

Correlation of Tourette Syndrome and Allergic Disease: Nationwide Population-Based Case-Control Study

Yu-Tzu Chang, MD,* Yu-Fen Li, PhD, MPH,† Chih-Hsin Muo, MS,‡ Shih-Chieh Chen, MD,§ Zheng-Nan Chin, MD,* Huang-Tsung Kuo, MD, PhD,* Hung-Chih Lin, MD,*|| Fung-Chang Sung, PhD, MPH,†‡ Chang-Hai Tsai, MD, PhD,*¶ I-Ching Chou, MD*#

ABSTRACT: *Objective:* Linkage between allergy and increased immune response activation in Tourette syndrome (TS) has been reported. We performed a matched case-control study to evaluate correlation between allergic diseases and TS. *Methods:* Data in this case-control study were from the Taiwan National Health Insurance Research Database. The sample comprised 845 2- to 18-year-old patients with newly diagnosed TS in 2003–2007 and 3378 controls frequency matched with cases on age, sex, and urbanization level. Unconditional logistic regression estimated odds ratios (ORs) and 95% confidence intervals (CIs) of the association between allergic disease (e.g., allergic rhinitis, atopic dermatitis, asthma, and allergic conjunctivitis), the number of allergic comorbidities, and TS. *Results:* The majority (76.0%) of incident TS cases were boys; the 4 allergic diseases strongly correlated with higher risk of TS. In a model simultaneously considering all 4 allergic diseases, subjects with allergic rhinitis showed double the risk of TS (adjusted OR = 2.18, 95%CI 1.83–2.59; $p < 0.0001$); adjusted ORs were 1.82, 1.61, and 1.33, respectively, for asthma (95% CI 1.47–2.24; $p < 0.0001$), dermatitis (95%CI 1.32–1.95; $p < 0.0001$), and allergic conjunctivitis (95% CI 1.13–1.57; $p < 0.001$). Risk increased with number of comorbidities ($p < 0.0001$); this association was positively modified by age ($p < 0.0001$). *Conclusions:* Our data showed significant correlation between allergic diseases and TS. Risk also increased with number of allergic comorbidities and with age. Further studies on the mechanism of neuroimmunology of TS are required.

(*J Dev Behav Pediatr* 32:000–000, 2011) **Index terms:** Tourette syndrome, allergy, neuroimmunology.

Tourette syndrome (TS) is a neuropsychiatric disorder characterized by the presence of involuntary motor and phonic tics that grow stronger and then become weaker. In this heterogeneous disorder, genetic, environmental, immunological, and hormonal factors interact to establish vulnerability. Immune and nervous systems have delicate, complex, and dynamic interaction, both in healthy and diseased individuals.¹ Mounting evidence suggests that besides affording communication between immune cells, specific cytokines play a role in signaling

the brain to produce neurochemical, neuroendocrine, neuroimmune, and behavioral changes.^{2–5} Cytokines may act as neuromodulators and immunomodulators;² the signaling may be part of a generalized and comprehensive mechanism to mobilize resources in the face of physical and/or psychological stress and to maintain homeostasis. On the clinical level, advances in cytokine research have helped us understand pathophysiology of medical conditions and identification of new treatments.⁶ These developments are particularly relevant to immune-related disorders such as infection, allergy, autoimmune disease, and cancer. Neurobiological research has revealed several possible alternations; evidence points to immune dysregulation as involved in pathogenesis of tic disorders.

Likewise, environmental factors triggering immune response have been proposed for a subgroup of patients with TS and pediatric-onset obsessive-compulsive disorder (OCD). Possibility of such a link is partly based on similarity of TS to Sydenham chorea, which occurs after group A β -hemolytic streptococcal infections.^{7–8} In brief, immunological research indicates that infections like pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections may induce or reinforce tics and associated features in susceptible individuals, possibly via abnormal humoral immune re-

From the *Children's Medical Center, China Medical University Hospital; †Department of Public Health, China Medical University; ‡Management Office for Health Data, China Medical University Hospital; §Division of Pediatric Immunology, Children's Medical Center, China Medical University Hospital; ||School of Chinese Medicine, College of Chinese Medicine, China Medical University; ¶Department of Healthcare Administration, Asia University; #Graduate Institute of Integrated Medicine, College of Chinese Medicine, China Medical University, Taichung, Taiwan.

Received April 2010; accepted October 2010.

This study was supported partly by the National Science Council, Executive Yuan, Taiwan, Republic of China, grants NSC 95-2625-Z-039-002, NSC 96-2625-Z-039-003, and NSC 97-2625-M-039-003; China Medical University Hospital grant IMS1; and Taiwan Department of Health Clinical Trial and Research Center for Excellence grant DOH99-TD-B-111-004.

Address for reprints: I-Ching Chou, MD, Children's Medical Center, China Medical University Hospital, No. 2, Yuh-Der Road, North District, Taichung 40447, Taiwan; e-mail: icking@mail.cmuh.org.tw.

Copyright © 2011 Lippincott Williams & Wilkins

sponse directed against self-tissue antigens.⁸⁻¹⁴ Linkage between group A β -hemolytic streptococcal infections and onset or worsening of pediatric OCD, TS, and tic disorders has been corroborated by cross-sectional⁸⁻¹⁰ and longitudinal¹¹⁻¹² reports.

Association of allergies with TS has been described in literature.¹⁵⁻¹⁹ Ho et al¹⁵ cited patients who show clinical evidence of allergy in the Multiple Allergens Simultaneous Tests positive group (56.9%) of patients with TS as displaying a significant difference from controls. Prevalence of allergy in patients with TS has proven significantly higher than in the general population. However, after comparing 247 patients with TS with selected controls, Comings and Comings²⁰ concluded that no significant difference in frequency of allergies between these groups existed.

To calculate association between allergy and TS, we hypothesize the role of allergy in TS and performed nationwide population-based case-control study to correlate rhinitis, asthma, atopic dermatitis, and conjunctivitis with TS.

MATERIALS AND METHODS

Study Subjects

We gleaned data from the National Health Research Institutes Dataset established in January 1996. The National Health Insurance program of Taiwan is an island-wide system established by the Bureau of National Health Insurance of the Department of Health. Implemented as of March 1995, it had a coverage rate of over 99% in 2007 (<http://www.nhi.gov.tw>). This dataset consisted of insurance claims by 10,000,000 individuals randomly selected among all insured individuals in 2005. These claims, retrospectively collected since 1996 and prospectively recorded up to 2007, contained basic demographic information on insured residents (sex, age, region, and so on), along with medical records (including inpatient and ambulatory visits). We used the International Classification of Disease, Ninth Revision (ICD-9) to define status of Tourette syndrome (TS) in individuals aged 2 to 18 years. We identified 845 incident cases as newly diagnosed patients with TS (ICD-9: 307.2) in 2003-2007. In each case, 4 controls were matched for age, sex, and urbanization level among children with no history of TS. Using 1:m case-control studies is to increase the power and to control possible confounding. As the statistical efficiency does not gain much when $m > 4$, we decide to conduct a 1:4 matched case-control study. Urbanization level was defined according to population density (persons/km²) for each township and district (Department of Statistics, Ministry of the Interior, Executive Yuan of the Republic of China, <http://sowf.moi.gov.tw/stat/year/list.htm>). Number of matchable controls came out too short—3378 controls included in analysis. We identified the status of each subject's allergic conjunctivitis (ICD-9: 372.05, 37.210, and 372.14), allergic rhinitis (ICD-9: 477), asthma (ICD-9: 493 and 494), and atopic dermatitis (ICD-9: 691) during

the study period. Cumulative effect of multiple allergic comorbidities was evaluated by the number of allergic comorbidities.

Statistical Analysis

Chi-square and *t*-tests rated the difference between case and control groups. The odds ratio (OR) and 95% confidence interval (CI) were estimated using unconditional logistic regression with adjustment of confounders. The mutually adjusted model tested all 4 allergic diseases simultaneously, while adjusting for sex, age, and urbanization. Analyses were performed by SAS software version 9.1 (SAS Institute Inc., Carey, NC), and significance level was set at 0.05.

RESULTS

Among 845 incident cases diagnosed with Tourette syndrome (TS) in 2003-2007, the majority was boys (76.0%) with a mean age of 8.37 (SD = 2.97) years (Table 1). Compared with matched controls, cases were more prone to allergic conjunctivitis (64.6% vs 53.0%), allergic rhinitis (58.1% vs 32.9%), asthma (26.0% vs 10.8%), and atopic dermatitis (26.6% vs 15.2%). Adjusted logistic regression analysis of TS and associated factors are presented in Table 2. Model 1 refers to multivariate logistic regression of each comorbidity, adjusted for sex, age, and urbanization. Model 2 serves as a mutually adjusted model. Four allergic diseases positively correlated with risk of TS. In the model simultaneously considering all 4 allergic diseases, subjects with allergic rhinitis showed more than twice the risk of TS (adjusted odds ratio [OR] = 2.18, 95% confidence interval [CI] 1.83-2.59; $p < 0.0001$); adjusted ORs were 1.82, 1.61, and 1.33, respectively, for asthma (95% CI 1.47-2.24; $p < 0.0001$), dermatitis (95% CI 1.32-1.95; $p < 0.0001$), and allergic conjunctivitis (95% CI 1.13-1.57; $p < 0.001$).

Individuals can simultaneously manifest several allergic comorbidities; we thus rated cumulative effect by counting allergic comorbidities each individual suffered, adjusted for age, sex, and urbanization level. Risk increased with number of comorbidities, exhibiting an OR of 1.74 (95% CI 1.62-1.87; $p < 0.0001$). However, cumulative effect was positively modified by age ($p < 0.0001$; Fig. 1). For individuals without indexed allergic diseases, TS risk decreased with age (adjusted OR = 0.96, 95% CI 0.92-1.01; $p = 0.08$) but increased with age (adjusted OR = 1.06, 95% CI 1.04-1.09 per year and per indexed allergic disease; $p < 0.0001$) for individuals with indexed allergic diseases, especially among those with 3 or 4 allergies, as depicted in Figure 1. Relative to a 10-year-old patient without allergic diseases, a 15-year-old patient with allergic diseases displayed 40 times the risk.

DISCUSSION

The connection between the immune system and neuropsychiatric disease has become increasingly clear.²⁰ More and more studies suggest immune abnormality as associated with Tourette syndrome (TS): e.g., autoimmune re-

T1, AQ:C

T2, AQ:D

F1

Table 1. Comparisons in Sociodemographic Factors and Comorbidities Between Cases with Tourette Syndrome and Controls

	Total (n = 4223)	Tourette Syndrome		p
		No (n = 3378)	Yes (n = 845)	
Age (yr)				.98
Mean	8.38	8.38	8.37	
SD	2.96	2.96	2.97	
Sex				.99
Girls	1015 (24.0)	812 (24.0)	203 (24.0)	
Boys	3208 (76.0)	2566 (76.0)	642 (76.0)	
Urbanization				.99
Mean	7063	7064	7060	
SD	6094	6094	6097	
Comorbidity				
Allergic conjunctivitis				<.0001
No	1887 (44.7)	1588 (47.0)	299 (35.4)	
Yes	2336 (55.3)	1790 (53.0)	546 (64.6)	
Allergic rhinitis				<.0001
No	2621 (62.1)	2267 (67.1)	354 (41.9)	
Yes	1602 (37.9)	1111 (32.9)	491 (58.1)	
Asthma				<.0001
No	3637 (86.1)	3012 (89.2)	625 (74.0)	
Yes	586 (13.9)	366 (10.8)	220 (26.0)	
Atopic dermatitis				<.0001
No	3486 (82.6)	2866 (84.8)	620 (73.4)	
Yes	737 (17.5)	512 (15.2)	225 (26.6)	

Tourette syndrome = International Classification of Diseases, Ninth Revision (ICD-9) code: 307.2; allergic conjunctivitis = ICD-9-code: 372.05, 372.10, and 372.14; allergic rhinitis = ICD-9 code: 477; asthma = ICD-9 code: 493 and 494; atopic dermatitis = ICD-9 code: 691. Values are presented as n (%) unless otherwise indicated.

sponses, altered cytokine profiles, and correlations of inflammatory mediators with symptom exacerbation. This study revealed people with allergic diseases like rhinitis, asthma, and conjunctivitis at risk for TS, which increased

Table 2. Associations Between Risk Factors and Tourette Syndrome, OR, and 95% CI

	Model 1		Model 2	
	OR	95% CI	OR	95% CI
Allergic conjunctivitis				
No	1	reference	1	reference
Yes	1.62	1.39–1.89*	1.33	1.13–1.57**
Allergic rhinitis				
No	1	reference	1	reference
Yes	2.83	2.43–3.30*	2.18	1.83–2.59*
Asthma				
No	1	reference	1	reference
Yes	2.90	2.40–3.50*	1.82	1.47–2.24*
Atopic dermatitis				
No	1	reference	1	reference
Yes	2.03	1.70–2.43*	1.61	1.32–1.95*

OR, odds ratio; CI, confidence interval. Model 1: each comorbidity adjusted for sex, age, and urbanization; Model 2: mutually adjusted. **p* < 0.0001; ***p* < 0.001.

with comorbidities and with age. Association between allergy and TS has been mentioned in previous studies. In 1999, Ho et al stated that 64% of their patients with TS proved atopic,²⁰ showing prevalence of allergy in patients with TS definitely higher than in the mainstream popula-

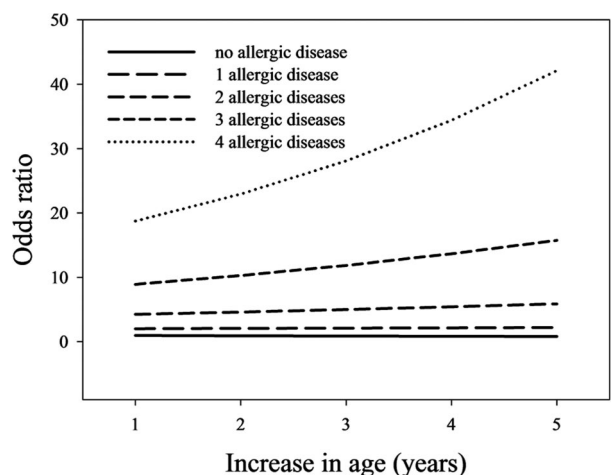


Figure 1. A statistical graph representing the relative risk (in terms of odds ratio) for Tourette syndrome as age increases by the number of allergic diseases (*p* for interaction <0.0001). The reference group is individuals with no allergic disease at a certain age.

AQ: I

AQ: E tion. Allergens in food may play a role in both allergic disease and TS, which may be alleviated by avoiding demonstrable offending dietary factors. Evidence that certain foods could enhance production of a specific neurotransmitter has also been reported.^{1,21-23} By reviewing 3300 patients with TS, Bruun²¹ stated that in his clinical experience, symptom exacerbation is often associated with seasonal allergic responses or ingestion of allergens in foods, as well as by medication used to treat allergies. Allergic diseases are more chronic in winter than in summer; in addition, these may improve during puberty. Course of these diseases is similar to tic disorders that grow stronger and then become weaker. Finegold¹⁶ reported 4 patients with TS showing higher serum IgE levels and positive skin test. He stated that symptoms of patients with TS may mimic allergies or combine with allergic illness. He suggested linkage between these 2 disorders. In 1986, Mandell reported 80% incidence of allergy in investigations of patients with TS,²³ linking allergy and TS.

AQ: G Allergic disease may lead to stress for patients. Psychosocial stress has emerged as a powerful predictor of future tics, obsessive-compulsive disorder (OCD), and depressive symptom severity.²⁴ Other environmental triggers (infection, stress, allergen, and so on) involve the dopamine release system,²⁴⁻²⁷ increasing cytokine and autoantibody release, whose interactions with the central nervous system may be involved with the onset or worsening of tics and obsessive-compulsive symptoms.²⁴ Animal studies prove that immunosuppression elicited by stressor can be modified by drugs influencing serotonin and dopaminergic systems. The authors view stress-induced alternation of immune response as arising from changed neurochemical patterns of the brain and disturbance of the mechanism via psychoneuroimmunomodulation.²⁸ Furthermore, stress could aggravate symptoms of TS and allergies.^{18,24,29} This may be the reason why more allergic comorbidity means higher risk of TS, as exhibited in this study.

Interpretations of our study have some limitations. Children with TS often suffer tics along with concomitant psychopathologies: attention-deficit-hyperactivity, mood disorders, OCD, episodic outbursts, learning difficulties, sleep disturbance, and other behavioral problems. Clinical impact on affected patients is quite significant and can presumably get more scrutiny in their care and pediatric visits as compared with control subjects. Risk of controls to develop allergic disorder may be underestimated, because children with minor allergic disorder may not go to pediatric clinics.

CONCLUSION

Incidence of allergic diseases are correlated with occurrence of Tourette syndrome (TS). Possible immunopathogenic mechanisms in TS include genetic expression, immune response, the role of cytokine, environmental influence, or stress-related responses. Nevertheless, although the precise mechanism is largely unknown at present, available evidence points

to allergic disease affecting individuals with tic disorders. Ongoing large-scale longitudinal studies could provide definite answers to this intriguing topic.

REFERENCES

1. Kerr D, Krishnan C, Pucak ML, Carmen J. The immune system and neuropsychiatric diseases. *Int Rev Psychiatry*. 2005;17:443-449.
2. Kronfol Z, Remick DG. Cytokines and the brain: implications for clinical psychiatry. *Am J Psychiatry*. 2000;157:683-694.
3. Rothwell NJ. *Cytokine in the Nervous System*. Georgetown, TX: PG Landes; 1996;47-71.
4. Ransohoff RM, Benveniste EN, eds. *Cytokines and the CNS*. Boca Raton, FL: CRC Press; 1996.
5. Plotnikoff N, Murgu A, Faith R, Good R, eds. *Cytokines: Stress and Immunity*. Boca Raton, FL: CRC Press; 1999.
6. Kunkel SL, Remick DG, eds. *Cytokines in Health and Disease*. New York, NY, Marcel Dekker; 1992.
7. Kiessling LS, Marcotte AC, Culpepper L. Antineuronal antibodies in movement disorders. *Pediatrics*. 1993;92:39-43.
8. Swedo SE, Leonard HL, Garvey M, et al. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: clinical description of the first 50 cases. *Am J Psychiatry*. 1998;155:264-271.
9. Cardona F, Orefici G. Group A streptococcal infections and tic disorders in an Italian pediatric population. *J Pediatr*. 2001;138:71-75.
10. Church AJ, Dale RC, Lees AJ, Giovannoni G, Robertson MM. Tourette's syndrome: a cross sectional study to examine the PANDAS hypothesis. *J Neurol Neurosurg Psychiatry*. 2003;74:602-607.
11. Murphy ML, Pichichero ME. Prospective identification and treatment of children with pediatric autoimmune neuropsychiatric disorder associated with group A streptococcal infection (PANDAS). *Arch Pediatr Adolesc Med*. 2002;156:356-361.
12. Luo F, Leckman JF, Katsovlis L, et al. Prospective longitudinal study of children with tic disorders and/or obsessive-compulsive disorder: relationship of symptom exacerbations to newly acquired streptococcal infections. *Pediatrics*. 2004;113:e578-e585.
13. Hoekstra PJ, Anderson GM, Limburg PC, Korf J, Kallenberg CG, Minderaa RB. Neurobiology and neuroimmunology of Tourette's syndrome: an update. *Cell Mol Life Sci*. 2004;61:886-898.
14. Trifiletti RR, Packard AM. Immune mechanisms in pediatric neuropsychiatric disorders. Tourette's syndrome, OCD, and PANDAS. *Child Adolesc Psychiatr Clin N Am*. 1999;8:767-775.
15. Ho CS, Shen EY, Shyur SD, Chiu NC. Association of allergy with Tourette's syndrome. *J Formos Med Assoc*. 1999;98:492-495.
16. Finegold I. Allergy and Tourette's syndrome. *Ann Allergy*. 1985;55:119-121.
17. Kim H, Moote W, Mazza J. Tourette's syndrome in patients referred for allergy evaluation. *Ann Allergy Asthma Immunol*. 1997;79:347-349.
18. Freeman RD, Connolly JE, Baird PA. Tourette's syndrome: update. *Can Med Assoc J*. 1984;130:1554-1557.
19. Jankovic J: Tics and Tourette's syndrome. In: Tolosa E, Koller WC, Gershanik OS, et al, eds. *Differential Diagnosis and Treatment of Movement Disorders*. Boston, MA: Butterworth-Heinemann, 1998;99-108.
20. Comings DE, Comings BG. A controlled study of Tourette syndrome. VI. Early development, sleep problems, allergies, and handedness. *Am J Hum Genet*. 1987;41:822-838.
21. Bruun RD. Gilles de la Tourette's syndrome. An overview of clinical experience. *J Am Acad Child Psychiatry*. 1984;23:126-133.
22. Wurtman RJ. Effects of foods on the brain. Possible implications for understanding and treating Tourette Syndrome. *Adv Neurol*. 1992;58:293-301.
23. Allergy and Tourette's syndrome. *Ann Allergy*. 1986;56:507-508.

AQ: H

24. Martino D, Dale RC, Gilbert DL, Giovannoni G, Leckman JF. Immunopathogenic mechanisms in tourette syndrome: A critical review. *Mov Disord.* 2009;24:1267-1279.
25. Robertson MM. The Gilles de la Tourette syndrome: the current status. *Br J Psychiatry.* 1989;154:147-169.
26. Kurlan R. Hypothesis II: Tourette's syndrome is part of a clinical spectrum that includes normal brain development. *Arch Neurol.* 1994;51:1145-1150.
27. Hyde TM, Weinberger DR. Tourette's syndrome. A model neuropsychiatric disorder. *JAMA.* 1995;273:498-501.
28. Idova G, Cheido M, Devoino L. Modulation of the immune response by changing neuromediator systems activity under stress. *Int J Immunopharmacol.* 1997;19:535-540.
29. Gustafsson PA, Bjorksten B, Kjellman NI. Family dysfunction in asthma: a prospective study of illness development. *J Pediatr.* 1994;125:493-498.

AUTHOR QUERIES

AUTHOR PLEASE ANSWER ALL QUERIES

1

- A—Please confirm whether apostrophe s removed from Tourette’s syndrome, per style, is OK.
- B—Please confirm whether the sentence “Number of matchable controls came...” is OK as edited.
- C—Please confirm whether values for Urbanization in Table 1 are presented as “n”, as they are greater than the Total number and same under all column heads.
- D—Please confirm whether linked footnotes in Table 2 are OK as edited.
- E—Please note that in the sentence “In 1999, Ho et al stated that...” author name does not match with reference number. Please check.
- F—Please confirm whether the uncited Ref. 22 cited in the line “Evidence that certain foods could..,” as Ref. 21–23, is appropriate.
- G—Please note that in the sentence “In 1986, Mandell reported 80%. . . ” author name does not match with Ref. number. Also Mandell, 1986 is not present in reference list. Please check.
- H—Please provide chapter title and editor name for Ref. 3.
- I—Please confirm whether figure legend is OK as edited.
- J—Please provide department/division name (if any) for 1st, 3rd, 5th, and 7th affiliation.
- K—Please confirm whether grant information is OK as given.
- L—Please confirm whether correspondence information is OK as edited.
-