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Childhood urticaria and angioedema: pathogenesis, diagnosis and therapy

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Summary

Urticarial disease is characterized by transient erythematous, swelling and pruritic lesions. Classification of the disease as acute and chronic urticeria provide a comprehensive approach to detect the etiological factors and estimate the prognosis. In this paper, clinical classification of urticeria, pathogenesis, related factors with disease and therapy options were reviewed. *(Turk Arch Ped 2012; 47: 232-236)*

Key words: Angioedema, child, urticeria

Introduction

The lifetime occurrence of any type of urticaria is estimated to be 25% (1). Acute urticaria usually occurs secondarily to ingestion of food or medicine and has a self-limiting clinical course, while chronic urticaria may cause disruption of the quality of life because of persistent pruritus and chronic skin lesions. Chronic urticaria which occurs with a two-fold higher frequency in women usually continues 3-5 years and may last for a lifetime in 20% of the patients (2,3). Inability to determine the pathogenesis accurately increases the failure of treatment. Although successful results have been achieved with novel treatment methods in recent years, lack of adequate number of studies related to this subject and the high cost of these novel treatment methods arise as the main problems.

Clinical definition

Acute urticaria is characterized by superficial swelling, erythema and pruritus on any area of the skin. It usually fades in a short time (1-24 hours). It may rarely last up to six weeks. In chronic urticaria, the findings last more than six weeks. Swelling in the subcutaneous tissues and mucosa is defined as angioedema and occurs in 40% of the patients with urticaria (1). Chronic urticaria occurs in adults more frequently. However, 0,1-3% of the children may develop chronic urticaria (4). Knowledge of the pathogenesis and causes in chronic urticaria is important in terms of providing treatment.

Pathogenesis

The pathophysiology in urticaria is explained by release of vasoactive mediators from activated mast and basophil cells. Histamine is responsible of erythema, swelling and axon reaction which leads to expansion of reaction observed in urticaria. In addition, substances including prostaglandin D, leukotrien C and D, complement system elements (C3a, 4a, 5a) and bradykinin are involved in the occurrence of the findings. Another mechanism which is non-IgE-mediated and which is mostly effective in chronic urticaria is related with release of histamine releasing factors from mononuclear cells. These factors include monocyte chemotactic peptide-1, RANTES and macrophage inflammation peptide (MIP-1). In this way basophils, eosinophils and T lymphocytes aggregate in the skin. In some patients with chronic urticaria, the number of blood basophils was found to be decreased and it was emphasized that this was related to the activity of the disease (1,3,5,6).

In recent years, anti-IgE autoantibodies have been blamed in the pathogenesis of autoimmune chronic urticaria and IgE type anti-IgE autoantibodies are found against the α subunit of the highly sensitive IgE receptor on the mast cell in 40% of the patients and against IgE molecules in 5-10% of the patients (7). A part of the cases with idiopathic urticaria is explained with this mechanism. As a result of binding of autoantibodies, histamine, triptase-like proteases, chemotactic factors, leukotriens and cytokines (TNF-α, IL–1, IL–4, IL–5) are released from basophils

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and mast cells. At the same time the complement system is activated and hence histamine release increases further. Neutrophils, eosinophils and monocytes aggregate and the number of CD4+ cells increases in the skin by mediation of C5a which has chemoattractant property. Studies performed found an increase in the rates of IL-4, 5 and IFN-γ cytokines together with an increase in Th1, Th2 and Th0 cells in the skin in cases with chronic urticaria. When the histologic skin properties of the cases with autoimmune and idiopathic chronic urticaria are examimed, polymorphonuclear cells are observed with a higher rate in the autoimmune group (5,8).

Another mechanism which is blamed in chronic urticaria is disruption of the intrinsic activity of basophils o mast cells. Among these Syk, SHIP-1 and SHIP-2 proteins were examined and Syk was found to be involved in increasing IgE receptor activity and the other two proteins were found to be involved in decreasing this activity (9,10).

Classification

Variability of the causes of urticaria and the clinical findings makes it difficult to classify urticaria accuretely. Idiopathic urticaria constitutes approximately 80% of all cases of chronic urticaria (3,11). After idiopathic urticaria physical urticaria is the second most frequently observed urticaria. In recent years, it has been shown that chronic urticaria is not rare in children and the approximate frequency has been shown to be 30% (12). Therefore, a part of chronic idiopathic urticaria has shifted into this group. The final guideline emphasized that evaluation of the activity level and quality of life is as important as classification of urticaria. Again according to this guideline conditions which are accompanied by urticaria including pigmented urticaria (cutaneous mastocytosis), urticarial vasculitis, familial cold urticaria and non-histaminergic angioedema (congenital or aquired C1 esterase inhibitor deficiency) were not included in the classification of urticaria, because they are caused by different mechanisms (13,14). The classification of urticaria and graduation of activity are shown in Table 1 and 2.

History and etiologic causes

Detailed history is important in cases of urticaria. The points which should be noted in the history including the onset, frequency, variability during the day, distribution, relation with the environment of the findings, presence of angioedema, presence of triggering factors (cold, hot, pressure, vibration, sun, stress, water), familial tendency, problems related to the gastrointestinal system (gastritis, ulcer, dispepsia), placement of a permanent foreign body related to the teeth or following any surgical procedure, drug usage (nonsteroid antiinflammatory drugs, antibiotics, laxatives, rectal drugs), nutritional history, exposure to smoking, relation with menstrual cyclus, relation with movement and stress, response to previous treatments and treatment period should be interrogated in detail (1,14).

Type 1 hypersensitivity reaction caused by foods is mostly related with acute urticaria. In the early infancy, milk, eggs, dried nuts and fruits, sea food, tomato and strawberry may lead to acute urticaria (15,16).

Although infectious agents usually cause acute urticaria, they may also lead to chronic urticaria. The main causes include hepatitis A, B, C, EBV, enterovirus, streptococci and parasitic infections. Chronic urticaria may develop in presence of dental abscess, urinary tract infection and H.pylory (16,17,18).

Systemic vasculitis and autoimmune diseases may lead to chronic urticaria. In 25% of the cases with chronic urticaria, thyroid autoantibodies and antinuclear antibody were found to be positive. However, thyroid dysfunction does not accompany in most cases despite high autoantibodies. In patients with thyroid dysfunction, Hashimato thyroiditis is usually found. More rarely, Graves disease, Celiac disease, type 1 diabetes mellitus and vitiligo may be observed in these patients (19,20). Anti-IgE antibodies have been mostly associated with chronic urticaria in adulthood and its incidence has been found to be 45%. Very few studies have been conducted in the subject of pediatric autoimmune chronic urticaria. In these studies, the incidence of chronic urticaria has been reported to range between 31% and

Tabe 1. Classification of urticaria

Type	Subtype
Spontaneous urticaria	Acute and chronic spontaneous urticaria
Physical urticaria	Cold urticaria Delayed pressure urticaria Hot urticaria Solar urticaria Dermographism Vibration urticaria
Other	Aquagenic urticaria Cholinergic urticaria Contact urticaria Exercise induced anaphylaxis-urticaria

Table 2. Grading of activity in urticaria

Score	Severity of pruritus	Number of hives
0	None	None
1	Mild, recognizes little. The patients can endure pruritus	<20/ 24 hours
2	Moderate, the patient barely endures	20-50/ 24 hours
3	Very severe, the patient can not endure	>50/24 hours

Score range: 0-6

40% (12). Generally, the findings in the patients with autoimmune chronic urticaria have a more severe course (5,8).

Since a definite relation between chronic urticaria and cancer has not been shown until the present time, it is not recommended to make investigations in terms of cancer in patients who have no sypmtoms suggesting cancer. However, some studies have suggested that urticarial plaques may occur as a result of antigen-antibody complex related to cancer (21).

Physical urticaria generally occurs as a result of a physical stimulus and the most common form is dermographism. It affects 2-5% of the population. More rare types include pressure, cholinergic, solar, cold, aquagenic and vibratory urticaria (22).

Diagnosis

If the clinical diagnosis is definite in patients presenting with acute urticaria, laboratory tests directed to the etiology are not necessary. Detailed tests are not recommended either in patients with chronic urticaria who have mild disease or who respond to treatment.

Tests which are recommended to be performed at the first presentation (23):

- Complete blood count, erythrocyte sedimentation rate, C-reactive protein
- Liver function tests, stool examination, complete urinalysis

Tests to be ordered at the secondary care:

- Detailed biochemical tests
- Thyroid hormones, thyroid autoantibodies, antinuclear antibody, antigliadin antibody
- Hepatitis serology
- Complement system analysis (C2, C3, C4)
- Skin tests or serum IgE level, if antigen sensitivity is considered
- Skin biopsy in patients in whom vasculitis is suspected: the lesions last for more than 24 hours, are painful and usually heal by leaving hyperpigmentation on the area of the lesions in urticarial vasculitis (24).
- Autolog serum test, basophil histamine release test, ELISA, Western blot test, if autoimmune chronic urticaria is considered.

In cases of chronic autoimmune urticaria, the presence of autoantibodies can be demonstrated by different methods. Autoantibodies can be found in the peripheral blood sample with ELISA, Western blot method and basophil histamine release test. However, it is difficult to perform these methods in practice because of limited area of application and limited availability. The sensitivity of autolog serum skin test is lower compared to the other methods, but its negative predictive value is considerably high in terms of determining functional autoantibodies if performed accurately. It is preferred because of its convenience and low cost (14,25).

- There are diagnostic tests defined for physical urticaria (26).

1. Dermographism: Occurrence of eryhtema and swelling in a few minutes after the skin is marked with a solid object indicates presence of dermographism.

2. Cholinergic urticaria: Swelling by metocholin stimulation in the skin and eryhtema and pruritus by exercise, hot, bathing, hot food.

3. Cold urticaria: Pruritus, eryhtema, swelling and accompanying angioedema in a short time after exposure to cold. Ice is applied on the forearm for five minutes. If no reaction occurs in five minutes, ice application should be performed for 10 minutes. Large, pruritic plaques are considered positive. However, the test should be performed on different parts of the skin decreasing the test period by one minute each time to find the shortest time causing plaques to form.

4. Solar urticaria: Occurrence of erythema, swelling and a sense of burning in a few minutes after exposure of the skin to sun supports the diagnosis.

5. Aquagenic urticaria: The diagnosis is made by observing point lesions of 1-2 cm a short time after contact with water.

6. Delayed pressure urticaria: Occurrence of erythema and swelling in the late period (generally after 4-6 hours) in the areas where continuous pressure is applied. The lesions may last up to 48 hours. Special measurement devices are available for the diagnosis.

Treatment

The general approach in cases of urticaria is removing the suspicious factors primarily. If there are foods (preservatives, tomato, cake), allergens, drugs (NSAI drugs, aspirin, ACE inhibitors), infectious and physical agents which are know to cause urticaria, removal or minimization of these factors should be planned (14).

Drugs used for symptomatic treatment in urticaria:

- **Antihistaminics:**

These are the first-line drugs in treatment. They are efficient in resolving both swelling and pruritus. First-generation H1 receptor antagonists achieve receptor blockage in a dose-dependent fashion. Their anticholinergic effects last for a long time and their effect of sedation lasts more than 12 hours. They cause sleep problems, performance and learning difficulties. Since their effects are dose-dependent, the dose should be increased according to the extensiveness of the lesion. Because of these reasons the accepted approach is to use non-sedative second-generation antihistaminics instead of first-generation antihistaminics in the first-line treatment. Second-generation antihistaminics show lower central nervous system and anticholinergic effects. However, cetrizine which belongs to this group has central nervous system effects in 10-14% of the cases. Since they bind to H1 receptors with high affinity and independent of the dose, a single daily dose provides treatment compliance. The final treatment guideline recommends

increasing the dose up to four fold according to the response obtained in patients in whom the complaints continue despite two-week treatment with second-generation antihistaminics. The recommended time for a change of treatment has been noted to be 1-4 weeks. After the disease is under control the patients should be evaluated every 6 months. In cases where no response is obtained, combination treatments may be tried. Combination treatment as a second-generation antihistaminic in the morning and a first-generation antihistaminic in the night and combination of H1 and H2 receptor antagonists may be tried. However, there is no sufficient information about the efficiency of these treatments (1,14,15,17,22).

Combined use of tricyclic antidepressant drugs (doxapine) can also be efficient by H1 and H2 receptor blockage. Monitoring in terms of QT prolongation by electrocardiogram is recommended with regular intervals during use of this drug (14,27,28). Doses of antihistaminic drugs are given in Table 3.

● **Corticosteroids:**

They act by blocking histamine release. Although their efficiency has not been demonstrated definetely in urticaria, they may be given as a short-term therapy in patients who do not respond to treatment and who have severe urticaria and angioedema. A dose of 0,5 mg/kg should be administered daily for 3-7 days. Long-term use is not recommended because of side effects (1,4,14).

● **Adrenergic agents:**

They are not used except for in urticaria and angioedema which cause respiratory distress. Adrenaline autoinjector is recommended for patients with a history of life-threatening attack (1).

● **Other treatment options:**

Other treatment options may be tried in cases resistant to antihistaminic treatment. Leukotrien receptor inhibitors may be tried especially in patients who have developed reaction against aspirin and non-steroid antiinflammatory drugs. Nonstandardized treatments include calcium channel blockers, cholchicine, dapson, sulphasalazine, IVIG, TNF-alpha blocker agents and methotrexate. However, there are no controlled studies showing the efficiency of all these treatment options. It has been demonstrated that combined use of cyclosporine with antihistaminics is effective in placebo-controlled studies (25). However, it should only be used in severe cases because of its side effects. In recent years, it has been emphasized that anti-IgE (omalizumab) monoclonal antibody treatment among new treatment options acts by specifically binding to IgE antibody preventing binding with highly sensitive IgE receptors and thus highly sensitive IgE receptors expressed on mast and basophil cells decrease by negative feedback and omalizumab is useful in treatment of chronic urticaria (14,29-34).

Treatment in physical urticaria (1,14,26):

● **Dermographism:** Treatment is usually not necessary, but resolving the dryness of the skin and use of antihistaminics may be useful in patients with symptomatic pruritus. The most efficient antihistaminic treatment is provided by hydroxyzine.

● **Cholinergic urticaria:** Hot bathing, stress, excessive exercise and consumption of hot foods should be avoided.

Table 3. Doses of antihistaminic drugs

Drug	Adult	Pediatric
Diphenhydramine	25-50 mg/dose, 3-4 times a day, PO, IV, maximum dose: 400 mg/day	5 mg/kg/day, in 3-4 doses, maximum dose: 300 mg/day
Hydroxyzine	25-50 mg/dose, 3-4 times a day, maximum dose: 300 mg/day	PO: 0,6 mg/kg/dose, in 4 doses IM:0,5-1 mg/kg/dose, in 4 doses.
Doxapine	10-150 mg/day, PO, in 1-3 doses	>12 years: 10-50 mg/day, PO., in 1-3 doses, maximum dose: 100 mg/day
Ciproheptadine	2-4 mg/dose,PO, in 3 doses	2-6 years: 2 mg/dose,PO, in 3 doses 7-17 years: 2-4 mg/dose, PO, in 3 doses
Cetirizine	5-10 mg PO, single dose	<30 kg: 5 mg, single dose >30 kg: 10 mg, single dose
Loratadine	10 mg PO, single dose	2-5 years: 5 mg PO, single dose 6 years: 10 mg PO, single dose
Desloratidine	5 mg PO, single dose	>12 years: 5 mg PO, single dose
Levocetirizine	5 mg PO, single dose	6-12 years: 2,5 mg PO, single dose >12 years: 5 mg PO, single dose
Fexofenadine	60 mg PO, dose, in 2 doses	6-11 years: 30 mg PO, dose, in 2 doses >11 years: 60 mg PO, dose, in 2 doses
Ranitidine	150 mg/dose, in 2 doses	1,5-2 mg/kg, dose, PO in 2 doses

Antihistaminics may be given in symptomatic cases. In very severe cases, danazol and beta-blocker treatment may be tried.

- **Cold urticaria:** It occurs rarely in children. In compliant patients, cold tolerance treatment may be performed. Among antihistaminics ciproheptadine and doxapine may be useful.
- **Solar urticaria:** Oral or local antihistaminic agents are efficient. Rarely, topical steroid treatment may be given to patients in whom antihistaminics are not efficient. Tolerance treatment with Psoralen Ultra-Violet A may be administered.
- **Delayed pressure urticaria:** Generally, preventive measures are useful. Although antihistaminics, steroids, non-steroid antiinflammatory agents and colchicine have been shown to be useful in different studies, the response varies from person to person.

Prognosis

The prognosis of urticaria is heterogeneous and varies from person to person. Although acute urticaria heals in 24 hours in most cases, it may last for up to six weeks rarely in some cases. Chronic urticaria generally lasts for 3-5 years and becomes permanent for a life time in 20% of the cases. Treatment response varies from person to person and the clinical prognosis is better in children compared to adults (25).

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