

Can allergy patch tests with food additives help to diagnose the cause in childhood chronic spontaneous urticaria?

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Abstract

Introduction: Chronic spontaneous urticaria (CSU) is characterized by the onset of symptoms which are not induced by specific triggers, but are rather spontaneous. A considerable number of patients report that foods or food additives might be responsible for their chronic urticaria.

Aim: To determine the prevalence of sensitization to food additives in children with CSU using atopy patch tests (ATP).

Material and methods: Atopy patch tests for 23 different food additives were applied to 120 children with CSU and 61 healthy controls.

Results: Seventeen (14.1%) children with CSU were sensitized with food additives. None of the control group had positive APT. *Azorubine* and *Cochineal red* were the food additives detected with the highest sensitization rates (5.8% ($n = 7$) and 6.7% ($n = 8$), respectively).

Conclusions: There can be an association between food additives and CSU. APT tests may be a helpful tool in the assessment and management of CSU so that easier to follow diets and effective treatments can be offered to families.

Key words: chronic urticaria, children, food additives.

Introduction

Chronic urticaria (CU) has been defined as daily or nearly daily occurrence of wheals and/or angioedema, occurring over a period of ≥ 6 weeks [1].

This condition affects 0.1–0.3% of the children and includes different subtypes [2]. CU is currently classified into two main subtypes, that is one with a known, inducible cause such as physical urticarias and the other of unknown origin. The latter is called chronic spontaneous urticaria (CSU). It is characterized by the onset of symptoms which are not induced by specific triggers, but are rather spontaneous. In recent years, various causes of chronic spontaneous urticaria have been described. It can be provoked by a wide variety of different causes or may be the clinical presentation of certain systemic diseases such as allergies, autoimmune diseases, infectious diseases and malignancies. In practically 50% of

the patients with CSU, the cause cannot be identified. Activation of basophiles or mast cells causing histamine release is quite specific to CSU [1–3].

A considerable number of patients report that foods might be a cause of their CSU because of the variations in the diet, especially containing high levels of spices, seasonings and natural histamine like amines aggravated their symptoms. For this reason, unnecessary food restriction is common among these patients. Restriction of the basic nutritional requirements is harmful to health especially in children and also reduces quality of life and well-being of the whole family [4]. Therefore, it is important to determine the causative triggers in CSU patients [5].

For patients with CSU, food ingredients and food additives such as food colorants, sweeteners, preservatives, dyes and antioxidants may also be important causatives. Thousands of additives, either synthetic

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or natural are used worldwide [6]. The Food and Drug Administration (FDA) keeps publishing online updated lists of more than 3000 food additives [7]. The European Commission gives permission to use about 390 different food additives in European food industry [8]. In Turkey regulations of food additives are based on the European Commission rules [9].

There are a limited number of studies dealing with sensitization to food additives.

Aim

In this study we aimed to determine the prevalence of sensitization to food additives using atopy patch tests in children with CSU.

Material and methods

Study population

Patients diagnosed with CSU, who attended Istanbul University, Istanbul Faculty of Medicine, Divisions of Paediatric Allergy Outpatient Clinics from July 2015 to March 2015 were enrolled in the study. Children were defined as CSU according to the following criteria: 1) children aged 3–18 years with urticaria except for physical urticaria lasting for > 6 weeks, 2) children treated only with oral antihistamines and montelukast for their CSU, 3) patients who did not have an etiological cause for urticaria.

Paternal schooling, family income, daily life problems (school attainment, occupational or academic failure), family problems (conflicts and/or quarrels with family members), disease-related variables (frequency of hospitalization for CSU attacks in the previous year), some demographic and clinical characteristics (age, sex, patient's medical history, and family history of allergic diseases in first-degree relatives) and symptoms associated with foods history were investigated.

Ethics

The study was performed in accordance with the tenets of the Declaration of Helsinki and good clinical practice, and was approved by the Istanbul University, Istanbul Faculty of Medicine Ethical Committee, (2014/989). All study patients and their parents were given information about the study, and signed consent was obtained from the parents.

The control group consisted of 61 children, aged 3–18 years, chosen from those who were periodically attending the paediatric welfare clinic of the same hospital for regular check-ups. They were evaluated with regard to chronic and/or severe infections, autoimmune disorders, familial history of atopy, eosinophil counts and total IgE level and skin prick tests. Children with a negative personal/familial history of atopy, having no signs or

symptoms of any atopic disorder and negative skin prick test results were included in the control group.

CSU survey

All patients underwent laboratory examinations, including complete blood count, erythrocyte sedimentation rate, liver transaminases, serum levels of complement C4 and free thyroxin, thyroid stimulation hormone, serum total immunoglobulin E, antinuclear antibody (ANA), anti-thyroid peroxidase antibodies (anti-TPO), anti-thyroglobulin antibodies (anti-TG), hepatitis surface antigen, antibody titres for hepatitis B and C viruses, urine analysis, *Helicobacter pylori* IgG antibodies, autologous serum skin test (ASST), microscopic investigation of stool for parasites' ova and skin prick test (SPT) for common aero and food allergens. Patients with a serum total IgE level > 100 kIU/l and/or positive to at least one allergen in SPT were accepted as atopic.

Atopy patch test for food additives

The patch test was applied on the upper back of all the patients enrolled in this study using twenty three allergens present in food additives series (aspartame, azorubine, amaranth, benzoic acid, Butylhydroxyanisole, Butylhydroxytoluene, brilliant black, cochineal red, carmine, Erythrosine b, Formic acid, patent blue VF, pectin, quinoline yellow, sorbic acid, sodium glutamate, sodium diphosphate, sodium nitrite, saccharine, sodium disulphite, sodium alginate, sodium formiate, tartrazine) produced by Stallergenes Ltd® Paris. The Finn chamber with petrolatum was used as the control test. We made sure that the families had been informed that they should avoid giving antihistamines to the children for 3 days preceding the application of the patch test. We also advised them not to apply creams/ointments containing corticosteroids in the week before the test. After applying the patch test, the patient was asked to come after 48 h and 72 h for evaluating the results. In case of any doubtful reactions, patients were advised to return on the fifth day. Results were interpreted by a single investigator according to the American Academy of Dermatology for APT, with a scale ranging from +1 (weak reaction) to +3 (strong reaction). Reactions of +2 and +3 were considered positive [10]. APT was applied to all CSU patients and controls.

We recommended food additive-free diet for 4 weeks for APT positive patients (Table 1). All patients asked to fill in a diet diary. After 4 weeks' diet, a small questionnaire concerning urticaria was performed during follow-up examination.

Statistical analysis

Statistical analysis was performed using SPSS statistical software (version 19; SPSS, Chicago, IL). All data are presented as means ± standard deviations or as medians

Table 1. Recommended carmine/cochineal red/azorubine-free diet

Packaged chips, fried potatoes
Flavoured or fruit yoghurts
Candies, lollipops
Packaged fruit juices, fizzy drinks
Ketchup, packaged sauces
Sausages, salami
Packaged fruit based sauces, marmalades, jams

Table 3. APT results in the CSU group

Food additives	% (n)
Azorubine	6.7 (8)
Cochineal red	5.8 (7)
Amaranth	3.3 (4)
Butylhydroxyanisole	2.5 (3)
Butylhydroxytoluene	2.5 (3)
Carmine	1.7 (2)
Sodium diphosphate	0.8 (1)
Sodium nitrite	0.8 (1)
Aspartame	0.8 (1)
Benzoic acid	0.8 (1)
Tartrazine	0.8 (1)

CSU – chronic spontaneous urticaria, APT – atopy patch test.

for non-normally distributed variables. Student *t* tests, Pearson χ^2 tests and Mann Whitney *U* tests were used to compare statistical differences between groups. For all analyses, $p < 0.05$ was considered as a statistically significant difference.

Results

One hundred and twenty children with CSU (52 girls and 68 boys; mean age was 9.14 ± 4.44 years) and 61 healthy controls were enrolled to the study. A causative factor such as auto reactivity, chronic infection

Table 2. Clinical and laboratory characteristics of the CSU group ($n = 120$)

Parameter	N (%)
Family history of atopy	22.5 (27)
Angioedema	26.6 (32)
Parental report of food-related urticaria	30.8 (37)
Parental report of stress-related urticaria	43.3 (52)
Other atopic conditions (asthma, AD, AR)	15 (18)
Skin prick test positivity to aeroallergens	10.8 (13)
Skin prick test positivity to food allergens	1.6 (2)

CSU – chronic spontaneous urticaria, AD – atopic dermatitis, AR – allergic rhinitis.

could only be identified nearly in 25% ($n = 29$) of the patients; no underlying causes could be detected in the rest of children ($n = 91$). There were 21 children with detectable auto antibodies including ANA, anti-TPO, anti-TG and ASST; 8 children had chronic infection such as *Helicobacter pylori* and amebae.

Some clinical characteristics of the CSU group are shown in Table 2. There was no statistically difference between the control and CSU groups in terms of age and sex. Median serum total IgE was 266.35 ± 435.80 (8–2000) and blood eosinophil percentage was 2.38 ± 2.98 (0.1–15) among CSU patients, and 50.5% ($n = 46$) of them were atopic.

APT with food additives was applied to all CSU patients and controls. Seventeen (14.1%) of 120 children with CSU had positive APT results, while none of the controls had any positivity to any item ($p = 0.001$). In the CSU group, 17 of 120 individuals (11 boys, 6 girls) had 32 positive results to 11 different food additives. There were no positive results to other 12 food additives. Positive APT results for Azorubine and Cochineal red were highest; 5.8% ($n = 7$) and 6.7% ($n = 8$), respectively. No triggering factor such as thyroid autoantibody, ANA positivity, positive tests for *H. pylori* was detected among the patients with positive APT results. Results of APT for food additives are shown in Table 3. No significant difference was found in age, serum total IgE, blood eosinophil percentage, sensitivity in skin prick tests

Table 4. Demographic and laboratory characteristics of the CSU group according to APT results

Parameter	APT positive ($n = 17$)	APT negative ($n = 103$)	P-value
Age	9.52 ± 3.82	9.38 ± 4.35	0.32
Age of onset [month]	72.45 ± 42.85	72.45 ± 49.17	0.205
Serum total IgE	266.95 ± 323.92	251.63 ± 425.59	0.86
Eosinophil %	3.33 ± 3.50	2.65 ± 3.39	0.47
Skin prick test positivity to aeroallergens	7	6	0.39
Skin prick test positivity to food allergens (banana)	1	1	0.33

CSU – chronic spontaneous urticaria, APT – atopy patch test.

to both aeroallergens and food allergens, other atopic conditions between APT positive and negative patients with CSU (Table 4).

Among these 17 patients with positive APT test results, parents of 10 children believed that pruritus was related with food ingestion (Table 5).

We recommended food additive-free diet for 4 weeks to patients with APT positive results. After 4 weeks, they were examined and asked for any symptoms. Fourteen of 17 (82.3%) APT positive patients filled in a diet diary and none had any complaints after the diet. We could not contact other 3 APT positive patients or see their diet diaries.

Discussion

Our cross-sectional data show that an overall prevalence of hypersensitivity to food additives is 14.1% in children with CSU. A noteworthy finding is that none of the control group has positive APT to food additives. Additionally, no children with a positive result to a causative factor such as thyroid autoantibody, ANA positivity, or positive tests for *H. pylori* had positive APT tests among the CSU patients. Recent and past literature on the prevalence of food additives in children with CSU using APT is very limited [11]. Also, there is no published study primarily focused on prevalence of food additives and associated risk factors in children with CSU. This is the first paper to investigate the prevalence of hypersensitization to food additives in children with CSU by means of APT.

Over the years, depending on innovations in food technology, consumption of commercially prepared foods and exposure to various food additives has increased. Similarly, the prevalence and incidence of CSU has also increased. It is reported that the annual prevalence of CSU ranged from 0.02% in 2002 to 0.38% in 2013 and the incidence was 0.10–1.50 per 1000 person-years respectively in 2002 and 2013 [12].

Chronic spontaneous urticaria describes the commonest form of CU. In our study, the cause was unknown in nearly 75% of patients, which is compatible with other studies [13, 14].

Food additives are commonly used for flavouring and colouring and also for their antimicrobial effects [15]. Although they are blamed for triggering or worsening CSU symptoms, the exact role of food additives in CSU is unclear [16]. Foods can much more likely be triggering factors for acute urticaria rather than the chronic form [14]. However, food additives can evoke urticarial lesions in a subgroup of patients with CSU [17, 18]. The reactions to food additives are given various terms like pseudo-allergy and non-allergic hypersensitivity since it is believed that they are not based on any immunologic mechanisms [16]. Skin and laboratory tests are not objective diagnostic tools for pseudo-allergy [19]. There is no recommendation for the diagnostic approach to pseudo-allergic reac-

Table 5. Parents' opinion about the presence of symptoms related with food ingestion in the APT positive group ($n = 17$)

Parameter	Yes (n)	No (n)	P-value
Angioedema	4	13	0.205
Parental report of food-related urticaria	10	7	0.079
Parental report of stress-related urticaria	9	8	0.451
Other atopic conditions (asthma, AD, AR)	2	15	0.858

APT – atopy patch test, AD – atopic dermatitis, AR – allergic rhinitis.

tions. There is a great need for further investigations on this matter.

Atopy patch tests have been used for many years for evaluation of contact dermatitis, more recently they have been used in the assessment of mixt and non IgE mediated food allergy in atopic dermatitis, eosinophilic esophagitis and food protein induced enterocolitis syndrome [20, 21]. Previously Catlı *et al.* reported that it might be useful to perform APT with food additives in atopic dermatitis in children [22]. Hession *et al.* suggested that APT may be helpful to evaluate contact allergens like nickel sulphate in CSU patients for whom the previous workup has failed to detect an etiological cause [23]. But to our knowledge, there is no study in the literature investigating APT for food additives in children with CSU. In our study, 17 of 120 patients with CSU had positive reactions to food additives, but no positivity was detected in healthy controls. However, in clinical practice, the use of APT may have limitations due to subjective evaluation and variations between assessment of the results. However, standard interpretation according to guidelines would prevent contradictory results [24].

Several food additives including colorants, sulphites, monosodium glutamate, benzoates have been reported to cause adverse reactions such as asthma, urticaria and anaphylaxis [15, 25]. In a large study with a survey of Danish school children, intolerance to food additives was found in 2% of atopic children and 0.13% of the entire population [26].

Positivity to cochineal red and azorubine were the most accountable food additives in our study. Cochineal red is a natural food colorant derived from female cochineal insects. Azorubine is a synthetic azo dye derived from tar. These popular red colouring agents are used in many commercially prepared foods like jams, candies, yoghurts, ice creams, juices, salami and sausages. Not only type 1 hypersensitivity reactions but also type 4 hypersensitivity reactions have been reported to cochineal red and/or carmine. It is reported that several food additives as carmines, cochineal red, allura red, erythrosine can trigger chronic urticaria and angioedema [15].

It is believed that in most CSU patients symptoms will improve by giving careful attention to their diet. While different mechanisms and possible triggers were considered, pseudo-allergen-free diet and low histamine diet are thought to be effective to reduce symptom severity and improve patients' quality of life [27, 28]. On the other hand, unnecessary dietary restrictions may have a negative impact on the quality of life of the patients and their families. In the present study, we observed that patients who had positive APT tests stayed free of symptoms during the 4 weeks' interval of restricted diet for food additives. This finding may support that exposure to culprit food additives can aggravate urticarial lesions in patients with CSU without a known aetiology, but who are already sensitized to those food additives.

The current diagnostic approach to food allergy and sensitization to food additives are based on skin prick tests and double blind placebo controlled challenge tests [28]. But when pseudo-allergy is concerned, authors recommend a low pseudo-allergen diet for 3 weeks, and if there is an improvement the patient is then exposed to a pseudo-allergen-rich diet as a challenge [29]. It is a fact that the challenge tests should be designed with the use of purified extracts of food additives so as to be safe and free of bias. In our study, challenge tests with food additives could not be performed because purified extracts of these could not be provided.

Despite this limitation, APT to food additives may be useful in individuals with CSU patients who report having or worsening symptoms such as pruritus after ingestion of commercially prepared foods especially containing red colorants like carmine, cochineal red or azorubine. Low pseudo-allergen and low histamine diets are overlapping recommendations for red colorants-free diet but a large variety of permitted foods makes it easier to follow the diet for patients. APT with food additives is also a reliable, easy-to-use test for CSU, suggesting hypersensitivity to food additives in chronic urticaria patients. Demonstrating these sensitivities may encourage patients to avoid these food additive containing foods.

Conclusions

Food additive sensitization diagnosed with the APT test was shown in patients with CSU. Although our study group consists of a low number of patients, clinicians should be aware of the association between food additives and CSU. Even such comprehensive investigation involving a larger number of patients is needed. We think that APT tests may be a helpful tool in the assessment and management of CSU, so that easier to follow diets and effective treatments can be offered to families.

Conflict of interest

The authors declare no conflict of interest.

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