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Prevalence of atopic diseases in children with papular urticaria

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Abstract
Background: Papular urticaria is a hypersensitivity reaction characterized by chronic and recurrent papular erythema. It occurs as a result of the bites of mosquitoes, fleas, bed bugs, and other insects; and it is generally seen in children. This study examines the prevalence of atopic diseases in patients with papular urticaria.
Methods: The medical records of 130 pediatric patients with the diagnosis of papular urticaria between August 2017 and August 2019, whose disease progression was followed in two tertiary care centers, were reviewed retrospectively. The patients were divided into two groups: under 5 and above 5 years old. The prevalence of the atopic disease in children with papular urticaria was compared with those in age-matched controls without papular urticaria.
Results: The study included 130 patients who were diagnosed with papular urticaria (64 males, 66 females, median age: 60 months). The prevalences of atopic disease, recurrent wheezing, and atopic dermatitis were higher in the group under 5 years old with papular urticaria than in the same-age control group (p=0.001, 0.002, and 0.001, respectively). The prevalences of atopic disease, asthma, allergic rhinitis, and atopic dermatitis were higher in the group above 5 years old with papular urticaria than in the same-age control group (p=0.001, 0.001, 0.001, and 0.007, respectively).
Conclusions: Many children with papular urticaria are atopic children. These patients should be assessed not only in terms of papular urticaria but also in terms of comorbid atopic diseases.

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Introduction

Papular urticaria consists of papules or vesicles accompanied by recurrent itching and varying degrees of local edema. These reactions are generally hypersensitivity reactions that occur as a result of an insect bite. A great number of insects, such as mosquitoes, flies, ticks, and caterpillars, are associated with papular urticaria. Papules typically cluster on the extensor sides of extremities and the non-stocking part. Children are more prone to papular urticaria.[1] The prevalence of papular urticaria in children between the ages of 1 and 6 years is 20%.[2] It has recently been suggested that papular urticaria can be an early indicator of the atopic march.[3]

The word "atopy" refers to antibody production in immunoglobulin against small amounts of protein allergens in the structures of pollens, mites, and food. The presence of atopy is expressed as an increased risk of one or more atopic diseases such as asthma, allergic rhinitis, and atopic dermatitis.[4] The atopic march expresses the natural course of atopic diseases. The atopic march typically consists of atopic dermatitis in early childhood, comorbid food allergies and asthma that develop later, and allergic rhinitis following these conditions in adulthood.[5] This study examines the prevalence of atopic diseases in patients with papular urticaria.

Materials and methods

This retrospective chart review was conducted in the Gaziosmanpasa Education and Research Hospital, Pediatric Allergy and Immunology Department and in the İnönü University Medical Faculty, Department of Pediatric Allergy and Immunology between August 2017 and August 2019. As a control group, same-age children without papular urticaria who were referred to the Bakırköy Sadi Konuk Research and Training Hospital's Pediatric Unit were included in the study. The serum eosinophil count and total immunoglobulin E (IgE) levels of these patients were taken from their electronic chart.

Study group

One hundred and thirty patients with papular urticaria were included in the study. All patients were diagnosed with papular urticaria by pediatric allergists. Demographic data regarding the age of onset of papular urticaria, diagnosis age of papular urticaria, number of lesions, lesion type, lesion diameter, annual number of episodes, coexistence of angioedema, family history, recovery time, seasonal distribution, lesion localization, regular breast milk intake (>6 months), exposure to tobacco smoke by parents, accompanying atopic disease, family history (parents and/or siblings) of atopic disease (e.g., asthma, allergic rhinitis, atopic eczema), and pet exposure at home—were obtained from patients' electronic files. Total serum IgE and peripheral eosinophilia values of all patients and controls were measured upon admission. The laboratory results were obtained from patients' electronic charts.

Atopic disease assessment

The patients were divided into two groups—under 5 and over 5 years of age—and compared with children without papular urticaria in similar age groups in terms of atopic disease. In order to discover the prevalence of the atopic disease in patients with papular urticaria, a questionnaire form was filled in. While preparing this questionnaire, the Global Initiative for Asthma (GINA) diagnostic criteria were used for asthma, whereas guides such as Allergic Rhinitis and its Impact on Asthma (ARIA) were used for allergic rhinitis, and updated Hanifin and Rajka diagnostic criteria were used for atopic dermatitis.[6–8] Serum eosinophil levels and total IgE levels were checked in all patients. Following this, a skin prick test including the most frequent aeroallergens (mite, pollen, mold, animal feather, and cockroach) was conducted for patients who were found to have an atopic disease. For the control group, the children whose hemogram and total IgE levels were examined were included in the study. After the control group was examined, their questionnaires were filled in with their parents. A skin prick test was not performed on the control group.

Statistics

We performed a statistical analysis using the Statistical Package for Social Sciences (SPSS) 21.0 software (SPSS Inc., Chicago, IL, USA). Descriptive statistics were expressed in terms of frequency and percentage for categorical variables, whereas quantitative data were expressed in terms of a median for non-normally distributed data and as a mean for normally distributed data. We used the Mann-Whitney U-test to compare the two groups and the Chi-square test to compare the categorical variables.

Ethical considerations

Ethical approval was granted in decision no. 2019/391 (dated 12/11/2019) by Inonu University's Ethics Committee of Medical Research.

Protection of human and animal subjects

The authors declare that no experiments were performed on humans or animals for this investigation.

Confidentiality of data

The authors declare that no patient data appear in this article.

Right to privacy and informed consent

The authors declare that no patient data appear in this article.

Table 1 Demographics of children with papular urticaria.

	n (%)
Male	64 (49.2)
Diagnosis age, median, (min-max) months	60 (3-156)
Disease onset age, median, (min-max) months	36 (1-120)
Breast-feeding, regular (>6 months)	99 (76.2)
Tobacco exposure	69 (53.1)
Pet exposure	17 (13.1)
History of atopic disease, in family	60 (46.2)
Skin prick test positivity	66 (50.7)
Acarus	32 (24.6)
Pollen	8 (6.1)
Multiple inhalants	26 (20.0)
Serum IgE elevation, (0-100) IU/mL	71 (54.6)
Serum IgE level, median (min-max), IU/mL	121 (1-3220)
Eosinophilia, (0-5) %	37 (28.5)
Eosinophil level, median (min-max) %	3.2 (0.4-19.6)
Total	130 (100.0)

Results

The study included 130 patients who were diagnosed with papular urticaria (64 males, 66 females, median age: 60 months). The median onset age of papular urticaria was 36 months. The demographic characteristics of the patients who were diagnosed with papular urticaria are summarized in Table 1. Also, the demographic characteristics of the patients under 5 and over 5 years old are given in Table 2.

In 124 (95.4%) patients, the lesion type was papular. In 110 (84.6%) patients, the lesion had occurred in the summer months, and the most prevalent localization was extremity involvement, seen in 122 (93.8%) patients. Fifty (38.5%) patients had more than 10 lesions, and the diameters of the lesions measured between 6 and 10 mm in 76 (58.5%) patients. Twelve (9.8%) patients also had angioedema. The characteristics of the papular urticaria lesions are shown in Table 3.

Under 5 years group

The prevalence of the atopic disease, recurrent wheezing, and atopic dermatitis was higher in patients with papular urticaria than in the control group (p=0.001, 0.002, 0.001, respectively). Atopic disease history in the family was higher in patients with papular urticaria than in the control group (p=0.003). Elevated serum IgE and IgE levels were more common in patients with papular urticaria than in the control group (p=0.001, 0.028, respectively). Elevated serum eosinophil and eosinophil levels were more common in patients with papular urticaria than in the control group (p=0.033, 0.001, respectively). No statistically significant differences were found between the papular urticaria group and the control group in terms of gender, diagnosis age, exposure to tobacco, breast-feeding regularity, or exposure to pets (p=0.120, 0.063, 0.071, 0.328, 0.865, respectively). The comparison of atopic disease in children under 5 years old with papular urticaria and age-matched healthy controls are given in Table 4.

Table 2 Demographics of children with papular urticaria according to age groups.

	n (%) (<5 years old)	n (%) (≥5 years old)
Male	23 (38.3)	41 (58.6)
Diagnosis age, median, (min-max) months	36 (3-57)	96 (60-136)
Disease onset age, median, (min-max) months	22.5 (1-56)	72 (3-120)
Breast-feeding, regular (>6 months)	41 (68.3)	58 (82.9)
Tobacco exposure	31 (51.7)	38 (54.3)
Pet exposure	8 (13.3)	9 (12.9)
History of atopic disease, in family	27 (45.0)	33 (41.7)
Atopy	41 (68.3)	53 (75.7)
Recurrent wheezing (>3 episodes/year)	30 (50.0)	-
Asthma	-	42 (60.0)
Allergic rhinitis	-	43 (61.4)
Atopic dermatitis	19 (31.7)	16 (22.9)
Skin prick test positivity	29/51 (56.9)	37 (54.4)
Acarus	17/51 (33.3)	15 (22.1)
Pollen	2/51 (3.9)	6 (8.8)
Multiple inhalant	10/51 (19.6)	16 (23.5)
Serum IgE elevation, (0-100) IU/mL	31 (51.7)	40 (57.1)
Serum IgE level, median (min-max), IU/mL	106 (2-3220)	132.5 (1-2291)
Eosinophilia, (0-5), %	14 (23.3)	23 (32.9)
Eosinophil level, median (min-max) %	3.2 (0.6-19.6)	3.1 (0.4-11.9)
Total	60 (100.0)	70 (100.0)

Over 5 years group

The prevalences of atopic disease, asthma, allergic rhinitis, and atopic dermatitis were higher in patients with papular urticaria than in the control group (p=0.001, 0.001, 0.001, 0.007, respectively). In the patient group, pet exposure was lower than in the control group (p=0.045). Elevated serum IgE and IgE levels were more common in patients with papular urticaria than in the control group (p=0.001, 0.001, respectively). Elevated serum eosinophil levels were more common in patients with papular urticaria than in the control group (p=0.035). No statistically significant differences were found between the papular urticaria group and the control group in terms of gender, diagnosis age, exposure to tobacco, breast-feeding regularity, family history of atopic disease, or eosinophil count (p=0.058, 0.592, 0.052, 0.128, 0.060, and 0.102, respectively). The comparison of atopic disease in children over 5 years old with papular urticaria and age-matched healthy controls are given in Table 5.

Table 3 Characteristics of papular urticaria lesions.

	n (%)
Number of lesions	
0-5	35 (26.9)
6-10	45 (36.4)
>10	50 (38.5)
Type of lesion	
Papular	124 (95.4)
Vesicular	4 (3.1)
Bullosa	2 (1.5)
Diameter of lesion	
0-5 mm	21 (16.2)
6-10 mm	76 (58.5)
>10 mm	33 (25.4)
Number of episodes per year, median (min-max)	2 (1-5)
One episode	64 (49.2)
Two episodes	40 (30.8)
Three episodes	18 (13.8)
Four episodes	6 (4.6)
Five episodes	2 (1.5)
Coexistence of angioedema	12 (9.8)
Is there anyone else in the family	11 (8.5)
Recovery time, days, median (min-max)	15 (3-180)
Season	
Summer	110 (84.6)
Spring	17 (13.1)
Winter	15 (11.5)
Autumn	19 (14.6)
Localization	
Head and neck	41 (31.5)
Trunk	24 (18.5)
Extremities	122 (93.8)
Total	130 (100.0)

Table 4 Comparison of atopic disease in children under 5 years old with papular urticaria and age-matched healthy controls.

	Patient	Control	p
	n (%)	n (%)	
Male	23 (38.3)	30 (52.6)	0.120
Diagnosis age, median, (min-max) months	36 (3-57)	36 (4-48)	0.063
Tobacco exposure	31 (51.7)	20 (35.1)	0.071
Breast-feeding, regular (>6 months)	41 (68.3)	34 (59.6)	0.328
Pet exposure	8 (13.3)	24 (19.8)	0.865
History of atopic disease, in family	27 (45.0)	11 (19.3)	**0.003**
Atopy	41 (68.3)	17 (29.8)	**0.001**
Recurrent wheezing (>3 episodes/year)	30 (50.0)	13 (22.8)	**0.002**
Atopic dermatitis	19 (31.7)	3 (5.3)	**0.001**
Serum IgE elevation (0-100)	31 (51.7)	18 (31.6)	**0.028**
Serum IgE level, IU/mL	106 (2-3220)	28 (2-1157)	**0.001**
Eosinophilia (0-5)	14 (23.3)	5 (8.8)	**0.033**
Eosinophil level, %	3.2 (0.6-19.6)	1.9 (0.2-15.3)	**0.001**
Total	60 (100.0)	57 (100.0)	

Chi-square and Mann-Whitney U-tests were applied. Values written in bold are statistically significant.

Discussion

Papular urticaria is a hypersensitivity reaction characterized by chronic and recurrent papular erythema that occurs as a result of the bites of mosquitoes, fleas, bed bugs, and other insects and is generally seen in children.[9] It is not seen during the neonatal period. It peaks at the age of two, and tolerance develops generally through the age of 10.[10] It can rarely be seen in adolescents and adults. It does not discriminate based on race or sex. Type I and type IV hypersensitivity reactions generally coexist in reactions.[11] Lesion sizes generally range between 3 and 10 mm. Lesions generally occur in the late spring and summer months. Although the lesions can occur on any part of the body, they frequently tend to occur on the extensor side of extremities.[12] Although the lesions are generally in the form of papules, they can also be in the form of vesicles, pustules, or crusting.[2] In our study, the characteristics of papular urticaria lesions were found to be similar to those described in the literature; 95.0% of the lesions had papular characteristics, 94.0% were located on extremities, 85.0% had occurred in the summer months, and 58.0% had a lesion diameter of 6-10 mm.

Asthma is the most common chronic disease in children, and its prevalence is gradually increasing, along with that of other allergic diseases.[13] There are many risk factors influencing the prevalence of allergic diseases, mainly age, gender, genetics, air pollution, smoking, having pets, and one's area of residence.[14] In prevalence studies of allergic diseases, the physical examination results or the disease prevalence in patients who refer to the hospital can be used in addition to questionnaires.[15] The International Study of Asthma and Allergies in Childhood (ISAAC) shows the prevalence of childhood asthma and allergic disease worldwide. That study is the most extensive questionnaire study standardized for epidemiology studies.[16] In our study, instead of a questionnaire, previously determined diagnostic criteria for asthma, allergic rhinitis, and atopic dermatitis were used. The study attempted to discover the actual prevalence by making use of GINA, ARIA, and updated Hanifin and Rajka diagnostic criteria. In addition, a control group was used to minimize the risk factors influencing prevalence. According to the ISAAC Phase Three study, the global prevalences for current asthma, rhinoconjunctivitis, and eczema in the 6-7 years age group were 11.78.5, and 7.9%, respectively.[17] In a study with 14 centers conducted in our country in 2007, the mean prevalences of childhood asthma, allergic rhinitis, and atopic eczema were 13.4, 17.3, and 4.6%, respectively.[18] In this study, the rate of atopy was found to be 68.3 and 75.7% in the group below the age of five and in the group above the age of five, respectively. Also, recurrent wheezing (>3 episodes

Table 5 Comparison of atopic disease in children over 5 years old with papular urticaria and age-matched healthy controls.

	Patient	Control	p
	n (%)	n (%)	
Male	41 (58.6)	27 (42.2)	0.058
Diagnosis age, median, (min-max) months	96 (60-136)	96 (60-192)	0.592
Tobacco exposure	38 (54.3)	24 (37.5)	0.052
Breast-feeding, regular (>6 months)	58 (82.9)	46 (71.9)	0.128
Pet exposure	9 (12.9)	17 (26.6)	**0.045**
History of atopic disease, in family	33 (47.1)	20 (31.5)	0.060
Atopy	53 (75.7)	24 (37.5)	**0.001**
Asthma	42 (60.0)	16 (25.0)	**0.001**
Allergic rhinitis	43 (61.4)	19 (29.7)	**0.001**
Atopic dermatitis	16 (22.9)	4 (6.3)	**0.007**
Serum IgE elevation (0-100)	40 (57.1)	16 (25.0)	**0.001**
Serum IgE level, IU/mL	132.5 (1-2291)	41.5 (2-679)	**0.001**
Eosinophilia (0-5)	23 (32.9)	13 (20.3)	0.102
Eosinophil level, %	3.1 (0.4-11.9)	2.6 (0.2-18.5)	**0.035**
Total	70 (100.0)	64 (100.0)	

Chi-square and Mann-Whitney U-tests were applied. Values written in bold are statistically significant.

per year) and atopic dermatitis rates were 50.0 and 31.7%, respectively, in the under-five group, whereas in the control group, these rates were 22.8 and 5.3%, respectively. In our study, asthma, allergic rhinitis, and atopic dermatitis rates were 60.0, 61.4, and 22.9%, respectively, in the group above the age of five, whereas the rates in the control group were 25.0, 29.7, and 6.3%, respectively. Allergic diseases are on the rise.[19] Thus, it is not surprising that the rates of asthma and allergic rhinitis in the control group were higher than in previous years. Another reason for this may be the fact that the numbers of patients and the control group were limited in our study.

The risk factors associated with papular urticaria were the presence of fleas in the accommodation, use of mattresses without springs, daily use of public transportation, having a soil or earth floor in the main bedroom, and siblings with a history of atopic dermatitis. Protective factors were wooden floors, the presence of sewerage, no presence of neighboring houses, and private transportation. Although there are contradictory data in the literature about having pets at home, it is accepted as a risk factor.[2] In our study, no significant difference was found between the under-five group and the control group in terms of pet exposure. In the over-five group, the rate of pet exposure was lower than in the control group.

In a recent study, having a sibling with atopic dermatitis was assessed as a risk factor for papular urticaria. However, no associations have been found among asthma, allergic rhinitis, atopic dermatitis, and papular urticaria in patients with papular urticaria or their families.[2] In another study, papular urticaria caused by some arthropods, such as mosquitoes and caddisflies, has been found to be associated with allergic diseases.[1] In our study, the rate of atopic disease in both age groups was higher than that in the control group. In a study by Halpert et al.,[2] atopic disease was found in higher rates in children with papular urticaria. When both studies were examined, the mean ages of children with papular urticaria were found to be similar. The primary reason for the difference could be the great number of environmental and genetic risk factors influencing allergic disease prevalence.[14] Another factor could be the limited number of our patients. One more limitation of our study is the fact that the arthropod types causing papular urticaria were not determined.

An additional limiting aspect of our study is that some of our patient group members (all from the papular urticaria group) were collected from Malatya province. In a recent study in children aged 6–7 years in Malatya province, the prevalences of wheezing, allergic rhinitis, and atopic dermatitis were 20.0, 37.0, and 7.5%, respectively.[20] In our study, the prevalences of asthma, allergic rhinitis, and atopic dermatitis in the over-five control group were 25.0, 29.7, and 6.3%, respectively. However, the number of patients participating in the study from Malatya province was only a small group (22 patients). The possibility of this patient group affecting the study results can therefore be excluded.

Conclusions

We found that most children with papular urticaria were atopic children. These patients should be assessed not only in terms of papular urticaria but also in terms of comorbid atopic diseases.

Conflicts of interest

Each of the authors has contributed to, read and approved this manuscript. None of the authors has any conflict of interest, financial or otherwise. This manuscript is original and it, or any part of it, has not been previously published; nor is it under consideration for publication elsewhere.

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