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Review

Chronic urticaria and drug hypersensitivity in children

Carla Mastrorilli[1], Roberto Bernardini[2], Lucia Liotti[3], Fabrizio Franceschini[4], Giuseppe Crisafulli[5], Silvia Caimmi[6], Paolo Bottau[7], Francesca Mori[8], Fabio Cardinale[9], Francesca Saretta[10], Giovanni Simeone[11], Marcello Bergamini[12], Carlo Caffarelli[1]

[1] Clinica Pediatrica, Dipartimento di Medicina e Chirurgia, Azienda Ospedaliero-Universitaria, Università di Parma, Italy; [2] Paediatric Unit, "San Giuseppe" Hospital, Empoli, Italy; [3] Department of Pediatrics, Senigallia Hospital, Senigallia, Italy; [4] UOC Pediatria, Azienda Ospedaliero-Universitaria "Ospedali Riuniti", Ancona, Italy; [5] UO Allergologia, Dipartimento di Pediatria, Università di Messina, Italy; [6] Pediatric Clinic, Foundation IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy; [7] Pediatric and Neonatology Unit, Imola Hospital, Imola (BO), Italy; [8] Allergy Unit, Department of Pediatric Medicine, Anna Meyer Children's University Hospital, Florence, Italy; [9] UOC di Pediatria, Azienda Ospedaliera-Universitaria "Consorziale-Policlinico", Ospedale Pediatrico Giovanni XXIII, Bari, Italy; [10] Pediatric Department, AAS2 Bassa Friulana-Isontina, Palmanova-Latisana, Italy; Pediatric Allergy Unit, Department of Medicine, Udine, Italy; [11] Primary care Pediatrician, Local Health Unit of Brindisi, Brindisi, Italy; [12] Generalist Pediatrician, Local Health Unit of Ferrara, Ferrara, Italy

Summary. The cause of chronic urticaria remains often elusive. The association between chronic urticaria and intake of medications have been reported in children. However, the causative role of drugs has been rarely ascertained by onset of symptoms on drug provocation test. Chronic urticaria can be mediated by immunologic and nonimmunologic mechanisms. The diagnostic work-up of chronic urticaria includes a comprehensive evaluation of triggering factors such as drugs. A diagnosis is necessary in order to permit a safely administration of drugs in children with chronic urticaria. (www.actabiomedica.it)

Key words: drug hypersensitivity reactions, children, urticaria, skin test, specific IgE, basophil activation test, drug provocation test

Introduction

Chronic urticaria (CU) is a common dermatologic disease, defined as the sudden development of transient wheals and/or angioedema recurring at least two times a week and lasting longer than 6 weeks. CU affects up to 5% of the general population and it is more frequent in adults (1). Depending on whether the lesions appear spontaneously or are induced by specific triggers, current classification distinguishes spontaneous CU (sCU) and inducible CU (2). CU is considered a mast cell-driven disease that may be triggered by infections, food or drug intolerance, activation of the coagulation cascade, genetic disposition, or autoimmunity (3). Within the inducible subtype, there are physical and non-physical urticarias (4). Although, drugs are occasionally implicated in CU and they may be causative factors or aggravate CU (5). In the last years, urticaria has increasingly attracted notice to patients and their families, last but not least inspired by the involvement of allergy and adverse reactions to drugs, foods or additives. This report attempts to summarize the evidence on the role of drugs in eliciting CU in childhood. English-language studies published from 1978-November 2018 in PubMed and the Cochrane central register of controlled Trials were searched by using the following keywords: "children", "chronic urticaria", "drug allergy", "etiology", "ACE inhibitors", "nonsteroidal anti-inflammatory drugs", and "drug-induced urticaria". Systematic reviews, guidelines, clinical trials, cohort and cross-sectional studies were considered. Case reports and abstracts were

excluded. References from selected papers were also examined to find additional related articles. Identified papers were discussed and relevant articles were included in this review.

Frequency of drug-induced chronic urticaria

The association between CU and intake of medications has been investigated in several studies. However, the diagnosis has not been always demonstrated by drug provocation test that is the gold standard (6,7). In a systematic review, etiological factors of CU in children have been analyzed, mentioning drug allergy from 0 to17% of cases (Table 1) (8-12). Kozel et al (13) showed that 9% of 220 patients from secondary and tertiary referral centers had CU or angioedema caused by an adverse drug reaction that was confirmed by positive drug challenge and urticaria was cured by permanent elimination of the drug use. In a population-based study, drug intake caused CU in 1.8% of children (14). Moreover, CU was caused by drug allergy in 1/44 and 22/92 Turkish children aged 6-15 years in two different studies (15, 16). Furthermore, drugs were suspected as precipitating factors for CU among 423 patients in 7.3% of cases (17). In an observational study including 369 patients aged 5-74 years, a history of CU triggered by various medications was positive in 28.6% of patients (18). However, urticaria improved in only three cases after withdrawing the suspect medication. In a Turkish cohort of 222 children with CU, drugs were found to be the triggering factors by clinical history in 18 patients, but they were not confirmed by skin tests, if available, and drug provocation tests (19).

Which drugs?

Several drugs have reported to trigger CU in children. Volonakis et al (10) described the type of drugs, penicillin and phenobarbital, which provoked CU. Sánchez-Borges et al (17) showed that the most frequent drugs involved in CU were nonsteroidal anti-inflammatory drugs (NSAIDs) (4.2%), ACE inhibitors (1.1%), radiocontrast media (0.4%), oral contraceptives (0.2%), glyburide/metformin (0.2), losartan (0.2%), penicillin (0.2%), lorazepam (0.2%), oxcarbazepam (0.2%). Desferal was reported as offending drug by Sahiner et al (15). Sublingual immunotherapy (20), perioperative drug (21), probiotics (22,23) have not been related to CU.

Commonly, CU in adults is considered "allied" to particular conditions, such as the multiple drug allergy syndrome (MDAS) and hypersensitivity to multiple NSAIDs (24,25). Patients with MDAS report a history of reactions to several chemically unrelated antibiotic and nonantibiotic drugs. The clinical classification of cross-intolerant hypersensitivity reactions to NSAIDs includes two different cutaneous manifestations: NSAIDs-exacerbated cutaneous disease (NECD), urticaria and/or angioedema occurring in

Table 1. Characteristics of included studies on the etiologic role of drug allergy in children with chronic urticaria

Authors, year	Country	Study population (n)	Age (range, years)	Prevalence of drug allergy (%)	Diagnosis of drug allergy
Kauppinen et al. 1984 (9)	Finland	55	6 months – 16 y	0	Challenge
Volonakis et al. 1992 (10)	Greece	226	1-14	17	Challenge
Kozel et al. 1998 (13)	Netherlands	220		9	Challenge
Sackesen et al. 2004 (11)	Turkey	17	1-19	17	Clinical history
Jirapongsananuruk et al. 2009 (12)	Thailand	94	4-15	0	Clinical history
Sahiner et al. 2011 (15)	Turkey	25	0.7-17.2	1	Clinical history
Sánchez-Borges et al. 2014 (17)	Venezuela	423	2-85	7.3	Clinical history
Colgecen et al. 2015 (18)	Croatia	369	5-74	28.6	Clinical history
Uysal et al. 2016 (16)	Turkey	92	6-15	23.9	Clinical history
Lee et al. 2017 (14)	Korea	57	9.12±1.68	1.8	Clinical history
Yilmaz et al. 2017 (19)	Turkey	222	4.6-12.3	0	Skin test, Challenge

patients with a history of sCU and NSAIDs-induced urticaria/angioedema (NIUA), wheals and/or angioedema occurring in otherwise healthy children. Although NECD has been occasionally reported in patients affected by physical urticaria with persistent dermatographism, it is primarily defined in patients with sCU (26). Aspirin hypersensitivity has been reported in 24% of 58 children and adolescents with CU, performing single-blind placebo-controlled challenge (26). Aspirin caused CU or exacerbated CU in 10% to 40% of patients (27, 28).

Regarding the role of additives, allergic or pseudo-allergic reactions can be provoked by benzoic acid, butylated hydroxytoluene, sulfites, aspartame, coloring, tartrazine, and preservatives. The prevalence of reaction to food and drug additives ranges from 2%-68%. In this regard, Rajan et al (29) challenged 100 patients with CU, aged 14-67 years, to 11 different colored additives and preservatives, and found two positive responses on single-blind challenge. No patient had a positive urticarial response on double-blind placebo-controlled challenge.

Mechanisms

CU can be mediated by both type I (IgE mediated) and type II (autoantibodies) hypersensitivity reactions (30) and by nonimmunologic mechanisms. Several studies showed that up to 60% of patients with sCU had a positive intradermal autologous serum test. In these patients, serum histamine-releasing activity has been endorsed to the presence of circulating IgG autoantibodies specific either for the high-affinity IgE receptor, FceRI, or for IgE. Circulating autoantibodies would be responsible for histamine release from both basophils in healthy donors and human mast cells *in vitro* (3). The autoreactivity observed in most patients might also represent a pathogenic mechanism for allergic and pseudo-allergic reactions induced by drugs. Several studies reported that leukotriene antagonists were of benefit not only in asthmatics by perhaps reducing radical induced by peroxidation of arachidonic acid in the cell membrane such as 8-isoprostane (31) but also in patients with CU, especially due to NSAID intolerance (32), suggesting that the inhibition of cyclooxygenase (COX)-1 pathway may play a role in these drug-induced reactions (33, 34). This hypothesis was supported by the tolerance of selective COX-2 inhibitors by most patients. However, other mechanisms could be involved, and a pathogenic role may be sustained by the presence of circulating histamine-releasing factors (35,36). It may be hypothesized that offending drugs may increase or help the activity of circulating histamine-releasing factors, whereas such factors alone might not be enough to provoke symptoms.

Diagnostic work-up and management

It is challenging to ascertain a cause-effect correlation between CU and drug allergy only on the basis of history, especially at the emergency department (37). The approach to CU includes a comprehensive evaluation. It is essential to identify, when possible, the triggering factors of CU by clinical assessment. Thus, in the clinical history it must be taken into consideration the use of drugs (e.g., NSAIDs), injections, immunizations, hormones, laxatives, suppositories, ear and eye drops, and alternative remedies. Diagnostic tests to drugs (cutaneous, serum specific IgE, challenge) should be considered in case of convincing relationship between drug consumption and symptoms occurrence (38). If there is a suspicion that a medication has induced urticaria, international guidelines recommend as routine diagnostic tests a trial of withholding the drug (2). The suspected drug should be substituted by another class of agents if necessary (39). A correct diagnostic approach can be reached up after symptoms' improvement during the exclusion period and onset of symptoms on drug provocation test. Tests aimed at searching IgE sensitization to additives and pseudo-allergens are not useful (40). A diet without additives and colorants in foods and drugs additive-free diet should be recommended only when there is an history of additives ingestion associated with symptoms occurrence, or when diagnostic work-up does not allow the identification of other etiologies. If the diet is successful, an open challenge should be performed initially. If there is any objective evidence of reaction, then double-blind placebo-controlled challenge should be performed to

confirm the diagnosis (41). CU in children is often a self-limited disease, but the long-term natural history of drug hypersensitivity in children is unknown. There is no data on the evolution of drug allergy after the resolution of CU in children (42).

Conclusions

Drugs account only for a few cases of CU, but it is important to be recognized as a possible cause. Patients with CU should be asked whether they take ACE inhibitors, aspirin, and non-steroidal anti-inflammatory drugs which are the most common eliciting agents. A rapid diagnosis is necessary to permit that drugs are safely given to children with CU.

Conflict of interest: None to declare

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Correspondence:
Carlo Caffarelli
Clinica Pediatrica, Dipartimento di Medicina e Chirurgia,
Azienda Ospedaliero-Universitaria, Università di Parma,
Via Gramsci 14 - Parma, Italy
Tel. 0521702207
Fax 0521702830
E-mail: carlo.caffarelli@unipr.it