Recurrent urticaria

Lyn Ventilacion

Susan Leech

Abstract

Urticaria is characterized by the sudden development of wheals and/or angioedema. It is a common problem. Acute spontaneous urticaria is the most common form of urticaria, affecting up to 1 in 7 British children. About one-third will progress to chronic or recurrent urticaria. This article highlights the value of a good history and reviews the treatment options available for children.

The diagnosis is usually made on clinical grounds, by a thorough history of eliciting factors. Further investigations should be guided by the urticaria subtype and are often unnecessary. Acute spontaneous urticaria is usually secondary to a viral infection ± antibiotic use. Viral infections are usually responsible for flare-ups. In older children, chronic spontaneous urticaria may by associated with antibodies to the α chain of the high-affinity IgE receptor or, less commonly, other autoimmune disease. Dermographism and cold urticaria are the commonest forms of inducible urticaria in childhood.

Symptomatic relief is usually achieved by elimination of triggers and the use of non-sedating antihistamines. Tranexamic acid is useful to control isolated angioedema. Unresponsive cases may improve with the addition of a leukotriene receptor antagonist, anti IgE therapy or systemic immunosuppression (e.g. Ciclosporin A). Short courses of oral steroids are helpful to control acute episodes and severe exacerbations of chronic spontaneous urticaria. Urticaria remits over time. After 3 years, a quarter of children with chronic spontaneous urticaria are disease free and the vast majority are disease free after 7 years.

Keywords angioedema; antihistamines; childhood; dermographism; urticaria

Prevalence

Urticaria is common in childhood. Acute urticaria affects 4.5−15% of British children. The episodes last for less than 6 weeks. It may be spontaneous or occur in response to a viral infection and persist for several days. Chronic urticaria is less common, affecting 0.1−3%. Chronic urticaria is defined as an episode of urticaria and/or angioedema lasting for more than 6 weeks. Children may have episodic urticaria/angioedema lasting for hours or days and recurring over months or years. Of young children presenting to hospital with acute urticaria, 20−30% progress to chronic or recurrent urticaria. There is no gender bias.

Recent studies in children have provided information about the causes, eliciting factors and pathomechanisms. However, the distinction between acute and recurrent urticaria remains unclear and there are fundamental differences in populations studied (e.g. primary care, hospital based, selected from specialist clinics). In 2013, an international consortium updated the guidelines for the definition, classification, diagnosis and management of urticaria. This review uses this classification and applies it to childhood urticaria.

Definition

Urticaria is a manifestation of a heterogeneous group of diseases which share a common skin reaction, namely the sudden development of wheals and/or angioedema.

- A wheal consists of:
  - A central swelling of variable size, usually surrounded by reflex erythema
  - Associated itching or burning sensation
  - A fleeting nature; the skin usually returns to its normal appearance within 1−24 hours
- Angioedema is characterized by:
  - A sudden pronounced swelling of the lower dermis and subcutis
  - A swelling which is pale rather than pink and may be painful rather than itchy
  - Frequent involvement below the mucous membranes
  - Resolution that is slower than for wheals and can take up to 72 hours.

Mechanism

The wheal is a result of histamine acting on H1 receptors on endothelial cells. The neurogenic flare and pruritis arise from the action of histamine on sensory nerves. The wheal demonstrates oedema of the upper and mid dermis, with dilatation of the postcapillary venules and lymphatics of the upper dermis. In angioedema, the changes occur in the lower dermis and subcutis. Skin affected by wheals usually exhibits upregulation of endothelial adhesion molecules and a mixed perivascular inflammatory infiltrate of neutrophils, eosinophils, macrophages and T-cells. Mast cell numbers may be increased and urticaria involves dermal mast cell degranulation and histamine release. These changes are not specific, nor of diagnostic value.

When angioedema occurs in the absence of wheals (non-histaminergic angioedema), the mechanism usually involves overproduction of kinin. In children, C1 esterase inhibitor deficiency of hereditary angioedema should be considered. Other causes include stress, infection and drugs (classically angiotensin converting enzyme inhibitors). The management of this condition is not covered here.

Diagnosis of urticaria

The diagnosis of urticaria is made on clinical grounds. It is important to obtain a thorough history, including all possible eliciting factors. Questions should be asked regarding:

- Time of onset of disease
- Frequency and duration of wheals
- Shape, size and distribution of wheals
- Associated angioedema
- Associated subjective symptoms of lesion e.g. itch, pain

Lyn Ventilacion *MD MRCPCH is ST8 in the Department of Paediatric Allergy, Kings College Hospital, Denmark Hill, London, UK. Conflicts of interest: none declared.*

Susan Leech *FRCPCH is Clinical Lead for the Paediatric Allergy Service, Department of Paediatric Allergy, Kings College Hospital, Denmark Hill, London, UK. Conflicts of interest: none declared.*

- Precipitating factors including physical agents, exercise, relationship to food,
- Associated viral-type symptoms
- Diurnal variation
- Occurrence in relation to weekends and holidays
- Medication used and efficacy
- Effect on school and daily life
- Family and personal history of urticaria and atopy

Physical examination should include a test for dermatographism, where indicated by the history. Subsequent diagnostic steps depend on the nature of the urticaria subtype. In most cases, further investigations are unnecessary.

Classification of urticaria subtypes

The classification of urticarial subtypes is based on duration, frequency and causes. (Table 1). Two or more subtypes may co-exist in a single patient.

Spontaneous urticaria

Acute spontaneous urticaria

This is the commonest form of urticaria in children. It is usually generalized. Angioedema affects the eyelids and extremities in 60%. Pruritis is common (90%) and dermatographism less so (21%). Mild fever occurs in 50% of cases. Respiratory symptoms occur in 60% and gastrointestinal symptoms in 21%. Haemorrhagic lesions and arthralgia are more frequent in urticaria caused by infections. This may be misdiagnosed as erythema multiforme or anaphylactoid purpura and be alarming enough to cause hospital admission.

Investigation of acute spontaneous urticaria: thorough investigation of acute urticaria reveals a presumptive cause in most children. In younger children, the cause is usually a viral infection, possibly associated with antibiotic therapy. Viral causes include adenovirus, Epstein Barr virus, enterovirus and respiratory syncitial virus. Other infective causes include *Giardia* and *Escherichia coli*. The classic streptococcal cause of urticaria has been debated.

Acute urticaria may be associated with drug ingestion, usually antibiotics or antipyretics. It occurs between the 6th and 10th days of antibiotic therapy, with a drug which may have been used before without problem. Food ingestion, particularly egg, is associated with urticaria in 11%, particularly where the symptoms include angioedema of the lips and atopic dermatitis.

There are no diagnostic tests recommended for children with acute spontaneous urticaria. In routine clinical practice, the cause is usually unidentified.

Prognosis of acute spontaneous urticaria: intercurrent viral infections often cause flare-ups of urticaria. Following an acute episode, a quarter of patients will have a recurrence.

Chronic spontaneous urticaria

Chronic spontaneous urticaria (CSU) is characterized by daily or almost daily symptoms that persist for more than 6 weeks. It is less common in children than in adults, occurring in 8% of children under 3 years old, following acute urticaria.

Unlike the wheals of most physical urticarias, the wheals of chronic spontaneous urticaria usually last at least 6 hours. They fade without leaving a mark. 50–80% of children have accompanying angioedema. Oropharyngeal oedema is rarely life-threatening. A significant number (35–40%) of children with CSU are atopic, although the symptoms may not be associated with food ingestion (Figure 1).

Investigation of CSU: up to 40% of older children with recurrent or chronic urticaria have functionally active autoantibodies against the α-chain of the high-affinity IgE receptor (FCεR1) or against IgE, resulting in the promiscuous activation of dermal mast cells. Autoimmune urticaria can be demonstrated using the autologous serum skin test (ASST), where the intradermal injection of autologous serum elicits an immediate wheal and flare response and mast cell degranulation. This is not performed in routine clinical practice.

About 4% of children with CSU have antithyroid antibodies, although most are euthyroid. It is unclear if this association is causal. The urticaria often does not improve with thyroxine

Classification of urticaria (presenting with wheals and/or angioedema)

Types	Subtypes	Definition
Spontaneous urticaria	Acute spontaneous urticaria	Spontaneous wheals and/or angioedema <6 weeks
	Chronic spontaneous urticaria	Spontaneous wheals and/or angioedema >6 weeks
Inducible urticaria	Symptomatic dermographism	Eliciting factor: mechanical shearing forces (wheals arising after 1–5 minutes)
	Cold urticaria	Eliciting factor: cold objects/air/fluids/wind
	Delayed pressure urticaria	Eliciting factor: vertical pressure (wheals arising with a 3–12 hour latency)
	Heat urticaria	Eliciting factor: localized heat
	Solar urticaria	Eliciting factor: UV and/or visible light
	Vibratory angioedema	Eliciting factor: vibratory forces, e.g. pneumatic hammer
	Contact urticaria	Elicitation by contact with urticariogenic substance
	Cholinergic urticaria	Elicitation by increase of body core temperature due to physical exercise, spicy food, hot baths
	Aquagenic urticaria	Eliciting factor: water

Table 1