

Management of urticaria in children

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ABSTRACT

Urticaria is a common condition in children for which physicians are consulted. The management of childhood urticaria is similar as in adults; however, there are pediatric-specific features that must be taken into account for better management of childhood urticaria.

Key words: Antihistamines nonsedating, children, urticaria

DEFINITION

Urticaria is defined by the presence of wheals and/or angioedema.^[1] A wheal comprises a central swelling, pruritus or burning sensation, disappearing within a maximum of 24 h without residual lesion. Angioedema is characterized by swelling of the lower dermis and subcutis associated with a tingling sensation or pain, its resolution taking up to 72 h.

PATHOGENESIS

Activation and degranulation of basophils and/or mast cells leading to histamine release.

CLASSIFICATION

Urticaria is classified into four main types.^[1] The classification is based on the precipitating factors and duration

- Spontaneous acute urticaria
- Spontaneous chronic urticaria
- Physical urticaria
- Other urticarias.

SPONTANEOUS ACUTE URTICARIA

It lasts less than 6 weeks^[1] and is the most common

type of urticaria in children.^[2] It does not have a specific cause and has many potential trigger factors like infections, drugs, food hypersensitivity, etc. The possibility that a specific combination of several triggers is required to elicit acute urticaria could be an explanation for why symptoms never reappear. The overall success in finding the cause of acute spontaneous urticaria varies from 20% to 90% depending upon various factors.^[3,4]

The Precipitating Factors for Spontaneous Acute Urticaria Are

- Infections have been found to be the most commonly associated potential triggers in many studies.^[5] Upper respiratory tract infections, infections of the gastrointestinal tract, urinary tract infection due to viruses such as adenovirus, enterovirus, rotavirus, respiratory syncytial virus, Epstein–Barr virus, cytomegalovirus; bacteria like Streptococci, mycoplasma pneumonia; parasites like *Blastocystis hominis*, *Plasmodium falciparum*, *Anisakis simplex*. *Anisakis* nematode has a higher risk of recurrent acute urticaria but the association is controversial
- Drug hypersensitivity: It is the second most common cause of childhood acute urticaria. It is caused most commonly by antibiotics and nonsteroidal antiinflammatory drugs, but true drug hypersensitivity has to be confirmed by detailed patient and implicated drug history along with *in vitro* assays. If not contraindicated,

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drug provocation tests according to the patient's history. In cases of acute urticaria due to drug hypersensitivity, more than 90% patients could tolerate the suspected drug after a proper diagnostic workup^[6,7]

- Food allergy: Acute urticaria is the main manifestation in IgE mediated food allergy. Food allergy may occur after direct skin contact (form of contact urticaria), inhalation or digestion. Symptoms occur immediately in less than 1 h. Diagnostic workup is by allergen specific IgE quantification with total serum IgE and skin prick test regarding suspected food allergens. Oral food challenges are the gold standard for diagnosis. Acute urticaria is one of the main manifestations of IgE mediated food allergy, but food allergens are responsible for less than 7% of all cases of urticaria.^[8,9]

SPONTANEOUS CHRONIC URTICARIA

It has a duration of more than 6 weeks.^[1] The incidence of chronic urticaria in children can vary from 10-35%. Various suspected causes are:

- Infections: Many pathogens have been associated with chronic urticaria in children. Viruses like Epstein-Barr virus, bacteria like Streptococci, Staphylococci, *Helicobacter pylori*, *Escherichia coli* and parasites like *B. hominis* have been reported as causative factors^[10-12]
- Autoreactivity: It can be assessed *in vivo* by autologous serum skin test (ASST). ASST indicates presence of factors in patients own serum, responsible for the development of wheals. In order to demonstrate functional auto antibodies and their specificity, a basophil histamine release assay (western blot) and an ELISA should be performed.^[13] Some studies on chronic urticaria in children concerning with ASST have demonstrated a positive ASST in 38-47% patients.^[11,14] The patients with positive and negative ASST have similar clinical features, and hence there was no difference in their medications.^[11,14] Few studies have also demonstrated the presence of autoantibodies to IgE receptors in patients of chronic childhood urticaria.^[15] Understanding of the mechanism by which autoreactivity causes development of wheals requires further research and data analysis. Practically ASST has not been proven to enhance the identification of the underlying cause or is neither useful in predicting urticaria severity, duration or the best therapeutic approach

- Thyroid autoimmunity: Chronic urticaria is sometimes also associated with thyroid autoimmunity. It is hypothesized that children having chronic urticaria which is more severe or unresponsive to standard treatment may have associated autoimmune conditions. A study carried out in Italy by Caminiti *et al.* in antihistamine resistant cases of chronic childhood urticaria, 9.5% cases demonstrated antithyroid auto antibodies.^[16] At present laboratory examinations for thyroid hormones or antibodies are performed only if child's personal or family history is suggestive of thyroid dysfunction
- Other autoimmune conditions: Juvenile idiopathic arthritis, systemic lupus erythematosus, type I diabetes mellitus and coeliac disease have been reported to be associated with chronic urticaria in children. A study comparing 79 children with refractory chronic urticaria and 2545 controls suggested 5% cases had coeliac disease which was significantly more than in controls (0.67%). All these patients became symptom free within 5-10 weeks after being put on a gluten free diet^[16]
- Food hypersensitivity: IgE mediated food allergy is a rare cause of chronic urticaria in children.^[11,12] Psuedo, allergen-free diet,- may be beneficial to some patients with suspected hypersensitivity to food and food additives. Chronic urticaria reactions in children due to food hypersensitivity are mainly due to coloring agents and preservatives, monosodium glutamate and sweeteners.^[17] Food hypersensitivity must be documented by history and confirmed by supervised elimination in diet for 3 weeks, followed by oral challenge tests.
- Very rarely chronic urticaria has also been reported with pediatric malignancies.^[18] However, chronic urticaria in children does not warrant screening for malignancy.

PHYSICAL URTICARIA

They are the most common identified etiologies of childhood urticaria.^[19] According to eliciting trigger factors, physical urticaria is divided into the following subtypes; cold contact, heat contact, solar, dermatographic, delayed pressure and vibratory.

Dermographic Urticaria

It is elicited by mechanical shearing forces such as rubbing and scratching which rapidly induces wheals typically without angioedema. It may be idiopathic, related to systemic mastocytosis or may

be secondary to infections, infestations or drugs. Khakoo *et al.*^[20] studied inducible urticaria in children, and dermatographic urticaria was diagnosed in 38% patients. It is important to distinguish this condition from simple dermatographism, which is more common and requires no investigation or treatment.^[21]

Cold Contact

Cold (objects, air, fluid) induces immediate urticaria. It may be idiopathic or secondary to infections (viral) or cryoglobulinemia.^[22] Anaphylaxis due to cold exposure is reported in up to 50% cases.^[23] Atypical cold urticaria with immediate negative or uncharacteristic responses (systemic or prolonged reactions) to cold stimuli testing has been reported.^[24]

Avoidance of physical stimuli is crucial like avoidance of tight fitting or woolen clothing, aquatic activities, cold food, drinks, ice creams depending on the type of physical urticaria suspected.

OTHER URTICARIAS

These include cholinergic, exercise induced, aquagenic and contact.

Cholinergic Urticaria

It is the 2nd most common form of inducible childhood urticaria. It occurs within minutes after elevation of body temperature. The rise of body temperature may be active or passive. The wheals are typically less than 5 mm.

Exercise Induced Urticaria

It occurs on active elevation of body temperature due to active processes like exercise. Exercise-induced urticaria does not occur after a hot water bath and differentiation with cholinergic urticaria is necessary.^[21] There are larger wheals and evolution to anaphylaxis is frequent. Classic exercise-induced anaphylaxis predominantly occurs in young adults, adolescents within 30 min of exercise. It is typically preceded by cutaneous manifestation with a rapid progression to severe systemic reaction.^[25] Food dependent exercise-induced anaphylaxis is associated with IgE-mediated hypersensitivity to food and intake of these foods is tolerated in the absence of exercise which distinguishes it from food allergy.^[26] The commonly associated food products are wheat (most common), cereals, shellfish, nuts, vegetables, fresh fruit, eggs, and milk.^[26] Diagnosis is made with the help of isolated suspected oral food challenge, isolated exercise test (without food intake in previous 4 h) and

exercise test after suspected food intake. The high risk of severe reactions must be considered before performing this test as its sensitivity is only 70%.^[27] Specific IgE to omega-5 gliadin, a major wheat allergen has proved to be helpful in diagnosing this condition and avoiding the provocation test.^[28]

Contact Urticaria

Immediate hypersensitivity to exogenous proteins and chemicals can cause contact urticaria.^[29] Oral and perioral urticaria occurs after direct contact of the oral mucosa with food. Cross reactivity to pollen is common. Progression to systemic symptoms is severe and life threatening.^[29]

Aquagenic Urticaria

it is elicited by contact with water independent of temperature, and it is a rarity.

MANAGEMENT

Childhood urticaria management is currently the same as in adults.^[30] It consists of two essential steps;

Identification and Elimination of Eliciting Triggers or Underlying Causes

- Avoidance or elimination of urticarial triggers, underlying causes, is the only potentially curative therapy
- Comprehensive anamnesis and physical examination are the keys for identification of relevant eliciting factors. Patient tailored diagnostic tests may also be useful for identification of eliciting triggers.

Treatment Aimed at Providing Symptomatic Relief

- H1-type oral antihistamines are the most preferred drugs to induce symptom relief. 2nd generation antihistamines are preferred over older 1st generation antihistamine molecules. Cetirizine and its active enantiomer, levocetirizine, have been most extensively studied for childhood urticaria.^[31] Multiple double blinded placebo controlled trials have concluded that both are effective and safe for children as young as 1-year old. Other 2nd generation antihistamines that are being used in childhood urticaria are fexofenadine, loratadine, and desloratadine.^[32] The approach of a 4 fold increase in the antihistamine dose in children has not yet been validated. Better symptom control in difficult to treat chronic childhood urticaria can be achieved by changing over to an alternate 2nd generation antihistamine.^[33]

- First generation H1 antihistamines like hydroxyzine, diphenhydramine and chlorpheniramine have also been used. However, they are many adverse effects such as paradoxical excitement, irritability and hyperactivity in infants and toddlers. In older children sedation, impairment of alertness and memory, as well as behavioral changes, have been observed.^[34] Rare side effects include arrhythmias, dry mouth, urinary retention and constipation. Deaths due to accidental overdose have also been reported. Keeping all this in mind along with the unfavorable therapeutic index in children; the regular use of 1st generation antihistamines in childhood urticaria is not recommended
 - In chronic refractory urticaria leukotriene antagonists like montelukast have been used in combination with antihistamines.^[35] They are ineffective as monotherapy for urticaria, and further studies are needed to evaluate its efficacy when used in combination with antihistamines
 - H2 blockers like Ranitidine along with H1 antihistamines have also been used in chronic refractory childhood urticaria. However, further studies are needed to prove their efficacy
 - Other treatment options for chronic refractory urticaria in children include methotrexate, cyclosporine, immunoglobulins or omalizumab.^[36] There are case reports where these drugs have been used, but further studies are needed
 - Oral corticosteroids can provide symptom relief in urticaria. Due to the side-effects associated with long term corticosteroid use, they should be avoided in chronic urticaria.^[30] However, they may be used in acute urticaria as a short course
 - In selected cases of cold and cholinergic urticaria, therapeutic options like induction of tolerance can be considered^[30]
 - In refractory cases, the physician must carefully examine the patient, conduct relevant laboratory tests and consider the benefit versus risk ratio, before choosing one of the alternatives for treatment
 - Monitoring the urticaria activity score, determining the threshold for eliciting factors, and quality of life index for children are important tools during follow-up visits to judge the efficacy of treatment.
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