

Pediatric urticaria in the Emergency Department: epidemiological characteristics and predictive factors for its persistence in children.

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Abstract

Introduction: Acute urticaria (AU) in children is a common clinical manifestation responsible for admission to the emergency department (ED). We aimed to analyze the epidemiological characteristics of AU in children and to identify predictors of both severity and progression.

Material and methods: We evaluated 314 children admitted to the ED with a diagnosis of AU. We analyzed information concerning its onset, duration, severity, possible triggering factors and the persistence of symptoms after 1, 3, and 6 months.

Results: The most common etiological factors were infections (43.9%); in 32.4% of cases, AU was considered as idiopathic. AU was significantly most common in males and pre-school children. At the 6-month follow-up, 9.5% of children presented a persistence of urticaria, mainly those with contact (44.4%) or idiopathic (30.4%) forms.

Conclusion: The AU etiology identified by history in the ED may be a significant predictor of persistence after a first attack of AU.

Key words: acute urticaria; children; trigger factors; epidemiology; severity

Introduction

Acute urticaria (AU) is a common skin disorder characterized by itching, wheals, and/or angioedema with a duration <6 weeks. Urticaria is considered chronic when it is recurrent, with signs and symptoms recurring most days of the week, for six weeks or longer (chronic urticaria, CU) (1,2). AU is reported in childhood (3.4% UK, 4.4% Germany, 5.4% Denmark), and its persistence is even less probable (0.1%-0.3%) (3). The first treatment of urticaria is the elimination of any identified trigger factors and then the use of second-generation antihistamines and corticosteroids (2). A detailed history of the factors that may predict the time and the severity of urticaria will help physicians to perform an appropriate clinical assessment. Several studies described the demographics and the etiologies of AU in children (4,5), but the factors that may influence its duration and severity have not been well addressed.

Therefore, this study aimed to evaluate the prevalence of urticaria in children referred to Emergency Departments (ED) in Italy and to analyze the factors that may predict the duration of the first attack.

Material and Methods

We performed an observational clinical study on children with AU referred to Italian EDs from 1 October 2016 to 1 December 2017. The Local Ethics Committees approved the study protocol, and the work was conducted in compliance with the Institutional Review Board/Human Subjects Research Committee requirements and with the Declaration of Helsinki and the Guidelines for Good Clinical Practice criteria.

Population

Inclusion criteria: patients of both sexes and <18 years old, with a diagnosis of AU in agreement with international guidelines (2) and with no pharmacological treatment before ED evaluation, whose legal guardians signed the informed consent. Exclusion criteria: patients with CU or affected by autoimmune diseases or in treatment with corticosteroids; children whose legal guardians did not sign the informed consent.

Endpoint

The first endpoint was the evaluation of the characteristics of children with AU. The second endpoint was to determine the factors that could be used to predict the severity and duration of an initial episode of AU in children.

Experimental protocol

The diagnosis of AU and its management was made in agreement with the European Academy of Allergy and Clinical Immunology (EAACI) international guidelines (2). Children who satisfied the inclusion criteria were evaluated at 1, 3, and 6 months after the ED admission in order to obtain data

on the efficacy of treatment and persistence of symptoms. We used a questionnaire *ad hoc* that included questions concerning the onset of the acute attack, its duration and severity, and the possible triggering factors. The same questionnaire was repeated at follow-up. The etiological diagnosis was mainly carried out through history taking and physical examination. Laboratory investigations were performed based on history and physical examination to identify the underlying cause. The disease activity was assessed with the weekly Urticaria Activity Score (UAS7) score (2).

Statistical analysis

All data were analyzed using the SPSS statistical program (Microsoft, Redmond, WA, USA) by evaluating the arithmetic characteristics, e.g., mean, geometric mean, standard deviation (SD). Data parameters were checked for normality using the Shapiro-Wilk normality test. Data were analyzed by one-way ANOVA analysis of variance and the χ^2 test. Pearson's test was used to evaluate the correlation between urticarial and patients' characteristics. The threshold for statistical significance was set at $*p < 0.05$. SPSS (SPSS Inc., Chicago, USA) software was used for statistical analyses. We defined and labeled this study as exploratory; therefore we did not perform a power calculation.

Results

During the study, 314 children (148 females, 47.1%, and 166 males, 52.9%) aged <17 years (median 70 months, range 2-442 months) with a diagnosis of AU that fulfilled the inclusion criteria were enrolled. AU was more common in males than in females ($p < 0.05$), and in the age range of 0 to 5 years (50.3%).

Clinical evaluation and laboratory tests documented that the most common forms of AU were para-infectious (43.9%) and idiopathic (32.4%) (Table 1). In particular, the idiopathic form was most common in children 6-10 years old ($p < 0.05$) and the infectious form in children under five years (Table 2). Moreover, the frequency of AU was significantly lower ($p < 0.01$) in children older than ten years compared to the younger ones.

Mild urticaria was diagnosed in 40.4% enrolled children, moderate urticaria in 44.5%, and severe urticaria in 14.9%.

The correlation between the severity of AU and the age of children, sex, etiology and family history for allergic diseases is shown in Table 3. A positive family history for allergy was found in 114 children (36.3%), and it was significantly more frequent in those with AU induced by reactions to food ($n = 24$, 54.5%; $p < 0.01$), drugs ($n = 5$, 45.5%; $p < 0.05$) and contact ($n = 8$, 44.4%; $p < 0.05$) compared to children with idiopathic ($n = 31$, 30.4%) or infectious ($n = 46$, 33.3%) urticaria.

Drug treatment was given in 290 children (92.4%), and most commonly used drugs were antihistamines ($p < 0.01$) in monotherapy ($n = 166$; 57.3%) or with corticosteroids ($n = 110$; 37.9%). During follow-up, 10.8% of children presented a recurrence of urticaria in the first month, 11% at three, and 9.5% at six months.

The factors associated with the recurrence of AU are reported in table 4. Severity, sex and familiarity did not seem to correlate with the persistence of urticaria. The ages that had had a greater tendency to CU (in particular at six months) were 5-10 years old and 10-15 years old. In particular, urticaria recurrences were most common in the contact (44.4%) and idiopathic (30.4%) forms without differences during the follow-up (Figure 1).

Discussion

In this study, we analyzed epidemiologic data of children with AU admitted to ED; also, we evaluated several significant factors that may predict the severity of an initial episode of AU in children and its progression to a chronic form. AU is a common cause of admission of children to the ED, and it is estimated to affect 15% - 25% of people at some point in their life (4,6), commonly adult females (7, 8). In a register-based study, Ghazanfar et al. (9) recently documented that women were more frequently diagnosed with urticaria than men, probably because men are less likely to seek medical attention than women. In contrast, in our study, urticaria was more common in males and in pre-school children suggesting that probably age-related sex hormones can play a role in the pathogenesis of urticaria.

Previous studies reported that infections are involved in the development of AU in children (3-5,10). Infections were the most common potential triggers of attacks of AU in the present study, occurring in 43.9% of the patients and mainly represented by upper respiratory tract infections. The observed frequency rate is similar to that reported in other studies (11,12).

Bacterial infections of the mouth and the tonsils (e.g., with streptococci) and gastrointestinal infections (e.g., *Helicobacter pylori* infection) have been described as potential triggers of AU. Nevertheless, the exact role and pathogenesis of mast cell activation by infectious processes remains unclear (13).

Moreover, new episodes of infection are accompanied by reappearance or aggravation of urticaria symptoms causing chronic spontaneous urticaria (3,14).

In our study, a clear etiology of AU has not been identified in 32.4% of children (idiopathic urticaria), in agreement with literature data (15,16). AU secondary to food was found in 14% of the patients. The predominant foods that cause urticaria are milk, eggs, peanuts, tree nuts, fish, and shellfish. Foods were reported to be the possible cause of attacks of AU in 0.9% and 1.3%,

respectively, of patients in two previous studies (11,12); however, Juhlin reported that foods and drinks were associated with exacerbation of wheals in 30% and 18%, respectively, of patients with recurrent attacks of urticaria (17).

Drug treatment used in the management of urticaria was administered in agreement with international guidelines considering the severity of symptoms (e.g., intense pruritus and angioedema) (4,18). Therefore, we documented that antihistamines were the most common drug used. We did not record any adverse drug reaction, probably because the short duration of treatment.

We found that specific triggers of AU were not associated with severe urticaria, even if we found that unknown causes were significantly associated with mild urticaria and infectious triggers with a moderate one. Also, we found that pre-school children had more frequent mild urticaria ($p < 0.04$). AU has been defined as spontaneous wheals presenting for less than six weeks (1,19). However, its duration is related to the clinical presentation of disease (15,20). Therefore, a detailed understanding of the related factors that may influence the duration of AU will help primary physicians to perform a more appropriate clinical assessment. So, we aimed to determine if there were differences in demographic and clinical characteristics in children that had an AU that will progress more probably to CU, with the persistence of symptoms in follow-up at three and six months after the first attack.

We analyzed if there were some patient-related factors associated with persistent urticaria such as age, sex, etiology, severity, and family history. Sex was not a statistically significant factor associated with the duration of urticaria. Children 5-10 years old and 10-15 years old had a greater tendency to CU, with symptoms remaining at six months of 6% and 7%, respectively. About etiology, the higher prevalence of urticaria has been observed in the group with unknown etiology (10%). Severity and familiarity did not seem to correlate with the persistence of urticaria.

The present study has some limitations. Firstly, we have not recorded laboratory data (for example, white blood cell, c-reactive protein) because current guidelines do not recommend routine diagnostic tests or extended diagnostic programs in patients with acute urticaria. Moreover, we did not record the total number of accesses of urticaria in pediatric age in Italy, even if the reported data are recorded in several cities of Italy and probably could represent a model of Italian reality.

Conclusion

We believe that the identification of children with AU who have a high risk of progression to CU is essential for better diagnostic and therapeutic management. We think that a good quality standardized questionnaire aimed to identify specific high-risk factors, together with a detailed

physical examination, can provide important data related to the progression from AU to CU and guide the follow-up.

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Legend to figure

Figure 1: Detailed information on the relationship between etiologies of the first attacks of urticaria and recurrence of urticaria at one, three and six months.

Table 1. Clinical characteristic of urticaria in children enrolled in the study

| Urticaria | Total | Male | Female | % |
|------------------|--------------|-------------|---------------|----------|
| Idiopathic | 101 | 48 | 53 | 32.4% |
| Infectious | 139 | 75 | 64 | 43.9% |
| Food | 43 | 27 | 16 | 11.4% |
| Drugs | 12 | 9 | 3 | 3.5% |
| Poison | 1 | / | 1 | 0.3% |
| Contact | 18 | 7 | 11 | 5.7% |

Table 2. Difference in the age of children with urticaria enrolled in the study

| Urticaria | Total children (n) | Mean age (n) | | | |
|------------|--------------------|--------------|------------|-------------|-------------|
| | | 0-5 years | 6-10 years | 11-15 years | 16-20 years |
| Idiopathic | 101 | 38 | 42 | 20 | 1 |
| Infectious | 139 | 87 | 37 | 13 | 2 |
| Food | 43 | 21 | 11 | 9 | 2 |
| Drugs | 12 | 5 | 3 | 4 | 0 |
| Poison | 1 | 0 | 0 | 0 | 1 |
| Contact | 18 | 7 | 4 | 5 | 2 |

Table 3. Relationship between gravity of urticaria and sex, age, etiology and familiarity for allergy.

| | | GRAVITY | | |
|---|-------------|-----------------------|---------------------------|----------------------|
| | | MILD n.127 (40.4%) | MODERATE n.140 (44.5%) | HIGH n.47 (14.9%) |
| Physician- diagnosed cause of urticaria | Idiopathic | 46 | 39 | 16 |
| | Infectious | 55 | 70 | 15 |
| | Food | 18 | 14 | 11 |
| | Drugs | 6 | 5 | 1 |
| | Poison | 0 | 1 | 0 |
| | Contact | 2 | 10 | 5 |
| Sex | Female | 63 | 62 | 23 |
| | Male | 64 | 78 | 24 |
| Age | 0-5 years | 76 | 66 | 16 |
| | 6-10 years | 33 | 52 | 12 |
| | 11-15 years | 16 | 18 | 17 |
| | 16-18 years | 2 | 4 | 2 |
| With family allergic history | 43 | 51 | 20 | |

Table 4. Related factors associated with the recurrence of an initial episode acute urticaria in children

| RECURRENCE | | | | |
|--|-------------|-------------------|--------------------|--------------------|
| | | follow-up 1 month | follow-up 3 months | follow-up 5 months |
| Physician-diagnosed cause of urticaria | Idiopathic | 10 | 11 | 10 |
| | Infectious | 8 | 6 | 4 |
| | Food | 4 | 4 | 2 |
| | Drugs | / | 2 | / |
| | Poison | / | / | / |
| | Contact | 4 | 3 | 2 |
| Sex | Female | 13 | 13 | 10 |
| | Male | 10 | 13 | 8 |
| Age | 0-5 years | 9 | 13 | 8 |
| | 6-10 years | 9 | 6 | 6 |
| | 11-15 years | 5 | 5 | 4 |
| | 16-18 years | 3 | 2 | 0 |
| Severity | Mild | 11 | 9 | 4 |
| | Moderate | 10 | 11 | 8 |
| | High | 5 | 6 | 6 |
| With family allergic history | | 9 | 11 | 10 |

