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Prognosis of chronic urticaria in children

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ABSTRACT

Objective: Chronic urticaria (CU) is defined as the recurring presence of urticaria, angioedema, or both, for a duration of six weeks or more. In most patients, it is a self-limiting disease. The study aimed to investigate the clinical findings, comorbidities, laboratory results, response to treatment and prognosis in children with CU.

Material and Methods: Patients aged 0-18 years with CU followed up at the Pediatric Allergy and Immunology Outpatient Clinic of Selcuk University Faculty of Medicine Hospital between January 2022 and March 2024 were included, and their medical records were retrospectively analyzed.

Results: The study sample included 74 patients with CU. About 55.4% of the patients were girls. The mean age of the patients was 11 year (2.3-17.9). The mean follow-up period was 475 days (129-925). Sixteen patients (21.6%) had angioedema, while 15 patients (20.2%) reported presence of a trigger. Eleven patients (14.8%) had dermographism. Four patients (5.4%) were anti-thyroid peroxidase positive and seven patients (9.4%) were antinuclear antibody positive. Eosinopenia was present in 10 patients (13.5%), whereas basopenia was present in only two (2.7%) patients. Skin prick test detected positivity in 24 patients (32.4%). Sixty-eight patients (91.9%) responded to antihistamine and/or montelukast treatment, and omalizumab was prescribed to six patients (8.1%) showing no response to the conventional treatment.

Conclusion: In pediatric CU patients, the disease is often self-limiting without the need for treatment with omalizumab. Drug compliance should be evaluated in patients with poor disease control.

Keywords: Antihistamine, Chronic urticaria, Eosinopenia, Prognosis

INTRODUCTION

Urticaria is characterized by edematous papules/plaques involving the upper layers of the dermis, which are raised from the skin, fade with pressure, pink or red in color, with clear borders and usually surrounded by a ring of erythema (1). Chronic urticaria (CU) is broadly described as continuous or intermittent urticaria present for at least 6 weeks. The incidence of CU is estimated to be 1.4% per year, affecting 2-3% of the population and significantly impairing their quality of life. Previous studies indicate that the prevalence of CU is generally higher in females with a female-to-male ratio ranging from 7:3 to 4:1 (2,3).

Chronic spontaneous urticaria (CSU) accounts for around 50-75% of chronic urticaria cases, whereas chronic inducible urticaria (CIU) is responsible for approximately one-third of all cases (1). Epidemiological data derived from adult populations suggest that certain subtypes of CSU may have an underlying autoimmune etiology (3). In pediatric CSU patients, spontaneous remission occurs in 30% to 50% of cases within the first three-years following diagnosis (4).

The diagnostic workup for all urticaria patients should involve a comprehensive clinical history, the initial step crucial for accurate diagnosis and subsequent management. Clinicians should thoroughly collect all available information regarding the temporal aspects of symptoms (onset, frequency, and pattern), potential triggering factors, environmental exposures, presence of angioedema or other systemic manifestations, current and past medication use, and known allergies. Besides, urticarial lesions and angioedema often display an ephemeral nature they may not be evident during physical examination so it is of great importance to review documents detailing signs and symptoms, including photographic evidence of urticaria and/or angioedema (4-6). The third step in the diagnostic algorithm for CU involves a basic diagnostic workup with limited laboratory testing. Subsequent to these three steps, further diagnostic

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investigations may be performed, individually tailored based on previous findings, the specific type and subtype of urticaria identified, such as provocation tests for inducible urticaria (5,7).

The current treatment options for urticaria mainly focus on targeting mast cell mediators, such as histamine, or their activators including autoantibodies. The first line of treatment, as recommended by international guidelines, involves the administration of second-generation H1-antihistamines at standard doses for symptomatic relief (5). Leukotriene receptor antagonists (LTRA) particularly montelukast, which is the most extensively studied in this class have so far shown a favorable safety profile in numerous clinical trials, including those involving pediatric patients. However, their efficacy in CSU still remains rather limited, as we have no robust evidence to encourage LTRA use as monotherapy (8). For patients failing to achieve adequate symptomatic control with second-generation H1-antihistamines, omalizumab stands out as the only licensed drug therapy, thus representing the next echelon in the treatment algorithm. A monoclonal antibody targeting free immunoglobulin E (anti-IgE), omalizumab has been shown to be highly effective and safe in the management of CSU with reduced urticaria activity scores (9).

In this study, we aimed to investigate the factors affecting prognosis in children with chronic urticaria.

MATERIALS and METHODS

The sample of this retrospective study included pediatric patients aged 0-18 years who were evaluated and followed at the Pediatric Allergy and Immunology Outpatient Clinic of Selcuk University Faculty of Medicine Hospital from January 2022 to March 2024. Research data were retrieved from medical records and the hospital's electronic health record system. The following parameters were recorded for analyses: gender, age, family history, chronic diseases, duration of urticaria, type of urticaria, laboratory findings (complete blood count results, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level, thyroid function tests, antithyroglobulin and antithyroid peroxidase autoantibodies (anti-TPO), antinuclearantibody (ANA) level, urine analysis).

Drug therapies: Treatment regimens administered to the study cohort were also documented. In order to assess current therapeutic status and remission outcomes, patients were contacted via telephone for a standardized follow-up interview. The Urticaria Activity Score over seven days (UAS7) was employed as a validated instrument to quantify disease activity and evaluate remission status.

Hematological and immunological parameters were analyzed through established cut-off values from the literature: an eosinophil count below 0.05×10^9/L was considered eosinopenia, while basophil values below 0.01×10^9/L were interpreted as basopenia (10,11). Serum total IgE levels were classified as low if below 40 kU/L and high if above 100 kU/L (12).

Diagnostic procedures: Results of skin prick tests for common aeroallergens and food allergens, and provocation tests for physical urticaria were collected and included in the analyses. Skin prick testing was performed through standardized allergen extracts from Credisol® (Maharashtra, India) and Lofarma® (Milano, Italy). To reduce potential confounding effects, patients were instructed to discontinue antihistamines 15 days prior to testing, antidepressants seven days prior, and montelukast three days prior. Positive control agent was a histamine solution (10 mg/mL) and the negative control substance was physiological saline. Allergen solutions were applied to the volar aspect of the forearm through the prick-lancet technique. Measured 15 minutes after allergen application, a positive reaction was defined as the development of a wheal measuring 3 mm or larger in diameter at the allergen test site as compared to the negative control site (13). Inhalation allergens used in the skin prick test included house dust mites (Dermatophagoides farinea, Dermotophagoides pteronyssinus), pollen allergens representing various sources like trees (redwood, birch), grasses (rye, grass), and weeds (xanthium or cocklebur, common plantain, lamb's quarters, and other prevalent weeds), cat epithelium, dog epithelium, molds (Alternaria alternata, Aspergillus and Cladosporium) and cockroach debris. Food allergens included common allergenic foods like milk, eggs, tree nuts, peanuts, wheat flour, fish, tomatoes, and soy. In addition to the skin prick tests, the ice cube test was used to evaluate for cold urticaria, which involved placing an ice cube on the inner side of the forearm for five minutes and observing for the development of hives, which would indicate an allergic reaction to cold.

Statistical analysis

Statistical analyses were performed via IBM IBM SPSS Statistics for Windows, version 22 (IBM Corp., Armonk, N.Y., USA). After evaluating the conformity of the data to normal distribution by the Kolmogorov Smirnov test, an after evaluating the conformity of the data to normal distribution by the Kolmogorov Smirnov test, median (IQR or minimum-maximum) or mean (standard deviation) values were used to evaluate numerical data; frequency distributions and percentages were used to summarize categorical data. Mann-Whitney U tests were conducted to explore the differences between groups for data not conforming to normal distribution. Chi-square test was used to compare categorical data. Statistical significance level was accepted as $p<0.050$ in all tests.

RESULTS

Our study included 74 patients. The mean age at presentation was 11 year (2.3-17.9). Female patients constituted the majority with a rate of 55.4% (n=41). Patients were followed up for a mean duration of 475 days (129-925) after diagnosis.

Sixteen patients (21.6%) had angioedema associated with urticaria. When chronic diseases were questioned, asthma was the most common comorbidity. Among the comorbidities were allergic rhinitis, hypothyroidism, familial mediterranean fever (FMF), idiopathic thrombocytopenic purpura (ITP), and diabetes mellitus (DM). Fifteen patients (20.2%) reported urticaria after a trigger (hot water, water, cold, pressure). Of all CU patients, 60 (81.1%) were diagnosed with CSU and 14 (18.9%) with Chronic inducible urticaria. According to diagnostic provocation tests, the most common type among the 14 patients with CIU was symptomatic dermographism (78.6%), followed by aquagenic urticaria (21.4%). Demographic characteristics of the patients are summarized in Table I.

Laboratory results showed that 10 of 74 (13.5%) patients had eosinopenia, four (5.4%) eosinophilia and two (2.7%) basopenia. There were 24 patients (32.4%) with a positive skin prick test. Allergic sensitization via inhalation was detected in 13 (17.6%), food sensitization in eight (10.8%), and combined inhalation and food sensitization in three (4%) patients. ANA positivity was found in seven (9.4%) of all patients, and no patient developed rheumatologic disease during the follow-up period. Antithyroid peroxidase antibody positivity was detected in four patients (5.4%) and no autoimmune thyroiditis was detected during follow-up. Thirteen patients (4%) showed elevated ESR and seven (9.4%) elevated CRP as acute phase reactants. Urinalysis detected signs of infection in 11 patients (14.9%). The laboratory test results are presented in Table II.

Table I: Clinical characteristics of children with chronic urticaria

Variables	Children with Chronic Urticaria (n=74, %)
Age at presentation (year)*	11±5.1 (2.3-17.9)
Mean follow-up time (days)*	475±237.2 (129-925)
Gender†	
Female	41 (55.4)
Male	33 (44.6)
Presence of angioedema†	16 (21.6)
Presence of a trigger (hot water, water, cold, pressure)†	10 (13.5)
Hot water	5 (6.7)
Cold	2 (2.7)
Water	2 (2.7)
Stress	1 (1.3)
Dermographism†	11 (14.8)
Comorbidities†	
Asthma	7 (9.4)
Allergic rhinitis	2 (2.7)
Hypothyroidism	2 (2.7)
Familial mediterranean fever	1 (1.3)
Idiopathic thrombocytopenic purpura	1 (1.3)
Diabetes mellitus	1 (1.3)
Family history†	
Chronic urticaria (mother/father)	4 (5.4)
Asthma/Allergic rhinitis (mother/father)	2 (2.7)
Rheumatologic disease (mother/father)	1 (1.35)
Chronic spontaneous urticaria†	60 (81.1)
Chronic inducible urticaria†	14 (18.9)
Dermographism	11 (14.9)
Aquagenic (cold) urticaria	3 (4)

***:** *mean±standard deviation (min-max),* **†:** *n(%)*

Table II: Laboratory results of children with chronic urticaria

Variables	Children with chronic urticaria (n=74, %)
Eosinopenia	10 (13.5)
Eosinophilia	4 (5.4)
Basopenia	2 (2.7)
Mean IgE level, average*	133.87±152 (17-688)
Low IgE <40 kU/L	16 (21.6)
High IgE >100 kU/L	21 (28.4)
Positive for antithyroid peroxidase antibodies	4 (5.4)
Positive for antinuclear antibodies	7 (9.4)
Skin prick test positivity	24 (32.4)
Inhalant allergen sensitivity	13 (17.6)
Food sensitivity	8 (10.8)
Inhalation and food sensitivity	3 (4)
Elevated erythrocyte sedimentation rate	3 (4)
Elevated C-reactive protein	7 (9.4)
Urine analysis	
Leukocyturia	11 (14.7)
Hematuria	2 (2.7)
Proteinuria	2 (2.7)

***:** *mean±standard deviation (min-max)*

As a first line of treatment, all 74 patients received antihistamine therapy at the standard dose. For patients who did not respond, the dose was increased incrementally up to two, three, or four times the initial dose. Montelukast was added to the drug regimen in 28 patients with no partial response despite the increased antihistamine doses. Twenty-two patients responded well to combined therapy with antihistamine and montelukast. Omalizumab was commenced in six patients with partial response. The details of drug regimens administered to patients are presented in Figure 1. Among the six patients who received omalizumab therapy, one (16.7%) presented with angioedema, one (16.7%) asthma, one (16.7%) exhibited both eosinopenia and basopenia, two (33.3%) tested positive for ANA, and one (16.7%) patient showed elevated levels of both ESR and CRP.

We managed to contact 44 patients (59.4%) via telephone, and 22 (50%) of these patients had achieved complete remission. Of the other 22 patients, nine (20.4%) had well-controlled symptoms, six (13.6%) partially controlled and seven (16%) uncontrolled. When the patients were called by phone, 9-12 months had passed. All patients with partially controlled or uncontrolled signs and symptoms reported to experience drug compliance issues.

Table III presents a comparison of laboratory results across different disease control categories: remission-well-controlled

Table III: Comparison of laboratory parameters in children with chronic urticaria by disease control status: remission, good control, partial control, and no control

Variables	Remission and well controlled (n=31)	Partially controlled and uncontrolled (n=13)	p
Eosinopenia*	10 (13.5)	3 (23.1)	0.650
Eosinophilia*	-	3 (23.1)	
Basopenia*	2 (6.4)	-	
Elevated ESR*	2 (6.4)	-	
Elevated CRP*	3 (9.7)	1 (7.7)	
Positive for antithyroid peroxidase antibodies	2 (6.4)	1 (7.7)	
Positive for antinuclear antibodies	3 (9.7)	2 (15.4)	0.780
Skin prick test positivity*	13 (61.9)	5 (71.4)	0.690
IgE level†	104 (45.2-202)	68 (42-235)	0.700

**: n(%), †: median (interquartile range)*

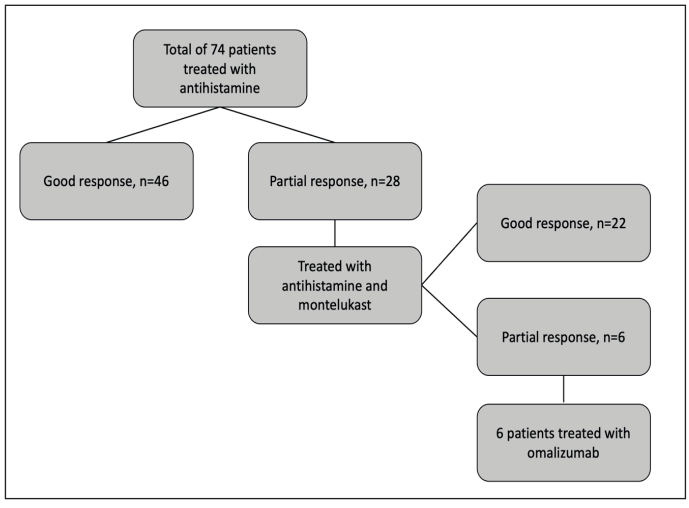

Figure 1: Treatment regimen flow chart for children with chronic urticaria}

and partially controlled-uncontrolled. Eosinopenia, ANA positivity, anti-TPO positivity were proportionally higher in patients achieving remission and exhibiting well-controlled chronic urticaria, although there was no statistically significant difference. Serum IgE levels were similarly higher in both patient groups, albeit with no significant statistical difference.

DISCUSSION

In this study, we evaluated the clinical and etiologic features, laboratory findings, and treatment response of 74 CU patients who were followed up in our clinic. The female patients constituted the majority of the sample. The most common accompanying symptom was angioedema, while the most common comorbidity was asthma. Family history included chronic urticaria, asthma and rheumatologic diseases. CSU was detected in about 80% of our patients, and the remaining ones were diagnosed with CIU by provocation tests. Evidence-based information from clinical trials or real-life studies on epidemiology, comorbidities and treatment outcomes in the pediatric population is scarce, thus there are gaps in the management of CU in children.

In literature, pediatric patients receiving a diagnosis of CU are predominantly female, with a mean age range of 8-11 years (14, 15). In our cohort, the majority of patients were female (55.4%), and the mean age was in accordance with the findings reported in the literature. Angioedema was observed in 21.6% of our patients. Prior research has documented comparable incidences of angioedema ranging from 30% to 50%, which renders it as the most frequently occurring symptom associated with CU (15) .

While the association between CU and atopy remains to be fully elucidated, some studies suggest a potential link. Previous research has demonstrated correlations between atopy, comorbid allergic conditions, and CU, with children diagnosed with CU exhibiting a higher prevalence of allergic diseases or sensitization (16). In our case series, atopy was observed in 32.7% of patients with CU, a figure consistent with previous findings (17). Furthermore, 14.9% of our cohort had a diagnosis of asthma and/or allergic rhinitis, while 32.4% demonstrated sensitization on skin prick testing. A family history of atopy was noted in 8.1% of patients. Although food sensitization was identified in some individuals, no specific association with food-induced urticaria was reported; therefore, food challenge testing was not conducted.

The potential role of autoimmunity in chronic urticaria should also be investigated. In line with the EAACI/WAO guideline diagnostic algorithm, assessment for autoimmunity (chronic autoimmune or autoantibody-associated CU) is recommended in selected patients with chronic spontaneous urticaria who exhibit an inadequate response to standard treatment (1). Within our sample, three patients (4%) presented with concomitant autoimmune conditions, including DM, FMF, and ITP; TPO antibodies were detected in four patients (5.4%), and seven (9.4%) tested positive for ANA. No patients developed any new autoimmune diseases during the follow-up period.

CSU accounts for 50-75% of chronic urticaria cases, and CIU represents about one-third of this subset. Dermographism is the most common manifestation of CIU (18). Our case series closely align with these literature findings, as 81.1% had CSU and 18.9% CIU, predominantly dermographism.

Current guidelines recommend antihistamines as first-line therapy for the management of chronic urticaria, while second-line treatment should involve up-titration to a maximum of four times the standard dose. Omalizumab is recommended for patients aged over 12 not responding to such therapies (7). Previous studies have reported that 7% to 10.7% of pediatric patients diagnosed with chronic urticaria require omalizumab (19, 20). In support of these data, 8.1% of our patients received omalizumab.

Even though chronic urticaria is often self-limiting, about 20% of patients experience symptoms for more than 5 years (21). In our study, 29.5% of patients remained partially controlled or uncontrolled after a mean follow-up period of 1.5 years, underscoring the importance of continued monitoring and improvement of treatment strategies.

In patients with chronic spontaneous urticaria, complete blood count results typically fall within the normal range, however the presence of eosinopenia (<50 mm^3) is often associated with a poorer response to antihistamines and omalizumab (11). Likewise, although the majority of CSU patients exhibit normal CRP and ESR levels, significant elevations in either marker could be linked to worse outcomes, including reduced quality of life and diminished antihistamine efficacy (22). For patients failing to respond to omalizumab therapy, generally cyclosporine is recommended, but none of our patients required cyclosporine as their urticaria was effectively managed with omalizumab.

This study is subject to several limitations. First of all, its retrospective design can inherently cause some recall bias. Secondly, failure to contact some patients for follow-up may have impacted the overall findings. Finally, the relatively small sample size should limit the generalizability of our results.

CONCLUSION

The findings suggest that chronic urticaria is often self-limiting without the need for omalizumab in pediatric patients. Drug compliance should be evaluated in patients with poor disease control. Although the number of patients treated with omalizumab was relatively low, they responded well to this therapy. More studies are needed to evaluate etiology and treatment response in patients with chronic urticaria.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. Ethical approval was obtained from the ethics committee of Selcuk University Faculty of Medicine (approval no: 2024/116 date: 27.02.2024).

Contribution of the authors

Yılmaz SY: Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***Külhaş Çelik İ:*** Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Reviewing the article before submission scientifically besides spelling and grammar. ***Artaç H:*** Constructing the hypothesis or idea of research and/or article, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar.

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Conflict of interest

The authors declare that there is no conflict of interest.

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