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Review Article

Chronic urticaria in children

兒童慢性蕁麻疹

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Urticaria is a fairly common paediatric disorder. The prevalence was reported to be 2.1-6.7%. Management of chronic urticaria in children can be challenging. A good clinical assessment with appropriate investigations will lead to a correct diagnosis. This article is a broad review of the approaches to assess and manage chronic urticaria in children.

蕁麻疹是頗為常見的兒科疾病。其患病率為 2.1-6.7% 。慢性蕁麻疹的處理甚具挑戰性。經良好的臨牀評估及適當的化驗研究可作出正確診斷。本文對兒童慢性蕁麻疹的評估及處理作廣泛的回顧。

Keywords: Angio-oedema, histamine H_1 antagonists, urticaria

關鍵詞：血管性水腫，H_1 型組胺拮抗劑，蕁麻疹

Introduction

Urticaria is derived from the Latin word 'urere' meaning 'to burn'. Urticaria usually manifests as a transient, itchy, polymorphic skin eruption. The disease has been recognised as a distinct disease entity for more than two thousands years. However, even now, the pathogenesis is still not fully understood.

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Urticaria can occur in any age group. It is not uncommon in children. The prevalence of urticaria has been reported to be 2.1-6.7% in children and adolescents.[1] This is even higher than the prevalence in adult population (0.05-0.5%).[1] By definition, chronic urticaria can persist longer than 6 weeks. Chronic urticaria is found less often in children in comparison to acute urticaria.[2]

Epidemiology

Boys and girls seem to be equally affected by chronic urticaria. In a retrospective study by Harris, sex distribution was equal in 94 children under 16 years old with chronic urticaria in United States.[3] The onset of urticaria range from 1 month old to 15.1 years old with a median age of 6.8 years.[3]

Aetiology

Although most cases of chronic urticaria are idiopathic, some may be associated with underlying causes. Physical factors have been reported to be responsible for chronic urticaria in 6.2-25% of children.[3-5] Symptomatic dermographism is the most common type of physical urticaria in children.[6] Wheals arise after firm stroking of the skin. Cholinergic urticaria is characterised by small, 2-3 mm wheals associated with sweating. It accounted for 2.7% of children aged 1 to 14 in Volonakis' series of chronic urticaria.[5] Idiopathic cold contact urticaria is reported in as many as 8.5% of cases in Harris' series.[3] It can be familial and acquired. Familial cold urticaria is a rare autosomal dominant disorder with varying penetrance. Children develop urticaria in infancy.[7] Acquired cold contact urticaria is more common. Alangari reported the mean and median ages of onset were 7 years old in a review of 30 patients with acquired cold urticaria, aged less than 18 years old.[8] Systemic symptoms, including headache, fatigue, fainting, dyspnoea, vomiting and diarrhoea are particularly common. Anaphylaxis happened in one third of the patients in Alangari's series. As physical urticaria is not associated with any systemic diseases or dietary factor, this diagnosis has important implications in management. The investigations for other associated factors can be stopped once a diagnosis of physical urticaria is established.[2]

A genetic predisposition has been reported in food allergy.[9] Food-provoked urticaria was held responsible for 9% of chronic urticaria and 12% of recurrent urticaria in Kauppinen's study of 163 children between 6 months and 16 years old.[4] In Volonakis' series, food accounted for 4% of chronic urticaria in children.[5] Apart from milk, nuts, egg and fish, food additives or acetylsalicylic acid were also important elicitors.[5,6] In Kauppinen's retrospective study, food additives accounted for 18% of chronic urticaria and 12% of recurrent urticaria in children.[4] Ehlers conducted a double-blinded, placebo controlled study on 16 children aged 3-17 years with chronic urticaria.[10] All of them were treated with a low-pseudoallergen diet for 3 weeks and then took food-additive containing capsules. Twelve out of 16 children developed disease exacerbation after taking capsules containing colouring agents, preservatives, monosodium glutamate and sweetener.

Infection is less often seen in chronic urticaria in comparison to acute urticaria. In Harris' retrospective study, infection including sinusitis and hepatitis accounted for 2% of chronic urticaria.[3] In Volonakis' series, infection accounted for 4.4% of chronic urticaria.[5] Sinusitis due to group A streptococcus and parasite infestation were the common causes.[5] However, Champion noted that urticaria usually did not respond to the elimination of worms.[11]

Drugs accounted for 1.8-2.5% of chronic urticaria.[4,5] The common offending drugs were penicillin and phenobarbitone. Aeroallergen accounted for 2.2% of cases.[5] Cat dander and pollens were the most common allergen. Most of these patients were highly atopic children.

Despite work up, 35% of chronic urticaria and 60% of recurrent urticaria remained idiopathic.[5]

The potential provoking factors of chronic urticaria are summarised in Table 1.

Clinical features

The clinical manifestations of chronic urticaria are similar to those of acute urticaria. Sixty-eight percent complained of pruritus over skin lesions.[12] Seventy-three percent described a burning sensation.[12] Six percent had concurrent arthralgia.[3]

Halpern suggested that the pattern of skin lesions remains constant if the aetiological agent remained unchanged.[13] Different patterns of urticaria are also reported for different eliciting

Table 1. Potential provoking factors of chronic urticaria

Provoking factors		Reported percentage in chronic urticaria
Physical urticaria	Pressure, friction, cold, light, water	6.2-25%
Cholinergic urticaria	Exercise, heat	2.7%
Idiopathic cold contact urticaria	Cold	8.5%
Food induced urticaria	Milk, egg, fish	4-9%
Food additives induced urticaria	Acetylsalicylic acid, colouring agents, preservatives, monosodium glutamate, sweetener	12-18%
Infection	Group A streptococci, parasite	2-4.4%
Drug	Penicillin, phenobarbitone	1.8-2.5%
Aeroallergen	Cat dander, pollens	2.2%
Idiopathic		35%

factors. For example, food-induced urticaria is described to be generalised, small, irregularly shaped wheals surrounded by slight flares which tend to fade rapidly.[5] Cholinergic urticaria commonly affects neck, flexural areas of elbows, wrists, knees and inner thighs but may affect other areas.[2]

6.6-9% of children develop angio-oedema without urticaria.[3,5] Angio-oedema manifests as swelling of eyelids, lips, mouth and tongue. The larynx, pharynx and intestine may also be involved. In Harris' series, 85% of patients had isolated chronic urticaria, 9% had isolated angio-oedema and the other 6% had both.[3] Volonakis' series had similar findings.[5] 78.4% of the children had chronic urticaria alone, 6.6% had angio-oedema alone and the other 15% had both.

Associated diseases

An atopic family history was more frequently found in children with chronic urticaria in comparison to adult patients.[8,14] Halpern reported 89% of children under 5 years old had an associated family or personal history of allergy.[13] Not only a positive family history but also a personal history of atopy was more common in children. Harris reported that atopic diseases coexisted in 30% of patients with chronic urticaria while it was only found in 18% of control subjects without chronic urticaria.[3] In a prospective study on 226 Greek children between 1 and 14 years of age, Volonakis reported asthma and/or rhinitis in 17.2% of children with urticaria and 10.1% of children with both urticaria and angio-oedema.[5]

Selective IgA deficiency is found in 3% of chronic urticaria or recurrent urticaria patients while it only happens in 1% of general population.[15] Bonifazi speculated that selective IgA deficiency led to parasite infestation which caused chronic urticaria in children.

There are also reports of association of chronic urticaria with various types of autoimmune diseases in children, including celiac disease, thyroid autoimmunity, insulin-dependent diabetes mellitus, systemic lupus erythematosus and juvenile rheumatoid arthritis.[3,16,17] This may be due to immune dysregulation in urticaria secondarily affecting other organs. Another possibility is that generalised immune disruption affects several organs independently. Leznoff and Sussman reported that 14% of 624 patients with chronic urticaria had positive thyroid autoimmunity as compared with 3% to 6% of controls.[18] In a recent

evaluation of data from 187 patients with chronic urticaria aged 7 to 17 years, Levy reported three (1.6%) cases of hypothyroidism during a 7.5 year follow-up period. One patient developed hypothyroidism five years after onset of chronic urticaria.[19]

History taking

The initial approach to chronic urticaria is a careful and thorough history taking. Clinical history is not easily obtained from children. Parents should be asked for the details of urticarial rash and associated symptoms. A good history should cover most aspects listed in Table 2.

Laboratory investigations

Investigations are based on clinical diagnosis drawn from history. The aim of investigation is to confirm the elicitor and screen for associated diseases. They are summarised in Table 3.

Table 2. Full history covering most aspects of urticaria

Subjects	Contents
Disease episode	Onset
	Frequency of attacks
	Daily pattern of attacks
	Seasonal pattern of attacks
Skin lesion	Morphology
	Size
	Body distribution
	Duration of individual lesions
	Complete skin recovery without residual pigmentation
Angio-oedema	Distribution (lips, eyelids, extremities)
	Duration of swellings
Joints swelling	Pattern of joint involvement
Systemic symptoms	Any breathing difficulty, wheezing, abdominal pain, vomiting, dizziness
Provoking factors	Infection
	Foods, food-exercise, food additives
	Drug exposure (aspirin, codeine, antibiotics including penicillin)
	Hot bath, sweating
	Friction, pressure
	Cold exposure
	Sunlight
	Water exposure
	Insect bites
Treatment	Name of medication
	Duration and usefulness of each medication
Life disturbance	School absence
	Effect on daily and leisure activities
	Peer group response
	Self perception

Table 3. Investigations for specific aetiological factors

Clinical problems	Investigations
Infection-induced urticaria	Full blood counts Liver function test CRP Urine microscopy and culture Stool for culture, virus, ova and cyst Viral titres, including CMV, EBV, Hepatitis B virus, Hepatitis C virus Throat and nasopharynx swab for virus Dental and sinus X-ray
Food-induced urticaria	RAST Skin prick test Elimination and provocation testing
Food additive-induced urticaria	Elimination and provocation testing
Drug-induced urticaria	RAST Challenge testing
Symptomatic dermographism	Light stroking of the skin
Cholinergic urticaria	Running stairs Jogging on the spot
Cold urticaria	Ice cube testing
Solar urticaria	Solar simulator
Aquagenic urticaria	Tepid water compress (35-36°C) to back for 40 minutes
Alleroallergen induced urticaria	Skin prick tests
Suspected autoimmune disease	ESR Thyroid function test Anti-nuclear factor C3, C4 Immunoglobulin pattern

Management

Parents and patients must be reminded to avoid aspirin, other non-steroidal anti-inflammatory agents and opiates as they can trigger histamine release. Codeine, pethidine, opioid analgesics, muscle relaxants, dextran and dye-containing radiocontrast media are also better avoided because these may also activate mast cells. There are specific precautions for specific types of urticaria. Those with symptomatic dermographism and chronic idiopathic urticaria should avoid tight clothing. Bedroom is to be kept cool all the time. Patients with cholinergic urticaria should understand that exertion, hot bath and anxiety can provoke attacks. Swimming in cold water should be forbidden in cold urticaria. It is probably safe to swim in a heated pool under supervision. Regular exposure of affected skin to cold can deplete the skin stores of antihistamine and induce cold tolerance. This may be useful in highly motivated adolescents. Sunlight provokes attacks in solar urticaria. Appropriate sunscreen is recommended.

Several simple topical measures may be useful to relieve itch. Tepid shower and application of cooling preparations such as 1% menthol in aqueous cream may be helpful.[2] Topical steroid was found to be useless.[3]

As H_1 receptor activation is mainly responsible for the itch, wheal and flare, H_1 antihistamine is used as the first-line treatment for urticaria. Non-sedating or low-sedating H_1 antihistamine (second-generation antihistamine) is the mainstay of therapy in children aged 6 years old or above. Simons compared the effectiveness of cetirizine and loratadine in abolishing histamine-induced wheal and flare in 15 children with mean age of 9 years.[20] Cetirizine (10 mg) had a more rapid onset of action than loratadine (10 mg). Although the use of cetirizine in children under 2 years old is not recommended by the pharmaceutical company, Spicak reported its successful use in infants and toddlers in a pharmacokinetic and pharmacodynamic study of cetirizine in 15 children aged 6 to 23.5 months.[21] In younger children, the pharmacokinetics of a single dose of cetirizine (0.25 mg/kg) is characterised by shorter elimination rate than in older children and adults.[21] The inhibition of a histamine-induced wheal was equally effective in toddlers. However, side effects, such as sleepiness, irritability and vomiting were noted in three children. Loratadine is recommended for children aged 2 or above. In a study of loratadine given to 60 children aged 2 to 5 years with allergic rhinitis or chronic idiopathic urticaria, no electrocardiographic abnormality was demonstrated.[22] However, in another study performed in 94 children aged 6-12 years, sedation, nausea, fever, headache, rash, dyspepsia, fatigue, change in taste and vomiting were reported.[23] Loratadine is metabolised by hepatic cytochrome P450. Concomitant administration of drugs which inhibit or are metabolised by these enzymes may elevate plasma concentrations of either drug. The other second-generation antihistamines including terfenadine and astemizole have become less popular because of their potential side-effect of ventricular arrhythmias.[24-26]

First-generation antihistamines seem to be less effective than the second-generation antihistamine, except hydroxyzine.[27] First generation antihistamines can be added if patients do not respond to non-sedative H_1 antihistamine. Hydroxyzine is a potent classical antihistamine. Although the soporific effect is strong, most children tolerate classical sedative antihistamine better than adults. Hydroxyzine is particularly good for dermographism in children as the effect seems long-lasting.[6] In general, regular daily dose of oral antihistamine is advocated to 'build-up' a therapeutic effect.[2] Tachyphylaxis towards soporific effect may occur with prolonged administration.[3] This makes day-time usage possible. Apart from soporific side effect, the anticholinergic effects and paradoxical excitation are potential unwanted effects. Moreover, all antihistamines may potentially aggravate urticaria by paradoxical histamine release.[27]

When combined H_1 antihistamine therapy failed, Harris reported that addition of H_2 antagonist is sometimes useful.[3] However; Greaves believed that additional therapeutic effect from addition of a H_2 antihistamine is unproven.[2] The value of using combined H_1 and H_2 antihistamines remains controversial.

The pharmacology of commonly used antihistamines is summarised in Table 4.[21,27-30]

Doxepin is a tricyclic antidepressant with potent antihistamine activity. It is a particularly useful nighttime treatment for those with sleep disturbance or agitation.[27] Side effects include sedation, lethargy, dry mouth and constipation. Calcium-channel antagonist, such as nifedipine and beta-2-agonist, such as terbutaline have been advocated in patients with chronic urticaria but their effect is not proven. Ketotifen and terbutaline were reported to be useful in cold urticaria but are not particularly useful in practice.[31,32] Self-injectable epinephrine devices are recommended for children with cold urticaria and those with history of anaphylaxis.

Table 4. Pharmacology of commonly used antihistamines

Name of medication	Chlorpheniramine	Hydroxyzine	Diphenhydramine	Cetirizine	Loratadine
Trade name	Piriton	Atarax	Benadryl	Zyrtec	Clarityne
Generation	First	First	First	Second	Second
Formulation	Syrup (2 mg/5 ml) Tablet (4 mg)	Syrup (10 mg/5 ml) Tablet (10, 25 mg)	Elixir (10 mg/5 ml) Capsule (25, 50 mg)	Solution (5 mg/5 ml) Tablet (10 mg)	Syrup (5 mg/5 ml) Tablet (10 mg)
Paediatric dosage	0.35 mg/kg/24h, in divided doses q4-6h	1 mg/kg/24h, in divided doses q6-24h	2.5-5 mg/kg/24h, in divided doses q4-6h	3-6 years: 5 mg/day >6 years: 10 mg/day	2-5 years: 5 mg/day 6-12 years: 10 mg/day
Adult dosage	4 mg q4h	25 mg at night to 25 mg qid	25-50 mg tid	10 mg daily	10 mg daily
Onset of action	30 minutes	15-30 minutes	15 minutes	30-60 minutes	2 hours
Peak of action	1-2 hours	2 hours	2-4 hours	2 hours	1-2 hours
Duration of action	4-6 hours	6-24 hours	4-6 hours	24 hours	12-24 hours
Adverse effect	Sedation, anticholinergic effects: dry mouth, urinary retention, constipation; rarely, tachycardia, QT interval prolongation, heart block, arrhythmia.			Less sedative, anticholinergic effects; rarely, arrhythmia.	

Oral steroid has no role in the long-term management of chronic urticaria in children. However, a short tapering course may be beneficial in those with severe angio-oedema. After the discovery of the roles of autoantibodies, anti-FcεRI and anti-IgE in some patients, immunosuppressive or immunomodulating agents become the second line therapy for chronic urticaria in adults. Cyclosporin is a cyclical peptide with immunosuppressive activity. Greaves stated that cyclosporin is probably also effective in autoantibody-negative chronic idiopathic urticaria.[2] Intravenous immunoglobulin and plasmapheresis are theoretically beneficial but have not generally been used in children.[33,34]

Apart from pharmacological measures, a low pseudoallergen diet can be tried in those who suffer from chronic idiopathic urticaria. It is a list of foods which are free of all artificial colourings, flavours and preservatives. Kemp reported that a diet with only lamb, chicken, beef, lettuce, carrots, parsley, pears, rice, plain flour, semolina, matzo crackers, Carr's table water biscuits, sugar, golden syrup, honey, vinegar, salt, pepper and coffee for two weeks followed by controlled reintroduction of food can be useful.[35] In Kemp's study, 39% of children showed marked remission and 39% had less urticarial lesions during the second week of elimination diet. After normal food was reintroduced, 45% of children continued to have disease remission. Ehlers also reported that 16 patients with chronic urticaria could stop medication after they had adhered to low-pseudoallergen diet.[10] It is difficult to comply with an elimination diet. Kemp reported a non-compliance rate of 22%.[35] Moreover, some food product, especially snack; do not have a full label of their ingredients and additive constituents. This can put patients at risk.

Outcome

The long term outcome is generally good in children. Half of the children become symptom-free when followed up for two to four years.[3,4] The median duration of disease is 16 months.[3] Harris reported that children under 8 years old had higher resolution rate of 50% in comparison to 22% in those aged 8 to 15.9 years old.[3] Among 163 children aged 6 months to 16 years old with a mean follow-up time of 3.8 years, all those with urticaria related to insect bite, parasite and drug resolved.[4] Eighty-one percent of those with infection-induced urticaria was resolved.[4] Fifty percent of those with food and food-additives or acetylsalicylic acid group was resolved.[4] Forty-three percent of those children with physical urticaria resolved.[4] Physical urticaria has been reported to last for 2 to 4 years in children.[36]

Conclusion

Until now, chronic urticaria in children is still not well understood. Much of the information is based upon extrapolation from the research on adult subjects. However, urticaria and angio-oedema in children seem to differ from that seen in adults in some aspects. For example, delayed pressure urticaria is rare in children, contact urticaria is not commonly reported, physical urticaria seems to be documented more frequently and the prognosis of chronic urticaria in children tends to be better than in adults. Further population-based studies on epidemiology, aetiology and natural history of urticaria in children are necessary to improve our understanding of this disease.

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