Etiological Assessment of Acute Urticaria in Children

Çocuklarda Akut Ürtikerin Etiyolojik Değerlendirilmesi

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ABSTRACT

Objective: Acute urticaria is one of the most common causes of admission to hospitals in children. The aim of the study is to evaluate the etiology of acute urticaria in patients who admitted to pediatric allergy outpatient clinics.

Material and Methods: The patients who were diagnosed as acute urticaria in pediatric allergy outpatient clinics between January 1, 2016 and December 31, 2016 were included in the study. Patient information was recorded retrospectively from medical files.

Results: In this study, 469 patients with acute urticaria were evaluated. The median (min-max) age of the patients was 7 years (2 months-18 years), and 48.8 % of them were male. Angioedema was accompanying in 20 % of the patients. Recurrent acute urticaria was seen in 33.5 % (n = 157) of the patients. In the history, infections were the triggers in 37.5 % (n=176) of the patients, drugs in 17.9 % (n=84), food in 10.9 % (n=51), insect bites in 3.2 % (n=15), and 0.2 % (n=1) of them had the vaccine. When the patients were evaluated with the medical histories, physical examination and laboratory findings; triggers could not be detected in 59 % (n=276) and these patients were diagnosed as idiopathic acute urticaria. Infections (37.5 %; n=176) were in the first place in patients with triggers. Food and drug allergies were confirmed in only one patient each. Considering the etiological distribution according to age groups, it was seen that idiopathic acute urticaria was more common in the 12-18 age group and infection-associated acute urticaria in the group under 2 years old (p=0.009).

Conclusion: Mostly, triggers cannot be found in children who apply to the allergy clinic due to acute urticaria. In patients who can be identified triggers, infections are in the first place. However, patients' clinical histories may also include food or drug(s) as a suspected trigger, and it is important to evaluate these patients with diagnostic allergy tests. Thus, misdiagnosis of patients and unnecessary food or drug restrictions would be prevented.

Key Words: Acute Urticaria, Children, Etiology, Infection, Trigger

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ÖZ

Amaç: Akut ürtike rçocuklarda hastane başvurularının en sık nedenlerinden biridir. Çalışmanın amacı çocuk alerji polikliniğinde akut ürtiker tanısı alan hastaların etiyolojik açıdan değerlendirilmesidir.

Gereç ve Yöntemler: Çalışmaya 1 Ocak 2016 - 31 Aralık 2016 tarihleri arasında hastanemizin çocuk alerji polikliniklerinde akut ürtiker tanısı alan hastalar alındı. Hasta bilgileri dosya kayıtlarından geriye dönük olarak kaydedildi.

Bulgular: Çalışmada akut ürtiker tanısı alan 469 hasta değerlendirildi. Hastaların yaş ortancası (min-maks) 7 yıl (2 ay-18 yıl) olup, %48.8'i erkekti. Hastaların % 33.5'inde (n=157) tekrarlayan akut ürtiker öyküsü vardı ve % 20'sine anjiyoödem de eşlik ediyordu. Öyküde tetikleyici olarak hastaların % 37.5'ünde (n=176) enfeksiyonlar, % 17.9'unda (n=84) ilaç, % 10.9'unda (n=51) besin, % 3.2'sinde (n=15) böcek ısırığı ve % 0.2'sinde (n=1) aşı bulunuyordu. Hastalar anamnez, fizik muayene ve laboratuvar bulguları ile değerlendirildiğinde; %59'unda (n=276) tetikleyici saptanamadı ve bu hastalar idiopatik akut ürtiker olarak tanı aldılar. Tetikleyici saptanan hastalarda enfeksiyonlar (% 37.5; n=176) ilk sırada yer alıyordu. Besin ve ilaç alerjisi ise sadece 1'er hastada doğrulandı. Yaş gruplarına gore etiyolojik dağılıma bakıldığında, 12-18 yaş grubunda daha çok idiyopatik akut ürtiker, 2 yaş altı grupta ise enfeksiyonla tetiklenen akut ürtiker olduğu görüldü (p=0.009).

Sonuç: Akut ürtiker nedeniyle alerji kliniğine başvuran çocuklarda çoğunlukla tetikleyici bulunamamaktadır. Tetikleyici tespit edilebilen hastalarda ise enfeksiyonlar ilk sırada yer almaktadır. Ancak hastaların klinik öykülerinde şüpheli tetikleyici olarak yiyecek veya ilaç(lar) da bulunabilir ve bu hastaların tanısal alerji testleri ile değerlendirilmesi önemlidir. Böylece hastaların yanlış tanı almaları ve gereksiz besin veya ilaç kısıtlamaları önlenebilecektir.

Anahtar Sözcükler: Akut Ürtiker, Çocuk, Etiyoloji, Enfeksiyon, Tetikleyici

INTRODUCTION

Urticaria are skin lesions that can appear in any part of the body, they are characterized by itchy and erythematous plaques and usually they are healed within 24 hours. When the deeper of the dermis is involved and there is also a subcutaneous involvement accompanied by pain rather than itchiness, then this version is called angioedema. With a very rough definition, urticaria is a vascular reaction that develops against various stimulants and is formed with various mechanisms (immunologic or non-immunologic). Symptoms in acute urticaria last shorter than 6 weeks while in chronic urticarial they last longer than 6 weeks (1).

Acute urticaria can be observed in all age groups. It has been reported that around 20 % of the general population suffers at least one acute urticaria attack during their lifetime (2). There are not many studies available on acute urticaria prevalence in children but it is reported to be 2-6.7% (3).

Infections, drugs, food and bites are among the most common reasons behind acute urticaria. Acute urticaria may develop during or after viral or bacterial infections particularly in children. In some pediatric series, infections have been found to be related to more than 80 % of acute urticaria cases (8). However, it is not always possible to detect etiology in acute urticaria and in almost half of the cases etiology is never determined (4). The aim of this study is to make an etiology assessment of the patients applying to pediatric allergy outpatient clinics with acute urticaria.

MATERIAL and METHOD

The population of our study was <18-year-old patients who applied to our hospital's pediatric allergy outpatient clinic between 1 January 2016 and 31 December 2016 and received acute urticaria diagnosis.

The study has been approved by Health Sciences University Ankara Pediatric Health and Diseases Hematology Oncology Training and Research Hospital's ethical board (2017-073/ 12.06.2017).

Patient files have been reviewed to record their demographic characteristics (age, gender, family and individual atopy history), duration of urticaria, triggering factors, accompanying findings, physical examination and laboratory tests conducted to determine etiology (complete blood count, liver and kidney function tests, erythrocyte sedimentation rate, c reactive protein, full urine test, urine culture, throat culture, fecal parasite screening and lung X-rayresults).

Patients with suspected drugs or food in their history have been invited to clinic and diagnostic tests had been invited to the cliinic and had undregone allergologic tests to confirm or rule out allergy.

Skin prick test: Patients without dermographism have been subjected to skin prick test. Histamine (10 mg/mL) was used as a positive control and diluent (temolin) as a negative control for the test. Skin prick tests were performed on the volar forearm, and were read after 20 min. SPT results were considered positive if a wheal size was ≥3 mm compared with the negative control.

Allergens used in skin prick test (Stallergenes SA, 92160, Antony, France): - Food allergens (cow's milk, egg white and yolk, wheat, soya, hazelnut, peanut, orange, banana) - House dust mites (Dermatophagoides farinae, Dermatophagoides pteronyssinus) - Pollen: grass-pollen mixture of 5 (Perennial ryegrass, Cynodondactylon, Timothy grass, Sweet vernal grass, Bluegrass), grain-pollen mixture of 4 (oat, wheat, barley, maize), tree pollen mixture (Cupressus sempervines, Salix caprea, Olea europaea, Betula alba, Platanus vulgaris), weed polen (Salsola kali, Chenopodium album, Parietaria judaica, Artemisia vulgaris,

Ambrosia elatior, Plantago, Compositae) - Mold (Aspergillus mixture [Aspergillus fumigatus, Aspergillus niger, Aspergillus nidulans], Cladosporium mixture [Cladosporium cladospories, Cladosporium herbarum], Alternaria alternate) - Epithelium (cats and dogs) - Cockroach (Blatella germanica) - Latex.

Diagnostic assessment for drug allergy: A guide prepared by the European Academy of Allergy and Clinical Immunology (EAACI) association has been used for the drug allergy assessment of the patients (5). Accordingly, a skin prick test with the parenteral form of the suspected drug has been conducted, and if the skin prick test was negative, intradermal test has been conducted. If the intradermal test was also negative, drug provocation test has been conducted orally with the suspected drug. Patients who did not display any reactions during provocation have been kept under observation for at least 2 hours. Drug allergy has been ruled out if no reaction was detected. However, detection of any objective findings during or after the provocation led to the acceptance of drug allergy.

Diagnostic assessment for food allergy: Prick test has been performed with the suspected food. Patients with a negative skin prick test were subjected to food oral provocation test. Observing any findings in the patient related to skin (urticaria, angioedema), cardiovascular (hypotension, confusion, tachycardia), respiration (wheezing, hoarseness, cough, dyspnea), gastrointestinal (nausea, vomiting, stomach ache), neurologic (dizziness, vertigo, fainting) systems during provocation test or following the final dosage meant the test was deemed positive and terminated.

Consent of patients and / or their families has been taken prior to skin tests and provocation tests.

Statistical Analysis

All findings have been evaluated with SPSS 17 (SPSS Inc, Chicago, IL, 2009) program. Discrete variables are given in numbers and percentages, continuous variables are given in minimum, maximum, mean±standard deviation and median. Chi-square test has been used for the comparison of discrete variables. T-test has been for the comparison of continuous variables of the two groups conforming to normal distribution, and Mann Whitney-U test has been used for normal the comparison of continuous variables not conforming to normal distribution. $p<0.05$ value has been considered statistically significant.

RESULT

In this study, 469 patients with acute urticaria were evaluated. The median age (min-max) of the patients was 7 years (2 months-18 years) and 48.8% were male. Urticaria was generalized in more than half of the patients. Ninety-four (20%) patients had accompanying angioedema. The most accompanying extracutaneous symptom was fever (Table I).

Table I: Symptomsofpatients.

Symptoms	n (%)
Onlyskinsymptoms	293 (62.5)
Urticaria	199 (42.5)
Urticaria+Angioedema	94 (20)
Localization of urticaria	
Generalized	190 (40.5)
Extremities	129 (27.5)
Extremities + Trunk	65 (13.9)
Head and neck region	55 (11.7)
Trunk	30 (6.4)
Localization of angioedema	
Periorbital area	26 (27.7)
Periorbital area + lips	26 (27.7)
Extremities	21 (22.3)
Lips	20 (21.3)
Genital area	1 (1)
Skin +other symptoms	176 (37.5)
Fever	95 (20.3)
Fever+Cough	63 (13.2)
Dysuria	8 (1.7)
Diarrhea	5 (1.1)
Analzone itching	3 (0.6)
Toothache	2 (0.4)

Infections were the first (37.5%) among the possible triggers in the clinical history (Table II). In 17.9% (n=84) of the cases with acute urticaria, there was a history of drug use as a possible trigger (Table II). Diagnostic testing was planned for all patients with possible drug-related urticaria. However, 18 patients later had used the same drug without any reactions. The parents of 20 patients did not consent for drug tests. The remaining 46 patients were evaluated to drug allergy tests. 11 patients with suspected penicillin allergy were checked for specific IgE and it was found negative. Drug skin tests and provocation tests were negative in 45 patients while drug allergy was confirmed only in 1 patient. This patient was positive penicillin skin test.

In 10.9% (n=51) of the patients, there was food as a possible trigger in the history (Table II). 8 of those patients had not developed any symptoms when they consumed the same food afterward. No diagnostic test with suspected food was performed on these patients. The remaining 43 patients have been subjected to skin prick test and provocation test with suspected foods and only one case had a positive skin test result, who was tested with green lentil. The history of this patient included acute urticaria recurring with consumption of green lentils.

The most common abnormal laboratory findings were elevation in C-reactive protein. The other abnormal laboratory findings are shown in Table III.

Among patients evaluated with clinical history, physical examination, and laboratory data 58.8% (n=276) of the patients did not have any trigger, while there were 193 (41.2%) patients

Table II: Possible Triggers in History

	n (%)
Infection	176 (37.5)
Respiratory tract infection	163 (92.7)
Urinary tract infection	8 (4.5)
Acute gastroenteritis	5 (2.8)
Drug	84 (17.9)
Antibiotics	56 (66.7)
Amoxicillin clavulanate	44 (52.4)
Clarithromycin	4 (4.8)
Cefdinir	3 (3.6)
Metronidazole	2 (2.4)
Ceftriaxone	1 (1.2)
Cefixime	1 (1.2)
Cefuroxime	1 (1.2)
Nonsteroidal anti-inflammatory drugs	20 (23.8)
Ibuprofen	11 (13.1)
Paracetamol	8 (9.5)
Methimazole	1(1.2)
Others	8 (9.5)
Pseudoephedrine+Dextromethorphan	3 (3.6)
Fish oil	2 (2.4)
Sumitrin	1 (1.2)
Lidocaine	1 (1.2)
Carbamazepine	1 (1.2)
Food	51 (10.9)
Chocolate	11 (21.6)
Milk and products	5 (9.8)
Strawberry	3 (5.9)
Spice	3 (5.9)
Egg	3 (5.9)
Honey	2 (3.9)
Fish	2 (3.9)
Sunflower seeds	2 (3.9)
Hazelnut	2 (3.9)
Lentil	2 (3.9)
Dessert	2 (3.9)
Eggplant	2 (3.9)
Chicken	2 (3.9)
Other foods	20 (39.2)
Beeorin sectbites	15 (3.2)
Vaccine (Hepatitis Bvaccine)	1 (0.2)
Unknown	142 (30.3)

Table III: Patients with abnormalities in laboratory tests.

	Abnormal results / Number of patients under going test (%)
Complete Blood Count	
Leukocytosis	69/349 (19.8)
Anemia	61/349 (17.5)
Eosinophilia	39/349 (11.2)
Thrombocytosis	26/349 (7.5)
Thrombocytopenia	3/349 (0.9)
Biochemical tests	
Abnormal liver function tests	44/270 (16.3)
Abnormal renal function tests	2/164 (1.2)
Acute phase reactants	
Elevated C-reactive protein	53/137 (38.7)
Elevated erythrocyte sedimentation rate	7/57 (12.3)
Elevated total IgE	77/239 (32.2)
Abnormal lung X-ray	3/25 (12)
Microbiological tests	
Urine culture positivity	9/305 (3)
Throat culture positivity	8/30 (26.7)
Group Abetahemolytic streptococci	

Table IV: Confirmed etiology of acute urticaria (n=193).

	n (%)
Infection/infestation	176 (91.2)
Upper respiratory tract infection	149 (77.2)
Urinary tract infection	9 (4.7)
Acute otitis media	5 (2.6)
Acute gastro enteritis	4 (2)
Pneumonia	3 (1.6)
Parasitosis	3 (1.6)
Tooth abscess	2 (1)
Varicella	1 (0.5)
Insect bite	15 (7.8)
Food allergy (Green lentils)	1 (0.5)
Drug allergy (Penicillin)	1 (0.5)

Table V: Comparison of age groups by etiology.

Age groups	Idiopathic n (%)	Infection n (%)	Other n (%)	p
≤2 years (n=43)	15 (34.9)	31 (48.8)	7 (16.3)	0.009
2-6 years (n=94)	52 (55.3)	37 (39.3)	5 (5.3)	
6-12 years (n=203)	117 (57.6)	74 (36.4)	2 (1)	
12-18 years (n=129)	92 (71.3)	34 (26.4)	3 (2.3)	

with confirmed acute urticaria etiology. Infections were seen to be the first in the etiology of acute urticaria (Table IV).

In terms of age groups, most common triggers in patients under 2 years were infections while in 12-18 age group the most common trigger was idiopathic acute urticaria (Table V).

23.3% (n = 100) of the patients had recurrent acute urticaria. In these patients the urticaria recurrence median was 2 (minimum 1- maximum 5). There was no statistical difference between the patients with first episode acute urticaria and recurrent acute urticaria in terms of age, gender and etiology (Table VI).

DISCUSSION

Etiology was found in only 41% of the patients in the study assessed for acute urticaria. Infections were the leading factor triggering acute urticaria.

Table VI: Comparison of patients with first episode and recurrent acute urticaria.

	First episode (n=369)	Recurrent acute urticaria (n=100)	p
Age groups, n(%)			
≤2 years	30 (69.8)	13 (30.2)	
2-6 years	72 (76.6)	22 (23.4)	0.298
6-12 years	160 (78.8)	43 (21.2)	
12-18 years	107 (82.9)	22 (17.1)	
Gender, n (%)			
Male / Female	185 (50.1) / 184 (49.9)	44 (44) / 56 (56)	0.276
Etiology, n(%)			
Idiopathic	220 (59.6)	52 (52)	0.328
Infection	112 (30.4)	38 (38)	
Other	37 (10)	10 (10)	

Acute urticaria can be seen in both children and adults. It has been reported that around 20% of the general population suffers at least one acute urticaria attack during their lifetime (2). There are not many studies available on acute urticaria prevalence in children but it is reported to be 2-6.7% (3). A study conducted by Ricci et al. (6) reported that acute urticaria is observed at a higher rate in 0-24 months old children and prevalence is reduced by age. The age of the patients participating in our study ranged between 2 months and 18 years but the majority of the patients (39.7%) were between 6 to 12 year olds.

Acute urticaria in adults is mostly seen in women but in pediatric patients the distribution between genders is equal. Despite the fact that some studies on pediatric patients are reporting a higher incidence, there are no significant differences in terms of prevalence in pediatric patients (7). Our study group consisted of 48.8% of boys and 51.2% of girls and there was no significant difference between gender distributions in terms of age groups.

Determining etiology in patients with an acute urticaria diagnosis is important as it would have an impact on the treatment approach. However, it is not always possible to determine etiological. In a collection of studies on the subject, the rate of etiology in acute urticaria in pediatric age groups ranged between 20-90% determining (8). In our study, an etiologic cause was found only in 41% of the patients. Hence, majority of the patients were idiopathic cases. In etiology identified most common cause are infections. Over 80 percent of acute urticaria cases in some pediatric series have been found to be related to infections. Different studies have indicated that viral, bacterial and parasitic infections can be related to acute urticaria (9). Particularly in children, acute urticaria can develop during or after viral or bacterial infections. It is thought that this is related to complement activation resulting from immune complexes that develop during an infection (10). The most frequent infections in acute urticaria etiology are viral upper respiration tract infections. In 91.2% of the patients with a defined etiology in our study, infections and in particular upper respiratory tract infections are found to be acute urticaria triggers. A study by Sackesen et al. (4) has pointed out urinary tract infections in acute urticaria etiology. Interestingly, in about 70% of the patients with a diagnosed urinary tract infection (16.2%) there were no symptoms to indicate urinary tract infection and they suggested routine urinary test in etiologic assessment. There were 9 (4.7%) patients with a urinary tract infection diagnosis in our study. A symptomless urinary tract infection has been detected only in one of these patients.

Food and drugs are among the common suspicious agent in acute urticaria etiology in our study. However, confirming the allergy through allergy work-up indicates that these rates are not so high. It is difficult to distinguish the etiologic reason in urticaria that occurs after use of drug in acute infection. It is generally though that the reaction is due to infectious agents or the interaction between the drug and infectious agent (11). Confirming drug allergy in these patients is important as it will prevent getting a wrong drug allergy diagnosis. In our study the rate of drug allergy confirmation was only 1.2% (n=1), while the rate of food allergy confirmation was only 2% (n=1). A study by Sackesen et al. (4) reported a food allergy confirmation rate of 3% and a drug allergy confirmation rate of 5%. As it is seen, even though they are considered to be highly suspicious in etiology, drug and food allergy are actually very low in acute urticaria etiology. However, especially in etiology, it is very difficult to prove there is no drug allergy. There are drugs such as antibiotics and antipyretic (paracetamol, ibuprofen) that can be simultaneously used during acute infection. When acute urticaria occurs in such a case it is not possible to say that the only cause is infection. These patients must be subjected to allergy tests at least 4-6 weeks after the reaction to see whether there is any drug allergy.

Another cause in etiology is bite /sting. Papular urticarial resulting from bug bite is included in acute urticaria. Therefore, particularly in the presence of papular urticarial, bug bites must be taken into consideration. Papular urticaria frequency in children is ranging between 3.3 and 4.7% Similar to literature, popular urticaria rate has been concluded as 3.2% in our study (12).

Age seems to be an important factor in determining etiology in acute urticaria. Majority of the patients with defined etiology in our study are children under 2-year-old. The rate of determining etiology in under 2 year olds is 65.1% while the rate in patients

over 12 is 28.7%. Therefore, more detailed tests could be necessary when searching for etiology in younger children.

21.3% (n=100) of the patients assessed in our study for acute urticaria had recurring acute urticaria. No age, gender or etiologic differences have been observed in patients with first attack and recurring acute urticaria. A study conducted by Mortureux et al. (13) monitored post -acute urticaria children and reported chronic or recurring acute urticaria in 30% of the children.

It is a limitation that our study is retrospective. However, a high number patients were evaluated. Unlike other similar studies, allergy tests were performed on patients with suspected drug and / or food allergies to clarify whether there is an allergy. These are the strengths of our study.

In conclusion, the most important point in detecting etiology in acute urticaria is getting a detailed clinic history of the patient and performing a comprehensive physical examination. It is not necessary to have routine laboratory tests in all patients. Laboratory tests must be planned on the basis of clinical findings of each patient. Infections occupy an important place in etiology particularly in etiology in younger children. Therefore, infection-related tests could be performed on younger children even if there are no clinical suspicions. Unlike the popular belief, the rate of confirmed food and drug allergy is not very high. Diagnostic tests must be performed if there are suspected food or drugs in the story. This will prevent unnecessary food or drug restrictions.

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