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RESEARCH ARTICLE

Lack of Association of Group A Streptococcal Infections and Onset of Tics

European Multicenter Tics in Children Study

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Abstract

Background and Objectives

The goal of this work was to investigate the association between group A streptococcal (GAS) infections and tic incidence among unaffected children with a family history of chronic tic disorders (CTDs).

Methods

In a prospective cohort study, children with no history for tics who were 3 to 10 years of age with a first-degree relative with a CTD were recruited from the European Multicentre Tics in Children Study (EMTICS) across 16 European centers. Presence of GAS infection was assessed with throat swabs, serum anti–streptolysin O titers, and anti-DNAse titers blinded to clinical status. GAS exposure was defined with 4 different definitions based on these parameters. Cox regression analyses with time-varying GAS exposure were conducted to examine the association of onset of tics and GAS exposure during follow-up. Sensitivity analyses were conducted with Cox regression and logistic regression analyses.

Results

A total of 259 children were recruited; 1 child was found to have tic onset before study entry and therefore was excluded. Sixty-one children (23.6%) developed tics over an average follow-up period of 1 (SD 0.7) year. There was a strong association of sex and onset of tics, with girls having an ≈60% lower risk of developing tics compared to boys (hazard ratio [HR] 0.4, 95% confidence interval [CI] 0.2–0.7). However, there was no statistical evidence to suggest an association of any of the 4 GAS exposure definitions with tic onset (GAS exposure definition 1: HR 0.310, 95% CI 0.037–2.590; definition 2: HR 0.561, 95% CI 0.219–1.436; definition 3: HR 0.853, 95% CI 0.466–1.561; definition 4: HR 0.725, 95% CI 0.384–1.370).

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Class of Evidence
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European Multicentre Tics in Children Study (EMTICS) coinvestigators are listed at links.lww.com/WNL/B751.

Glossary

ADB = anti–DNAse B; **ASOT** = anti–streptolysin O titer; **CTD** = chronic tic disorder; **DSM-IV-TR** = *Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision*; **EMTICS** = European Multicentre Tics in Children Studies; **GAS** = group A streptococcal; **TS** = Tourette syndrome.

Discussion

These results do not suggest an association between GAS exposure and development of tics.

Classification of Evidence

This study provides Class I evidence that group A streptococcal exposure does not associate with the development of tics in children with first-degree relatives with chronic tic disorder.

The etiology of chronic tic disorders (CTDs) and Tourette syndrome (TS) is still unclear, despite significant advances in genetics[1] and neuroimaging.[2] There are clear contributions from genetic factors,[3-5] but environmental factors, including noxious exposures during prenatal and perinatal stages, for example, maternal smoking, exposure to certain drugs such as amphetamines and other CNS stimulants, as well as psychosocial stress, have also been speculated to contribute.[6-9] Since the description of the first 50 cases of tic-like behaviors in the context of group A streptococcal (GAS) infections,[10] there has been an ongoing controversy regarding the possible role of GAS infections in tic disorders. Several cross-sectional studies have found elevated anti-streptococcal antibody titers in patients with tics.[11,12] Findings from 1 case-control study indicated a correlation between levels of anti-streptococcal antibodies and tic severity,[13] in contrast to results from another case-control study.[14] Retrospective population studies based on data from health care registries from the United States, Denmark, and Taiwan reported associations between the onset of tics and GAS exposure.[15-18] On the other hand, longitudinal studies based on clinical data did not suggest a temporal link between a recent GAS exposure and onset or clinical worsening of tic disorders.[19-25] Previous studies have been retrospective or register based or had limited sample sizes. Considering that the average age at onset of TS is 7 years (and the prevalence and severity reach a peak at ≈9–12 years of age)[26] and that GAS throat infections are common in this age group, clear associations are difficult to establish in small samples. Laboratory-confirmed prospective studies in this field are difficult to conduct because GAS infections are frequently not documented with laboratory tests and may go undiagnosed. In addition, tic onset is insidious, and tics can be unnoticed outside a specialist setting for many years.[27] We set out to prospectively study the association of onset of tics, assessed bimonthly, with GAS infections detected with throat swabs and serology (serum anti–streptolysin O titer [ASOT] and anti–DNAse B [ADB] antibody titer) in a large high-risk sample of 3- to 10-year-old children, namely first-degree relatives of patients with TS or CTDs who were followed up for up to 48 months. Therefore, for the current study, the primary research question was to explore whether there is an association between GAS infections and development of tics in children with first-degree relatives with a CTD independently of age, sex, and parental education level.

Methods

Study Design

The European Multicentre Tics in Children Studies (EMTICS) is a prospective cohort study exploring the role of environmental and genetic factors in pediatric CTDs. The methods of this study have been described previously.[28] The main objective of the ONSET arm of the study was to investigate the association between environmental and genetic factors and the onset of tics in children who are first-degree relatives of patients with an established CTD.

Participants

A total of 260 children 3 to 10 years of age who were first-degree relatives of individuals with a CTD (criteria according to the DSM-IV-TR)[29] but themselves free of tics were recruited between 2013 and 2016 from 16 (child and adolescent) psychiatry and pediatric neurology outpatient clinics (1 of the EMTICS centers did not collect data for the current study, and 1 child was removed because he had tics before study entry). Children were excluded if at baseline they had a serious medical or neurologic illness or were unable to understand and comply with study procedures. Children were allowed to receive treatment for mental health problems. The detailed inclusion and exclusion criteria are published elsewhere.[28,30]

Standard Protocol Approvals, Registrations, and Patient Consents

All local Ethics Committees of the participating centers provided approval for the study. Parents and their child (children) provided written informed consent and assent as appropriate according to ethics regulations.

Study Procedures

Participants were evaluated every 2 months, alternating between scheduled hospital visits and telephone interviews.

Parents were also instructed to communicate any possible sign of tic onset to the study center as soon as possible (e.g., by phone or email). All symptoms indicative of a possible onset of tics were explained to parents at the baseline visit. If parents reported possible onset of tics outside of planned visits, an unscheduled tic onset evaluation telephone interview was held by the study clinician to investigate whether possible onset of tics had occurred. Data collection was structured on 3 levels of observation: (1) through a weekly diary in which parents were asked to indicate possible symptom onset, aimed at the earliest possible detection of onset of tics throughout the whole study duration (parents were instructed to contact the study clinician immediately whenever they suspected the onset of tics); (2) scheduled telephone interview once every 4 months with review of the weekly diaries since the last assessment and clinical evaluations of possible tic onset performed by the study clinician to parents; and (3) visits in hospital every 4 months over the 3-year duration study period, which comprised clinical evaluation and collection of biological samples (i.e., throat swab and ASOT and ADB titers).

Tic onset was defined as the first occurrence of any sudden, rapid, recurrent, nonrhythmic involuntary movement or vocalization noticed on at least 3 separate days within a period of 3 weeks. If the evaluation pointed to a possible tic onset, in any case, an onset of tics hospital visit was scheduled, preferably within 1 week or at the earliest opportunity, for extended clinical evaluation, including the Yale Global Tic Severity Scale[31] to confirm the onset of tics and to collect biological material. If an onset of tics was confirmed, no further planned assessments were conducted until a final follow-up visit at 1 year after the tic onset visit. Otherwise, the originally scheduled visits were continued. The detailed follow-up process is given in the study protocol.[28] Moreover, to establish the possible onset of tics after the end of the study period, further follow-up telephone calls were made 2 years after the end of the study to 200 unaffected participants.

Laboratory Measures

The main microbiological measures were GAS colonization by throat swabbing and processing using a standardized methodology. To ensure homogeneity in laboratory procedures, the protocol was harmonized, and all centers participated in cross-center training and external quality control co-led by 2 microbiological units in the EMTICS consortium. Exposure to GAS in study participants was also investigated by measuring ASOT and ADB. A significant rise of ASOT was identified when ASOT > 200 and $[\log10\ (ASOT_{current\ visit}) - \log10\ (ASOT_{prior\ visit})] \geq 0.2$ (variation between log10 for 2 consecutive measurements is ≥0.2); a significant rise of ADB was identified when ADB >300 and $[\log10\ (ADB_{current\ visit}) - \log10\ (ADB_{prior\ visit})] \geq 0.2$ (variation between log10 for 2 consecutive measurements is ≥0.2). ASOT and ADB titers were centrally measured in the laboratory of the University Hospital Munich (Ludwig-Maximilians-Universität). For determination of ASOT, the immunoturbidimetric test from Beckman Coulter (Brea, CA) was used with a lower limit of quantification of 100 IU/mL. For determination of ADB titers, an immunonephelometric method performed on a BN Prospec analyzer by Siemens Healthineers (Erlangen, Germany) was used for which the lower limit of quantification was 71 U/mL. A detailed summary of laboratory measurements is listed in the protocol article.[28] Laboratory analyses were performed by investigators blinded to clinical status.

Four combinations of measures were used to classify GAS exposure: (1) new definite GAS exposure, characterized by a newly positive throat swab regardless of serologic test results; (2) new possible GAS exposure, characterized by negative or missing throat swab but significant rise of anti-streptococcal antibody titers, that is, ASOT or ADB; (3) ongoing definite GAS exposure, characterized by persistently positive throat swab over at least 2 time points, regardless of serologic test results; and (4) ongoing possible GAS exposure, characterized by significant rise of either of the 2 anti-streptococcal antibody titers and negative or missing throat swab but positive throat swab at the previous time point. On the basis of these classifications, we used 4 definitions of varying stringency for analysis, with definition 1 being the most conservative and definition 4 being the most lenient definition. Definition 1 included only a new definite GAS exposure; definition 2 included either a new definite or a new possible GAS exposure; definition 3 included either a new (definite or possible) GAS exposure or an ongoing definite GAS exposure; and definition 4 included either a new (definite or possible) GAS exposure or an ongoing (definite or possible) GAS exposure.

Other Measurements

Covariates measured at baseline were age in years, sex, and parental education level. Parental education level was based on the highest education level of the 2 parents and consisted of 2 levels: low level vs high level. This was dichotomized at whether the parents received a college degree (i.e., low-level parental education: maximum education level was A-level or 2-year college degree; high-level parental education: at least a 4-year college/university degree). Clinical site was categorized by geographic region, that is, Northern (UK, Denmark), Central (Germany, Netherlands, Switzerland, Hungary), and Southern (Spain, Italy, Israel) Europe. Psychotropic medications included first- and second/third–generation antipsychotics and α-agonists and were checked 2 weeks before each follow-up time point by clinicians (results are listed in eTables 1–3, links.lww.com/WNL/B750).

Power Calculation

The current study originally aimed to recruit 500 participants who were 3 to 10 years of age and were first-degree relatives of patients with a tic disorder. The finally achieved sample size of 260 still provides 80% power to detect an odds ratio of 2.85 for GAS carriers compared to noncarriers with respect to the event onset, assuming an estimated GAS carriage rate of 15% in childhood,[32] and an estimated risk of 30%[33] for a first-degree relative of patients with TS or other CTDs to be affected by tics at $\alpha = 0.05$ (2 sided). Detailed information on power analysis is published elsewhere.[28]

Statistical Analyses

Participants' characteristics were summarized with descriptive statistics. Continuous variables were expressed as mean and SD. Categorical variables were reported as counts and percentages. For each of the different definitions of GAS exposure, the following analyses were performed. The main analysis used was a Cox regression model with time to tic onset as outcome and GAS exposure as a time-varying risk factor; this allowed us to take an individual's change of GAS exposure over time into consideration. For this analysis, missing data on GAS exposure were imputed with the technique of the last observation carried forward. To test the impact of missing GAS exposure on the outcome of interest, a sensitivity analysis was carried out by excluding visits with missing data on GAS exposure. We also ran additional sensitivity analyses testing possible associations of GAS exposure and tic onset: a Cox regression analysis with time to tic onset as outcome and baseline GAS exposure was conducted to examine the relationship of GAS exposure at baseline with subsequent tic onset, and a logistic regression was performed to test the association between tic onset and GAS exposure at any time during follow-up. For each of the above analyses, we first present univariable results and subsequently adjusted for age, sex, and parental education. In additional analyses, we also adjusted for site and psychotropic medication use. Results of the sensitivity analyses are listed in eTables 4–6, links.lww.com/WNL/B750. All statistical tests were 2 sided, and a value of $p < 0.05$ was considered statistically significant. Statistical tests were implemented in STATA version 16 (StataCorp LP, College Station, TX).

Data Availability

Deidentified participant data related to all demographic, clinical, and laboratory variables will be shared after request by any qualified investigators to the study authors.

Results

Sample Descriptive

The mean age of the 259 participants at baseline was 6.8 (SD 2.1, range 2.8–10.9) years, and more than half were female. About 57% of participants' parents had received at least college/university–level education (Table 1). Follow-up time was on average 1.6 (SD 1.0, range 0–3.8) years. Overall, there were 61 onset tic cases during the study period, and the average time from baseline until tic onset was 1 (SD 0.7) year. At baseline, a total of 44 (17.0%) participants tested positive on GAS, and 204 (78.8%) participants tested negative, while no throat swab was available for 11 (4.2%) participants. Blood samples were collected from 207 participants at baseline to examine ASOT and/or ADB titers (eTable 1, links.lww.com/WNL/B750).

Table 1 Baseline Characteristics of Participants

		No tic onset (n = 198)	Tic onset (N = 61)	Total (N = 259)
Age, y	Mean (SD)	6.9 (2.2)	6.8 (1.9)	6.8 (2.1)
Sex, n (%)	Male	77 (38.9)	38 (62.3)	115 (44.4)
	Female	121 (61.1)	23 (37.7)	144 (55.6)
Parental education, n (%)	Low	83 (43.0)	27 (45.0)	110 (43.5)
	High	110 (57.0)	33 (55.0)	143 (56.5)

During the study follow-up period, there were a total of 1,944 visits, including 939 telephone interviews (928 scheduled and 11 unscheduled, respectively) and 1,005 clinical visits. Throat swab and serum ASOT/ADB analyses were available for 422 (42%) and 564 (56%) of 1,005 study visits, respectively. The number of cases of confirmed positive GAS exposure during follow-up was 59, 102, 125, and 138 relating to definition 1, 2, 3, and 4, respectively. Detailed distribution of GAS exposure across clinic visits by tic onset visits without any missing data on GAS exposure can be found in Table 2.

Results of Regression Analyses

There was no evidence of an association of tic onset with GAS exposure in univariable Cox regression analysis with time-varying GAS exposure used for any definitions of GAS exposure (Table 3). Adjustment for age, sex, and parental education level did not reveal any significant associations between tic onset and GAS exposure (Table 3). However,

Table 2 Distribution of GAS Exposure Status by Tic Onset Visits (Without Any Missing Data on GAS Exposure)

Definition		No tic onset visit (n = 874), n (%)	Tic onset visit (n = 56), n (%)
1	No GAS exposure	817 (93.5)	54 (96.4)
	GAS exposure	57 (6.5)	2 (3.6)
2	No GAS exposure	777 (88.9)	51 (91.1)
	GAS exposure	97 (11.1)	5 (8.9)
3	No GAS exposure	757 (86.6)	48 (85.7)
	GAS exposure	117 (13.4)	8 (14.3)
4	No GAS exposure	744 (85.1)	48 (85.7)
	GAS exposure	130 (14.9)	8 (14.3)

Abbreviation: GAS = group A streptococcal.
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 rise of anti-streptococcal antibody titers, that is, anti–streptolysin O titer or anti–DNAse B titer. Definition 3: new definite GAS exposure or new possible GAS exposure or ongoing definite GAS exposure, the last 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 last characterized by significant rise of either of the 2 anti-streptococcal antibody titers and negative or missing throat swab but positive throat swab at the previous time point.

Table 3 Time-Varying Cox Regression Analyses Testing the Association Between Tic Onset and GAS Exposure

Definition of GAS exposure	HR (95% CI)	*p* Value
GAS exposure (definition 1)		
Univariable	0.619 (0.130–2.940)	0.546
Multivariable	0.310 (0.037–2.590)	0.279
GAS exposure (definition 2)		
Univariable	0.731 (0.272–1.966)	0.535
Multivariable	0.561 (0.219–1.436)	0.228
GAS exposure (definition 3)		
Univariable	1.062 (0.616–1.833)	0.828
Multivariable	0.853 (0.466–1.561)	0.607
GAS exposure (definition 4)		
Univariable	0.936 (0.527–1.662)	0.822
Multivariable	0.725 (0.384–1.370)	0.322

Abbreviations: CI = confidence interval; GAS = group A streptococcal; HR = hazard ratio.
In all multivariable analyses, sex was found to be a significant factor associating with the development of tic onset, with girls less likely to develop tics than boys (HR 0.4, $p < 0.01$). 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 rise of anti-streptococcal antibody titers, that is, anti–streptolysin O titer or anti–DNAse B titer. Definition 3: new definite GAS exposure or new possible GAS exposure or ongoing definite GAS exposure, the last 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 last characterized by significant rise of either of the 2 anti-streptococcal antibody titers and negative or missing throat swab but positive throat swab at the previous time point. All analyses were run first with GAS exposure as the only independent variable (univariable analyses) and then adjusted for all covariates, including age, sex, and parental education level (multivariable analyses).

there was a strong association in all analyses between tic onset and sex, with girls being 60% less likely to develop tics compared to boys (all $p < 0.01$).

The sensitivity analysis using Cox regression analysis to examine the association of tic onset with GAS exposure at baseline also showed no evidence of an association of tic onset with baseline GAS exposure (eTable 4, links.lww.com/WNL/B750); the logistic regression analysis also did not show an association of tic onset with GAS exposure (eTable 5). Results from the analysis after excluding visits with missing data on GAS exposure were consistent with the main findings (eTable 4). Analyses with further adjustment for clinical site and psychotropic medication use were also in line with the main findings (eTable 6).

During the additional 2-year follow-up after the end of the study, 7 patients were reported to have had onset of tics. Replication of all analyses with these additional cases did not change the results (data not shown).

Classification of Evidence

The study provides Class I evidence that GAS exposure is not associated with the development of tics in children with first-degree relatives with a CTD.

Discussion

In this large cohort of children at risk of tics, GAS infection was not associated with tic onset in either univariable or multivariable time-varying Cox-regression analyses adjusted for age, sex, and parental education level. The results from a series of sensitivity analyses confirmed the results from the main analyses. On the other hand, our finding confirms the strong sex difference in terms of tic onset after controlling for age, GAS exposure, and parental education level, with boys being significantly more likely to develop tics in this cohort. This is in line with previous studies.[21,34,35]

The association between GAS exposure and tic onset remains controversial, with some studies reporting a significant association,[15-17] and others not.[20-22] Our results do not support an association between GAS exposure and onset of tics. One possible explanation for differences between our study and others is that there are substantial study variations with regard to study population, design, and GAS measurements. For example, most studies reporting a significant association between GAS exposure and tic onset were based on health insurance data.[15-17] The identification of GAS infection and the diagnosis of tic disorder in these studies were based on information from routine care, for which a number of factors related to health care systems and health care seeking need to be considered, rather than standardized prospective assessments in an at-risk population. Therefore, it is possible that the relation found between GAS infection and onset of tics was influenced by different health care–seeking behaviors of patients and differences in diagnostic procedures for diagnosis of GAS-related throat infections. Moreover, information from studies using health records might be subject to misclassification, and the recorded dates of disease onset may differ from the true timing of disease onset. In our study, we were able to prospectively follow up children who had first-degree relatives with a CTD but were free of tics at baseline and to conduct standardized examinations for GAS infection independently of health care practices and examination by experienced clinicians following standardized procedures.

Our results do not support an association between GAS throat infection and onset of tic disorders. It is interesting to note that a large population-based cohort study reported that regardless of streptococcal test results, children who had testing for streptococcal status because of throat infections had a higher risk of tic disorders than those who were not being tested for streptococcal infections. However, the risk of any mental disorder and obsessive-compulsive disorder was more elevated after a streptococcal throat infection than after a nonstreptococcal infection.[36] Another recent large Danish

population-based cohort study found that children with infections requiring hospitalizations had an increased risk of mental disorders, including tic disorders, obsessive-compulsive disorder, and attention-deficit/hyperactivity disorder, but not those without hospitalization.[18] Taken together, these studies suggest that either pathogens other than GAS or infection-induced inflammatory mechanisms are linked to development of tics and other mental disorders in children. Future studies into other pathogens and immunologic factors are needed to investigate whether these play a specific role in the development of tics.

The key strength of this study is the prospective evaluation of unaffected children at risk of developing tics not relying on health care–seeking behavior. Further strengths of the study include the comprehensive evaluation of GAS exposure and tic onset. We used multiple definitions of GAS exposures, varying in stringency, to minimize false-negative findings. A 3-level observation and data collection scheme was performed to allow an accurate diagnosis of tic onset in a timely manner (and therefore reduce the rate of misclassification) and to minimize recall bias. The timely examination of participants with GAS exposure was particularly important because findings from a previous study suggested that the impact of GAS exposure on tic development might be influenced by the time window between GAS infection and tic onset.[15] To account for the potential influence of the time between GAS exposure and tic onset, we used time-varying Cox regression models taking into account changes of GAS exposure status over time and performed several sensitivity analyses assessing the association of tic onset with GAS exposure at baseline and during follow-up.

One of the potential limitations is that our participants were from 16 study centers across Europe, which could result in a great heterogeneity in terms of clinical and microbiological assessments. However, we used several strategies in the study design to mitigate this limitation, including clinical procedure harmonization, across-center clinical training, and external quality control co-led by 2 microbiological units in the EMTICS consortium, as well as correction of the analysis for site. Furthermore, there were missing data for laboratory tests largely as a result of insufficient volume or hemolysis of the collected specimens or unavailability of participants for specimen collection. However, we performed sensitivity analyses with complete cases only (i.e., excluding visits with missing data on GAS exposure), and the results from sensitivity analyses were consistent with the main findings. The width of the 95% confidence intervals of the hazard ratio estimates in primary analyses was relatively large, suggesting that a type II error may exist. However, according to our power analysis, the size of study population was sufficient for detection of a moderate association between GAS exposure and tic onset.

This prospective study did not find evidence for an association between prospectively studied GAS exposure and tic onset in children who are the first-degree relatives of patients with a CTD. This finding may have implications for both clinical and pathophysiologic aspects of tic disorders. From a clinical perspective, because GAS exposure was not found to be associated with tic onset, our study does not support the widespread ongoing clinical practice by many primary care physicians of ordering throat swabs and antibody tests for GAS or treating with antibiotics when a child presents with a new onset of tics. Moreover, because our companion EMTICS study[25] reported no significant association between GAS exposure and tic exacerbations, investigation or recommendation of active management of GAS infection is unlikely to help modify the course of tics. Because the study participants were recruited from a high-risk population of first-degree relatives, results from this study may suggest that GAS exposure at least in those with genetic risk factors does not play an important role in the occurrence of tics. The lack of association between GAS exposure and tic onset suggests that future research needs to examine the relationships between tic onset and a wider range of factors, including other pathogens.

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Appendix 1 Authors

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Anette-Eleonore Schrag, MD, PhD	Department of Clinical Neuroscience, UCL Institute of Neurology, University College London, UK	Design and conceptualized study; analyzed the data; drafted the manuscript for intellectual content; corresponding author
Davide Martino, MD, PhD	Department of Clinical Neurosciences, Cumming School of Medicine and Hotchkiss Brain Institute, University of Calgary, Alberta, Canada	Design and conceptualized study; revised the manuscript for intellectual content
Hanyuying Wang, PhD	Department of Clinical Neuroscience, UCL Institute of Neurology, University College London, UK	Interpreted the data; performed statistical analysis; revised the manuscript for intellectual content

Continued

Appendix 1 *(continued)*

Name	Location	Contribution
Gareth Ambler, PhD	Department of Statistical Science, University College London, UK	Interpreted the data; revised the manuscript for intellectual content
Noa Benaroya-Milstein, MD, PhD	Child and Adolescent Psychiatry Department, Schneider Children's Medical Centre of Israel, Petah-Tikva, Affiliated to Sackler Faculty of Medicine, Tel Aviv University	Major role in the acquisition of data
Maura Buttiglione, PhD	Department of Biomedical Sciences and Human Oncology, University of Bari "Aldo Moro," Bari, Italy	Revised the manuscript for intellectual content
Francesco Cardona, MD	Department of Human Neurosciences, University La Sapienza of Rome, Italy	Major role in the acquisition of data
Roberta Creti, PhD	Department of Infectious Diseases, Istituto Superiore di Sanità, Rome, Italy	Major role in the acquisition of data; participated in design of microbiological analyses; advised on interpretation of results
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
Tammy Hedderly, MD	Evelina London Children's Hospital GSTT, Kings Health Partners AHSC, London, UK	Major role in the acquisition of data
Isobel Heyman, MBBS, PhD, FRCPsych	Psychological Medicine, Great Ormond Street Hospital NHS Foundation Trust, London, UK	Major role in the acquisition of data and advised on results' interpretation
Chaim Huyser, MD, PhD	Levvel, Academic Center for Child and Adolescent Psychiatry, Amsterdam, the Netherlands; Amsterdam UMC, Department of Child and Adolescent Psychiatry, the Netherlands	Major role in the acquisition of data
Pablo Mir, MD, PhD	Unidad de Trastornos del Movimiento, Instituto de Biomedicina de Sevilla, Hospital Universitario Virgen del Rocío/CSIC/Universidad de Sevilla, Spain; Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas, Madrid, Spain	Major role in the acquisition of data
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Appendix 1 *(continued)*

Name	Location	Contribution
Natalie Moll, MSc	Institute of Laboratory Medicine, University Hospital LMU Munich, Germany	Major role in the acquisition of laboratory data
Norbert E. Müeller, MD	Department of Psychiatry and Psychotherapy, University Hospital, LMU Munich, Germany	Major role in the acquisition of data
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Renata Rizzo, MD, PhD	Child and Adolescent Neurology and Psychiatry, Department of Clinical and Experimental Medicine, University of Catania, Italy	Major role in the acquisition of data
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Markus J. Schwarz, MD, PhD	Institute of Laboratory Medicine, University Hospital LMU Munich, Germany	Major role in the acquisition of laboratory data
Zsanett Tarnok, PhD	Vadaskert Child and Adolescent Psychiatric Hospital, Budapest, Hungary	Major role in the acquisition of data
Susanne Walitza, MD, MSc	Department of Child and Adolescent Psychiatry and Psychotherapy, University of Zurich, Switzerland	Major role in the acquisition of data
Andrea Dietrich, PhD	University of Groningen, University Medical Centre Groningen, Department of Child and Adolescent Psychiatry, the Netherlands	Design and conceptualized study; acquisition of data; data curation; revised the manuscript for intellectual content
Pieter J. Hoekstra, MD, PhD	University of Groningen, University Medical Centre Groningen, Department of Child and Adolescent Psychiatry, the Netherlands	Design and conceptualized study; analyzed the data; revised the manuscript for intellectual content

Appendix 2 Coinvestigators

Coinvestigators are listed at links.lww.com/WNL/B751

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Lack of Association of Group A Streptococcal Infections and Onset of Tics: European Multicenter Tics in Children Study

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