



Childhood urticaria

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Purpose of review

The present article reviews childhood urticaria. It provides an update on the current understanding of its pathophysiology and highlights the current practice in the management of this condition.

Recent findings

Progress has been made in understanding the pathophysiology of urticaria with the elucidation of an autoimmune basis in a significant proportion of children with chronic spontaneous urticaria. H1-antihistamines remain the mainstay of therapy, but there is increasing awareness on the risks of sedating first-generation antihistamines. Omalizumab is increasingly being used off-license in the most refractory cases.

Summary

Urticaria is a common disease that affects children and adults. However, paediatric urticaria has specific features and remains poorly understood. Acute spontaneous urticaria is the most common clinical presentation in childhood. It is caused by viral infection in most cases with an identifiable trigger. By contrast, chronic spontaneous urticaria in children may be autoimmune, but more studies are needed to understand the clinical significance of functional autoantibodies in this subgroup of patients. Investigations should always be guided by history. Treatment remains largely symptomatic. H1-antihistamines are the mainstay of therapy but are insufficient to control symptoms in all patients. There is an urgent need for more efficacious therapies.

Keywords

antihistamines, childhood, chronic autoimmune urticaria, omalizumab, urticaria

INTRODUCTION

Urticaria is a disease characterized by itchy weals, angio-oedema, or both, and presents with specific clinical patterns. Most of the literature pertains to urticaria in adults. Published data on urticaria in children are scarce and mostly derived from extrapolating information obtained in adults. There is a great degree of incongruity amongst studies on urticaria, which is largely because of inconsistencies in its classification in the literature. Urticaria has traditionally been classified as either acute or chronic based on its duration, with acute urticaria lasting fewer than 6 weeks and chronic urticaria lasting 6 weeks or more. The importance of this distinction has been questioned as it is difficult to predict which patient with acute urticaria will progress to chronic disease and how frequently this happens [1^{••}]. The term 'chronic spontaneous urticaria' has been proposed as an alternative to 'chronic idiopathic urticaria' to emphasize the clinical behaviour of the disease rather than its causes. Diseases related to urticaria like urticarial vasculitis and syndromes which can present with urticaria are not included in current classification

[2]. Paediatric urticaria studies involve children with a median age range of 6–11 years. However, urticaria may occur at any age from infancy to adulthood [3].

QUALITY-OF-LIFE CONSIDERATIONS

In children, urticaria was found to produce a decline in the quality of life greater to that seen in many chronic diseases of childhood including epilepsy and diabetes [4]. There are currently no validated questionnaires that address the impact of urticaria on everyday life in children, though the effects may be debilitating as they impinge on education and learning. In one survey, up to 7.4% of children with urticaria missed an average of 7.5 ± 18.5 school days per year. Children with urticaria were more likely to

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KEY POINTS

- Childhood urticaria most commonly presents as a single acute episode, often triggered by respiratory viral infection.
- Chronic spontaneous urticaria in children may be autoimmune.
- Investigations of childhood urticaria are often unrewarding.
- Antihistamines are the mainstay of therapy.
- There is increasing awareness on the risks of sedating first-generation antihistamines.

have bad school performance when compared with those from the rest of the sample [5].

SPONTANEOUS URTICARIA

Different causes have been implicated. Individual swellings usually occur without an obvious trigger. In children, urticaria most commonly presents as a single acute episode lasting a few weeks, with only a small percentage of patients reported to progress to a more chronic form of the condition, especially during adolescence [6].

Epidemiology

There are no paediatric epidemiologic studies based on the current recommended classification for urticaria. Henz and Zuberbier [7] give a range of 2.1–6.7% for all forms of childhood urticaria. In contrast with adults, both sexes seem to be equally affected. Atopy seems to be more prevalent in patients with urticaria (with the exception of autoimmune urticaria) when compared with the general population [8¹¹]. In a recent study [9¹²] of childhood acute urticaria, a similar epidemiological pattern was found in northern and southern Europe regardless of genetic, geographic, and environmental differences.

Clinical presentation, natural course and prognosis

A small number of studies have reported the clinical manifestations of urticaria in childhood, its natural course and associated comorbidities [10¹³]. According to a series of 226 children with chronic urticaria, Volonakis *et al.* [11] identified weals alone in 78.4% and angio-oedema without weals in only 6.6% of patients, the remaining children showing a combination of both. In a recent prospective study [12] of 94 Thai children with chronic urticaria, 51% had

associated angio-oedema. By contrast, Liu *et al.* [13] reported that 8.8% of 1120 children with an initial episode of acute urticaria had coexisting angio-oedema. The latter group seemed to have a more severe clinical course when compared with the group of children with hives alone. Most cases of acute urticaria in children are transient and resolve without sequelae. In the large series by Liu *et al.* [13], only 5.4% of children continued to experience symptoms for more than 15 days. In chronic urticaria, rates of remission are variable across published studies. In general, however, chronic spontaneous urticaria appears to have a good prognosis. In one series of 80 children with chronic urticaria, remission occurred in 36% of cases during the 3-year study. However, the investigators could not establish predictors of disease remission [14]. Sahiner *et al.* [15¹⁶] showed that one out of two children with chronic urticaria were symptom free within 5 years. The recovery rate seemed to be better for boys than girls and for children under 10 years of age, but the difference did not reach statistical significance. In contrast to adults, preliminary data indicate that there is no significant difference between children with autoimmune and idiopathic urticaria with respect to disease severity, medication requirement, and disease remission [3,12].

Aetiology

Successful identification of a trigger for urticaria is difficult. In paediatric chronic urticaria (including physical urticaria in the classification), rates ranging from 21 to 83% have been reported [11,15¹⁶,17]. The considerable variations in the frequencies of a specific cause are mainly because of different criteria being used for the confirmation of suspected causes as well as a difference in population selection.

Infections

Infections are widely accepted as the leading cause of acute urticaria in the paediatric age group. In particular, upper respiratory viral infections appear to be the culprit in the majority of cases [13]. In a recent study [9¹²], it was demonstrated that the seasonality of several acute respiratory viral infections coincided with the seasonal fluctuation in acute urticaria incidence, supporting a potential cause–causality relation. In chronic urticaria, acute viral infections are believed to play an exacerbating role in some cases, but viruses have not been established as a direct cause per se of the condition [10¹³]. Chronic bacterial infections have also been implicated in the pathogenesis of spontaneous urticaria. In one study [18], group A β -haemolytic

streptococcus was documented in as many as 40% of 32 children with acute urticaria screened for streptococcal pharyngitis. Similarly, a role for *Mycoplasma pneumoniae* has been mentioned in few reports [19,20]. Sackesen *et al.* [6] highlighted the contribution of silent bacterial infections, especially urinary tract infections, to a significant number of acute and chronic cases of paediatric urticaria and reported resolution of urticaria following antibiotic treatment. However, many authors believe that bacterial infections are unlikely to have a significant role in chronic spontaneous urticaria [11,14,21,22]. More studies are necessary to determine the relevance of chronic infections in children with chronic urticaria as this may affect management. A clear association between parasitic infections and chronic urticaria is not established so far. In the UK, investigation for parasites is not recommended unless there is unexplained eosinophilia and a history of travel to endemic areas [23]. In one study [12] from a tropical country, parasitic infections were found in 5 out of 94 children with chronic urticaria but no clinical correlation was established.

Food

In one study [9[¶]] from two European cities, food allergy accounted for only 5.3% of all cases of acute urticaria, representing the least common identifiable cause. Foods implicated in younger children include egg, milk, soy, peanut, and wheat, whereas in older children triggering foods include fish, seafood, and nuts [24]. In chronic urticaria, Harris *et al.* [21] reported that although 27% of children or their parents regarded food a causative factor, food allergy was confirmed in only 2 out of 94 (2.1%). More recently, Du Toit *et al.* [14] demonstrated lower food allergen sensitization in a series of 80 children with chronic urticaria when compared with a control group with atopic eczema. In addition, they reported that dietary elimination of suspected foods did not affect disease course. In adults, it is now considered that most food-related chronic urticaria is pseudoallergic in nature and that allergy as a cause is exceptional [25]. Intolerance reactions to foods may also be relevant to children with chronic urticaria. In one study [26], up to 75% of children were found to have pseudoallergen-induced urticaria. Colouring agents and preservatives were most commonly implicated.

Drugs

Antibiotics and nonsteroidal anti-inflammatory drugs are the most commonly implicated drugs in

childhood urticaria. In one study [6] about the cause of different forms of urticaria in children, medications were implicated in 5 and 17% of acute and chronic urticaria cases, respectively. The authors admit, however, that no objective tools were used to demonstrate a causal relationship. In the study by Liu *et al.* [13], medications are mentioned as a cause of acute urticaria in up to 12.4% of children. Medications, in addition to infections, were linked with a more severe clinical course of urticaria than other physician-diagnosed causes. However, as in food-related urticaria, genuine drug allergy is an uncommon cause of urticaria. In a prospective study of benign skin rashes following penicillin use in children, Caubet *et al.* [27[¶]] concluded that the majority of rashes were not the result of β -lactam allergy and that viral infections, for which the antibiotics were prescribed, played an important role in many of these reactions. The authors based their conclusion on negative oral challenges to the implicated antibiotics. Similarly, Seitz *et al.* [28[¶]] excluded drug hypersensitivity in 40 out of 43 children and adolescents with suspected allergy to various drugs by performing appropriate testing.

Autoimmunity

The frequency of autoimmune urticaria in children and adults appears to be similar. In 2004, Brunetti *et al.* [29] demonstrated that children may produce functional autoantibodies to the alpha chain of the high-affinity IgE receptor (Fc ϵ RI α) or IgE itself, as in adults. They demonstrated that testing for autoreactivity using the autologous serum skin test (ASST) and the basophil histamine release assay (BHRA) significantly reduced the diagnosis of idiopathic urticaria from 52 to 29%. These results were reproduced in subsequent studies [12,14]. Chronic urticaria has been linked to a higher incidence of autoimmune diseases, especially autoimmune thyroid disease. In a recent study [3] from Turkey, it was found that 14.8% of children with chronic spontaneous urticaria have thyroid autoimmunity, a figure significantly higher than the rates of autoimmune thyroiditis in children without history of urticaria (0.35–1.6%). Although this figure remains lower than rates reported in adults, the authors recognize that autoimmunity is an evolving process which increases with age. Coeliac disease has been also associated with urticaria in children. In one case–control study [30], coeliac disease was found in 5% of children with chronic urticaria and in 0.67% of controls. Furthermore, the association was considered to be causal as a gluten-free diet resulted in symptom remission in these children.

Other autoimmune diseases mentioned in association with childhood urticaria include juvenile rheumatoid arthritis, arthralgia with a positive ANA, and insulin-dependent diabetes mellitus [21,31].

INDUCIBLE URTICARIA

This umbrella term includes a heterogeneous group of physical urticarias and cholinergic urticaria [32]. Although most of the current literature refers to physical urticarias under chronic urticaria, it has been proposed that the term 'chronic urticaria' should be restricted to patients with spontaneous disease [8²²]. In the largest reported study [33] of physician-diagnosed physical urticaria in children, dermatographic urticaria accounted for 38% and cholinergic for 19% of all cases. Interestingly, mixed types of urticarias (mainly dermatographic and cholinergic) were found in 17% of children, highlighting that overlap amongst subtypes is not uncommon. There was no sex predominance and associated angio-oedema was reported in 67% of cases. The average duration of urticaria was 47 months and only 38.4% were free of symptoms after 5 years, indicating that children with physical urticarias have longer and more severe disease courses than previously thought. A history of atopy and more frequent episodes were associated with poorer prognosis. Cold urticaria remains rare [11,21]. Alangari *et al.* [34] described the clinical features of cold urticaria in 30 children. No prognostic factors for disease remission could be identified. Importantly, the authors found that one-third of patients experienced anaphylactic reactions and accordingly recommended the provision of an epinephrine autoinjector to all children diagnosed with cold urticaria. Delayed pressure urticaria usually coexists with chronic spontaneous urticaria, as in adults. It remains, however, uncommon in children. Regarding solar urticaria, it is very rarely reported in children and appears to affect those above 10 years of age [35].

INVESTIGATIONS

Disease history and physical examination remain the best tools in identifying an underlying cause of urticaria. They are fundamental to direct further investigations, which are rarely useful [23]. In acute urticaria, laboratory investigations are not required in the majority of cases. Physicians can try to confirm a suspected infection or allergic trigger only where clinically significant. Importantly, allergy tests must always be guided by history to avoid the generation of false-positive results. If

autoimmunity is suspected, the ASST is a useful screening test. In children, the in-vitro BHRA is considered a more acceptable alternative to the ASST because of the potential discomfort of the latter [14]. However, both tests are mainly research tools which are not readily available in daily practice. Furthermore, there is no single test available to date that is diagnostic of autoimmune urticaria. There is ongoing research in this field, but more needs to be done [36]. Physical provocation tests are the gold standard for the diagnosis of subtypes of inducible urticaria [32]. They are also valuable for establishing trigger thresholds which are important to determine disease severity and response to treatment [1²²]. In a chart audit of 172 paediatric cases with chronic urticaria, Thomas *et al.* [37] separated laboratory investigations into two groups: allergy tests and 'additional investigations' (including blood, urine, and provocation tests). They reported that 83% of children underwent at least one investigation. Importantly, only 5.2% of the 'additional investigations' were found to be positive reflecting a very low positive outcome rate. The authors suggested that most 'additional investigations' are being performed unnecessarily and concluded by recommending a limited and step-wise approach to investigations as per current guidelines, awaiting further more validated studies.

MANAGEMENT

The first step in the management of a child with urticaria is the identification of potential triggers, where possible, and their subsequent avoidance. Pharmacological therapy remains largely symptomatic and in addition to antihistamines, most agents are currently used off-license. Most cases of acute urticaria are transient and uncomplicated. They respond to antihistamines and can be managed in the primary care setting. A critical step in the initial evaluation of a child with an acute episode of urticaria is to differentiate it from anaphylaxis as urticaria may be its first manifestation. However, hospitalization is only indicated if either respiratory distress (wheezing or stridor) or other signs of anaphylaxis (hypotension, hypotonia, or gastrointestinal symptoms) are observed [38]. In one study [13], it was shown that the combined treatment with oral plus intravenous antihistamines or corticosteroid is associated with the shortest duration of an initial episode of acute urticaria when compared to single treatment. Despite first-generation antihistamines having a lower therapeutic window than second-generation drugs, they are still widely available and still preferred by many physicians in children as young as 2 years of age. However, it is now well

established that they may not only cause anticholinergic adverse effects, but also are responsible for cognitive impairment and disrupted sleep patterns [39]. In a recent GA2LEN position paper, the potential risks of first-generation antihistamines, in addition to their risk of interference with education, were highlighted [40]. The nonsedating second-generation antihistamines should be considered the cornerstone of urticaria therapy. They are recommended by the EAACI/GA2LEN/EDF/WAO as a first-line therapy with the possibility of escalating the dose up to four times if the standard dose is not effective. Although these guidelines are suggested to be applicable in children (with weight adjustment), it remains a weak recommendation because it is mainly founded on extrapolated evidence from rhinitis studies as urticaria in especially young children is rare and only a limited number of randomized controlled trials (RCTs) have been conducted in this age group [10¹¹]. The first RCT that looked at the efficacy of second-generation antihistamines in childhood urticaria demonstrated the efficacy of cetirizine in reducing the frequency of acute urticaria in toddlers aged 12–24 months with atopic dermatitis [41]. Studies [42–46] in young children of efficacy and safety of other second-generation antihistamines, mainly levocetirizine, followed. There is some evidence that levocetirizine and fexofenadine might be more effective than desloratadine at inhibiting wheal and flare response to histamine in human skin *in vivo* [47,48]. However, well designed head-to-head comparison trials are needed, especially in the paediatric population, to determine which antihistamine confers an advantageous risk–benefit profile. Autoimmune urticaria is not common in children and there is no consensus on the use of immunomodulatory therapy in this age bracket. There is a very limited experience with ciclosporin. However, its use should be limited to those with the most debilitating and refractory disease because of its potential adverse events. The first paediatric case series on its use in chronic urticaria was published in 2009. Ciclosporin at a dose of 3 mg/kg/day was well tolerated and induced remission in all patients after several months of therapy [49]. Omalizumab is a promising new therapeutic modality. Trials are ongoing to establish its efficacy and safety in adults and adolescents (above 12 years) with chronic idiopathic urticaria. However, its exact mechanism of action in urticaria remains elusive [50¹¹].

CONCLUSION

In this review, we have exposed the scarcity of available literature on the subject of childhood

urticaria. We have noted that urticaria in children has specific features and that extrapolation of adult data to children should be undertaken carefully. We have highlighted the need for further research on various aspects of urticaria, especially in children. Treatment of urticaria remains largely symptomatic rather than curative because it is currently difficult to identify underlying causes. New generation antihistamines are still the first-line therapy for all types of urticaria in adults and children alike. However, a good proportion of patients are still symptomatic even when increasing the antihistamine dose as per approved guidelines. Clearly, there is a need for alternative, more efficacious, yet safe therapeutic modalities.

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Conflicts of interest

There are no conflicts of interest for any of the authors in relation to this publication.

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