

# Study protocol to investigate the correlation between Tourette syndrome and allergy in children and adolescents

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## Abstract

**Objective:** Noting that the usefulness of cases diagnosed in administrative registers is dependent on diagnostic validity, in this study, we aim to elucidate the correlation between Tourette syndrome and allergy in children and adolescents, specifically with regard to incidence of asthma, allergic rhinitis, allergic conjunctivitis, and atopic dermatitis.

**Methods:** Based on a set of inclusion and exclusion criteria, we intend to enroll 200 children and adolescents aged 18 years and younger, accompanied by their parents, for a duration of 2 years. We will administer an anonymous questionnaire in a case–control study. We will use the chi-squared test to evaluate differences between cases and controls.

**Results:** According to the European Review for Medical and Pharmacological Sciences, the proportion of allergic diseases expected in patients with Tourette syndrome is 53.1% (17/32) and 22.9% (8/35) in the controls. Setting the type I error to 0.05 and the power to 0.8, we will ensure a 1:2 case-to-control ratio.

**Conclusions:** This study protocol describes our analysis of anonymous questionnaire responses. Comorbidity rates, environmental factors, and genetic factors for various allergens, allergies, and other neuropsychiatric disorders will be studied.

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## Keywords

Allergen, allergic disease, neuropsychiatric disorders, Tourette syndrome, children and adolescents, survey

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## Introduction

The incidences of various allergies have risen concomitantly with an increase in global air pollution. A study using Taiwan's National Health Insurance Research Database has identified a positive correlation of Tourette syndrome with allergic rhinitis, allergic conjunctivitis, asthma, and atopic dermatitis.<sup>1</sup> Atopic constitution can be detected using several methods, such as the skin prick test, blood tests to detect IgE levels, and assessment of eosinophils. Accordingly, one study found that although there were no significant differences between a group with Tourette syndrome and a healthy control group in terms of IgE and eosinophil levels, the incidence of allergic rhinitis was higher in patients with Tourette syndrome.<sup>2</sup> Considering the rising severity of air pollution, we aim to investigate whether there is a similar increase in the correlation between Tourette syndrome and allergies. Blood tests that can identify specific allergens are currently available can be used to help in educating patients regarding ways to prevent allergic reactions. Additionally, owing to the development and convenience of the Internet, people have changed the way they work, communicate, and spend leisure time. Long periods of exposure to mobile phones, computers, or other radiation-emitting devices can harm the human body,<sup>3,4</sup> which may affect the immune system and result in allergies.

The incidence of Tourette syndrome ranges from 0.85% to 1% and is

characterized by multiple motor tics and one or more vocal tics. The disease is usually most severe at age 10 to 12 years.<sup>5</sup> Comorbid mental illnesses are common in patients with Tourette syndrome and their lifetime comorbidity rate is 85.7%. Groth et al.<sup>5</sup> interviewed 314 patients with Tourette syndrome (age range: 5–19 years) from 2005 to 2007 and 2011 to 2013 ( $n=227$ ) in the National Tourette Clinic in Denmark to examine the course of psychopathologies and the severity of comorbidities in Tourette syndrome. In an interview, 146 patients completed the Development and Well-Being Assessment questionnaire, used to diagnose coexisting psychopathologies. The study results demonstrated that among all comorbid mental illnesses that persist until adolescence, attention deficit hyperactivity disorder (ADHD) was most common (in approximately one-third of study participants), followed by obsessive-compulsive disorder (approximately one-fourth of participants). At follow-up, 63% of adolescents had comorbidities.<sup>5</sup>

In Finland, Leivonen et al.<sup>6</sup> reported an association between parental psychiatric disorders and Tourette syndrome and chronic tic disorder in the children. The presence or absence of these disorders in the offspring is predominantly affected by the mother. Environmental and maternal genetic factors play a role in Tourette syndrome and chronic tic disorder.<sup>6</sup> Family, twin, and isolation studies have provided valuable evidence regarding the hereditary

characteristics of Tourette syndrome. Family studies on Tourette syndrome and obsessive-compulsive disorder have demonstrated that early-onset obsessive-compulsive disorder may share common genetic factors with Tourette syndrome. Although an etiological relationship is evident between Tourette syndrome and ADHD, no genetic factors are shared between the most common forms of these disorders.<sup>7</sup>

Based on the above background, we aim to use a questionnaire survey to analyze the correlation of Tourette syndrome with four major allergic diseases (allergic rhinitis, allergic conjunctivitis, asthma, and atopic dermatitis), allergens (food and airborne), and environmental factors (e.g., pets, carpets, television/computer irradiation, living environment). The usefulness of cases included in administrative registers is dependent on diagnostic validity. We will administer an anonymous questionnaire for enrolled children and adolescents, to be completed by participants or their parents, in a case-control study. The survey data will be statistically analyzed to assess the correlation between the parameters and Tourette syndrome and to identify their clinical importance. Specifically, the survey will query information regarding neuropsychiatric disorders in the parents of participants, to examine the correlation with Tourette syndrome in their children. This questionnaire will also be used to analyze the correlation between the time spent using radiation-emitting devices and the prevalence of associated diseases in children and adolescents.

## Methods

### *Ethics approval and consent to participate*

We obtained verbal informed consent from all participants or their parents. There are no side effects expected in the conduct of

this questionnaire-based study. During data analysis, each participant's identity will be replaced by a code, and the personal information of participants will not be revealed at any time. This study has been reviewed and was approved on 18 October 2018. All experimental protocols have been approved by the Institutional Review Board (IRB: No. 10733), Tsaotun Psychiatric Center, Ministry of Health and Welfare, Taiwan. All methods shall be carried out in accordance with relevant guidelines and regulations of the Declaration of Helsinki, Declaration of Lisbon on the Rights of the Patient, and Declaration of Geneva. Informed consent shall be obtained from all participants or from a parent and/or legal guardian if the participant is under age 18 years.

### *Study duration*

The study period will be 2 years, between 18 October 2018 and 17 October 2020, and will be extended for a longitudinal study if necessary.

### *Study venue*

The study site will be the Psychiatry Department and the Children and Adolescent Psychiatry Outpatient Clinic at Taichung Hospital, Ministry of Health and Welfare, Taiwan.

### *Experimental design and data statement*

Pediatric patients with Tourette syndrome from outpatient clinics will be included in the experimental group, whereas patients without Tourette syndrome will be included in the control group. This proposal is for a questionnaire-based study, to be completed by included participants or the parents of participants under age 18 years. The study aim is to understand the correlation between Tourette syndrome and allergy in children and adolescents by focusing on the

incidence of asthma, allergic rhinitis, allergic conjunctivitis, and atopic dermatitis, and to explore their association with various environmental allergens.

Using the study results of Yuce et al. as reference,<sup>2</sup> we expect that the estimated proportion of allergic diseases in the experimental group will be 53.1% (17/32) and 22.9% (8/35) in the control group. Setting the type 1 error to 0.05 and the power to 0.8 will ensure that the case-to-control ratio is 1:2. We estimate that at least 30 and 60 participants will be required in the case and control groups, respectively. With a case-to-control ratio of 1:1, at least 40 participants will be needed in each group. Considering that the collected data may be incomplete or biased, 200 or more participants will be recruited.

### **Study implementation**

A questionnaire will be used, and we will adopt a case-control study design. The participants will receive a verbal introduction and explanation before administration of the survey.

Participants who fulfill the following inclusion criteria will be eligible to participate in the study: (A) children and adolescents with Tourette syndrome, or the adult parents of participants under age 18 years, who complete the questionnaire survey; and (B) children and adolescents who do not have Tourette syndrome, or the adult parents of participants under age 18 years.

Participants who meet the following exclusion criteria will not be eligible for the study: (A) participants or their parents who are unable to read or complete the questionnaire; (B) pediatric patients with major illnesses (congenital metabolic diseases, heart disease, cerebral palsy, and so), genetic diseases or chromosomal abnormalities, or organic mental disorders;

(C) adult parents of children with intellectual disabilities; and (D) adult parents aged 20 years or younger.

### **Statistical methods**

Data will be reported as mean  $\pm$  standard deviation. The chi-squared test will be used to assess differences between the group with Tourette syndrome and the control group. Logistic regression will also be used to infer odds ratios and 95% confidence intervals between the two groups. SAS software (SAS Institute Inc., Cary, NC, USA) will be used to analyze and compare the data and to assess the correlation between the parameters and their clinical significance.

### **Discussion**

For many years, Tourette syndrome has been considered a rare disorder, but tics and Tourette syndrome are now recognized as fairly common childhood-onset conditions.<sup>8</sup> Tourette syndrome is a complex neuropsychiatric disorder that is characterized by tics. Bilateral globus pallidus internus deep brain stimulation had been considered to be an effective treatment for refractory Tourette syndrome.<sup>9</sup> Tourette syndrome has been found to be correlated with a number of allergies, specific allergens, and parental neuropsychiatric disorders.<sup>1</sup>

In the proposed study, anonymous questionnaires will be completed by enrolled children and adolescents, or the parents of those under age 18 years, in a case-control study. The comorbidity rate, environmental factors, and genetic factors of various allergens, allergies, and other neuropsychiatric disorders will be examined. Simultaneously, we will study the family history of neuropsychiatric disorders, to further determine the influence of genetic factors.

We hope that this study will increase awareness of the government and the public about Tourette syndrome and that the study findings will serve as a foundation to assist individuals with Tourette syndrome and their families in receiving suitable medical care and social support. We also hope to carry out related studies using Taiwan's National Health Insurance Research Database in the future, thereby avoiding possible biases in participant recruitment and questionnaire results.

## Conclusions

A study using Taiwan's National Health Insurance Research Database identified a positive correlation of Tourette syndrome with allergic rhinitis, allergic conjunctivitis, asthma, and atopic dermatitis.<sup>1</sup> The present study protocol describes our plan to explore the relationship between Tourette syndrome and allergies among children and adolescents, in an analysis of the results of an anonymous questionnaire.

According to the European Review for Medical and Pharmacological Sciences,<sup>2</sup> the estimated proportion of allergic diseases among patients with Tourette syndrome is 53.1% and 22.9% in controls. Setting the type 1 error to 0.05 and power to 0.8, we will ensure a 1:2 case-to-control ratio. The chi-squared test will be used to assess the differences between case and control groups, and we will conduct statistical analysis to compare the data between groups and to assess the correlation between the included parameters and their clinical importance.

## Authors' contributions

All authors have contributed to this work and are in agreement with the content of the manuscript. Dr. Tsai and Prof. Lue conceived and

designed the experiments; Dr. Tsai and Prof. Lin wrote the paper; Prof. Lin revised the paper.

## Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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