Original Article

1) TITLE

ACUTE URTICARIA IN CHILDREN: FROM PEDIATRIC EMERGENCY DEPARTMENT TO ALLERGOLOGY CONSULTATION AT A CENTRAL HOSPITAL

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4) Abstract

Background. Acute urticaria is a common condition in the pediatric emergency department (ED) and no data is available in Portugal.

Objective. We aimed to characterize the prevalence, etiology and management of acute urticaria in children presenting at an ED of a portuguese central hospital and report the follow-up investigation when drug or food allergy was suspected.

Methods. Retrospective study of clinical records from children admitted to the ED with acute urticaria during one year period.

Results. 250 children were included, mean age of 7.4 ± 4.9 years (0-17 years). The most frequently suspected etiological factors were infections (22%), foods (12%), insect bites (9%) and drugs (8%), of which, upper respiratory tract infections, seafood and β-lactam antibiotics were the most frequent. In 44% of cases, the etiology of urticaria was not determined. After ED discharge, of the 50 patients with suggestive drug or food allergy, only 48% were sent to allergological workup and the allergy confirmed in 6 of them (2.4% of the 250 children).

Conclusion. These data suggest that allergy is not the main trigger of acute urticaria in ED children, but when suspected, reference to an allergy department to complete allergological workup was insufficient.

5) Highlights box

Acute urticaria in children can be caused by a wide variety of factors, such as infections, food or drug hypersensitivity, physical triggers, insect bites and idiopathic causes. There is a lack of childhood acute urticaria detailed information in Portugal, with no data available. In our study we characterize the prevalence, etiology and management of acute urticaria in children presenting at an emergency department of a portuguese central hospital and reported the follow-up investigation when drug or food allergy was suspected.

This study supports the opinion that allergy is not the main trigger of acute urticaria in children, representing 2.4% of the children admitted to the ED with acute urticaria. Most importantly, we found that in 52% of patients with suspected drug or food allergy, reference to an allergy department to complete allergological work-up was not performed.

It is important that physicians practising emergency medicine provide appropriate aftercare instructions to patients with suspected allergy, and refer these patients for allergological evaluation, in order to provide a complete and careful diagnostic work-up that is essential for a correct diagnosis. In fact, underestimated allergy diagnosis could lead to an increased risk in truly allergic patients, and overestimated diagnosis of allergy could contribute to an overrated avoidance measures in non-allergic children.

6) Manuscript

1. Introduction

Urticaria is a skin condition defined by the presence of wheals and/or angioedema (1). The diagnosis of this disorder is based on detailed clinical history and physical examination. By definition, acute urticaria lasts less than 6 weeks, is usually self-limiting and resolves typically within 30 minutes to 24 hours (1).

Acute urticaria in children can be caused by a wide variety of factors, such as infections, food or drug hypersensitivity, physical triggers, insect bites and idiopathic causes (2). It can be managed by the family physician, but this disease worries parents and children are frequently taken to the pediatric emergency department (ED). In a 2-year study, G. Ricci et al reported 2.4% of children (aged 0-14 years) with urticaria referred to an Italian ED (1.1 accesses/day) (3). J.Y. Kim et al found that urticaria and angioedema were the most common cutaneous disease treated in children and adults in a Korean ED, during an 8-year period from 2003 to 2010 (4). In an Italian study, the prevalence of acute urticaria in children and adults ED in a 1-year period was 1.01% of the total ED visits, corresponding to 1.2 admissions per day (5).

Although the allergic cause is minor (3,5), in case of suspicion an allergological evaluation is recommended.

There is a lack of childhood acute urticaria detailed information in Portugal, with no data available.

The aim of this study was to characterize the suspected aetiology and management of acute urticaria in children presenting to the ED of a portuguese central hospital covering an area of about 700,000 inhabitants. We also aim to analyse the follow-up investigation when drug or food allergy was suspected.

2. Materials and methods

2.1 Patient population

This retrospective study was conducted from January to December 2017. The database of pediatric patients aged less than 18 years presenting to the Centro Hospitalar Vila Nova de Gaia/Espinho ED was searched for "urticaria" (code 708) and subtypes (708.0 "allergic urticaria", 708.1 "idiopathic urticaria", 708.8 "other specified urticaria" and 708.9 "urticaria, unspecified") by International Classification of Diseases, Ninth Revision (ICD-9) codes.

2.2 Methods

Patient characteristics were collected from medical records and included age, gender, clinical manifestations, suspected trigger, personal allergic history, treatments and follow-up.

Children were divided into four age groups: infant (1 month to 1 year), preschool age (2−6 years), school age (7−12 years) and adolescent (13−17 years).

In addition to urticaria, the clinical presentation of children could include fever, respiratory tract symptoms (nasal obstruction, rhinorrhoea, sore throat, cough, dyspnoea and wheezing), gastrointestinal symptoms (nausea, vomiting, diarrhoea, constipation and abdominal pain), urinary tract symptoms (frequency, dysuria and pyuria), cardiovascular symptoms (tachycardia and palpitations) or others. Patients presented with anaphylaxis were excluded. Anaphylaxis was defined by the European Academy of Allergy and Clinical Immunology as "a severe, life-threatening generalized or systemic hypersensitivity reaction, which is characterized by being rapid in onset with life-threatening airway, breathing or circulatory problems, and is usually associated with skin and mucosal changes" (6).

The suspected etiological factors of acute urticaria were divided into 7 major categories based on the ED medical record: infections, drugs, foods, insect bites, contact allergens, physical agents and undetermined.

The personal allergic history of children included atopy, rhinitis, asthma, atopic dermatitis and food, drug and hymenoptera venom allergy. The term atopy as defined by World Allergy Organization "when individuals have an IgE sensitization as documented by IgE antibodies in serum or by a positive skin prick test"(7). Patients with chronic urticaria were excluded. The types of medical treatment and their methods of administration were recorded. The patients were discharged from the ED to home, a medical appointment or required hospitalization.

In an allergology consultation, a detailed clinical history was recorded and additional data were collected from the patient's hospital and personal health records. Children with a clinical history compatible with drug or food allergy/hypersensitivity were proposed to continue the allergology evaluation, based on specific IgE determination, prick and intradermal skin testing for drugs, and prick and prick-to-prick skin tests for foods. Finally, a provocation test was performed if not contra-indicated and if all other investigations were inconclusive. If parents reported symptoms that were not consistent with allergy/hypersensitivity, or the child could tolerate the suspected food or drug, they did not undergo further assessment. Skin tests and provocation tests were considered positive if EAACI and AAAI criteria were met (8,9).

The study was approved by the local ethical committee.

2.3 Statistical analysis

Descriptive statistics were produced for each relevant variable. Categorical variables are presented as frequencies and percentages, and continuous variables as means and standard deviations. Normal distribution of variables was checked using skewness and kurtosis. Differences in the prevalence of the aetiologies were analysed among the four age groups by the χ^2 test. A P value <0.05 was regarded as statistically significant. Analysis was performed with the use of IBM® *SPSS* Statistics version 24.

3. Results

Epidemiology, demographics and personal history

A total of 252 children with acute urticaria were included, which corresponds to 0.58% of the 43107 pediatric ED visits, between January and December 2017. There were 127 (50.8%) boys. The mean age was 7.4 ± 4.9 years, from neonate to 17 years. The majority of children were in the preschool-aged group (38.8%), followed by the school-aged (31.2%), adolescent (19.2%) and infant (10.8%) groups.

Considering personal allergic history, atopy was confirmed in 17 patients (6.8%). Rhinitis (10.8%) was the most prevalent disease, followed by asthma (10.4%) and atopic dermatitis (6.8%).

Clinical manifestations

Regarding clinical manifestations, 60% of reports had skin lesions only, and the remaining 40% had other clinical symptoms. Respiratory tract symptoms were the most commonly-associated symptoms (16.8%). Others included gastrointestinal symptoms (8%), fever (6.4%), cardiovascular symptoms (1.6%), urinary tract symptoms (0.4%) and others. Urticaria coexistent with angioedema was observed in 26 children (10.4%).

Detailed demographic and clinical characteristics of the patients are summarized in **Table I**.

Suspected aetiologies

Infections were the most common suspected etiological factor (22.2%), followed by foods (12.0%), insect bites (9.2%) and drugs (8.0%). Other suspected triggers were physical agents (4.0%) and contact allergens (0.8%). In 110 cases (44.0%), the cause of acute urticaria was not determined. Concerning the detailed aetiologies, upper respiratory tract infections were the most frequently documented infections associated with acute urticaria in children (13.2%). Other infectious causes included acute gastroenteritis (5.3%), skin infections (1.2%) and lower respiratory tract infections (0.8%). Foods were the second most common aetiology in our study with shrimp (2.4%) being the most common allergen. Egg (2%), milk (1.6%), fruits (1.2%), fish (1.2%), meat (1.2%) and peanut (0.8%) were the least common food-related allergens. Regarding insect bites, none was caused by hymenoptera insects. Of the drug-related causes, β-lactam antibiotics were the most common (6.0%). Analysis of aetiologies in different age groups showed that no determined etiology was more frequent in the preschool-aged group; and infections were more frequent in the preschool and school-aged groups than in the other groups. Suspected food allergy was more frequent in school-aged, followed by preschool-aged and adolescent groups. Suspected allergy to milk was only present in infants and preschool-aged groups. In the school-aged group, egg was the most suspected food trigger. Seafood, fish and peanut were more frequently suspected in the adolescent group. Drug-related aetiologies were higher in school-aged and adolescent groups. **Table II** describes all the suspected etiological factors.

The prevalence of the various aetiologies did not differ significantly between gender groups ($p>0.05$).

Treatment

The therapy most frequently prescribed in the ED was H1-antihistamine in 62.8%, followed by corticosteroids in 41.2%. Antihistamines in association with corticosteroids were

prescribed in 98 cases (39.2%). In both therapies, the oral form was used more commonly than injection form. All antihistamines used were first-generation H1 antagonists. Of the 250 reported enrolments in this study, in 88 cases (35.2%), no therapy was established (**Table II**). In addition, no one had received intramuscular epinephrine injections in ED.

The therapy at discharge was antihistamines only in 46.6% of cases, followed by antihistamines plus corticosteroids (35.3%). Intramuscular adrenalin injections were prescribed to 4 children (1.6%), and corticosteroids only to 2 children (0.8%). In 15.7% of cases, no treatment was prescribed (**Table III**).

Discharge from ED

Of the 250 patients enrolled in this survey, 217 (86.8%) were discharged home, 32 (12.8%) to a medical appointment and 1 (0.4%) required hospitalization for intravenous fluid therapy associated to acute gastroenteritis.

Allergy evaluation

Among the 50 children whose ED doctors suspected they had a drug or food allergy, 24 (48.0%) were sent to an allergy department for further investigation. After a detailed anamnesis, 2 patients (8.3%) had already tolerated subsequent ingestion of suspected foods (1 milk, 1 egg). The remaining 22 children (91.7%) had a compatible clinical history of food or drug allergy and required further evaluation. Six (25%) refused the diagnostic procedures (3 amoxicillin, 2 shrimp, 1 nuts). Thus, 16 children (66.7%) agreed to proceed with diagnostic tests. Specific IgE (sIgE) and/or skin tests were carried out in all patients. Thirteen provocation tests were performed in 11 patients with the suspected trigger; the drugs tested were β-lactams in 7 patients (5 amoxicillin/clavulanic acid, 1 amoxicillin, 1 cefixime) and acetaminophen in 1 patient. Five provocation tests with foods were performed (1 shrimp, 1 nuts, 1 fish, 1 milk and 1 egg) (**Figure 1**).

After complete evaluation, allergy was documented in 6 of 16 patients (37.5%), including 2 patients with positive sIgE (shrimp, amoxicillin); 2 with positive skin tests (amoxicillin, amoxicillin/clavulanic acid); 1 patient with positive sIgE, skin prick test and ImmunoCAP™ *ISAC* assay compatible with Lipid Transfer Protein syndrome; and one with positive provocation test (amoxicillin/clavulanic acid) (**Figure 1**).

Overall, from the 24 evaluated patients, 6 (25%) refused the diagnostic procedures, 12 (50%) had a negative allergological work-up and could actually tolerate the suspected trigger, and 6 (25%) had confirmed allergy. In conclusion, in the total 250 urticaria ED episodes, 2.4% had allergy confirmation (**Figure 1**).

4.

5. Discussion

Acute urticaria is a common disease in the pediatric ED. Ricci et al estimated that 2.4% of 33917 children referred to the emergency room were diagnosed with acute urticaria in a 2-year italian survey (3), but in our study only 0.6% of the emergency visits were due to acute urticaria episodes. Our explanation relies on codification system used on ED that can cause underdiagnosis.

In our study, the prevalence of acute urticaria was higher in preschool-aged group (39%), which is consistent with the literature (2,10), although other studies had found urticaria prevalence to be higher in children aged 0-24 months (28%), progressively decreasing thereafter (3).

Infections were the most common aetiologies (22%), being more frequent in the preschool and school-aged groups than in the other groups, with upper respiratory tract infections and acute gastroenteritis being the major infectious causes. This finding is compatible with those reported in previous studies (2,3,10–12), despite differences on age distribution. One study showed that infections as a cause of urticaria decreased as the age of children increased (2). In contrast, in a 1-year Italian survey, infections were the cause of urticaria in less than 3% of the children, however the authors did not discriminate the age distribution of the children (5). As for foods, our results agree with previous reports (2,10,13), showing that foods were the second most common trigger, with shrimp and egg being the most frequently involved allergens. Suspected food allergy was more frequent in school-aged group (egg), followed by preschool-aged (egg, milk, meat) and adolescent (seafood, fish and peanut) groups. In infant group, the only suspected food trigger was milk. In contrast to other study that found that foods were more predominant with increasing age of children (2). One italian study reported that food allergy showed two peaks of age prevalence: the first in children under 2 years (cow's milk or egg) and the second in those older than 5 years (nuts) (3). We reported very few cases due to peanuts, in contrast to other studies (2). In the opinion of the authors this is due to the fact that in Portugal most children do not eat nuts traditionally. A recent 10-year Portuguese anaphylaxis survey reported that in children nuts was the second most frequent cause of anaphylaxis due to foods, following milk (14). This founding showed that prevalence of nuts allergy is increasing in our country. Similar to other studies (3,5), we found that in most cases (43.6%), the aetiology of acute urticaria in children could not be determined, mainly in the preschool-aged group. The differences between studies regarding the distribution of aetiologies of acute urticaria in each age group may be due to several causes: the inclusion criteria was different because of the use of different classification on ED; the population

included had different age distribution; and regional differences regarding food consumption between the different countries, for example Portugal and Italy have similar food habits (Mediterranean diet) but different from Taiwan. Non-hymenoptera insect bites were the third most frequent aetiology, and we reported a higher prevalence (9.2%) when compared to other studies (2,3,13). The authors think that there may have been episodes of prurigo estrivalis that were misdiagnosed as urticaria. Although some studies have shown that drugs were an important cause of childhood urticaria (3,5), in our survey they were only the fourth most common trigger (8%). Drug-related aetiologies were higher in school-aged and adolescent groups. In a Taiwan study, the adolescent group had more suspected drug allergies (2). Antibiotics and nonsteroidal anti-inflammatory drugs (NSAIDs) were the most frequent culprit drugs involved (2,11,12). However in our study, only one patient had urticaria due to NSAIDs; with β-lactam antibiotics being the major drug-related aetiology (3%). These findings suggest that detailed medical history is extremely important in the study of children with acute urticaria, and the presence of infections in particular should be explored, especially those of the respiratory and gastrointestinal tracts. In addition, a possible relationship with food and drugs should always be evaluated.

The first level of acute urticaria treatment includes the use of non-sedating oral H1-antihistamine (1). In accordance with these guidelines, oral H1-antihistamines were administered to 55.2% of the children. Regarding treatments at discharge, H1-antihistamines were prescribed to 81.9% of the patients, 35.3% of which in association with a systemic corticosteroid. Similar results were found in other studies (2,3,13). Although adrenaline was not administered in the ED, it was prescribed to 4 patients at discharge, all of them with food as the suspected trigger. The authors can speculate that ED doctors suspected a possibly more serious future reaction, with criteria for anaphylaxis.

In our study, the majority of children (86.8%) were discharged home. Almost 13% were referred to a medical appointment for further investigation. Only 1 patient (0.4%) was hospitalized. In the Ricci et al survey, 3.8% required hospitalization for either the disease or for serious associated infections.

Acute urticaria usually does not require a diagnostic workup, because the major cause is infection. Detailed history and physical examination are the most important steps towards establishing a diagnosis, identifying an underlying cause, and determining the need for further investigation. Allergological evaluation is recommended if there is a clinical history of allergy in order to confirm or exclude an allergic cause and identify the culprit drug, food or insect venom (1).

The results from the survey indicated that drug or food allergens were suspected triggers in 20% of acute urticarial cases. Contrary to our expectations, only 48% of them were referred to an allergy department for further investigation. Previous studies reported a prevalence of these suspected triggers between 17% to 36% (2,3,5,10). However, these studies were not used to firmly demonstrate the allergy diagnosis. In our study, when a proper diagnostic work-up was carried out, allergy was excluded in most patients and diagnosed in only 6 of 24 cases (25%). Some studies reported that many children with adverse drug reactions are misdiagnosed as having drug allergy (15,16).

However, identification of true drug hypersensitivity is uncommon, with 2 studies of more than 40 children with a history of drug allergy showing that more than 90% tolerate the drug after appropriate workup (15,17). In line with this finding, Caubet and colleagues (18) were able to reproduce an urticarial reaction in only 6.8% of the 88 children presenting to the ED within 72 hours of ingesting b-lactams. As for foods, in a 10-year survey, only 1 out of 3 children had positive oral food challenges. Shrimps were the most common food involved, especially among children older than 3 years of age, followed by wheat, cow's milk and egg (19). In a birth cohort study, cow's milk allergy was suspected in 358 children and confirmed in 55, resulting in an overall incidence of challenge-proven cow's milk allergy of 0.54% (20).

The remaining 52% of patients that experienced a drug or food reaction resembling allergy, were catalogued as being allergic, without any further investigation. This leads to over-diagnosis of drug or food allergy/hypersensitivity that could contribute to an overrated avoidance measures in non-allergic children. However, underestimated allergy diagnosis could lead to an increased risk in truly allergic patients. Misdiagnosis has important undesirable consequences for the patients, but also a negative impact at socio-economic level.

There are some limitations in this study. Firstly, it was a retrospective study. Secondly, the usage of ICD-9 codes may lead to underdiagnosis or overdiagnosis of acute urticaria evaluated at ED. The exclusion of anaphylaxis is another limitation in this study, because the criteria used could lead to possibly misdiagnosis, particularly in the presence of active infection. Lastly, aetiology could not be easily determined in children with acute urticaria who were prescribed antibiotics and NSAIDs during infection. In these cases we always considered the drug as the suspected trigger, despite being the least likely.

6. Conclusions

In conclusion, children with acute urticaria were referred to the ED in 0.58% of the total pediatric ED visits and in most cases the aetiology was not determined. Upper respiratory tract infections were the most common etiological factor.

This study supports the opinion that allergy is not the main trigger of acute urticaria in children, with only 6 patients having a confirmed diagnosis of drug or food allergy, among the 50 patients with a suggestive clinical history. Most importantly, we found that in 52% of patients with suspected drug or food allergy, reference to an allergy department to complete allergological work-up was not performed.

It is important that physicians practising emergency medicine provide appropriate aftercare instructions to patients with suspected allergy and refer these patients for allergological evaluation, in order to provide a complete and careful diagnostic work-up that is essential for a correct diagnosis. We reinforce the need of formation of doctors in pediatric ED concerning allergic diseases and the implementation of criteria for proper referral to allergology workup.

Conflict of interests

The authors declare that they have no conflict of interest.

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