

R E V I E W

Urticaria in childhood

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Abstract. Histaminergic urticaria-angioedema is a common complaint in children. According to clinical criteria, it is classified as acute and chronic urticaria. A further clinical classification relies on triggering factors. We focus on diagnosis and therapeutic strategies. We report the main progresses in the field and issues that remain to be understood. (www.actabiomedica.it)

Key words: urticaria, angioedema, food allergy, anaphylaxis, asthma, allergic rhinitis, IgE antibodies, children, vaccination

Introduction

Urticaria is characterized by the sudden appearance of itching erythematous wheals with sometimes inner pallor and typically with ringing erythema. Wheals have variable shape and size. In 40% of patients, wheals are associated with angioedema. Angioedema is characterized by pale, non-erythematous swelling, with a feeling of tension and/or pain that disappears in 72 hours. It is mainly located in areas with more abundant subcutaneous tissue such as face, genitals and extremities. In 10% of cases, angioedema is isolated. Urticaria-angioedema syndrome is typically the result of mast cells activation. Stimulated skin mast cells release histamine, prostaglandins, leukotrienes, tryptase, platelet activating factor, and cytokines. Histamine and vasoactive mediators cause itching and edema. Urticaria is classified as spontaneous or com-

mon in up to 70-80% of cases or inducible when there is the possibility of inducing symptoms by exposure to a triggering agent. The form is spontaneous as the cause remains unknown. In the remaining cases, mast cells can be activated by numerous factors: infections, allergies, contact with allergens or irritants, physical stimuli (1,2). Urticaria is arbitrarily classified in acute urticaria (AU) if the lesions persist less than 6 weeks, and chronic urticaria (CU) more than 6 weeks. The 6-week period represents the period in which hives usually resolve. Less than 1/3 of cases are chronic. CU remits in 40-70% of cases within 5 years (1).

Acute urticaria

Infections are considered the more common cause of AU and they elicit up to 80% of cases. Viral dis-

eases affect also the airways (herpes virus, cytomegalovirus, Epstein-Barr virus) and less often the gastrointestinal tract besides skin. It has also been observed an association with streptococcus pyogenes infections and mycoplasma pneumoniae. Parasites generally induce AU with eosinophilia. Other microorganisms including helicobacter pylori, have not been confirmed.

Urticaria and/or angioedema during infections have been mainly described in younger children and last several days. An IgE-mediated allergic reaction can induce AU and/or angioedema that can be isolated or part of a systemic reaction (anaphylaxis). When hives are triggered by food allergens, the most common eliciting foods are milk, egg, fish, nuts(3). Additives such as Na benzoate, can be a trigger. Hives develop within 30' (2 hours) after food ingestion and they can be associated with asthma (4), allergic rhinitis (5), oral allergy syndrome (6), and anaphylaxis. However, reactions to alfa-gal that is contained in mammalian non-primate meat and in the Fab of the heavy chain of cetuximab, occur 2-6 hours after exposure.

Drugs (7,8) and vaccine for infectious diseases (9) induce hives by an IgE-mediated mechanism, especially betalactams, muscle relaxants, or by direct mediator release from mast cell, i.e. opioids, radiocontrast agents. Nonsteroidal anti-inflammatory drugs (NSAIDs) trigger urticaria-angioedema by an IgE-mediated mechanism or by inhibiting cyclooxygenase 1 that increases cisteinyl-leucotrienes resulting in hives.

IgE-mediated urticaria to latex and hymenoptera venom is less frequent and it can be associated with a systemic clinical hypersensitivity reaction. Hives can be elicited by contact or may coexist with hypersensitivity to pollens (10), latex, foods, furred animals. Physical factors infrequently cause AU. Among physical stimuli, dermographism, increasing body temperature and cold are more common, while delayed pressure, heat and sunlight are less frequent.

Chronic urticaria

AU that becomes chronic is spontaneous in most patients. Among aetiological factors of CU (1,2), physical stimuli are more common while infective and

allergic causes are sporadically reported. However, chronic spontaneous urticaria (CSU) is resolved in a minority of cases after eradicating the infection. CSU can coexist with physical urticaria, especially dermographism and delayed pressure and can be exacerbated by NSAIDs.

Histamine-releasing IgG autoantibodies to the IgE receptor (anti-FcεRIα) or to the FC region of IgE (anti-IgE) are found in about half of CSU (1). IgG autoantibodies can be detected by basophil histamine releasing assay (BHRA) that is not standardized. Western Blot and ELISA assays may also be used but they have low specificity and sensitivity. In vivo, the autologous serum skin test (ASST) detects several factors (including IgG autoantibodies) that activate mast cell. ASST results positive in about 50% of children with CSU. Those patients do not respond to particular treatment or have a different disease course. Autoimmune CSU is diagnosed when a biological test, an immunoenzymatic assay and ASST are all positive. Some autoimmune conditions, especially thyroid disorders and celiac disease are more common in children with CSU. CSU can be associated with thyroid peroxidase autoantibodies or antimicrosomal autoantibodies. Thyroid supplementation in autoimmune thyroiditis with hypothyroidism or wheat avoidance in celiac disease may heal concurrent CSU in some children.

Diagnostic work-up

The diagnosis (1,2) of urticaria is based on the appearance of skin lesions. No laboratory reference standard is available. Wheals are present in diseases that must be differentiated from urticaria as they have different mechanisms. They include mastocytosis (urticaria pigmentosa), papular urticaria (strophulo), urticaria vasculitis, cryopyrin-associated periodic syndrome (CAPS) and tumor necrosis factor receptor 1 periodic syndrome (TRAPS). Isolated histaminergic angioedema should be distinguished from bradykininergic angioedema. Bradykininergic angioedema is induced by ACE inhibitors and it is found in hereditary or acquired angioedema due to reduced function with low (type I) or normal (type II) levels of serum C1 inhibitor and decreased serum C4. In adult type

III, C1INH and C4 are normal. Besides cutaneous angioedema, intestinal and laryngeal edema are also present. Hypoproteinemic edema and lymphedema during malignancies must also be distinguished from isolated histaminergic or bradykininergic angioedema. Laboratory tests to identify the cause of urticaria are not recommended when there is no convincing history of a triggering agent. If the single wheal persists > 24 hours it can be due to delayed pressure, and the challenge should be performed. If wheal lasts <24 hours and a physical, allergic or infectious cause is suspected the relevant diagnostic tests should be carried out. In children with recurrent isolated angioedema, serum levels of C1INH and C4 should be measured. When history and physical examination are negative, it may be considered to perform blood count with formula, CRP, ESR. Investigations for associated autoimmune diseases (thyroiditis, celiac disease) are advisable. Finally, it can be assessed whether it is useful to perform the ASST to verify an autoimmune pathogenesis.

Treatment

Whenever possible, the sensitization to offending allergens should be prevented (11) and the triggering factors should be avoided (1,2,12). Questionnaires on quality of life (1) permit to understand how daily occupations, social relationships, leisure time are hampered by the illness. Severity can be assessed by UAS7 score. Second-generation H1 antihistamines are the cornerstone of therapy (1,2). They have a longer action, less sedation and anticholinergic properties, since they do not cross blood-brain barrier, compared with old H1 antihistamines. Antihistamines should be taken for 7-15 days in AU. The treatment should be reassessed every 3-6 months. In CU, anti-H1 is effective in about 50% of cases. A short course of systemic glucocorticoids can be given in AU, in the exacerbations of CU and in the delayed pressure urticaria. If anti-H1 does not control CU, data in adults indicate that symptoms can be cured by increasing the dose up to 4 times. Omalizumab (13) is an anti-IgE monoclonal antibody approved as adjunctive treatment in CU refractory to anti-H1 in patients > 12 years of age. In most cases, symptoms resolve in the first week of omalizumab

administration, in other cases the response is slower. There is no effect in 10-20% of cases. Even in some physical forms, omalizumab may help. Cyclosporin A (14) can be used in resistant cases. Montelukast has some efficacy in addition to anti-H1 in adults. Several other drugs have been used in CU, but evidence lacks to recommend their routine use.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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