E. Novembre, A. Cianferoni[1], F. Mori, S. Barni, C. Calogero, R. Bernardini, L. Di Grande, N. Pucci, C. Azzari, A.Vierucci

Urticaria and urticaria related skin condition/disease in children

Department of Pediatrics, University of Florence, Italy; [1] Children's Hospital, Philadelphia, USA

Key words

UA = Urticaria-angioedema,
AST = autologous serum test,
VU = vasculitic urticaria,
HAE = hereditary angioedema

Summary

Urticaria is a rash, that typically involves skin and mucosa, and is characterized by lesions known as hives or wheals. In some cases there is an involvement of deep dermis and subcutaneous tissue that causes a skin/mucosa manifestation called angioedema. Urticaria and angioedema are very often associated: urticaria-angioedema syndrome. The acute episodic form is the most prevalent in the pediatric population, and it is often a recurrent phenomenon (recurrent urticaria). Acute episodic urticaria it is usually triggered by viruses, allergic reactions to foods and drugs, contact with chemicals and irritants, or physical stimuli. In many instances it is not possible to identify a specific cause (idiopathic urticaria). Chronic urticaria is a condition that can be very disambling when severe. In children is caused by physical factors in 5-10% of cases. Other trigger factors are infections, foods, additives, aeroallergens and drugs. The causative factor for chronic urticaria is identified in about 20% of cases. About one-third of children with chronic urticaria have circulating functional autoantibodies against the high affinity IgE receptor or against IgE. (chronic urticaria with autoantibodies or "autoimmune" urticaria). It is not known why such antibodies are produced, or if the presence of these antibodies alter the course of the disease or influence the response to treatment. Urticaria and angioedema can be symptoms of systemic diseases (collagenopathies, endocrinopathies, tumors, hemolytic diseases, celiachia) or can be congenital (cold induced familiar urticaria, hereditary angioedema). The diagnosis is based on patient personal history and it is very important to spend time documenting this in detail. Different urticaria clinical features must guide the diagnostic work-up and there is no need to use the same blood tests for all cases of urticaria. The urticaria treatment includes identification of the triggering agent and its removal, reduction of aspecific factors that may contribute to the urticaria or can increase the itch, and use of anti-H1 antihistamines (and/or steroids for short periods if antihistamines are not effective). In some instances an anti-H2 antihistamine can be added to the anti-H1 antihistamines, even if the benefits of such practice are not clear. The antileucotriens can be beneficial in a small subgroup of patients with chronic urticaria. In case of chronic urticaria resistant to all the aforementioned treatments, cyclosporine and tacrolimus have been used with good success. When urticaria is associated to anaphylaxis, i.m epinephrine needs to be used, together with antihistamines and steroids (in addition to fluids and bronchodilatators if required).

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Definition

Urticaria is a rash, that typically involves skin and mucosa, and is characterized by lesions known as hives or wheals. A hive is a pruritic plaque usually erythematous and edematous; the edematous, central area (wheal) can be pale in comparison to the erythematous surrounding area (flare). These lesions blanch with pressure, and are the result of dilation of small venules and capillaries located in the superficial dermis. Similar pathologic alterations that occur in the deep dermis and subcutaneous tissue cause a skin/mucosa manifestation called angioedema. Urticaria and angioedema are very often associated: urticaria-angioedema syndrome (UA). UA is a skin condition with a very high prevalence among the general population, 10-20% of the general population experiences UA at least once in life. In children the prevalence is 2-6% (1).

Pathophysiology

The cells responsible for causing urticaria include mast cells and basophils. These cells are able to release histamine, the most important mediator in the urticaria pathogenesis.
Mast cell and basophiles produce many other factors that may also play a role in the UA pathogenesis.
Mast cells mainly reside in tissues, and in addition to histamine, produce other preformed mediators, such as tryptase, proteoglicans, heparin and chondroitin sulphate A and B. Basophiles are usually found both in the circulation and in tissues during an active allergic inflammation process, and express chondroitin sulphate A as well as histamine and preformed mediators. Upon stimulation mast cells and basophiles are able to synthesize leukotriens (LTB_4 and LTC_4), whereas only mast cells are able to secrete prostaglandin D_2 (PGD_2). Both mast cell and basophils can express IL-4, IL-13, but, in addition, mast cells express IL-5, IL-6, GM-CSF and TNF-alfa (2).

Classification

A classification of urticaria for clinical use has been recently published in a EAACI guideline (3). Spontaneous urticaria is defined as acute if wheals last less than 6 weeks, and chronic if wheals last 6 weeks or more. Physical urticaria includes cold contact, delayed pressure, heat contact, solar, dermographic, and vibratory urticaria. Other urticaria disorders include acquagenic, cholinergic, contact and exercise induced urticaria (Tab. 1).

Table 1 - Classification of urticaria

Spontaneous urticaria	- acute urticaria - chronic urticaria
Physical urticaria	- cold contact urticaria - delayed pressure urticaria - heat contact urticaria - solar urticaria - urticaria factitia - vibratory urticaria
Other urticaria disorders	- acquagenic urticaria - cholinergic urticaria - contact urticaria - exercise induced urticaria

The acute episodic form is the most prevalent in the pediatric population, and it is often a recurrent phenomenon (recurrent urticaria). Acute episodic urticaria is usually triggered by viruses, allergic reactions to foods and drugs, contact with chemicals and irritants, or physical stimuli. In many instances it is not possible to identify a specific cause (idiopathic urticaria) (4).
Chronic urticaria in children is caused by physical factors in at least 6% of cases (5, 6). Less often, infections (4%), foods (4%), additives (2.6%), aeroallergens (2.2%) and drugs (1.6%), are found to be the trigger factors.
In some patients with chronic urticaria, auto-reactivity functional auto-antibodies directed against the immunoglobulin E (IgE) receptors have been described in both adults and children (chronic urticaria with auto-antibodies or autoimmune urticaria) (7, 8). Nevertheless, the causative factor for chronic urticaria is identified in only 22% of cases (5). Urticaria and angioedema can be a symptom of systemic diseases (collagenopathies, endocrinopathies, neoplasias, hemolytic diseases, celiachia). (4). Syndromes that include urticaria/angioedema are: Muckle-Well syndrome, Schnitzler's syndrome, Gleich syndrome, Well's syndrome (3). In other cases, urticaria is related to other diseases as a result of the patient's history (urticaria pigmentosa, urticarial vasculitis, cold induced familiar urticaria, hereditary angioedema) (3).

Urticaria "Management"

Urticaria management should start with a check list to adequately characterize the clinical and anamnestic features of the episode (9) (Tab. 2).

Table 2 - Anamnestic and clinical features of the urticaria episodes

1)	Lesion first appeared: _____		
2)	Duration of urticaria:	☐ < weeks	☐ ≥ 6 weeks
3)	Duration of individual wheals:	☐ < 24 hours	☐ ≥ 24 hours
4)	Size of wheals: _____		
5)	Colour: _____		
6)	Skin's appearance after wheals have faded: _____		
7)	Frequency of whealing: _____		
8)	Diurnal variations? _____		
9)	Particular parts of body affected? If yes, which? _____	☐ YES	☐ NO
10)	Swelling of:	☐ eyelids ☐ tongue	☐ lips ☐ face ☐ throat
11)	Are lesions brought on by:	☐ rubbing ☐ exercise ☐ cold ☐ immersion in cold and warm water	☐ pressure ☐ heat ☐ exposure to UV light
12)	Are there associated symptoms?	☐ fever ☐ weight loss	☐ joint pain ☐ abdominal pain
13)	Are initiating or provoking factors (food or emotions) present? _____		
14)	History of injections, insect bites or recent illness: _____		
15)	History of drug use: _____		

Once episodic or chronic urticaria has been established, a specific diagnostic algorithm can be followed (Tab. 3-4). Different urticaria clinical features must guide the specific diagnostic test, especially if a physical factor is suspected (Tab. 5). There is no need to use the same blood tests for all cases of urticaria (Tab. 6)! Blood examinations (blood cell count with differential, ESR, CRP hepatic and thyroid function, BUN and glicemia, antistrept titer, complement, total and specific IgE), skin tests for common inhalants, food or drug allergens, food or additive challenges, elimination diets, auto-antibodies, infectious disease work-up (hepatitis B e C, TORCH, Epstein-Barr, urea-breath test for the diagnosis Helicobacter Pylori infection, urine culture, stool culture, nasal or pharyngeal or vaginal culture beta hemolytic streptococcus and staphylococcus) should be considered part of an extended diagnostic programme only in the case of chronic spontaneous urticaria and according to the patient's history (3, 4) (Tab. 6).

Infection induced urticaria

Infections can trigger acute urticaria and exacerbations of chronic urticaria. Infections do not seem to be the cause, per se, of chronic urticaria.

Viruses, such as HBV, HCV, HAV, EBV, and in particular adenovirus and rhinovirus have been reported to be causes of acute urticaria and exacerbations of the chronic form. Little is known of the pathogenetic mechanism responsible for virus induced urticaria. The most likely explanation is that the virus induced release of pro-inflammatory lymphokines and cytokines may increase mast cell and basophile "releasability", facilitating their degranulation (6,2).

Chronic persistent bacterial infections such as H.Pylori, streptococci, staphylococci, or Yersinia can also trigger urticarial symptoms (10). Bacterial infection (streptococcus and staphylococcus) may induce acute urticaria that often evolves into the chronic type.

Table 3 - Acute urticaria: diagnostici algorythm

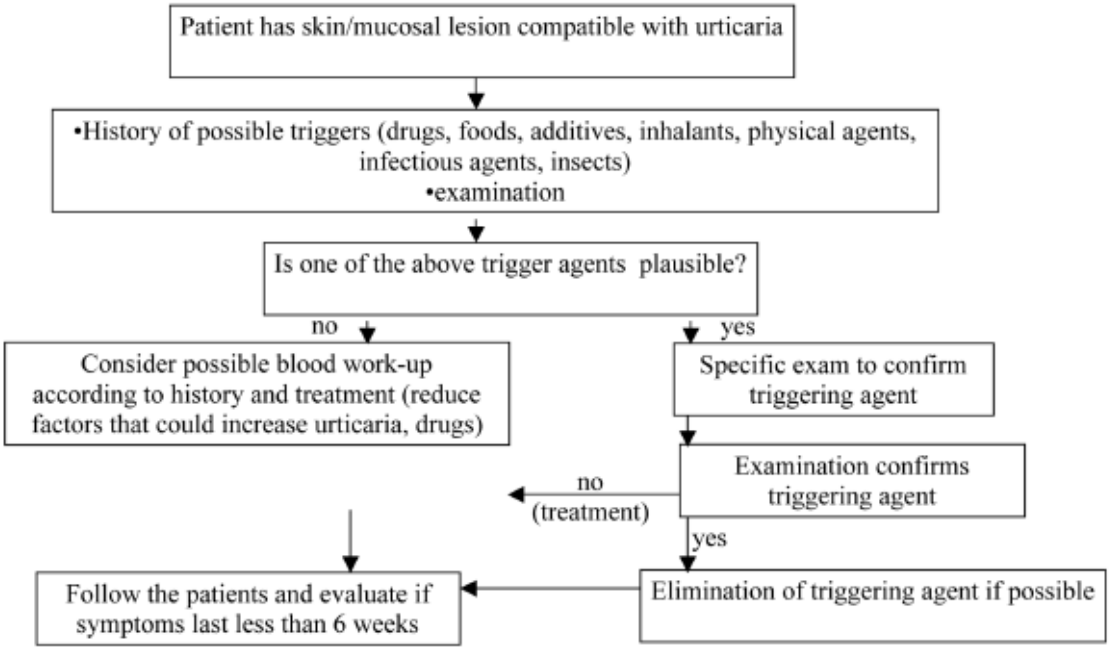

Table 4 - Chronic urticaria: diagnostici algorythm

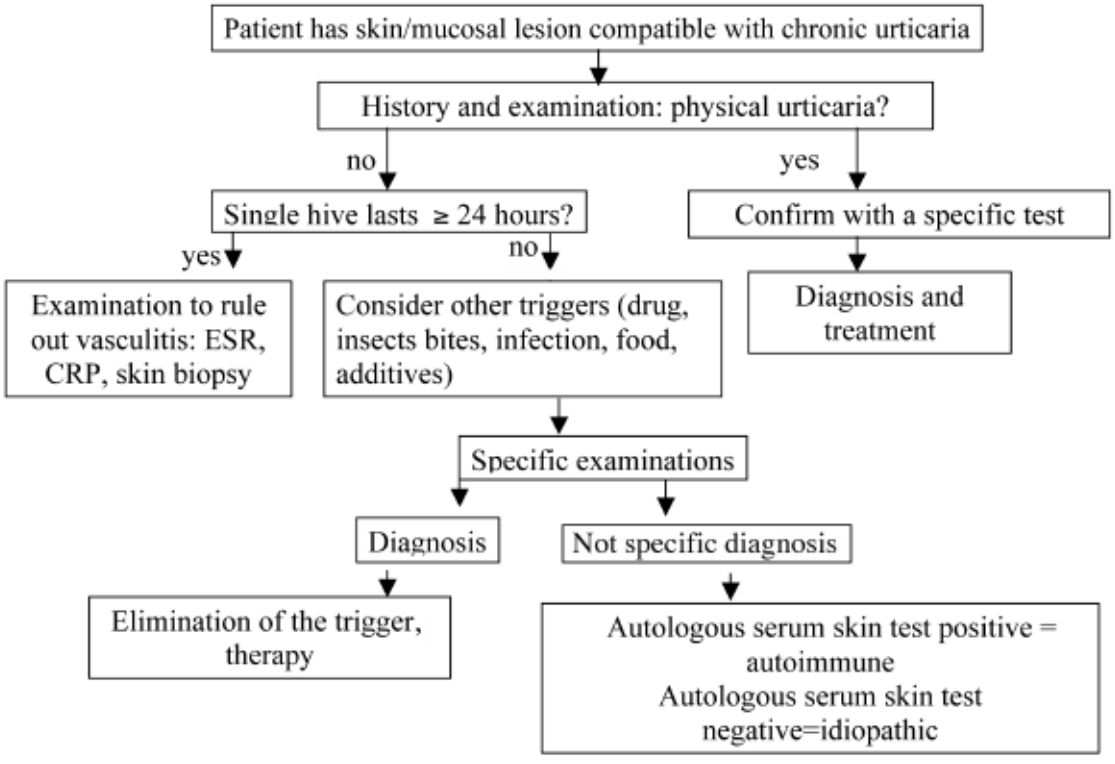

Table 5 - Clinical features and specific tests in some types of urticaria

Urticaria type	Clinical features	Test
Pressure	Erythematous, edematous, painful and itchy lesion, often big in size, at the site of pressure (soles of feet, palms of hands, waist) that last ≥ 24 hours, not associated with angioedema	Apply pressure for 10 minutes increasing pressure (500 g/cm^2, 1000 g/cm^2 1500 g/cm^2) at 90 degrees on the skin or a weight (6 kg) for 20 minutes on the extensor aspect of the thigh ("reading" at 30 minutes, 3 hours, 6 hours, 24 hours): positive test = lesion erythematous and persistent
Cold	Erythematous, edematous, itchy lesion in the area in contact with cold liquid or cold object. Can be generalized. Can be associated with angioedema.	Apply an ice cube for 10 minutes on the forearm, within 5 - 10 minutes after removing the ice a wheal should appear. Stay in a cold room (4 C°) for 10 - 30 minutes
Colinergic	Small, monomorphic, pruritic, pallid or pink wheal, mostly on trunk, neck and limbs associated with angioedema.	Excercise Intradermal test with methacolin
Autoimmune	Without specific clinical feature can be chronic	Autoinjection: intradermal with 50 μl of patient serum (positive if wheal volume is ≥ 9 mm^3 compared to the control after 60 minutes, positive if the wheal diameter is ≥ 1,5 mm compared to the control after 30 minutes). Reduction in peripheral basophils. Histamine release from basophils
Dermografism	Immediate (starts 2-5 minutes after the stimulus, and lasts 30 minutes), intermediate (starts after 30 minutes-2 hours and lasts 3-9 hours), delayed (starts after 4-6 hours and lasts 24-48 hours).	Scratch (back or forearm) with dulled point or nail with moderate pressure (from 3200 to 4900 g/cm^2) for a length of 10 cm

As antibiotics and NSAIDs are often prescribed during viral or bacterial infections, the infection-induced urticaria is often mistakenly attributed to the drug instead of the infective agent.

The most common skin manifestation associated with infection or reactions to drugs are maculopapular or erythematous exanthemas, which typically start at the trunk or areas of pressure, and subsequently spread to the limbs. Itch and fever may or may not be present. Occasionally drug-induced erythematous exanthemas may progress into far more severe skin manifestations (erithrodermia, Stevens, Jhonson Syndrome). For an accurate diagnosis of adverse reaction to drugs, the patient's history is the most useful tool available, such as cause-effect relationship between drug administration and beginning of symptoms, morphology and distribution of lesions. For example, an episode of hives shortly after administration of an antibiotic or angioedema shortly after NSAIDs intake is highly indicative of an allergic reaction. The presence of a sign not involving the skin is suggestive of an adverse drug reaction (fever, malaise, lymphoadenopathy, diarrhea, arthralgia, tachycardia, hypotension, dyspnea); the correct use of lab tests (i.e. eosinophil count, hepatic function, viral tests) may offer some assistance in the differential diagnosis between viral exanthema and adverse reactions to drugs (11). However, very often the viral exanthema and the drug reaction cannot be differentiated, and a prudent change of antibiotic or suspension of treatment may be warranted.

The role of H. pylori (Hp) in chronic urticaria is debated (7).

Even if the rate of Hp infection in patients with chronic urticaria is similar to that found in the general population, the immune response to Hp in patients with chronic urticaria seems to be different and characterized by a higher IgE secretion. Moreover, in some papers eradication of Hp was associated with a resolution of urticaria (10). However, no convincing demonstration of a causative role of Hp in chronic urticaria is presently available.

Table 6 - Laboratory evaluation of urticaria and angioedema

Suspected etiology	Procedures
General screening:	Complete blood count, sedimentation rate urinalysis
Vasculitis:	Ig, antinuclear factor, immune complexes skin biopsy
Infections:	Cultures, serological studies, liver function tests, stool for ova and parasites, x-ray
Allergic:	IgE, skin tests, eosinophil count, challenge, elimination diet, tryptase
Physical:	
Cholinergic	Metacholin test, running
Dermatographism	Spring-loaded dermographometer
Cold	Ice cube test
Solar	Light exposure
Heat	Warm water immersion
Hereditary angioedema	C3-C4, C1 esterase inhibitor
Other	T3-T4-TSH, skin biopsy, urea breath-test

Table 7 - Therapeutic management of urticaria

Remove identifiable	
Non-drug	Drug therapy
Explanation and information Avoid FANS	First line- all patients: - anti-H1 Second line- special indications: - anti-LT, anti-H2, Corticosteroids
Minimize stress, over-heatingalcohol	- Adrenaline
Exclusion diet when indicated	Third line- specialist use only: - Cyclosporin and tacrolimus - Ig - Cyclophoshamide

The role of parasitic infections in the pathogenesis of chronic urticaria is very uncertain (10).
In conclusion, even if the relationship between urticaria and infection is often suspected clinically, the lack of double blind studies makes it difficult to prove such an association, especially in a setting of different stimuli that can induce urticaria.

Allergic Urticaria

Allergic urticaria is the best known urticaria type. The pathogenetic mechanism is well known. Affected individuals are sensitized to specific allergens (most often foods, penicillins, cephalosporins or inhalant allergens), towards which they produce specific antibody of IgE class (6). Such antibodies bind to the IgE high affinity receptor present on mast cells and basophiles. The allergen binds to the IgE attached to the receptor, induces the cross linking of receptors, and subsequent degranulation of mast cells and basophiles. Examples of this urticaria type are: food induced urticaria/angioedema in subjects with food allergy, penicillins or cephalosporin induced urticaria in subjects that produce IgE against such drugs.
The patient's history establishes a temporal relationship between food or drug intake and the onset of urticaria. All types of food can induce urticaria in sensitized individuals, however the foods most often involved are eggs, milk, seafood and fruit. The drugs that most often cause urticaria are the beta lactams. Non-steroidal-antinflammatory drugs (NSAIDs) can cause urticaria by inducing degranulation of mast cells and basophiles, but not in an IgE mediated fashion. NSAID induced urticaria is typically associated with angioedema. These episodes are most often acute, recurrent and only seldomly chronic.
The most useful tools for diagnosis are skin tests (prick test), measurement of serum specific IgE, challenge and occasionally elimination diets (12).

Pseudo food allergy and urticaria

Pseudo food allergies are quite prevalent and seem to be re-

sponsible for chronic urticaria more often than food allergy (13). Pseudo food allergies are due to histamine release from skin mast cells and seem to be triggered by several agents (NSAIDs, additives such as salicylates and benzoates, and food colours such as tartrazine) (14). In rare cases urticaria can be the consequence of inhalation of volatile aromatic compounds found in white wine and tomatoes (15).
Diagnosis in these cases is based only on challenges and elimination diets, as in these instances skin tests are often not reliable.

Insect bite induced urticaria

This is probably the most common type of urticaria in children. It is characterized by groups of pruritic hives or papules on the exposed parts of the body (arms, legs). Several insects, including mosquitoes and fleas, can cause hives or papules. The pathogenetic mechanism can be either immuno-mediated (an IgE mediated response is followed by a delayed response) or, most often, irritative. After several insect bites, children may develop tolerance.
Hymenoptera sting-related allergic reactions can be more severe. In sensitized subjects hymenoptera stings can induce urticaria and angioedema either at the site of injection or systemically, and they can also cause anaphylaxis. Venom immunotherapy is recommended not only for life-threatening reactions, but also for urticaria if risk factors or quality of life impairment are present (16).

Contact urticaria

Contact urticaria can be immune mediated or not immune mediated.
The non immune-mediated form does not require prior exposure to the trigger agent, appears usually within 45 minutes after exposure, and is caused mainly by artificial or natural chemicals. The diagnosis is carried out with application tests.
The immunologic form needs a prior exposure to the offending agent, appears within 10-20 minutes after the exposure, and is caused by protein (animal, vegetal, plant etc). The diagnosis is carried out with the use of skin tests (prick test) or measurement of specific serum IgE (CAP) (1). Occasionally the same substance (as for example in the case of the Thaumetopeoa pityocampa- pine tree parasite-) can cause urticaria in a toxic/irritative manner and/or with a immunomediated mechanism (17).

Physical urticaria

Physical urticaria can be triggered by mechanical, thermal or light stimuli (Tab. 5).
Dermatographism is the most common type of physical urticaria, and it can be elicited by applying pressure to the skin by scratching it with a dull point at a pressure point of 3200-4900 g/cm^2 (18).
Cholinergic urticaria is usually triggered by warmth, exercise, or emotions. It can be localized or generalized. It is rare in children; in fact, it only represented 2.7% in a pediatric series (5). Usually it is localized on the neck, flexor aspect of elbow and knee, and arm pits. Typically the eruption lasts 30-60 minutes.
Cold induced urticaria can be typical or atypical. This form is very rare in children .

Autoimmune urticaria

The presence of histamine releasing factors was first reported in patients with chronic idiopathic urticaria, in whom the intradermic injection of autologous serum determined a wheal and flare response (19). These histamine releasing factors were recently identified as auto-antibodies against IgE or IgE receptors (1).
Auto-antibodies are found in up to 30-40% of children with chronic urticaria (8), but in none of those with other allergic diseases such as atopic dermatitis. Such auto-antibodies are found in other autoimmune diseases such as bullous pemphigous, vulgar pemphigous and dermatomyositis. Such auto-antibodies are often present in allergic or drug induced urticaria, and in children and adults (mostly women) with similar-allergic respiratory symptoms (20).
Although the effect of urticaria therapy does not change according to the presence of a positive or negative autologous- skin test (4), it has been reported that adult patients with positive AST tend to have a more severe disease (21). Therefore in these cases a more aggressive treatment could be justified.
Indeed it could be even hypothesized that auto-antibodies are not actually pathogenetic, but are secondary to the presence of urticaria in individuals with a predisposition to develop autoimmunity. Moreover, their presence does not change the therapeutic approach or the prognosis of the disease, therefore their presence does not have a high clinical significance.
Autoimmune urticaria is characterized by hives that last at least 8-12 hours (but always < 24 hours), with daily re-

currence, to which angioedema can be associated. From a diagnostic point of view, other causes of chronic urticaria (particularly the physical urticaria), must be excluded.
The diagnosis is based on the autologous serum -skin test that must be performed during the acute phase of the urticaria. Another useful test is the histamine release from basophiles induced by the serum from the affected patient. The concordance between those 2 tests is about 80% (8). There are no clinical features that can help in distinguishing between chronic urticaria with auto-antibodies as opposed to the one without auto-antibodies. Moreover children, as opposed to adults with chronic autoimmune urticaria, do not have other autoimmune diseases associated or sign of autoimmune thyroid disease, celiac syndrome or HP infection (21). On the other hand, chronic urticaria in children can be associated with other autoimmune diseases, mostly of the thyroid (22).

Vasculitic Urticaria (VU)

Vasculitic urticaria is rare in children; it can be associated with an immunocomplex disease, such as serum sickness or autoimmune disease such as sistemic lupus erithematosus or Henoch-Schoenlein purpura, or can be idiopathic. The skin biopsy, which is necessary for the diagnosis, typically shows a necrotizing vasculitis of small vessels, and immunocomplexes and complement deposits.
Hives last more than 24 hours, and leave purpuric signs. VU is often associated with arthalgias, abdominal symptoms, and elevated inflammatory markers. It does not respond to antihistamine treatment (1).

Urticaria Pigmentosa (cutaneous mastocitosis)

Cutaneous mastocitosis, is a rare disease in children. It usually appears in the first 2 years of life, and the most common manifestation is an isolated mastocitoma, a brownish lesion, sometimes mistakenly considered a mole, that can become red or can be itchy. Cutaneous mastocitosis can occur also as pigmentosa urticaria, i.e as an itchy generalized maculopapular rash. Scratching the lesion may cause a wheal and flare reaction (Darier sign).
The diagnosis of systemic mastocitosis needs the help of highly specialized laboratories, and is based on the presence of a major sign (multifocal dense infiltrates of > 15 mast cells in the bone marrow or in other extracutaneus organs) + one minor sign (serum alfa- tryptase levels > di 20 microgram/mL, CD2 o CD25 expression in bone marrow or other c-kit positive tissues mast cells, c-kit mutations in mast cells, presence of > 25% spindle-shaped bone marrow or other c-kit positive tissues mast cells) o three minor signs (23). Urticaria pigmentosa has a benign prognosis in most patients. Rarely, more severe symptoms can be present (rash, diarrhea, gastrointestinal bleeding and bronchospasm).

Hereditary Angioedema (HAE)

HAE is not a real form of urticaria. It can be congenital or acquired. The hereditary form (Quincke edema) is due to a reduced level or reduced function of C1 esterase inhibitor. This is a very rare type of angioedema, with a prevalence of 1/50.000 in the general population, and is transmitted in an autosomical dominant way. Only 10% of cases are new mutations. The clinical picture of this rare disease is characterized by recurrent angioedema attacks that can be potentially lethal if they involve the submucosal tissue of the glottis. Those patients need an adequate clinical and diagnostic follow up. The treatment of the severe attacks is based on the administration of the concentrated purified inhibitor. Intubation and mechanical ventilation of patients may be needed (24).

Skin diseases similar to urticaria

Scabies, especially in small children, can be similar to urticaria particularly the urticaria pigmentosa (25).
Herpetiform dermatitis (bullous skin disease very pruritic, which mainly involves the extensor aspect of limbs and is associated with celiac disease) can be similar to urticaria (26).
Other skin conditions similar to urticaria are psoriasis guttata, pitiriasi rosae, erithema nodosum, and eritmema multiforme. On the other hand, the angioedema can be similar to hypoproteinemic edema, due to erroneous diets (27), periorbital cellulitis, contact dermatitis, Gleich syndrome.

Therapy

The urticaria treatment includes (4, 28)(Tab. 6)
1. Identification (if possible) of the triggering agent and its removal
2. Reduction of nonspecific factors that may contribute to the urticaria or increase the itch

3. Use of antihistamines (and/or steroids for short periods if antihistamines are not effective). Second –generation antihistamines must be considered as first line symptomatic treatment for urticaria (29).
   All patients must choose between 2 antihistamines as the effectiveness and tolerance are different among different individuals.
   Before considering alternative treatment, higher dosages should be used. (29). Before increasing the dosage, a careful evaluation of risk/benefit ratio should be carried out, as higher doses of antihistamines certainly expose the patient to an increased risk of side effects (30).
   It is also possible to combine a non-sedative antihistamine with a sedative one in unresponsive cases.
   In some instances an antiH2 antihistamine can be used, even if the benefits of such practice are not clear. The antileucotriens can be beneficial in a small subgroup of patients with chronic urticaria (18).
4. In cases of insect related urticaria, treatment includes prevention (removal of possible sources of insects, such as pets, use of repellents), antihistamines, use of topical antibacterial drugs if there are signs of infection.
5. In cases where urticaria is associated with anaphylaxis i.m epinephrine needs to be used, together with antihistamines and steroids (+ fluids and bronchodilatators if required).
6. In case of chronic urticaria resistant to all the aforementioned treatments, cyclosporine and tacrolimus have been used with good success (28).
7. In case of HAE due to C1 esterase inhibitor deficiency the elective treatment is with anabolic steroids (stanazolol and danazol) or tranexamic acid. During acute episodes fresh frozen plasma and purified concentrated inhibitor can be used (31).

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