifested or worsened after group A streptococcal (GAS) infections and viral infection. They responded to plasmapheresis, intravenous immunoglobulin, or prednisone. Allen and colleagues[2] coined the term *PITANDs* (pediatric infection-triggered, autoimmune, neuropsychiatric disorders). Later, Swedo et al[3] evaluated 50 children who had the presence of OCD or tic disorders with temporal association with group A streptococcal infections. They proposed the existence of PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections) together with its diagnostic criteria. Cardona and Orefici[4] found that in children with tics, mean antistreptolysin O (ASO) titer was significantly higher compared with that of control subjects, and 17% of children with tics had throat cultures positive for GAS infection.[4] In children with obsessive-compulsive and tic disorders, Murphy et al[5] found positive correlations between streptococcal titers and obsessive-compulsive severity rating changes. In a case-control study[6] of children between 4 and 13 years old, patients with OCD, Tourette syndrome, or a tic disorder were shown to be more likely to have had a GAS infection in the 3 months before the disorder onset date. Using health insurance claims data, Leslie et al[7] reported that subjects with newly diagnosed OCD, Tourette syndrome, or tic disorder were more likely than controls to have had a diagnosis of streptococcal infection in the previous year. Murphy et al[8] also found that children with PANDAS were more likely to have had dramatic onset, definite remissions, and remission of neuropsychiatric symptoms during antibiotic therapy; history of tonsillectomies/adenoidectomies; and evidence of group A streptococcal infection as compared with children without PANDAS. These lines of evidence support an association of GAS infection with OCD and tic disorders. However, there are also studies with

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Clinical Points

- The association between group A streptococcal (GAS) infections and neuropsychiatric disorders, as well as the underlying autoimmune-mediated antibody-antigen hypothesis, is still not completely convincing.
- Our findings of increased risk of neuropsychiatric disorders after moderate- to high-frequency GAS infection confirmed an association between previous GAS infections and neuropsychiatric disorders and are consistent with an autoimmune-mediated antibody-antigen mechanism.

results not supporting an association of GAS infection with OCD and tics. In 2 longitudinal studies[9,10] of children with Tourette syndrome, although the tic/OCD groups did exhibit increased rates of GAS infection compared to controls, new GAS infections did not predict tics or other symptoms. In a 1-year follow-up of 30 children with Tourette syndrome or OCD, symptom exacerbation was not associated with new infections.[11] In a study of 40 matched PANDAS case-control pairs who were prospectively evaluated with laboratory testing for GAS infection and clinical measures for an average of 2 years, Kurlan et al[12] observed that most of the clinical exacerbations had no observable temporal relationship to GAS infection. Similarly, Leckman et al[13] also found no evidence for a temporal association between GAS infections and tic/OCD symptom exacerbations in children who meet the PANDAS diagnostic criteria. In a case-control study of a large primary care database, Schrag et al[14] found no overall increased risk of prior possible streptococcal infection in patients with a diagnosis of OCD, Tourette syndrome, or tics. Thus, this topic remains controversial. To further clarify the association between group A streptococcal infections and neuropsychiatric disorders, we examined the risk of patients developing tic disorders, OCD, and attention-deficit/hyperactivity disorder (ADHD) after GAS infection on a national scale by using Taiwan's National Health Insurance Research Database (NHIRD).

METHODS

Data Source

In 1995, the Taiwan government established the universal, single-payer National Health Insurance (NHI) program. The program is compulsory for all Taiwanese citizens and has covered nearly 99% of the country's 23 million citizens since 1998. Insured people pay relatively low premiums, and the government uses this revenue to pay a large part of patients' medical and medication costs to contracted health care institutions.

The Taiwan government appointed the National Health Research Institutes (NHRI) to organize and manage the NHIRD, which contains original annual claims data used for reimbursement. For this study, we used the Longitudinal Health Insurance Database (LHID), which is a subset of the NHIRD, to establish a study population. The LHID comprises a random sample of 1 million insured patients during 1996–2000 and provides information on the medical services used by the 1 million beneficiaries. The age and sex distributions of the patients in the LHID and those in the NHIRD are similar. The LHID contains up-to-date annual claims records, including beneficiary registries, records of outpatient and inpatient visits, drug prescription registries, and records of other medical services. To collate the files for each patient and protect personal privacy, the NHRI provides a scrambled and anonymous identification number for each patient's claims data before releasing them for research. This study was approved by the ethics review board at China Medical University (CMU-REC-101-012).

The NHIRD disease records are organized in accordance with the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) system. Disease histories were collected from inpatient and outpatient files.

Study Population

To investigate the association between GAS infection and the risk of pediatric neuropsychiatric disorders, namely tic disorders, OCD, and ADHD, we designed a retrospective, population-based cohort study in 2014. The GAS infection cohort was formed by collecting data on patients with a newly diagnosed GAS infection (*ICD-9-CM* codes 034 [streptococcal sore throat and scarlet fever] and 482.31 [pneumonia due to Streptococcus, group A]) from 2001 to 2010, and the initial GAS infection diagnosis date was set as the index date. All patients having GAS infection codes between 1996 and 2000 were excluded. The comparison cohort was constructed using data from people without GAS infection in the LHID and matched according to age (per 3 years), sex, urbanization of residence, and parental occupation to the GAS infection cohort at a 1:10 ratio. The comparison cohort's index dates were set using the years of the matched GAS infection cases and randomly allocated months and days. Both cohorts consisted of people aged younger than 18 years and excluded people with a history of neuropsychiatric disorders including tic disorders, ADHD, and OCD. The follow-up period extended until insurance was withdrawn, a neuropsychiatric disorder was diagnosed, or December 31, 2011.

The primary outcomes of this study were the overall neuropsychiatric disorder occurrence (*ICD-9-CM* codes 300.3 [obsessive-compulsive disorders], 301.4 [obsessive-compulsive personality disorder], 307.2 [tic disorder, unspecified], and 314 [attention deficit disorder]) and the occurrence of separate subtypes. Only the patients having neuropsychiatric events after the index streptococcal infection events were included. The severity and frequency of GAS infections were categorized for further analysis. Group A streptococcal infection severity was categorized into 3 groups: none (no GAS infection), outpatient (GAS infection requiring only outpatient treatment), and hospitalization (GAS infection requiring inpatient care). The mean frequency of GAS infections per year for each study subject was calculated as the total number of GAS infections within the follow-up duration divided by the

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follow-up duration (years). Group A streptococcal infection frequency was classified according to the mean number of GAS infection occurrences per year and classified into 4 groups: none, low frequency (< 3 GAS infections per person-year), moderate frequency (3–5 GAS infections per person-year), and high frequency (≥ 6 GAS infections per person-year).

Urbanization of residence was determined using a score calculated by incorporating variables indicating population density (people/km^2); the population ratios of people with different educational levels, older adults, and agricultural workers; and the number of physicians per 100,000 people.[15] Urbanization of residence was classified into 4 levels, with level 1 indicating the highest degree of urbanization and level 4 indicating the lowest degree. Parental occupations were classified into 3 groups: (1) a white-collar group comprising people with long indoor working hours, such as civil servants and businesspeople; (2) a blue-collar group consisting of people with long, outdoor working hours, such as industrial laborers and farmers; and (3) an "other" group containing retired people and those with a low income.

Statistical Analysis

We used the mean and standard deviation (SD) for age and the number and percentage for categorical variables to calculate the relationship between the GAS infection and comparison cohorts. We assessed the differences in the distributions of age and categorical variables between the cohorts by using the *t* test and χ^2 test, respectively. The cumulative neuropsychiatric disorder incidence rate was calculated by dividing the total number of people who developed a disorder by the sum of the observation time for each cohort per 10,000 person-years.

To compare the GAS infection and comparison cohorts' risks of developing a neuropsychiatric disorder, the hazard ratios (HRs) and 95% CIs were estimated using single-variable and multivariate Cox proportional hazards models. In a sensitivity analysis, the patients and controls were stratified into various demographic groups, and an adjusted Cox proportional hazards model was used to determine the HRs for the GAS infection cohort relative to the comparison cohort.

SAS 9.3 software (SAS Institute; Cary, North Carolina) was used to manage and analyze the data, and a 2-sided *P* value < .05 indicated significance.

RESULTS

This study established a 2,596-person GAS infection patient cohort and a 25,960-person comparison cohort (Table 1). Because the study and control populations were matched, the mean age of the GAS infection cohort was similar to the mean age of the comparison cohort (9.0 years), and there was no difference in the distributions of sex, urbanization, and parental occupation between the cohorts (all *P* values > .99). The mean frequency of GAS infection was 2.7 per person-year (SD = 5.0), and most GAS infection patients had < 3 per person-year infections (75.6%).

The incidence of neuropsychiatric disorders was 60.42 per 10,000 person-years in the GAS infection cohort and 49.32 per 10,000 person-years in the comparison cohort (Table 2). These neuropsychiatric disorders occurred a mean of 3.6 years (SD = 2.2) after the first GAS infection episode. Figure 1 shows the time distribution of the periods between GAS infection and neuropsychiatric disorders occurrence. The highest frequency of occurrence was 5 years after the first GAS infection episode. After adjusting for age, sex, urbanization, and parental occupation, we compared the

Table 1. Demographic Status Compared Between Comparison and Group A Streptococcal (GAS) Infection Cohort

Variable	Comparison Cohort (n = 25,960), n (%)	GAS Infection Cohort (n = 2,596), n (%)	*P* Value
Age, mean (SD), y[a]	9.0 (4.3)	9.0 (4.3)	.4424
Sex			> .99
Female	12,290 (47.3)	1,229 (47.3)	
Male	13,670 (52.7)	1,367 (52.7)	
Urbanization[b]			> .99
1	7,200 (27.7)	720 (27.7)	
2	7,910 (30.5)	791 (30.5)	
3	5,480 (21.1)	548 (21.1)	
≥ 4	5,370 (20.7)	537 (20.7)	
Parental occupation			> .99
White-collar	16,410 (63.2)	1,641 (63.2)	
Blue-collar	6,680 (25.7)	668 (25.7)	
Others	2,870 (11.1)	287 (11.1)	
Frequency of GAS infection			
Mean (SD)		2.7 (5.0)	
< 3 times		1,963 (75.6)	
3–5 times		413 (15.9)	
≥ 6 times		220 (8.5)	

[a]*t* test.
[b]Level 1 indicates the highest level of urbanization, and level ≥ 4 indicates the lowest level.

Table 2. Incidence of Neuropsychiatric Disorders and Hazard Ratios (HRs) Determined by Multivariate Cox Proportional Hazards Regression Analysis for Study Cohort

	Comparison Cohort			GAS Infection Cohort				
Type of Event	n	Person-Years	Rate[a]	n	Person-Years	Rate[a]	Crude HR, (95% CI)	Adjusted HR, (95% CI)[b]
Overall	898	182,059	49.32	110	18,207	60.42	1.23 (1.01–1.49)	1.22 (1.00–1.49)*
ADHD	739	182,059	40.59	86	18,207	47.23	1.17 (0.93–1.46)	1.16 (0.93–1.45)
Tourette syndrome and tics	122	182,059	6.70	20	18,207	10.98	1.64 (1.02–2.63)	1.63 (1.02–2.62)
OCD	37	182,059	2.03	4	18,207	2.20	1.08 (0.38–3.02)	1.08 (0.38–3.02)

[a]Incidence rate per 10,000 person-years.
[b]Model adjusted for age, sex, urbanization, and parents' occupation.
*P = .047.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, GAS = group A streptococcal, OCD = obsessive-compulsive disorder.

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risk of each type of neuropsychiatric disorder between the GAS infection and comparison cohorts. The results revealed that only the risk of tic disorders was increased after a GAS infection diagnosis (HR = 1.63; 95% CI, 1.02–2.62). For ADHD and OCD, the risks were mildly elevated (HR = 1.16 and 1.08, respectively), but the 95% CIs indicated they were not statistically significant. For children less than 6 years of age, the frequency of GAS infection may be underestimated, because these children often go undiagnosed with GAS infection as they present differently than older children (ie, present with more gastrointestinal symptoms).

Table 3 shows the association of GAS infection severity and frequency with neuropsychiatric disorder risk. Hospitalized GAS infection patients had a 1.96-fold increased risk of developing neuropsychiatric disorders compared with people without GAS infection (HR = 1.96; 95% CI, 1.23–3.12), whereas there was no difference in risk between outpatients diagnosed with GAS infection and the comparison group (HR = 1.14; 95% CI, 0.92–1.41). In the hospitalized patients, only 1 had pneumonia (*ICD-9-CM* code 482.31). Among the neuropsychiatric disorder subgroups, hospitalized patients with GAS infection had a significantly higher risk of ADHD than did people without GAS infection (HR = 1.82; 95% CI, 1.08–3.10). The risks of tic disorders and OCD were also higher for hospitalized patients with GAS infection (HR = 2.42 and 4.09, respectively), but the 95% CIs included zeros and therefore did not definitively indicate increased risk.

For patients with a low frequency (< 2 per year) of GAS infection–related clinic visits, neuropsychiatric disorder risk was not elevated compared with that of the control cohort. However, patients with moderate (2–4 per year) or high (≥ 5 per year) frequencies of GAS infection–related clinic visits had a much higher risk of developing neuropsychiatric disorders, tic disorders, and ADHD (all *P* values for trend < .05). This association was not observed for OCD, probably because too few OCD cases were included in this study.

Table 4 shows the relative risks of tic disorders after a GAS infection diagnosis according to various demographic factors. GAS infection significantly increased tic disorders risk in patients who were aged ≥ 6 years (HR = 2.67; 95% CI, 1.41–5.04), were female (HR = 2.60; 95% CI, 1.13–5.98), or lived in a rural area (HR = 2.82; 95% CI, 1.52–5.22).

DISCUSSION

Individual or serial cases of pediatric obsessive-compulsive behavior and tics have been associated with Sydenham chorea for decades.[16–18] In 1998, Swedo and colleagues[3] coined the term *PANDAS* for a subgroup of children diagnosed with OCD or tics associated with group A beta-hemolytic GAS infection but who did not fulfill the criteria for Sydenham chorea.[2] Despite these reported cases of tics and OCD exacerbations observed after GAS infection, the association between GAS infection and tics and OCD is difficult to be confirmed. Several retrospective studies[6,7] have shown that patients with OCD, Tourette syndrome, tic disorder, ADHD, or major depressive disorder were more likely to have had GAS infection than controls. Prospective studies examining this association have been largely inconsistent, failing to confirm a clearly higher rate of GAS infection–related exacerbations of tic disorder and/or OCD[12,13] or to verify an association between tics and GAS

Figure 1. Time Period of Group A Streptococcal Infection to Neuropsychiatric Disorder

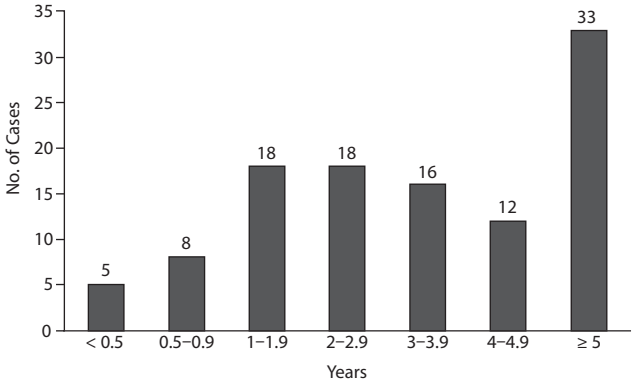

Table 3. Incidence of Developing Neuropsychiatric Disorder by Different Severity of Group A Streptococcal (GAS) Infection and the Neuropsychiatric Disorder Risk Associated With GAS Infection Severity Measured by Cox Proportional Hazards Regression Models

	Overall			ADHD			Tic Disorders			OCD		
Severity of GAS Infection	n	Rate	Adjusted HR (95% CI)[a]	n	Rate	Adjusted HR (95% CI)[a]	n	Rate	Adjusted HR (95% CI)[a]	n	Rate	Adjusted HR (95% CI)[a]
Care of GAS infection												
None	898	49.32	Reference	739	40.59	Reference	122	6.70	Reference	37	2.03	Reference
Outpatient	92	54.94	1.14 (0.92–1.41)	72	42.99	1.08 (0.85–1.38)	17	10.15	1.54 (0.93–2.57)	3	1.79	0.87 (0.27–2.81)
Hospitalized	18	123.23	1.96 (1.23–3.12)	14	95.85	1.82 (1.08–3.10)	3	20.54	2.42 (0.77–7.62)	1	6.85	4.09 (0.56–30.07)
Frequency of GAS infection visits per year												
None	898	49.32	Reference	739	40.59	Reference	122	6.70	Reference	37	2.03	Reference
< 2	91	51.13	1.04 (0.84–1.29)	73	41.01	1.02 (0.80–1.30)	14	7.87	1.18 (0.68–2.05)	4	2.25	1.10 (0.39–3.08)
2–4	12	402.34	5.78 (3.27–10.23)	8	268.23	4.53 (2.25–9.11)	4	134.11	15.52 (5.70–42.25)	0	0	NA[b]
≥ 5	7	634.02	8.64 (4.11–18.19)	5	452.87	7.18 (2.98–17.32)	2	181.15	18.61 (4.59–75.44)	0	0	NA[b]
P for trend			< .0001			.0041			< .0001			NA[b]

[a]Model adjusted for age, sex, urbanization, and parents' occupation.
[b]No patient fit this criterion.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, HR = hazard ratio, NA = not applicable, OCD = obsessive-compulsive disorder.

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Table 4. Incidence of Developing Tic Disorders by Demographic Status and the Tic Disorders Risk Associated With Group A Streptococcal (GAS) Infection Measured by Cox Proportional Hazards Regression Models Stratified by Baseline Characteristics

	Comparison Cohort			GAS Infection Cohort			Adjusted HR, (95% CI)[b]
Variable	Event	Person-Years	Rate[a]	Event	Person-Years	Rate[a]	
Age group, y							
<6	77	63,512	12.12	8	6,339	12.62	1.04 (0.50–2.15)
≥6	45	118,547	3.80	12	11,868	10.11	2.67 (1.41–5.04)
Sex							
Female	27	86,705	3.11	7	8,672	8.07	2.60 (1.13–5.98)
Male	95	95,354	9.96	13	9,535	13.63	1.36 (0.76–2.43)
Urbanization							
Urban	76	107,516	7.07	7	10,741	6.52	0.92 (0.42–1.99)
Rural	46	74,544	6.17	13	7,466	17.41	2.82 (1.52–5.22)
Parents' occupation							
White-collar	81	115,481	7.01	10	11,559	8.65	1.22 (0.63–2.36)
Blue-collar	27	46,697	5.78	6	4,677	12.83	2.24 (0.92–5.41)
Other	14	19,882	7.04	4	1,972	20.29	2.89 (0.95–8.77)

[a]Incidence rate per 10,000 person-years.
[b]Model adjusted for age, sex, urbanization and parents' occupation.
Abbreviation: HR = hazard ratio.

infection.[5,10] Furthermore, the relative risks of developing tics or OCD in children after GAS infection as compared to children without GAS infection are unknown.

Our study is the first to investigate the risks of tic disorders, OCD, and ADHD after GAS infection by using a nationwide population-based database. Our findings show that GAS infection in Taiwan is associated with a higher incidence of subsequent neuropsychiatric disorders (tic disorders, OCD, and ADHD; HR = 1.22) in patients younger than 18 years compared with people without GAS infection. Among tic disorders, OCD, and ADHD, only the risk of tic disorders was observed to be significantly increased (HR = 1.63) in the GAS infection cohort compared with that in the comparison cohort. Tics and OCD are the 2 conditions most strongly associated with GAS infection and are included in the diagnostic criteria for PANDAS.[3] Our results provide supporting evidence that GAS infection is associated with an increased risk of developing tic disorders.

An autoimmune-mediated interaction involving antibodies targeting basal ganglia antigens, similar to that of Sydenham chorea, has been proposed as the mechanism through which GAS infection is associated with neuropsychiatric disorders.[1,19–22] A study reported that the number of children with raised ASO titers was higher in a group of children with Tourette syndrome than in a control group.[23] Martino et al[9] found that patients with Tourette syndrome exhibited a higher frequency of GAS infection, higher ASO titers, and higher frequency of antibasal ganglia antibodies than the comparison group, and Cardona and Orefici[4] found that in children with tics, mean ASO titer was significantly higher compared with that of control subjects. On the other hand, Singer et al[24] examined serial serum samples of 12 children with PANDAS and found no correlation between clinical exacerbations and autoimmune markers. Murphy et al[25] evaluated patients for percentage of D8/17-positive B cells in childhood-onset OCD and/or tic disorders and healthy comparison subjects and found no differences between groups in the presence of antineuronal antibodies or high streptococcal titers.[25] Loiselle and colleagues[26] found that mean antistreptococcal titers did not differ between 41 children with Tourette syndrome and 38 controls. Singer[27] also found that measurements of antibasal ganglia antibodies do not differentiate between PANDAS and controls. Morris et al[28] found no significant differences in antistriatal antibodies in patients with PANDA as compared to controls.

Because of a nearly 100% NHI coverage in Taiwan, it is not very unusual for children with severe GAS infections symptoms to be hospitalized. We think hospitalization can be an indicator for severe GAS infections. Our results showed that patients who were diagnosed with severe GAS infection (requiring hospitalization) had a significantly higher risk of subsequently developing neuropsychiatric disorders as well as the 3 individual neuropsychiatric disorders compared with people who had only mild infections (requiring only outpatient visits). The risk in outpatients is slightly but not significantly elevated as compared with the comparison group. This may imply that if only mild GAS infection cases are included in a study, their association with neuropsychiatric disorders might not be revealed. Furthermore, the frequency of GAS infection was strongly associated with an increased risk of subsequent neuropsychiatric disorders, tic disorders, and ADHD. In a prospective, longitudinal study on school children, Murphy et al[29] also found that children with repeated streptococcus showed higher rates of behavior and distal choreiform observations. Our findings were consistent with the autoimmune-mediated antibody-antigen theory. It is reasonable to infer that multiple repeated exposures to, or an exposure to larger amounts of, streptococcal antigens could trigger more antibody responses than a single exposure or milder exposures. After a thorough review of the literature, we believe that this severity- and frequency-related association between GAS infection and neuropsychiatric disorders has not been reported previously.

In our study, neuropsychiatric disorders occurred a mean of 3.6 ± 2.2 years after the first GAS infection episode, contrasting more recent associations observed regarding PANDAS.[30,31] The cause of this relatively delayed occurrence

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is unclear. We propose that not all neuropsychiatric disorders that occur after GAS infection are the result of a single autoimmune episode. Some neuropsychiatric disorders may be secondary to accumulated antigen-antibody effects (eg, after multiple repeated exposures to streptococcal antigens) on the brain. Actually, OCD and tic disorders have also been reported to occur after infections other than GAS, such as mycoplasma infections or in association with chronic Lyme disease.[32–34]

In addition, our data showed that GAS infections increased the risk of tic disorders, primarily among patients who were 6 years of age or older, female, or in a rural area. The implications of these results are unclear.

Our study cohort included patients with pneumonia secondary to GAS infection (*ICD-9-CM* code 482.31), aside from streptococcal sore throat and scarlet fever (*ICD-9-CM* code 034). We presumed that autoimmune-mediated antibody-antigen reaction would occur irrespective of the location of GAS infections. However, there was only 1 patient with pneumonia secondary to GAS infection in our study cohort. For neuropsychiatric disorders, we included obsessive-compulsive personality disorder (OCPD) (*ICD-9-CM* code 301.4) as well as OCD (300.3). The reason for including OCPD is that we think newly onset OCPD subsequent to, but not before, GAS infection may still be related to GAS infection. However, the total number of events of OCD and OCPD is still very small, and this could affect our risk analysis considerably.

Our study was subject to limitations. First, the NHIRD does not provide detailed patient information on possible confounding factors such as lifestyle, body mass index, physical activity, socioeconomic status, and family medical history. Second, evidence derived from a cohort study, the design of which is subject to various biases related to adjustments for confounding factors, is generally of lower methodological quality than evidence from randomized trials. Despite our meticulous study design and adequate control of the confounding factors, a key limitation was that biases may have remained because of unmeasured or unknown confounders. Third, the NHI claims registries are primarily used for billing and are not verified for scientific accuracy. However, the diagnoses of GAS infection and pediatric neuropsychiatric disorders were made by psychiatrists and pediatricians, and thus were reliable. Finally, additional large, population-based, unbiased, randomized prospective studies are required to confirm our findings before firm conclusions can be drawn.

In conclusion, our results, including an increased risk of tic disorders after GAS infection, increased risk of ADHD after severe GAS infection, and greatly increased risk of tic disorders and ADHD after moderate- to high-frequency GAS infection, confirmed an association between previous GAS infections and neuropsychiatric disorders. The higher risk of neuropsychiatric disorders after more severe or frequent infections is consistent with an autoimmune-mediated antibody-antigen mechanism. The latency between GAS infection episodes and the occurrence of a neuropsychiatric disorder may suggest a cumulative antigen-antibody effect on the brain.

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