NULL HYPOTHESIS

Association of Group A *Streptococcus* Exposure and Exacerbations of Chronic Tic Disorders

A Multinational Prospective Cohort Study

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Abstract

Objective

To examine prospectively the association between group A *Streptococcus* (GAS) pharyngeal exposures and exacerbations of tics in a large multicenter population of youth with chronic tic disorders (CTD) across Europe.

Methods

We followed up 715 children with CTD (age 10.7 ± 2.8 years, 76.8% boys), recruited by 16 specialist clinics from 9 countries, and followed up for 16 months on average. Tic, obsessive-compulsive symptom (OCS), and attention-deficit/hyperactivity disorder (ADHD) severity was assessed during 4-monthly study visits and telephone interviews. GAS exposures were analyzed using 4 possible combinations of measures based on pharyngeal swab and serologic testing. The associations between GAS exposures and tic exacerbations or changes of tic, OC, and ADHD symptom severity were measured, respectively, using multivariate logistic regression plus multiple failure time analyses and mixed effects linear regression.

Results

A total of 405 exacerbations occurred in 308 of 715 (43%) participants. The proportion of exacerbations temporally associated with GAS exposure ranged from 5.5% to 12.9%, depending on GAS exposure definition. We did not detect any significant association of any of the 4 GAS exposure definitions with tic exacerbations (odds ratios ranging between 1.006 and 1.235, all p values >0.3). GAS exposures were

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Glossary

ADB = anti-DNase B; **ADHD** = attention-deficit/hyperactivity disorder; **ASOT** = anti-streptolysin O; **CTD** = chronic tic disorders; **CY-BOCS** = Children's Yale-Brown Obsessive-Compulsive Scale; **DSM-IV-TR** = Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision; **EMTICS** = European Multicenter Tics in Children Study; **GAS** = group A *Streptococcus*; **OCD** = obsessive-compulsive disorder; **OR** = odds ratio; **PANDAS** = pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection; **PANS** = pediatric acute neuropsychiatric syndromes; **SNAP-IV** = Swanson, Nolan, and Pelham IV; **TS** = Tourette syndrome; **YGTSS-TTS** = Yale Global Tic Severity Scale–Total Tic Severity Score.

associated with longitudinal changes of hyperactivity–impulsivity symptom severity ranging from 17% to 21%, depending on GAS exposure definition.

Conclusions

This study does not support GAS exposures as contributing factors for tic exacerbations in children with CTD. Specific workup or active management of GAS infections is unlikely to help modify the course of tics in CTD and is therefore not recommended.

Chronic tic disorders (CTD), encompassing Tourette syndrome (TS) and chronic motor or vocal tic disorders, are among the most common neurodevelopmental conditions, with a 0.3%–0.9% prevalence for TS[1] and multifactorial etiology.[2,3] Fluctuations in tic severity[4] have been related to psychosocial stress, infectious triggers, or their potential interaction.[5,6]

Group A *Streptococcus* (GAS)[7] has been investigated in CTD for over 2 decades. The interest in this association stems from the description of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS),[8,9] now incorporated in the pediatric acute neuropsychiatric syndromes (PANS),[10] in which tics constitute an accompanying feature.[11] Neither population-based[12–17] nor longitudinal clinical studies[5,18–30] could definitively establish whether tic exacerbations in CTD are associated with GAS infections.[24,25,27,28] A few studies including mixed populations of PANDAS and CTD[25,28] found that tic exacerbations were unrelated to GAS infection in the majority of cases, arguing against this association.[24,25,28–30] A prospective study of 168 children with CTD[27] did not demonstrate an effect of GAS on future tic or obsessive-compulsive symptom severity. However, the relatively long intervisit interval (4 months), the artificial bootstrapping procedure to define exacerbations, and the small sample size might have limited its sensitivity.

Our primary objective was to explore prospectively the association between GAS pharyngeal exposures and tic exacerbations in an in-depth assessment of a large, multicenter population of youth with CTD across the European Union/Israel (European Multicenter Tics in Children Study [EMTICS]). Secondarily, we evaluated the association between GAS exposure and the course of associated behavioral symptoms, i.e., obsessive-compulsive, inattentive, and hyperactivity/impulsivity symptoms.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

All the institutional ethical standards committees of the participating centers provided approval to the study. Parents and their children provided written informed consent and assent.

Study Design

EMTICS is a prospective pediatric cohort study exploring the association between CTD and environmental and genetic factors. Its detailed structure has been described by Schrag et al.[31] The main objective of one study arm (COURSE) was to investigate the association between environmental and genetic factors and clinically relevant exacerbations of tics (the other arm, not reported on here, focused on the onset of tics).

Participants

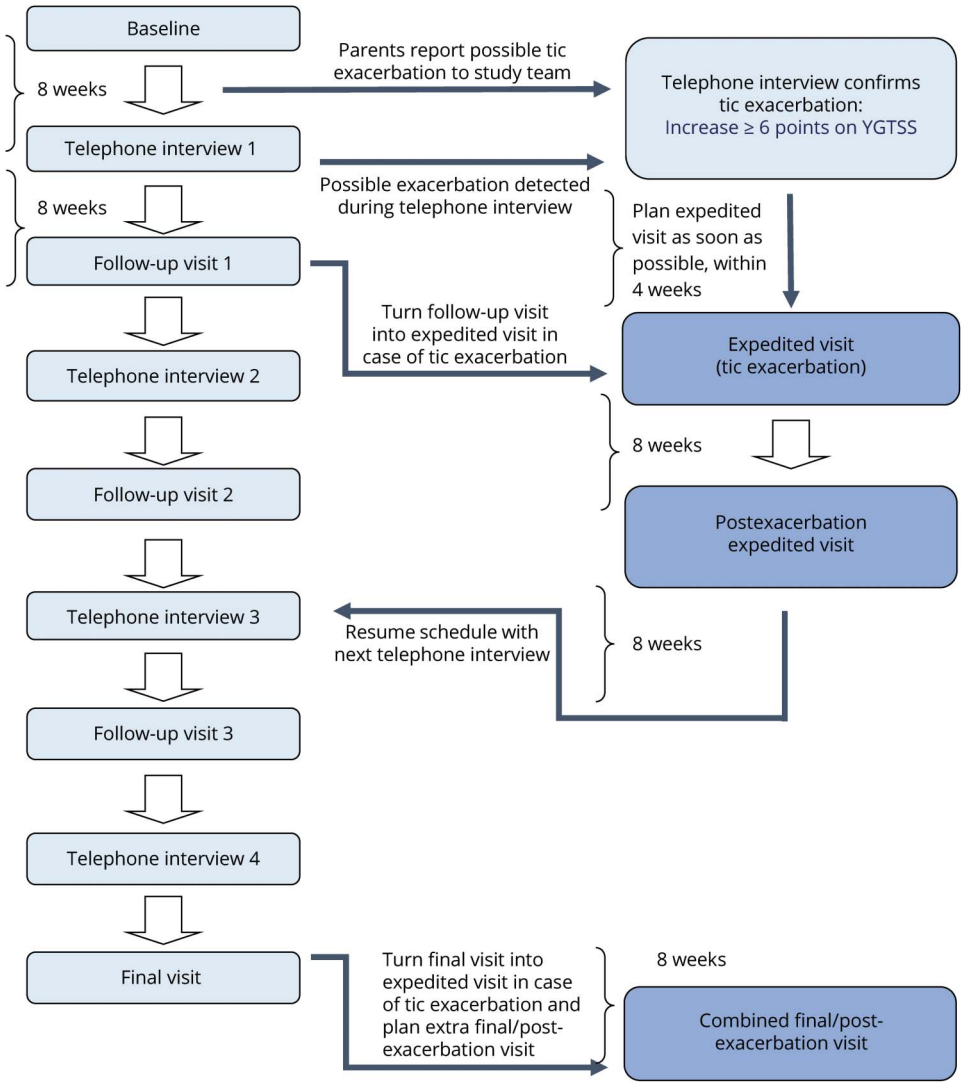
The COURSE arm of EMTICS included 715 children and adolescents aged 3–16 years with CTD, recruited between 2013 and 2016 by 16 child/adolescent psychiatry and pediatric neurology outpatient clinics (listed in appendix 2, links.lww.com/WNL/B326) or through advertisement to patient organizations and other health professionals.

Patients with an established diagnosis of TS or chronic motor or chronic vocal tic disorders according to DSM-IV-TR criteria[32] were recruited. Children with serious medical/neurologic illnesses or treated with antibiotics in the previous month were excluded. Use of medications or behavioral therapy for tics or comorbidities was not an exclusion criterion.

Study Visits

Data collection was structured on 3 observation levels: (1) scheduled 4-monthly face-to-face visits over 16 to 18 months, with clinical evaluation and collection of throat swabs and serum; (2) scheduled 4-monthly telephone interviews (2

Figure Flow Chart of the COURSE Arm Protocol of the EMTICS Study



EMTICS = European Multicenter Tics in Children Study; YGTSS-TTS = Yale Global Tic Severity Scale–Total Tic Severity Score.

months in between study visits) with review of weekly diaries completed since the previous assessment and evaluations performed by the study clinician interviewing the children's parents; and (3) a weekly diary in which parents were asked to indicate worsening of tics, aimed at the earliest possible detection of tic exacerbation (figure).[31] Tic exacerbations were defined by an increase of at least 6 points on the Yale Global Tic Severity Scale–Total Tic Severity Score (YGTSS-TTS) compared to the previous assessment (visit or telephone interview). This definition was supported by the only report published at EMTICS' start date, which identified a 6–7 point decrease on the YGTSS-TTS as clinically meaningful.[33] Tic exacerbations could be detected during scheduled 4-monthly study visits or telephone interviews, or through reporting in between scheduled visits/telephone interviews. Moreover, irrespective of the planned visit schedule, parents were instructed to report by phone/email any noticeable increase in tic severity, seemingly unrelated to a change in medication. Study clinicians then proceeded with an unscheduled telephone interview: if a tic exacerbation was suspected, an expedited tic exacerbation visit was arranged, preferably within 1 week from the interview. The tic exacerbation was definitely established during this planned visit only if the score change fulfilled the above definition of tic exacerbation.[31]

Clinical and Laboratory Measures

Clinical Measures

The primary outcome of tic exacerbation was based on changes on the YGTSS-TTS (range 0–50),[34] the most widely used instrument to rate tic severity,[35] which assesses past week tic severity combining motor and vocal tic subscores. Study clinicians were experienced in the evaluation and treatment of tic disorders and associated conditions. The severity of obsessive-compulsive disorder (OCD) and

Table 1 Demographic and Clinical Variables of the 715 Participants Enrolled in the Study

Variable	Mean ± SD or n (%)
Age at study entry, y	10.65 ± 2.83
Age at tic onset, y	5.15 ± 1.62
Male sex	549 (76.8)
Parental education level (higher level between the 2 parents)	
<7 years of school	1 (0.1)
7–9 years of school (or junior high)	44 (6.1)
General certificate of secondary education or high school diploma	146 (20.4)
A levels or 2-year college degree	160 (22.4)
4-year college or university degree	194 (27.1)
Postgraduate, graduate, or professional qualification	146 (20.4)
Geographic location	
Northern Europe (UK, Denmark)	86 (12)
Central Europe (Germany, Netherlands, Switzerland, Hungary)	320 (44.7)
Southern Europe (Spain, Italy, Israel)	309 (43.2)
Psychotropic medication use at baseline	
First-generation antipsychotics	32 (4.5)
Second/third-generation antipsychotics	130 (18.2)
Any antipsychotic	160 (22.4)
α-Agonists	20 (2.8)
Diagnosis	
Tourette syndrome	649 (90.8)
Chronic motor tic disorder	59 (8.2)
Chronic vocal tic disorder	7 (1)
Yale Global Tic Severity Scale at baseline	
Total severity score	19.5 ± 8.65
Overall impairment score	14.43 ± 11.95
Global score	33.94 ± 18.36
Psychiatric comorbidities[a]	
Obsessive-compulsive disorder	227 (31.7)
Attention-deficit/hyperactivity disorder	258 (36.1)

[a] Only the 2 most common psychiatric comorbidities are presented.

attention-deficit/hyperactivity disorder (ADHD) was established at baseline visits, telephone interviews, and follow-up visits using the Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS)[36] and the parent-reported Swanson, Nolan, and Pelham IV (SNAP-IV) questionnaire.[37] Clinicians checked psychotropic medication use during the 2 weeks prior to each follow-up time point. To harmonize clinical study procedures, collaborators were regularly trained in clinical assessments with a focus on the YGTSS by use of video recording of children with tics aimed at consensus scoring.

Laboratory Measures

Throat swabs and serum specimens were collected at each clinic visit, including expedited tic exacerbation visits. Throat swabs were assessed for GAS colonization using a consensus-defined methodology at each clinical site (pour plate method or

Table 2 Distribution of Group A *Streptococcus* (GAS) Exposure Across Clinic Visits, With and Without Exacerbation, Related Only to the 1,798 Clinic Visits Without Any Missing Data on GAS Exposure (Both Throat Swab and Serum Specimens Available)

Definition of GAS exposure	GAS exposure: upper row: 402 tic exacerbations; lower row: 1,396 time points without exacerbation, n (%)	No GAS exposure: upper row: 402 tic exacerbations; lower row: 1,396 time points without exacerbation, n (%)
Definition 1	22/402 (5.5)	380/402 (94.5)
	81/1,396 (5.8)	1,315/1,396 (94.2)
Definition 2	35/402 (8.7)	367/402 (91.3)
	127/1,396 (9.1)	1,269/1,396 (89.9)
Definition 3	39/402 (9.7)	363/402 (90.3)
	167/1,396 (12)	1,202/1,396 (88)
Definition 4	52/402 (12.9)	350/402 (87.1)
	228/1,396 (16.3)	1,168/1,396 (83.7)

Definition 1: new definite GAS exposure, characterized by a newly positive throat swab regardless of serologic test results. Definition 2: new definite GAS exposure or new possible GAS exposure, the latter characterized by negative or missing throat swab but significant elevation of antistreptococcal antibody titers, i.e., antistreptolysin O titer or anti-DNase B titer. Definition 3: new definite GAS exposure or new possible GAS exposure or ongoing definite GAS exposure, the latter characterized by persistently positive throat swab over at least 2 time points, regardless of serologic test results. Definition 4: new definite GAS exposure or new possible GAS exposure or ongoing definite GAS exposure or ongoing possible GAS exposure, the latter characterized by significant elevation of either of the 2 antistreptococcal antibody titers and negative or missing throat swab but positive throat swab at the previous time point.

through blood agar plates).[19] Before starting data collection, each center had to pass an external quality assessment co-led by 2 microbiological units in the EMTICS consortium. All positive throat swabs were *emm* typed. The *emm* typing method was performed centrally at the Istituto Superiore di Sanità, Rome, Italy, according to the Centers for Disease Control and Prevention protocol, as previously described[23,27]; further methodologic details are provided in table 6.

In serum, we measured anti-streptolysin O (ASOT) and anti-DNase B (ADB) antibody titers. A significant elevation of ASOT was identified when ASOT >200 and [log10(ASOT current visit) − log10(ASOT prior visit)] ≥0.2 (variation between log10 for 2 consecutive measurements ≥0.2); a significant elevation of ADB was identified when ADB >300 and [log10(ADB current visit) − log10(ADB prior visit)] ≥0.2 (variation between log10 for 2 consecutive measurements ≥0.2).[38] ASOT and ADB titers were centrally measured in the laboratory of the University Hospital Munich, Ludwig-Maximilians-Universität. ASOT was determined with the immuno-turbidimetric test from Beckman Coulter (Brea, CA), with a lower limit of quantification of 100 IU/mL. ADB titers were determined with an immunonephelometric method performed on a BN Prospec analyzer by Siemens Healthineers (Erlangen, Germany), where the lower limit of quantification was 71 U/mL.

Power Calculation

The COURSE study included 715 youth with CTD with a 3–16 years age range. Study power was calculated for $\alpha = 0.05$ assuming a yearly exposure frequency to a new GAS infection of 0.12[39] and a yearly rate of symptom exacerbation of 0.16 based on conservative estimates from prior longitudinal studies of TS.[27,28] The study sample size n = 715 yielded power $(1 - \beta)$ 95% chance, 89% chance, and 75% chance of detecting, respectively, an odds ratio (OR) of 2.5, 2.25, and 2 for participants exposed to a new GAS exposure compared to nonexposed for the event "tic exacerbation."

Statistical Analysis

Primary Outcome and Exposure Variables

The primary outcome variable was the occurrence of a tic exacerbation, whereas the primary exposure variable was exposure to GAS in the oropharynx. The latter was classified as follows: (1) new definite GAS exposure, i.e., a newly positive throat swab regardless of serologic results; (2) new possible GAS exposure, i.e., negative or missing throat swab but significant elevation of ASOT or ADB titers; (3) ongoing definite GAS exposure, i.e., persistently positive throat swab over at least 2 time points, regardless of serologic results; (4) ongoing possible GAS exposure, i.e., significant elevation of either of the 2 antistreptococcal antibody titers and negative or missing throat swab but positive throat swab at the previous time point. To define GAS exposure at each time point, we used 4 definitions of GAS exposure, with definition 1 being the most conservative and definition 4 the most lenient: definition 1 included only new definite GAS exposure; definition 2 included either new definite or new possible GAS exposure; definition 3 included either new (definite or possible) GAS exposure or ongoing definite GAS exposure; definition 4 included either new (definite or possible) GAS exposure or ongoing (definite or possible) GAS exposure.

Data Analysis

Descriptive data are presented as mean ± SD or n (%) of participants, as appropriate. We divided the main analysis in 2

Table 3 Logistic Regression Analyses Testing the Association Between Group A *Streptococcus* (GAS) Exposure and Tic Exacerbations

Definition of GAS exposure	Odds ratio	95% CI	*p* Value
Definition 1			
***YGTSS-TTS* ≥6**			
Adjusted for sex and age only	1.15	0.70–1.88	0.58
Multivariate	1.09	0.58–2.02	0.80
YGTSS-TTS ≥8			
Adjusted for sex and age only	1.26	0.72–2.20	0.42
Multivariate	1.34	0.64–2.80	0.44
Definition 2			
YGTSS-TTS ≥6			
Adjusted for sex and age only	1.23	0.83–1.84	0.30
Multivariate	1.05	0.63–1.75	0.86
YGTSS-TTS ≥8			
Adjusted for sex and age only	1.11	0.69–1.80	0.67
Multivariate	0.97	0.50–1.88	0.92
Definition 3			
YGTSS-TTS ≥6			
Adjusted for sex and age only	1.04	0.72–1.51	0.84
Multivariate	1.13	0.71–1.80	0.62
YGTSS-TTS ≥8			
Adjusted for sex and age only	1.37	0.91–2.06	0.13
Multivariate	1.34	0.87–2.08	0.19
Definition 4			
YGTSS-TTS ≥6			
Adjusted for sex and age only	1.03	0.74–1.43	0.86
Multivariate	1.01	0.66–1.53	0.98
YGTSS-TTS ≥8			
Adjusted for sex and age only	1.17	0.80–1.70	0.43
Multivariate	1.10	0.74–1.65	0.64

Abbreviation: CI = confidence interval.
Tic exacerbations are defined as an increase of the Yale Global Tic Severity Scale–Total Tic Severity (YGTSS-TTS) score of 6 or more (and, in the sensitivity analysis, of 8 or more) as detected at the same observation time point. All analyses were adjusted for age at visit and sex; all multivariate analyses were adjusted also for exposure to anti-tic medications (antipsychotics or alpha agonists), exposure to antibiotics, and geographical region (per individual center; results did not differ when geographical region was expressed as Northern, Central, or Southern Europe).

parts. First, we assessed the association between tic exacerbation and GAS exposure at the same observation time point. To avoid inaccurate duplication of time points during prospective observation, the information obtained from telephone interviews that prompted exacerbation visits, or that were followed by a follow-up visit by 4 weeks or less, was integrated with the information obtained at the following clinic visit and referred to as a single point in time. We evaluated strength and statistical significance of this association using age at visit- and sex-adjusted logistic regression analysis, in which "tic exacerbation" was the binary outcome variable and GAS exposure the main independent variable. Separate analyses were conducted for each of the 4 GAS exposure definitions. We then performed multivariate logistic regression analyses of the same outcome and independent variables, adjusting for exposure to anti-tic medications

Table 4 Survival Data Analysis of the Relationship Between Tic Exacerbations and Group A *Streptococcus* Exposure

Definition of GAS exposure	Hazard ratio	*p* Value	95% CI
Definition 1			
YGTSS-TTS ≥6 (including all visits)	1.11	0.56	0.78–1.59
YGTSS-TTS ≥6 (visits with missing data on GAS excluded)	1.16	0.43	0.81–1.65
Definition 2			
YGTSS-TTS ≥6 (including all visits)	1.20	0.28	0.87–1.65
YGTSS-TTS ≥6 (visits with missing data on GAS excluded)	1.16	0.34	0.86–1.56
Definition 3			
YGTSS-TTS ≥6 (including all visits)	1.06	0.71	0.79–1.40
YGTSS-TTS ≥6 (visits with missing data on GAS excluded)	1.15	0.36	0.85–1.55
Definition 4			
YGTSS-TTS ≥6 (including all visits)	1.15	0.32	0.88–1.50
YGTSS-TTS ≥6 (visits with missing data on GAS excluded)	1.19	0.20	0.91–1.55

Abbreviations: CI = confidence interval; YGTSS-TTS = Yale Global Tic Severity Scale–Total Tic Severity Score.
Multiple failure time analyses conducted using the Andersen-Gill method were always adjusted for sex, age at onset, exposure to psychotropic medications, exposure to antibiotics, geographical region, and number of visits completed in the time interval of interest, for each of the 4 working definitions of Group A *Streptococcus* (GAS) exposure.
The table includes results of the sensitivity analyses after exclusion of visits with missing data on GAS exposure.

(α-agonists, antipsychotics), antibiotics, and clinical site (individual and categorized by geographical region, i.e., North, Central, and Southern Europe).

The second part of the analysis investigated the primary outcome ("tic exacerbation") during prospective observations taking into account the risk of a new tic exacerbation being influenced by previous tic exacerbations occurring in the same participant. We modeled the association of GAS exposure with the risk of tic exacerbation using the Andersen-Gill extension of the Cox proportional hazards model. This approach is based on unstratified baseline hazards and is closely related to Poisson process theory for handling multiple failure time data.[40] We adjusted Andersen-Gill models for the same confounding variables, as well as for the nuisance variable "number of time points of data collection" (encompassing both study visits and telephone interviews) occurred during each modeled period of observation. Three different time periods were included, marked by the presence or absence of tic exacerbations: (1) time elapsed between study entry and study exit (if no exacerbation occurred); (2) time elapsed between 6 months prior to each exacerbation and time at exacerbation; (3) time elapsed between last exacerbation and study exit.

Finally, we explored the effects of GAS exposure on the changes in severity of tics, obsessive-compulsive symptoms, and ADHD symptoms, measured respectively as continuous variables with YGTSS-TTS score, CY-BOCS global score, and SNAP-IV scores for ADHD-combined, ADHD-inattention, and ADHD-hyperactivity-impulsivity. We estimated these effects through mixed effects linear regression models, using the 4 definitions of GAS exposure as independent variables, and always adjusting for age at visit, sex, presence of medication change, and geographical region.

Sensitivity Analyses

Given the relative arbitrariness of the cutoff used consensually to define tic exacerbation, logistic regression analyses were repeated adopting a more restrictive definition that had a ≥8 cutoff for YGTSS-TTS change. To take into account potential misclassification of visit status of "tic exacerbation" and "GAS exposure" due to excessively long intervisit intervals, we conducted logistic regression analyses after excluding all follow-up visits preceded by a greater than 20-week interval from the previous visit. All tests of statistical significance were 2-tailed. Data were analyzed using Stata v.14.

Data Availability

De-identified participant data related to all demographic, clinical, and laboratory variables will be shared following request made by any qualified investigators to the study authors.

Results

The baseline demographic and clinical characteristics of the 715 participants enrolled are shown in table 1. The mean age of patients at study entry was 10.65 ± 2.83 years, the majority (549; 76.8%) being male. The vast majority of participants

Table 5 Mixed-Effects Linear Regression Models Evaluating the Association Between Group A *Streptococcus* (GAS) Exposure Definitions and Longitudinal Changes of Tic, Obsessive-Compulsive, Inattentive, and Hyperactivity/Impulsivity Symptom Severity

Dependent variable: YGTSS-TTS	β	SE	z	$p > \|z\|$	95% CI
Predictor					
GAS definition 1	0.14	0.62	0.22	0.82	−1.08 to 1.36
GAS definition 2	0.48	0.44	1.09	0.28	−0.38 to 1.33
GAS definition 3	0.34	0.41	0.81	0.42	−0.47 to 1.15
GAS definition 4	0.15	0.41	0.36	0.72	−0.65 to 0.95
Dependent variable: CY-BOCS global score					
Predictor					
GAS definition 1	0.72	0.95	0.76	0.45	−1.14 to 2.59
GAS definition 2	0.15	0.67	0.22	0.82	−1.16 to 1.46
GAS definition 3	−0.16	0.62	−0.26	0.80	−1.39 to 1.06
GAS definition 4	−0.27	0.62	−0.44	0.66	−1.48 to 0.93
Dependent variable: average SNAP-IV ADHD-combined					
Predictor					
GAS definition 1	0.02	0.08	0.19	0.85	−0.15 to 1.18
GAS definition 2	0.1	0.06	1.72	0.09	−0.01 to 0.21
GAS definition 3	0.14	0.05	2.56	0.01	0.03 to 0.24
GAS definition 4	0.12	0.05	2.32	0.02	0.02 to 0.23
Dependent variable: average SNAP-IV ADHD-inattention					
Predictor					
GAS definition 1	−0.08	0.09	−0.91	0.37	−0.26 to 0.1
GAS definition 2	0.04	0.06	0.66	0.51	−0.08 to 0.17
GAS definition 3	0.07	0.06	1.21	0.23	−0.05 to 0.19
GAS definition 4	0.07	0.06	1.13	0.26	−0.05 to 0.18
Dependent variable: average SNAP-IV ADHD-hyperactivity-impulsivity					
Predictor					
GAS definition 1	0.13	0.09	1.47	0.14	−0.04 to 0.31
GAS definition 2	0.17	0.06	2.64	0.008	0.04 to 0.29
GAS definition 3	0.21	0.06	3.6	<0.001	0.1 to 0.33
GAS definition 4	0.19	0.06	3.24	0.001	0.07 to 0.3

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; CI = confidence interval; CY-BOCS = Children's Yale-Brown Obsessive-Compulsive Scale; SNAP-IV = Swanson, Nolan, and Pelham IV; YGTSS-TTS = Yale Global Tic Severity Scale–Total Tic Severity Score.
All models were adjusted for age at study visit, sex, psychotropic medication change, and geographical region (expressed as Northern, Central, or Southern Europe).

(649; 90.8%) had a diagnosis of TS, whereas the remainder fulfilled criteria for chronic motor or vocal tic disorder. OCD was diagnosed in 227 participants (31.7%) and ADHD in 258 patients (36.1%). Throat swab collection was available at baseline for 702 participants and was positive in 59/702 (8.4%).

After the baseline visit, the 715 participants generated 4,384 observation time points, comprising 2,272 study visits and 2,112 telephone interviews (2,017 scheduled and 95 unscheduled). The vast majority of study visits occurred less than 20 weeks after the previous visit (2,105/2,272 [92.6%]). Throat swab and serum specimens were not available for 135

Table 6 Distribution of *emm* Types Isolated From Positive Throat Swabs Collected at the 149 Visits After Baseline (2 of the 22 Tic Exacerbation Visits Associated With a Newly Positive Throat Swab Could Not be *emm* Typed due to Shipment Issues)

Tic exacerbation visits (total = 20) with positive throat swab		No tic exacerbation visits (total = 129) with positive throat swab	
***emm* Type**	**N (%)**	***emm* Type**	**N (%)**
1	1 (5)	1	15 (11.6)
2	0	2	1 (0.8)
3	4 (20)	3	8 (6.2)
4	2 (10	4	5 (3.9)
5	0	5	1 (0.8)
6	1 (5)	6	7 (5.4)
12	4 (20)	12	19 (14.7)
18	0	18	2 (1.6)
19	0	19	1 (0.8)
24	0	24	2 (1.6)
28	5 (25)	28	16 (12.4)
29	0	29	4 (3.1)
44	0	44	3 (2.3)
75	0	75	11 (8.5)
77	2 (10)	77	5 (3.9)
87	0	87	6 (4.7)
89	0	89	23 (17.8)
94	1 (5)	94	0

emm Gene amplified by PCR assay using oligonucleotide primers and PCR reaction conditions according to the protocol of the Streptococcal Laboratory of the Centers for Disease Control and Prevention (cdc.gov/streplab/groupa-strep/emm-typing-protocol.html).

(5.9%) and 393 (17.3%) of 2,272 study visits, respectively; overall, either throat swab or serum specimen was missing in 474/2,272 (20.9%) study visits, and for 2 or more study visits in 69/715 (9.7%) participants. These 69 participants did not differ significantly (all p values > 0.25) from the remaining 646 for age at study entry (10.8 ± 2.9 years vs 11.3 ± 2.8 years), sex (proportion male: 76.8% vs 76.7%), or frequency of tic exacerbation (22/250 visits [8.8%] vs 210/1,872 visits [11.2%]).

During follow-up, 405 tic exacerbations occurred in 308/715 participants (43.1%): 218 participants experienced only 1 exacerbation, whereas 84, 5, and 1 participants underwent, respectively, 2, 3, and 4 exacerbations during the entire study. Pharmacologic therapy had been withdrawn prior to 4/405 (0.99%) exacerbation visits and prior to 41/1,867 (2.2%) of all other visits (Fisher = 0.165), whereas it had been changed prior to 7/405 (1.73%) exacerbation visits and prior to 55/1,867 (2.95%) of all other visits ($\chi^2 = 2.05$, $p = 0.15$).

Table 2 shows the distribution of GAS exposure status, related to each of the 4 definitions adopted in the study, across visits that detected a tic exacerbation and those that did not. Compared to participants who developed only non-GAS-associated exacerbations (n = 259), those who developed a GAS-associated exacerbation (i.e., associated with any of the 4 GAS exposure definitions; n = 49), were younger at study exit (9.63 ± 2.4 years vs 11.4 ± 2.76 years, $p < 0.0001$), and had higher representation of males (46/49 vs 210/259, Fisher = 0.035). On logistic regression analysis (table 3), both age-/sex-adjusted and multivariate analyses failed to detect any significant association between tic exacerbation and any of the GAS exposure definitions (range of ORs 1.006–1.235; all p values > 0.3).

Multiple failure time analysis (adjusted for sex, age at onset, exposure to psychotropic medications, exposure to antibiotics, geographical region, and number of visits in the time interval of interest) confirmed the absence of a significant association between new or ongoing concurrent GAS exposure episodes and tic exacerbation events for any of the 4 definitions of GAS exposure (table 4).

Similar results on logistic regression analyses were obtained using the more restrictive definition of tic exacerbation,

i.e., YGTSS-TTS ≥8 (table 3). On these additional analyses, both univariate and multivariate models failed to detect any significant association between tic exacerbation and any of the 4 GAS exposure definitions (range of ORs 0.967–1.343; all p values > 0.18).

A subsequent sensitivity analysis conducted after excluding the 147 study visits that followed the previous clinic visit by more than 20 weeks did not yield different results from the primary analyses (range of ORs 1.012–1.289; all p values > 0.3).

Finally, the analyses based on mixed effects linear regression models showed lack of association between any of the 4 GAS exposure definitions and YGTSS-TTS score and CY-BOCS global score (all p values ≥ 0.28). GAS exposure defined using definitions 3 and 4 was significantly and positively associated with average SNAP-IV ADHD combined subscore ($\beta = 0.14$, $p = 0.01$ and $\beta = 0.12$, $p = 0.02$, respectively). When we tested the effect on the inattention and hyperactivity-impulsivity average SNAP-IV ADHD subscores, a positive association with GAS exposure definitions 2, 3, and 4 was detected only for the hyperactivity-impulsivity subscore ($\beta = 0.17$, $p = 0.008$, $\beta = 0.21$, $p < 0.001$, and $\beta = 0.19$, $p = 0.001$, respectively; table 5). Overall, the results of this analysis indicate that the presence of GAS exposure based on definitions 2, 3, and 4 is associated, respectively, with a 17%, 19%, and 21% increase in average SNAP-IV hyperactivity-impulsivity subscore.

GAS exposure after the baseline visit was associated with a positive throat swab in 149 visits, of which 103 characterized a new definite GAS exposure and 46 an ongoing definite GAS exposure. Of these 149 visits, 20 corresponded to tic exacerbations. Table 6 shows the distribution of *emm* types in exacerbation and nonexacerbation visits. We did not identify any *emm* type that was significantly overrepresented in exacerbation visits compared to nonexacerbation ones. Moreover, the frequency of rheumatogenic *emm* types (1, 3, 5, 6, 14, 18, 19, 24, 27, 29)[41] isolated from swabs associated with tic exacerbations (6 of 20) did not significantly differ from the frequency of rheumatogenic *emm* types swabs not associated with tic exacerbations (40 of 129; $\chi^2 = 0.008$; $p = 0.93$).

Discussion

In this study, we prospectively investigated the association between GAS pharyngeal exposures and tic severity exacerbations in a large cohort of youths with CTD. Changes in tic severity were monitored through telephone interviews and study visits at bimonthly intervals, with the integration of weekly diaries kept by parents. Changes in tic severity were judged as clinically meaningful using a definition based on Total Tic Severity score changes on the most used rating instrument for tics, the YGTSS, using a cutoff defined by a consortium of experts. We endeavored to measure GAS exposure as tightly temporally linked to tic exacerbations as possible, based on previous reports of a short-term effect of these infections on tic severity.[5,42] In order to minimize the risk of a false-negative finding with regard to an effect of ongoing GAS exposures, we tested associations using 4 different definitions of GAS exposure. We took into account the influence of a prior tic exacerbation on the risk of developing a new one in the same individual, by applying an extension of the Cox proportional hazards model that allows handling of multiple failure time data.[40] We also conducted sensitivity analyses using a more restrictive definition of tic exacerbation. The results of these analyses showed the absence of an association between new or ongoing GAS exposures and tic exacerbation in youth with CTD. Also, we did not find any GAS *emm* type to be significantly overrepresented in tic exacerbations compared to visits without tic exacerbations. This suggests that GAS exposures are highly unlikely to exert an independent effect on the risk of clinically relevant tic exacerbations. We did not detect an association between GAS exposures and obsessive-compulsive symptom severity but found a positive association between GAS exposures (using the most lenient definitions) and changes in severity of hyperactivity-impulsivity symptoms. This finding is in line with a longitudinal study of children from pre-kindergarten to 6th grade age groups.[30] In that study, Murphy et al.[30] collected data for 8 months from 693 community children exploring combined behavior/GAS associations that included tics and other hyperkinetic symptoms: they did not observe an association between GAS and tics, but reported a relationship between GAS and hyperactive behaviors consistent with ADHD (balance/swaying and non-tic grimacing). This association, supported by an earlier cross-sectional study linking antistreptococcal antibodies to ADHD,[43] corroborates the link between GAS and behavioral patterns of motor hyperactivity, previously described also in rheumatic chorea.[44] New prospective investigations of cohorts of youth with ADHD would provide further details on the relationship between GAS and the natural history of ADHD.

Our study presents a number of strengths. Based on our power analysis, our sample size would have allowed the observation of a moderately strong association between event of interest and primary exposure variable. Our study population had demographic and clinical characteristics (age at onset, sex distribution, comorbidity profile, exposure to pharmacologic treatments) that are representative of youth with CTD followed up by specialist tertiary services,[45,46] with the exception of a lower rate of ADHD comorbidity than typically reported in clinical populations.[46] We adopted a prospective data collection plan, whereby families had to directly contact clinical centers every 2 months, were requested to keep track of symptom changes via structured weekly diaries, and were encouraged to contact the clinic if potentially relevant increases in tic severity occurred in between visits or telephone interviews. Our definitions of GAS exposures integrated existing diagnostic criteria[38] to

discriminate between new and ongoing exposures, a distinction that can be challenging in the absence of highly frequent throat swab and serum collection. In planning our analysis, we were cognizant of the different hurdles posed by an intensive data collection from a multicenter prospective cohort. We took into account in our primary and sensitivity analyses the different levels of diagnostic certainty in the definitions of our primary outcome variable, i.e., tic exacerbation, and of GAS exposure. This approach did not alter the general findings of our study. A clinical study published following the definition of our protocol proposed as clinically meaningful a 25% change on the YGTSS-TTS.[47] Based on this and on the descriptive measures of the distribution of YGTSS-TTS scores at baseline in our population, there is a possibility that our study might have failed in detecting an association between GAS exposure and smaller tic severity changes over time. However, the lack of association between longitudinal tic severity changes and GAS exposure was confirmed by our analysis based on mixed model linear regression analysis.

Some important limitations of our study should be acknowledged. The multicenter design led to data collection from specialist clinics from different EU countries and Israel, which could potentially differ in clinical and microbiological assessment procedures. To mitigate this potential limitation, we applied adequate training, procedure harmonization, and external quality assessments across all centers, as indicated in our methods. A limitation concerning our GAS exposure definition is that we did not account for the presence and severity of clinically overt GAS infections but adjusted our analyses for a surrogate variable of presence of GAS infection, i.e., concurrent antibiotic exposure. Finally, we acknowledge that our methodology to ascertain GAS exposure might have missed a few infections in conjunction with the small number of visits with missing throat swab collection, given that an elevation of ASOT and ADB titers may not be observed in up to one-third of new GAS acquisitions.[48]

Our results have clinical and pathophysiologic implications for CTD. Descriptive studies advanced the characterization of PANS maintaining tics as an additional clinical feature.[8] A subtype of PANS could be triggered by immunologic mechanisms driven by GAS, i.e., the PANDAS subtype of PANS. However, the clinical and pathophysiologic commonalities between these syndromes and the acute exacerbation of tics in established CTD remain controversial.[9] A rapid worsening of tic severity is concerning for patients and families, often prompting them to seek urgent help from community and hospital physicians and discuss potential triggers for these events. In this scenario, detecting an ongoing or recent GAS infection might lead one to assume a cause–effect relationship. However, this was not corroborated by our large prospective cohort study. Our observation of lower age at study exit likely reflects the demographic distribution of GAS exposure in the general population.[49] At the same time, we cannot completely rule out a potential association between GAS exposure and tic exacerbations in younger children with CTD and shorter disease duration, for which our study was not sufficiently powered. Overall, based on our results, a diagnostic workup for GAS exposure in young patients with a tic exacerbation would yield the same chance of detecting an infection in a clinically stable condition. Our analysis suggests that detecting GAS exposure during an exacerbation is likely to be a coincidental finding that may prompt active management of the infection per se, depending on management guidelines for this type of infection, but not the expectation that treating the infection would have therapeutic benefit on the tic exacerbation.

It is known that immune activation may concur with tic severity in youth with CTDs,[50] and that psychosocial stress levels may predict short-term future tic severity in these patients.[5] Our findings suggest that GAS is unlikely to be the main trigger for immune activation in these patients. Future analyses from our cohort will explore whether other pathogens might exert a relevant contribution to these immunologic changes and their relationship with clinical course.[30] Moreover, future analyses will investigate whether the interaction of psychosocial stress and GAS infections contributes more to tic exacerbations than psychosocial stress alone, as suggested by a previous study on a substantially smaller clinical sample.[5,30] The negative findings of our study might lead to alternative explanations. For instance, if co-occurring psychosocial stress and infection-triggered immune activation are followed by an increase in tic severity, their interaction need not be related to a specific pathogen.

Our study of the largest prospective cohort of youth with CTDs ever documented to date provides evidence against a temporal association between GAS exposure and clinically relevant tic exacerbations. This result indicates that specific diagnostic workup or active management of GAS infections in the context of worsening of tic severity in patients with CTDs is not warranted.

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Androulla Efstratiou, PhD	WHO Global Collaborating Centre for Reference and Research on Diphtheria and Streptococcal Infections, Reference Microbiology, Directorate National Infection Service, Public Health England, London, UK	Participated in design of microbiological analyses and advised on results' interpretation
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Continued

Appendix *(continued)*

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