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Association of Tourette syndrome and obsessive-compulsive disorder with allergic diseases in children and adolescents: a preliminary study

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Abstract. – OBJECTIVES: To investigate the rate of allergic diseases including asthma, allergic rhinitis and eczema in children and adolescents diagnosed with obsessive-compulsive disorder (OCD) (n:26) and/or Tourette syndrome (TS) (n:32) [OCD plus TS, n:13] compared to control subjects (n:35) [total, n:80].

PATIENTS AND METHODS: The symptoms of any allergic disease were assessed using the ISAAC questionnaire form. Allergy diagnoses were made by a pediatric allergy specialist. Skin prick tests were applied, and IgE levels and eosinophil counts were measured.

RESULTS: While only one-fifth of the control subjects had allergic diseases, more than half of the children with TS and/or OCD had comorbid allergic diseases. Positive skin prick tests were greater in OCD patients compared to control subjects. There were no significant differences between the groups in terms of eosinophil counts or IgE levels. Among the allergic diseases, while allergic rhinitis was diagnosed at significantly higher rates in TS patients, eczema was significantly higher in OCD patients compared to control subjects.

CONCLUSIONS: This preliminary study shows an association between allergic diseases and TS and/or OCD. The results revealing differences in associations between types of allergic disease (rhinitis or eczema) and neuropsychiatric disorder (tic disorder or OCD) need to be investigated in further studies with higher numbers of participants, and immune markers should be examined.

Key Words:
Children, Tourette syndrome, Obsessive-compulsive disorder, Allergy.

Introduction

Tourette Syndrome (TS) is a neuropsychiatric disorder with onset in childhood or adolescence involving multiple motor and vocal tics[1]. Tic severity rises and falls, the peak generally occurring in early adolescence[1]. In addition to tics, most cases of TS also exhibit other psychiatric features, such as Obsessive-Compulsive Disorder (OCD), Attention Deficit-Hyperactivity Disorder (ADHD), or other behavioral problems[2]. While the prevalence of TS is reported at 0.4-1%, the vast majority of cases are not diagnosed and do not receive appropriate treatment[3-5]. Previous studies have suggested that genetic mechanisms that disrupt the functions of the frontocortical-subcortical circuits cause tics and obsessions[2,6]. Similarly, reduced lenticular nucleus volume in children with TS may indicate an increased risk of persistence of TS symptoms into adulthood, in addition to an increased risk of developing OCD[7].

OCD is another neuropsychiatric disorder, in which obsessions are recurrent and intrusive thoughts or images may be followed by repetitive compulsive behaviors[8]. Although OCD was previously thought to be mainly an adulthood disorder, studies with adolescents have shown that the prevalence of OCD is 1-4% in adolescents, and that 80% of adult cases diagnosed with OCD exhibited symptoms before the age of 18[9,10]. On the other hand, OCD comorbidity is very high in TS

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patients[11]. Childhood-onset OCD and TS share several common features in terms of clinical, neurophysiological and neuroanatomical profiles[6]. For instance, both involve dysfunctions in dopamine and serotonin functions[6]. In addition to common genetic factors, several environmental variables, including psychosocial stress, factors associated with pregnancy and labor, duration of exposure to high levels of androgens, autoimmune mechanisms, etc., have been found to be associated with tics and obsessions[12,13].

Tics and obsessions forming part of the clinical picture of some diseases (especially Sydenham chorea, Lyme disease and mycoplasma pneumonia) and a recently defined disorder called Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcus (PANDAS) has encouraged research interest in immune mechanism disturbances in TS and OCD[14-16]. It has been suggested that PANDAS involves those cases of TS/OCD that are the result of an immunological response to a prior Group A Beta Hemolytic Streptococcal (GABHS) infection[8]. Although PANDAS diagnosis remains a controversial area of on-going research, one epidemiological study supports the concept[17].

Allergy is a hypersensitivity reaction initiated by specific immunological mechanisms. The European Academy of Allergology and Clinical Immunology defines atopy as a personal or familial tendency to produce immunoglobulin E antibodies in response to low doses of allergen, usually proteins, and, as a consequence, to develop typical symptoms such as asthma, rhinoconjunctivitis or atopic eczema/dermatitis[18].

In most studies, atopy is defined either as a positive serum allergen-specific IgE (sIgE) or a positive skin prick test[18-20]. Approximately one-third of children suffer from some kind of allergy, with varying prevalences, depending on diagnosis[21,22]. Allergic disease has become a major burden in westernized societies because of a recent rise in prevalence[23].

Asthma that begins early in life is usually associated with atopy[23]. The influence of emotional states and stress on pulmonary function in asthma has been studied for many years[24,25]. Environmental stressors may affect asthma morbidity through neuroimmunological mechanisms[25]. There is a substantial volume of literature demonstrating that psychological stress may influence inflammatory and immune cell trafficking, cell proliferation and cell function including cytokine and inflammatory mediator production[26-28].

There have been few studies exploring the association between allergy parameters and TS and OCD to date. Our clinical case load suggests that some allergic disorders such as asthma and eczema are more prevalent in TS and OCD patients. One study reported that TS patients with tics resembling asthma symptoms were diagnosed with asthma and received asthma treatments[29]. Specific cytokines are involved in communication between several immune cells, and these can change neuroimmunological functions and behavior via transporting signals to the central nervous system[30-32]. A significant positive correlation between TS and allergy has been reported[33-37]. On the other hand, one study of the relationship between allergic diseases and anxiety in children reported a significant association between panic disorder and allergy. No association was determined with other anxiety disorders, including OCD[38].

The purpose of this study was to investigate the rate of allergic diseases, including asthma, allergic rhinitis and eczema, and overall atopy in children and adolescents diagnosed with OCD and/or TS compared to control subjects.

Patients and Methods

Participants and Study Design

Children and adolescents aged 6-18 and diagnosed with OCD (n:13), TS (n:19) or OCD plus TS (n:13) [total, n:45] (OCD, total n:26; TS, total n:32) over a one-year period at a University Hospital Child And Adolescent Psychiatry out-patient Clinic in Turkey were included. Control subjects (n:35) were recruited from the Pediatric out-patient Clinic of the same hospital. All cases were evaluated by child and adolescent psychiatry and pediatric allergy specialists. Psychiatric diagnoses were based on DSM-IV-TR criteria. The Schedule for Affective Disorders and Schizophrenia for School Age Children-Present and Lifetime Version-Turkish Version (K-SADS-PL-TR), Children's Yale-Brown Obsessive-compulsive Scale (CY-BOCS), and Yale Global Tic Severity Scale (YGTSS) were used for psychiatric diagnoses[39-42].

Patients diagnosed with TS and/or OCD and the control subjects with no psychiatric diagnosis were referred to the Pediatric Allergy Out-patient Clinic. Symptoms of any allergic disease were assessed using the ISAAC questionnaire form. Allergy diagnoses were made by a pediatric al-

lergy specialist. Skin prick tests were applied. Test was considered positive if the mean wheal diameter was ≥ 3 mm compared with the negative control. Eosinophil counts were measured using a complete blood cell autoanalyzer. IgE levels were measured using nephelometric immunoassay. IgE levels above 100 IU/ml and eosinophil counts over 450/μL were regarded as increased. Overall atopy was defined as at least one of asthma, allergic rhinitis or eczema. Hanifin-Rajka criteria were used for the clinical diagnosis of atopic dermatitis[43].

The Institutional Review Board approved the protocol of this study. Informed parental consent was obtained for all children before their inclusion.

Schedule for Affective Disorders and Schizophrenia for School Age Children-Present and Lifetime Version-Turkish Version (K-SADS-PL-TR)

K-SADS-PL-TR is a semi-structured diagnostic assessment schedule based on DSM-IV-TR criteria of major psychiatric disorders[39,40]. It is effective for diagnosing all major childhood psychiatric disorders. The validity of K-SADS-PL-TR is excellent for elimination disorders, good for attention deficit hyperactivity disorder and tic disorders and fair for affective disorders, anxiety disorders and oppositional defiant disorder[39]. We used K-SADS-PL-TR in addition to comprehensive psychiatric clinical assessment to explore psychiatric diagnosis and comorbidity.

Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS)

The CY-BOCS is a clinician-rated, 10-item semi-structured inventory of pediatric obsession and compulsion severity rated over the previous week on a five-point Likert scale. It includes two primary sections, the Symptom Checklist and Severity Scale[41]. The 10 severity items are totaled to produce an Obsessions Severity Score (five items), a Compulsions Severity Score (five items), and a total score (sum of all 10 severity items). Studies of the psychometric properties of the CY-BOCS Severity Scale have demonstrated positive results[41,44,45]. Turkish validation of CY-BOCS was performed by Yucelen et al[45].

Yale Global Tic Severity Scale (YGTSS)

The YGTSS is an index of tic severity commonly used with children and adolescents.[42] It consists of a semi-structured clinician-rated interview designed to provide a global measure of tic severity over the previous 7-10 days. Tic severity is determined based on an evaluation of the number, frequency, intensity, complexity and interference of motor and phonic tics and a global impairment rating. Each dimension is scored on a 5-point scale, separately for vocal and motor tics. A total severity score is obtained by summing all scores across vocal and motor tics (range 0-50) or separately for vocal and motor tics. The instrument has demonstrated good internal consistency and convergent and divergent validity[42,46].

The ISAAC Questionnaire

The International Study of Asthma and Allergies in Childhood (ISAAC) is a standardized questionnaire designed to evaluate the prevalence and severity of symptoms of asthma, allergic rhinitis and atopic eczema[47]. Questionnaires were completed by the parents.

In the questionnaire, asthma is defined as asthma diagnosed by a doctor or a diagnosis of allergic bronchitis and/or ≥ 3 bronchitis episodes, and wheezing or whistling in the chest or asthma crisis in the previous 12 months. Allergic rhinitis diagnosis is based on a positive response to questions about experiencing problems with sneezing, or having a runny or blocked nose during the previous 6 months when the child does not have the common cold or flu. Eczema diagnosis is defined as recurrent erythema, and itching or rash on the body without fever in the previous six months[48,49]. Familial atopy was defined as a positive history or diagnosis of asthma, rhinitis, and/or eczema in one or both parents. Overall atopy was defined as at least one of asthma, allergic rhinitis or eczema as described above. Several other parameters are explored in the form, including familial history of allergic diseases, risk factors for allergy, number of people in the household, duration of breast feeding, tobacco smoke exposure, etc. The ISAAC questionnaire was adapted into Turkish and applied in previous Turkish prevalence studies to elicit the prevalences of asthma, allergic rhinitis and eczema[48,49].

Statistical Analysis

Variable distributions were examined for normality, and nonparametric statistics were used in cases in which the scores were not normally distributed. As we include two different psychiatric disorders (TS and OCD), and their comorbidity is very high, we had four different groups (TS only, OCD only, TS plus OCD and control) in some measurements. Where we focused on the results of one disorder (e.g., OCD) alone, we had

two groups (e.g., OCD and control subjects). Statistical differences between groups were assessed using chi square tests and Fisher's exact test for categorical variables, and using *t*-tests, one-way ANOVA, Mann-Whitney U and/or Kruskal-Wallis tests for continuous variables. All values are reported as either percentages, medians (25-75 percentile) or means ± standard deviation. SPSS 15.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical calculations.

Results

Mean age of the children and adolescents diagnosed with OCD (n:13), TS (n:19) or OCD plus TS (n:13) [total, n:45] (OCD, total n:26; TS, total n:32) and the 35 control subjects was 11.3±3.3 (6-18) years. Demographic features and median scores on CY-BOCS and YGTSS of the diagnosis groups are presented in Table I. As expected, CY-BOCS scores were significantly higher in the OCD group, and YGTSS scores were significantly higher in the TS group. However, we did not find any significant correlation between either IgE levels or eosinophil counts and YGTSS and CY-BOCS scores.

Group differences were identified in terms of the presence of any allergic disease (p: 0.02). The presence of any allergic disease was significantly higher in the TS plus OCD group (61.5%) (p: 0.018) and the OCD-only group (61.5%) (p: 0.018) compared to the control subjects (22.9%) (p: 0.02). However, the TS-only group did not exhibit significantly higher rates (42.1%) (p: 0.076). In total, 55.5% of the cases in the patient group had at least one allergic disease, significantly higher than in the control group (p: 0.006).

The TS plus OCD group had a higher positive skin prick test rate compared to the control group (p: 0.011). While the OCD-only and TS-only groups had no higher rates, the TS plus OCD group had higher rates of eczema diagnosis (p: 1, p: 0.294, p: 0.001, respectively). We determined no significant difference between the groups in terms of asthma diagnosis or family history of allergy ($p > 0.05$). Skin prick tests, IgE levels and eosinophil counts and allergy diagnosis rates of the diagnosis groups are presented in Table II.

Since we include two psychiatric disorders (TS and OCD), which have very high comorbidity, we focused on the results each disorder. The skin prick tests, IgE levels and eosinophil counts and allergy diagnosis rates of these are presented in Tables III and IV. While the TS-only group exhibited no higher rate of any allergic disease compared to the control group, the TS group did exhibit higher rates of allergy (Table III). On the other hand, IgE levels and eosinophil counts did not differ significantly between the diagnosis groups (Tables II to IV).

Among the allergic diseases, while allergic rhinitis was diagnosed at significantly levels in the TS patients (Table III), eczema levels were significantly higher in the OCD patients (Table IV) compared to the control subjects.

Discussion

This preliminary research is a pioneering study in terms of investigating the association between TS and OCD and allergic diseases in children and adolescents. The results reveal that while only one-fifth of the control subjects had allergic diseases, more than half of the children

Table I. Diagnosis groups' demographic features and median (25-75 percentile) CY-BOCS and YGTSS scores.

	TS only (n:19)	OCD only (n:13)	Both TS and OCD (n:13)	Control (n:35)	*p*
Gender boy (n) (%)	11 (57.9)	9 (69.2)	7 (53.8)	15 (42.9)	0.392[c]
Gender girl (n) (%)	8 (42.1)	4 (30.8)	6 (46.2)	20 (57.1)	
Age	12.7 ± 3.7	10.2 ± 2.4	12.4 ± 2.5	10.6 ± 3.5	0.157[b]
CY-BOCS – obsession score	0 (0-0)	13 (9.5-13.5)	10 (0-13.5)	–	0.186[a]
CY-BOCS – compulsion score	0 (0-0)	13 (9-14)	11 (8-12)	–	0.512[a]
CY-BOCS – total score	0 (0-0)	26 (19-27.5)	20 (11-25)	–	0.209[a]
YGTSS – motor score	7 (3.5-13)	0 (0-0)	6 (2.5-12)	–	0.805[a]
YGTSS – vocal score	3 (0-6.5)	0 (0-0)	5 (0-10)	–	0.509[a]
YGTSS – total score	10 (5-18.5)	0 (0-0)	13 (5-22)	–	0.680[a]

Notes: Superscript a indicates Mann Whitney U tests. Superscript b indicates Kruskal-Wallis tests. Superscript c indicates chi-square tests.

Table II. Diagnosis groups' skin prick tests, IgE levels and eosinophil counts and allergy diagnosis rates.

	TS only (n:19)	OCD only (n:13)	Both TS and OCD (n:13)	Control (n:35)	*p*	TS-C *p*	OCD-C *p*	TS+OCD-C *p*
Skin prick test positive (n) (%)	2 (10.5)	2 (15.4)	5 (38.5)	2 (5.7)	**0.03**[b]	0.607	0.294	**0.011**
IgE levels (median [25-75 per])	42 (20-150)	24.3 (16-65)	32.7 (15-139)	23 (17-38)	0.554[a]			
Eosinophil counts (median [25-75 per])	122.5 (100-178)	100 (65-268)	110 (80-320)	100 (100-200)	0.539[a]			
Presence of any allergic disease (n) (%)	9 (47.4)	8 (61.5)	8 (61.5)	8 (22.9)	**0.02**[b]	0.076	**0.018**	**0.018**
Asthma (+) (n) (%)	3 (15.8)	3 (23.1)	3 (23.1)	3 (8.6)	0.480[b]			
Allergic rhinitis (+) (n) (%)	8 (42.1)	5 (38.5)	5 (38.5)	6 (17.1)	0.174[b]			
Eczema (+) (n) (%)	1 (5.3)	5 (38.5)	2 (15.4)	2 (5.7)	**0.01**[b]	1	0.294	**0.001**
Family history of allergy (n) (%)	3 (15.8)	2 (15.4)	7 (53.8)	8 (22.9)	0.061[b]			

Notes: Superscript a indicates Kruskal-Wallis tests. Superscript b indicates chi-square tests. Bold figures indicate statistical significance. TS: Tourette Syndrome; OCD: Obsessive Compulsive Disorder; C: Control.

with TS and/or OCD had comorbid allergic diseases. This finding suggests a significant association between allergy and TS and OCD. Patients with TS and/or OCD had significantly higher possession of any allergic disease compared to the control subjects. Although all types of allergies were at higher levels in the TS and OCD patients, allergic rhinitis in particular was significantly higher in TS patients, and eczema in OCD patients. To corroborate a significant association between OCD and/or TS and allergy, we expected to find significantly higher IgE levels and eosinophil counts in TS and OCD patients compared to control subjects. However, although mean IgE levels and eosinophil counts were higher in the patient groups, and there was a tendency for patients to have higher levels, the difference was not significant. In accordance with these results, neither IgE levels nor eosinophil counts were significantly correlated with YGTSS and CY-BOCS scores.

Some authors[34] recommend clinicians evaluating allergy in children to take tic disorders into account. In agreement with their recommendation and our findings, a previous study of children with TS reported signs of allergy in 56.9% of cases[33]. In a letter, Finegold[36] reported four cases of TS with high IgE levels and positive skin prick test results. He postulated an association between TS and allergy[36]. A previous study using a large dataset in Taiwan reported a significant positive relation between TS and several allergic diseases in children.[37] That data analysis revealed that allergic rhinitis patients have a twofold risk for TS, and that other allergic diseases had similarly high, albeit lower, risks for TS[37].

Overall stress factors may increase asthma attacks[50]. Environmental and biological stress may also increase the severity of TS and OCD symptoms.

Immune system problems associated with TS have mostly been reported in studies investigating PANDAS[8,16]. In a previous study, PANDAS proponents pointed out that elevated antistreptolysin O titers had been described in 38% of 150 children with tics compared with only 2% of 150 controls[51]. Another study reported that 45% of children diagnosed with tic disorders, and 20% of control subjects, had antibodies against caudate nucleus in their blood samples[52].

In addition to PANDAS, previous studies have reported functional differences in immune systems in children and adolescents diagnosed with TS and/or OCD in association with several other

Table III. Skin prick tests, IgE levels and eosinophil counts and allergy diagnosis rates in the TS group compared to control subjects.

	TS (n:32)	Control (n:35)	p
Skin prick test positive (n) (%)	7 (21.9)	2 (5.7)	0.075[c]
IgE levels (median [25-75 per])	39.2 (15-123)	23 (17-38)	0.235[a]
Eosinophil counts (median [25-75 per])	120 (100-275)	100 (100-200)	0.687[a]
Presence of any allergic disease (n) (%)	17 (53.1)	8 (22.9)	**0.013**[b]
Asthma (+) (n) (%)	6 (18.8)	3 (8.6)	0.292[c]
Allergic rhinitis (+) (n) (%)	13 (40.6)	6 (17.1)	**0.033**[b]
Eczema (+) (n) (%)	3 (9.4)	2 (5.7)	0.664[c]
Family history of allergy (n) (%)	10 (31.2)	8 (22.9)	0.582[c]

Notes: Superscript a indicates Mann-Whitney U tests. Superscript b indicates chi-square tests. Superscript c indicates Fisher-exact tests. Bold figures indicate statistical significance.

infections (e.g. Herpes simplex virus, Varicella zoster virus, Borrelia burgdorferi and Mycoplasma pneumoniae)[53-55]. Supporting the conclusion that TS patients have immune system problems, some patients in various studies did not respond to antipsychotics, but did respond to ACTH, prednisolone and/or plasmapheresis[56,57]. Compared to children with tics, immune system disorders in children diagnosed with OCD have been insufficiently studied.

Allergic diseases, and especially asthma, are reported to be associated with several psychiatric disorders[24,25,50,58]. Previous studies assessing psychiatric problems in children with allergic diseases have reported significantly more anxiety disorders in these children compared to control subjects. For instance, Bussing et al[59] reported that 43.2% of children with asthma had an anxiety disorder. In another large study involving 102,353 subjects, children with asthma exhibited significantly higher levels of depressive disorder, attention deficit hyperactivity disorder and learning disorder compared to control subjects[60]. To the best of our knowledge, previous studies have not shown higher rates of OCD and/or TS comorbidity either in asthma patients or in patients with atopic dermatitis and allergic rhinitis. However, in agreement with our findings, some studies have reported that many children with TS were incorrectly diagnosed and treated for asthma[29,34]. Similarly, we suspect that some patients with TS are incorrectly diagnosed and treated for rhinitis. Nevertheless, our findings support the idea that around 40% of cases with TS have comorbid allergic rhinitis, while only one-sixth of the control subjects had allergic rhinitis.

Conclusions

This is a preliminary study investigating the association between TS and OCD and allergy. Our results suggest that OCD and TS are significantly associated with allergic diseases in children and adolescents. We identified allergic rhinitis as the leading allergic disorder in TS patients, while skin

Table IV. Skin prick tests, IgE levels and eosinophil counts and allergy diagnosis rates in the OCD group compared to control subjects.

	TS (n:32)	Control (n:35)	p
Skin prick test positive (n) (%)	7 (26.9)	2 (5.7)	**0.030**[c]
IgE levels (median [25-75 per])	24 (16-66)	23 (17-38)	0.839[a]
Eosinophil counts (median [25-75 per])	100 (73-296)	100 (100-200)	0.387[a]
Presence of any allergic disease (n) (%)	16 (61.5)	8 (22.9)	**0.003**[b]
Asthma (+) (n) (%)	6 (23.1)	3 (8.6)	0.152[c]
Allergic rhinitis (+) (n) (%)	10 (38.5)	6 (17.1)	0.061[b]
Eczema (+) (n) (%)	7 (26.9)	2 (5.7)	**0.03**[c]
Family history of allergy (n) (%)	9 (34.6)	8 (22.9)	0.391[c]

Notes: Superscript a indicates Mann-Whitney U tests. Superscript b indicates chi-square tests. Superscript c indicates Fisher-exact tests. Bold figures indicate statistical significance.

allergies are more prominent in patients with OCD. The results revealing differences in associations between types of allergic disease (rhinitis or eczema) and neuropsychiatric disorder (tic disorder or OCD) need to be investigated in further studies with higher numbers of participants in which immune markers are also examined.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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