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ORIGINAL PAPER

Association between allergic conjunctivitis and provisional tic disorder in children

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Abstract

Background Allergic diseases are associated with a higher risk of Tourette's syndrome (TS). Provisional tic disorder (PTD) and eye blinking are often reported as the initial symptoms both in TS and in allergic conjunctivitis (AC).

Objective To investigate the association between AC and PTD in children of 4–10 years of age in southwest China.

Methods This case–control study was carried out at the Children's Hospital of Chongqing Medical University between January 2016 and June 2017. Age- and gender-matched children without PTD were included as the control group. Intraocular pressure was measured by non-contact tonometry, tear film break-up time by slit-lamp examination, and allergens by skin prick test (SPT). Multivariable logistic regression analysis was applied to adjust for the simultaneous effects of AC, dry eye, and allergic history in children with PTD.

Results The frequency of AC was higher in the PTD group (74.3%, 52/70) than in the control group (17.1%, 12/70) ($P < 0.001$). The frequencies of positive SPT were found to be higher in the PTD group (80.0%, 56/70) than in the control group (20.0%, 14/70). AC, dry eye, and history of allergic rhinitis were significantly associated with PTD.

Conclusion The frequencies of AC are high in children with PTD. AC and dry eye may be both associated with PTD in children.

Keywords Allergens · Hypersensitivity · Tic disorders · Tourette syndrome · Conjunctivitis · Allergic

Introduction

About 10–15% of children in elementary schools have transient simple motor tics [1]. Provisional tic disorder (PTD) is characterized by tics for < 1 year and affects about 3% of the pediatric population [2]. PTD is also observed during the onset stage of Tourette's syndrome (TS), and motor and phonic tics are the core features of TS [3]. Increased eye blinking is often reported as the initial symptom of patients with TS [4].

A study was showed that allergic diseases were associated with TS [5]. Allergic conjunctivitis (AC) is associated with changes in tear film composition, predisposing to dry eyes [6]. Tear film dysfunction can also be a possible complication of ocular allergic disease [7]. In an earlier study by our group, the occurrence of dry eye was higher in young children with seasonal and perennial AC [8]. Frequent eye

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blinking is one of the most common symptoms of dry eyes [8].

Frequent blinking is one of the most common and important symptoms of AC in children, even when there are no particular complaints of uncomfortable eyes [8]. A form of dry eye associated with AC is characterized solely by decreased tear film break-up time (TFBUT), without symptoms [9]. Activities that decrease eye blinking (such as extended computer use, watching television, and reading) can trigger and/or exacerbate dry eye symptoms [10]. Interestingly, patients with TS show a two–threefold higher blink rate compared with controls during video watching [11]. Associations between allergy and increased immune response activation have been reported in TS [5]. Some of the allergic manifestations are similar to the oral and motor tics found in patients with TS [12].

The association between AC and PTD is poorly understood. Based on those previous observations, the present study aimed to investigate the association between AC and PTD in children of 4–10 years of age in southwest China. The results could help the management of children with PTD.

Subjects and methods

Study design and patients

This case–control study was conducted at the Outpatient Department of Ophthalmology and the Outpatient Department of Neurology of the Children's Hospital of Chongqing Medical University between January 2016 and June 2017. Patients diagnosed with PTD at the Outpatient Department of Neurology were included. Age- and gender-matched non-PTD children were included as the control group. Those healthy children underwent health checkup at the Outpatient Department of Ophthalmology. All participants included in the study were between 4–10 years of age. The exclusion criteria for both groups were: (1) history of ocular surgery; (2) ocular trauma; (3) trichiasis; (4) eyelid abnormalities; or (5) any active ocular infection.

PTD was diagnosed according to the tenth International Classification of Disease-10 (ICD-10) criteria and the fifth version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [3]. PTD is diagnosed when [3]: (1) there is a presence of one or more motor tics of vocal tics; (2) there is a presence of tics for < 12 months in a row; (3) the patients have tics that started before age 18 years; (4) the patients have symptoms that are not due to medicine or drugs, or to other conditions that can cause tics; and (5) the patients have not been diagnosed with TS or persistent motor or vocal tic disorder. AC was diagnosed on the basis of positive skin prick test (SPT) and clinical symptoms such as ocular itching, redness, and swelling of the conjunctiva [8, 13].

The study was approved by the ethics committee of the Children's Hospital of Chongqing Medical University (No. 116/2016). Written informed consents were obtained from the parents or guardians of the children. The study was conducted in accordance with the principles of the Declaration of Helsinki.

TFBUT test

Both eyes were assessed. The right eye was used for data analysis. TFBUT was assessed using a Burton's lamp with a cobalt blue filter. A drop of 2% sodium fluorescein was applied to the eye, and the patient was asked to blink five times. The patient was then asked to refrain from blinking, during which time the dry pots appear and are shown as black spots or lines. The interval between the last blink and the appearance of the first randomly distributed dry spot was taken as the TFBUT. Three measurements were recorded. A reference value of 10 s for TFBUT was used for the diagnosis of dry eyes [14, 15].

Intraocular pressure

In all cases, both eyes were assessed routinely. The right eye was used for analysis. Intraocular pressure (IOP) was measured using a non-contact tonometer (NCT), based on air puff (Topcon CT60, Topcon Corporation, Tokyo, Japan). Three measurements were taken on each patient, and the average of the readings was recorded as the final IOP.

SPT

The skin prick test was performed on the anterior part of the forearm. The sensitivity to twenty-three common air allergens was tested including *Dermatophagoides* (*D.*) *pteronyssinus*, *D. farina*, cotton

fiber, dog hairs, cat hairs, duck feather, cockroach, cigarettes, birch pollen, *Artemisia vulgaris*, corn pollen, *Saccharomycetes*, *Penicillium*, peanut, milk, egg, mango, apple, soybean, hairtail, beef, shrimp, and sea crab. The positive control solution was 10 mg/mL histamine hydrochloride, and the negative control solution was phenolated glycerol–saline solution. The largest diameter of the wheals was measured 20 min after pricking. A positive skin reaction was defined as a wheal at least 3 mm greater than the diameter of the negative control. The results were scaled from 1 to 4 according to the size of the wheal (+ 1, larger than the negative control by < 5 mm; + 2, by 5–7 mm; + 3, by 7–10 mm; and + 4, by > 10 mm and/or pseudopods). The same physician evaluated all included children.

Statistical analysis

Data were analyzed using SPSS 16.0 (IBM, Armonk, NY, USA). Continuous variables were presented as mean ± standard deviation (SD) and were analyzed using the independent Student's t test. Categorical variables were presented as frequencies and percentage and were analyzed using the Chi-square test of the Fisher's exact test, as appropriate. Multivariable logistic regression analysis was performed to adjust for the simultaneous effects of AC, dry eye, and allergic history in children with PTD. Two-sided P values < 0.05 were considered statistically significant.

Results

Patients

Seventy patients and 70 healthy children were included in this study. There were 54 males and 16 females in the PTD group and 50 males and 20 females in the control group ($P = 0.591$). The mean age was 6.82 ± 2.18 years in the PTD group and 6.90 ± 2.25 years in the control group ($P = 0.875$).

Analysis by groups

The frequency of AC was higher in the PTD group (74.3%, 52/70) than in the control group (17.1%, 12/70) ($P < 0.001$). The frequencies of dry eyes (assessed by TFBUT) were 78.6% (55/70) in the PTD group and 28.6% (20/70) in the control group ($P < 0.001$). TFBUT was significantly lower in the PTD group (6.5 ± 1.4 s) than in the control group (9.6 ± 1.6; $P < 0.001$). There was no difference in IOP between the two groups (17.3 ± 2.9 and 16.8 + 3.1 mmHg, $P = 0.576$).

The frequency of positive SPT was higher in the PTD group (80.0%, 56/70) than in the control group (20.0%, 14/70). Regarding allergy history, 48.6% (34/70) patients had history of allergic rhinitis (AR) in the PTD group, compared with 11.4% (8/70) in the control group ($P = 0.001$). History of asthma was present in 17.1% (12/70) patients in the PTD group and 2.9% (2/70) children in the control group ($P = 0.046$) (Table 1).

Fifty-eight (82.9%) patients had a history of allergy in the PTD group, compared with 18 (25.7%) in the control group ($P < 0.001$). In the PTD group, 22 (31.4%) patients were determined as having simple AC and 22 (31.4%) patients as having AC combined with AR; there were four (5.7%) patients having AC combined with asthma; there were two (2.9%) patients having AC combined with AR and asthma; and there were two patients with all four (conjunctivitis, asthma, rhinitis, and dermatitis). In the control group, only six (8.6%) patients were determined as having simple AC; there were two (2.9%) patients having AC combined with dermatitis, two (2.9%) patients having AC combined with AR and dermatitis, and two (2.9%) patients having AC combined with asthma and dermatitis.

Analysis by allergens

In the PTD group, the frequencies of AC (74.3%, 52/70) and positive SPTs (80.0%, 56/70) were high. In the patients with positive SPT, allergy to food (such as milk and beef) and seasonal allergens (such as cotton fiber and corn pollen) were not common. Allergens such as birch pollen, *Artemisia vulgaris,* and other food allergens were all negative. Regarding the non-seasonal allergens, *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* were the most frequent allergens, representing 57.1% (40/70) and 54.3% (38/70) of the patients, respectively.

In the control group, the frequencies of AC (17.1%, 12/70) and positive SPTs (20.0%, 14/70) were low. The most frequent allergens were, in decreasing order,

Table 1 Baseline characteristics

Variable	PTD group (n = 70)	Control group (n = 70)	P
Age (years), mean ± SD	6.8 ± 2.2	6.9 ± 2.3	0.875
Gender, n (%)			0.591
Male	54 (77.1)	50 (71.4)	
Female	16 (22.9)	20 (28.6)	
TFBUT (s), mean ± SD	6.5 ± 1.4	9.6 ± 1.6	< 0.001
IOP (mmHg)	17.3 ± 2.9	16.8 ± 3.1	0.576
Allergic conjunctivitis, n (%)	52(74.3)	12 (17.1)	< 0.001
Dry eye, n (%)	55 (78.6)	20 (28.6)	< 0.001
Positive SPTs, n (%)	56 (80.0)	14 (20.0)	< 0.001
History of allergic rhinitis, n (%)	34 (48.6)	8 (11.4)	0.001
History of asthma, n (%)	12 (17.1)	2 (2.9)	0.046
History of allergic dermatitis, n (%)	4 (5.7)	8 (11.4)	0.393

PTD provisional tic disorder, *TFBUT* tear film break-up time, *IOP* intraocular pressure, *SPT* skin prick test

Dermatophagoides pteronyssinus and *Dermatophagoides farina*, dog hairs, cigarette, and milk (Table 2).

Risk factors for PTD in children

AC and dry eye were more common in children with PTD compared with the matched controls. AC, dry eye, and history of allergic rhinitis were strongly associated with PTD (Table 3). AC was less frequent than dry eye in the PTD group (odds ratio (OR) 13.96, 95% confidence interval (CI) 4.37–44.57, $P < 0.001$; and OR 23.27, 95% CI 5.84–92.68, $P < 0.001$, respectively). There were no associations with other variables including history of asthma and allergic dermatitis.

Discussion

Previous studies on the risk factors for TS mainly focused on genetic [16] and environmental factors such as low birth weight [17] and maternal smoking or drug use during pregnancy [18]. Frequent blinking and

Table 2 Prevalence of the commonest allergens and their proportional frequencies in the two groups

Allergens[a], n (%)	Positive SPTs in the case group (n = 70)					Positive SPTs in the control group (n = 70)					P
	+	++	+++	++++	Total	+	++	+++	++++	Total	
Dermatophagoides pteronyssinus	4	28	4	4	40 (57.1)	2	4	0	0	6 (8.6)	< 0.001
Dermatophagoides farina	2	24	12	0	38 (54.3)	0	6	0	0	6 (8.6)	< 0.001
Cotton fiber	2	2	0	0	4 (5.7)	0	0	0	0	0	0.357
Dog hairs	6	2	0	0	8 (11.4)	2	2	0	0	4 (5.7)	0.588
Cat hairs	0	2	2	0	4 (5.7)	0	0	0	0	0	0.357
Cockroach	2	4	4	0	10 (14.3)	0	0	0	0	0	0.146
Cigarettes	2	0	0	0	2 (2.9)	0	0	2	0	2 (2.9)	0.368
Corn pollen	0	2	4	0	6 (8.6)	0	0	0	0	0	0.209
Milk	0	0	0	0	0	2	0	0	0	2 (2.9)	0.416
Sea crab	0	2	2	0	4 (5.7)	0	0	0	0	0	0.357

SPT skin prick test

[a]The other thirteen aeroallergens were negative

Table 3 Risk factors for PTD in children

Variable	Multivariate logistic regression	
	P	Odds ratio (95% CI)
Dry eye (yes/no)	< 0.001	23.27 (5.84–92.68)
Allergic conjunctivitis (yes/no)	< 0.001	13.96 (4.37–44.57)
Positive SPTs (yes/no)	< 0.001	16.00 (4.96–51.62)
History of allergic rhinitis (yes/no)	0.002	7.32 (2.13–25.15)
History of asthma (yes/no)	0.079	7.03 (0.80–61.87)
History of allergic dermatitis (yes/no)	0.402	0.47 (0.08–2.75)

PTD provisional tic disorder, *SPT* skin prick test

eye rolling are common reasons for referral to pediatric ophthalmologists and pediatric neurologists. Frequent blinking is one of the most common and important symptoms of AC in children [8], but also one of the features of PTD [2], which is commonly seen during TS onset [3, 4]. In the present study, the frequencies of AC and dry eye in the PTD group were higher than in the control group. In one of our previous studies, the frequency of dry eyes was higher in children with AC than in healthy children [8]. In PTD, tics are preceded by an unpleasant "premonitory urge" characterized by the feeling that a tic is about to occur [19]. This unpleasant "premonitory urge" may be the feeling of dryness, foreign body sensation, itching, burning sensation, eyelid heaviness, and ocular fatigue from dry eyes induced by AC.

The results showed that AC was less prevalent than dry eye in the PTD group. In children with PTD, the ocular tics always include abnormal and frequent blinking and wrinkling. An incomplete blink leads to inadequate lipid distribution (thin lipid layer) as well as consequent exposure of the inferior ocular surface, which may increase evaporation [20]. The blink rate has a large influence on the tear film [21]. Incomplete blinking induced by ocular tics in children with PTD leads to instability of the tear film and dry eye, and in turn, the dry eyes trigger the unpleasant "premonitory urge" of PTD.

It was hypothesized that AC and dry eyes could be involved simultaneously in childhood PTD. The results showed that AC, dry eyes, and history of allergic rhinitis were strongly associated with PTD. This suggests that AC and dry eyes are both contributing to PTD in children. Ocular surface and tear film abnormalities, even minor, can normally increase blinking [22]. The corneal reflex has trigeminal afferents (nasociliary and supraorbital) and somatic efferent fibers from the facial nerve [21]. The facial nerve innervates orbicularis, resulting in eyelid closure and blinking [23]. In a previous study, the frequency of dry eyes assessed by TFBUT was up to 97.5% in young children with AC [8]. In addition, a form of dry eyes associated with AC has been found to be characterized solely by decreased TFBUT, without symptoms [9]. Dry eye associated with AC may play a direct role in PTD.

Dry eyes and ocular allergy are interrelated conditions that share clinical and biochemical factors [24]. The present study also found that *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* were the most frequent allergens in the PTD group, but that sensitization to food allergens was not common. Li et al. also showed that house dust mites are an important cause of perennial AR and AC, in which house dust mite sensitization due to *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, and *Blomia tropicalis* was prevalent [25]. Those allergens can trigger AC without seasonal specificity or difference. Nevertheless, symptoms of AC can relieve or disappear when the allergens disappear. In the pediatric age, AC occurs frequently, with a peak age in late childhood and young adulthood [13]. PTD is usually mild and will likely go away over a few months [26], and not all children with PTD progress to TS [27]. On the other hand, the results of the present study were different from those of Bruun et al. [28], who reported that symptom exacerbation of TS is often associated with seasonal allergic responses or ingestion of food allergens. Different populations and environment may be responsible for this discrepancy. In southwest China, air pollution is more serious than in developed country. Outdoor air pollution is a major risk factor for conjunctivitis, and the key contributors are fuel combustion and dust storms

[29]. In addition, the climate is humid in southwest China, which provides favorable conditions for the growth of dust mites. These would explain why *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* were the most frequent allergens in the present study.

In addition, history of allergic rhinitis was higher in the PTD group than in the control group, and history of allergic rhinitis was associated with an increased risk of PTD. Previous studies showed that allergic rhinitis was associated with AC [13]. Cell mediators, cytokines, chemokines, chemotactic factors, and other factors released during allergic reactions can reach the nasal mucosa or conjunctiva through the nasolacrimal duct and lacrimal system or indirectly by their transport through the blood stream and could cause AC [30]. AR is characterized by sneezing, rhinorrhea, nasal congestion, and nasal pruritus, which are often accompanied by ocular pruritus, redness, and/or lacrimation in 60–70% of patients [31]. Facial tics in children with PTD may be associated with nasal itching and other abnormal feelings in AR. More data are needed to support this hypothesis.

The present study has several limitations. First, the patients were recruited from southwest China, which may lead to a selection bias. Because the frequency of AC in children varies geographically, studies are needed on whether AC plays an important role in PTD in children in other areas of the world. Second, we did not evaluate the effects of anti-allergy treatments and dry eye treatments in the PTD patients. The results of the current study only showed an association between AC and PTD, but could not determine the cause-to-effect relationship between dry eyes and PTD. In addition, the sample size was small and was from a single center. More patients from more hospitals would increase the statistical validity of the results. Finally, the present study did not examine inflammation and immunological markers of allergic reactions.

Conclusion

PTD is probably a different disease than other diseases characterized by chronic tic disorders such as TS [32]. The present study highlights that the frequencies of AC are high in the PTD population. AC may be associated with PTD in children. Proper diagnosis and treatment of PTD involve appropriate evaluation and recognition, not only of tics, but also of other associated conditions such as AC. Therefore, ophthalmologists could play an important role in the management of the disease.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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