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REVIEW PAPER

What do we currently know about urticaria in children?

Anna Góra, Majka Jaszczura, Małgorzata Morawiecka-Pietrzak, Magdalena Kleszyk, Edyta Machura

Department of Paediatrics, Faculty of Medical Sciences in Zabrze, Medical University of Silesia, Katowice, Poland

ABSTRACT

Urticaria is a common pediatric dermatosis characterized by local swelling, pruritus, and skin redness. The primary lesions include wheals and/or angioedema. By definition, acute urticaria lasts up to 6 weeks and usually occurs as a single episode in life. Chronic urticaria lasts over 6 weeks and is uncommon.

Urticaria is a heterogenous disease. The development of skin lesions depends on the action of mast cells and other cells of the immune system, and inflammation is common in all forms of urticaria. Autoimmune mechanisms and activation of coagulation and fibrinolysis also play an important role. The etiology usually remains unknown.

Urticaria, especially its chronic form, contributes to a significant decrease in quality of life due to prolonged discomfort and the necessity of long-term and sometimes expensive treatment.

This article presents an up-to-date review of the literature on the incidence, causes, diagnosis, treatment and prognosis of urticaria in children.

KEY WORDS:

children, diagnosis, treatment, allergy, urticaria.

INTRODUCTION

Urticaria is one of the most common skin disorders. It is characterized by sudden onset of wheals and/or angioedema. An urticarial wheal is caused by swelling of the dermis and is usually accompanied by pruritus. The lesion fades on compression and usually resolves without leaving a trace within 24 hours. If deeper skin layers or mucous membranes are involved, angioedema develops [1–3]. It is generally accepted that the duration of skin lesions in acute urticaria (AU) does not exceed 6 weeks, whereas in chronic urticaria (CU) the lesions persist for more than 6 weeks [1].

Urticaria, despite its frequent occurrence in the pediatric population, still poses diagnostic and therapeutic difficulties, which worsen the patients' quality of life. Therefore, it is necessary to constantly expand the knowledge about this disease.

PREVALENCE

Urticaria occurs at least once in the life of about 15–25% of the general population [4], with the disease most often taking an acute form. The prevalence of all types of urticaria in children is estimated at 3.5–8% [5]. In the Polish population, the proportion of children with urticaria is 3.3%, while the chronic form affects 2.1% of children [6]. The peak incidence of CU occurs between the ages of 20 and 40 years [7]. Depending on age, the progression of AU to CU is reported in 1.2–25% of children [8, 9]. The duration of CU usually does not exceed 5–10 years [4].

ADDRESS FOR CORRESPONDENCE:

Anna Góra, Department of Paediatrics, Faculty of Medical Sciences in Zabrze, Medical University of Silesia, Katowice, Poland, phone: +48 32 3704283, e-mail: a.szczepanek@o2.pl

PATHOMECHANISM OF URTICARIA

Urticaria is a heterogeneous disease entity [2, 10]. Activation of cutaneous mast cells and other immune cells is required for the development of urticarial lesions [11]. The signaling pathways for mast cells show great variability and are not yet fully understood [1]. Mast cells can be activated through immunological and non-immunological mechanisms. The first group includes IgE-mediated immediate hypersensitivity reactions and the mechanisms associated with the presence of autoantibodies specific either for the high-affinity IgE receptor (FcεRI) or for IgE. The non-immunological mechanisms include the action of substances that can directly stimulate mast cells, such as contrast agents, opiates, neuropeptides, reactive oxygen species, certain foods or complement system activity [11].

Mast cell degranulation results in the release of histamine, proteases, and cytokines, and stimulates the production of platelet-activating factor, prostaglandins, and leukotrienes [3]. The consequence of these mediators is a widening of the lumen and increased permeability of vessels, which causes redness, swelling and pruritus [3]. At the site of wheal formation, perivascular infiltrates are formed, consisting mainly of CD4+ lymphocytes, monocytes, neutrophils, eosinophils, and basophils [4, 12, 13]. Patients with urticaria exhibit increased inflammatory markers and an altered cytokine profile consisting mainly of increased expression of IL-4, IL-5, and IFN-γ [12, 14].

ETIOLOGY OF ACUTE URTICARIA

In the pediatric population, AU is mainly associated with infectious agents. Infections most commonly involve the upper respiratory tract and gastrointestinal tract, less commonly the lower respiratory tract or urinary tract [15, 16]. Viral infections, including those caused by adenoviruses, enteroviruses, RSV, cytomegalovirus (CMV), Epstein-Barr virus (EBV), herpes simplex virus, influenza and parainfluenza viruses, are the most common etiologic agents [15, 17]. Cases of urticaria in COVID-19 have also been reported [18]. The development of AU may also be associated with bacterial infections (*Streptococcus*, *Staphylococcus*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Helicobacter pylori*) and in a small percentage with parasitic infestations (*Ascaris lumbricoides*, *Giardia lamblia*, *Anisakis simplex*, *Toxocara canis*, *Echinococcus granulosus*, *Strongyloides stercoralis*) [11, 15, 17].

Contrary to popular belief, food allergies are not among the predominant factors in the development of AU. Many foods such as eggs, milk, soy, nuts, wheat, and seafood can trigger hypersensitivity reactions [4, 17, 19]. In children, this mechanism is observed more frequently than in adults. The development of acute generalized urticaria due to ingestion of a specific food in sensitized patients may warn of future anaphylaxis. This group requires special attention, making it necessary to search for the trigger among food allergens [1, 4].

Acute drug-induced urticaria, which is much rarer, may develop in immunological (most often allergy to β-lactam antibiotics) and non-immunological (direct activation of mast cells by non-steroidal anti-inflammatory drugs, β-blockers) mechanisms [17].

The causes of AU, as with CU, largely remain unknown [17].

ETIOLOGY OF CHRONIC URTICARIA

Chronic urticaria can be divided into chronic spontaneous urticaria (CSU) and chronic inducible urticaria [1]. Spontaneous urticaria is characterized by the absence of a specific trigger. Inducible urticaria, on the other hand, is associated with an identifiable trigger factor; this group includes physical urticaria resulting from stimuli such as pressure, scratching, heat, cold, exposure to sunlight and water, physical exercise, cholinergic stimulation, and contact urticaria [1, 20].

There are many factors involved in the development of CU. Among these, infections, intake of certain medications, and even emotional stress are considered [4, 11]. Currently there is no clear evidence that consumption of pseudoallergens (such as food additives and some spices) may be the cause of CU [1, 21].

The role of infectious factors in CU in children is still a subject of research. The prevalence of bacterial, viral, parasitic, or fungal infections in CSU is not higher than in the general population, and the effectiveness of the treatment of infectious foci is questionable [21]. A high rate of *Staphylococcus aureus* carriage in the nasal cavity of adult patients with CU is well documented [4, 22]. Some authors suggest a possible influence of pathogens on the development of the immune response [23, 24].

The microorganisms associated with CU include HHV-6 and other human herpesviruses, CMV, EBV, *Streptococcus* spp., *Staphylococcus* spp., *Yersinia enterocolitica*, *Chlamydia pneumoniae*, and *Helicobacter pylori* [4]. Selected reports suggest a beneficial effect of *Helicobacter pylori* eradication treatment [1, 11, 21, 25].

The prevalence of parasitic infestations in children with CU ranges 0–37.8% [21, 26]. However, antiparasitic treatment in children rarely leads to the resolution of skin lesions [21]. Coexistence of CU with *Blastocystis hominis*, *Giardia lamblia*, *Dientamoeba fragilis*, *Ascaris lumbricoides*, *Strongyloides stercoralis*, *Toxocara canis*, and *Anisakis simplex* has been described [4, 15, 21].

Routine testing for viral, bacterial and parasitic infections is not recommended in most cases of urticaria and does not change the patient outcomes [1]. The aforementioned diagnostics should be performed only in patients with a suggestive history or laboratory tests [21].

The relationship between food and the occurrence of CU remains unclear [4]. IgE-mediated reactions to

food are a very rare cause of CU [1]. The prevalence of food allergy confirmed by history data, detection of IgE-specific antibodies in blood and by challenge tests ranges 8–10% [4]. Approximately 20% of patients with CSU have positive skin tests for hypersensitivity to food allergens [11]. Obtaining a positive skin prick test (SPT) result does not prove the diagnosis of food allergy, for which it is necessary to perform diagnostic elimination diets and/or oral food challenges [21]. The false-positive SPT results in patients with dermographism should be taken into consideration [27].

Data on the influence of non-allergic hypersensitivity reactions on the development of CU are conflicting. It is believed that so-called pseudoallergens contained in foods, food additives and some spices may promote the onset, recurrence or exacerbation of urticarial lesions [1, 4, 6]. It has been suggested that a diet with restriction of histamine-rich foods such as aged cheeses, cured meats, seafood, tomatoes, strawberries, citrus, egg white, chocolate, and alcohol may help to reduce symptoms in adult patients with urticaria [28, 29], but the effectiveness of a histamine-reduced diet has not been confirmed in well-designed studies [1].

An additional factor influencing the development of urticaria is the use of nonsteroidal anti-inflammatory drugs (NSAIDs). Almost a quarter of patients with CSU have been diagnosed with acetylsalicylic acid hypersensitivity, which is associated with increased severity of symptoms after exposure to NSAIDs [30]. Angiotensin-converting enzyme inhibitors may contribute to the development of bradykinin-mediated angioedema [10, 11].

According to various sources, approximately 30–40% of CU cases are associated with an autoimmune mechanism, as evidenced by, among other things, a positive autologous serum skin test (ASST) [4, 11]. In this group of patients the presence of IgG class antibodies directed against the high affinity receptor for IgE (FcεRIa) or, more rarely, antibodies against IgE itself has been documented [11].

Activation of the immune system makes CU associated with an increased risk of autoimmune thyroiditis, type 1 diabetes, systemic lupus erythematosus, or celiac disease [10, 11, 21]. Antinuclear antibodies are detected in about 10% of children [5], while antithyroid antibodies (against thyroperoxidase and/or thyroglobulin) are present in 4.3–17.3% of children [4].

Current scientific reports indicate that in addition to autoimmune processes, an important pathogenetic factor in CU is the activation of the coagulation and fibrinolysis systems, and a common link is the presence of inflammation [8, 31].

The mechanisms involved in the development of urticaria depend on the action of a number of immune cells, including granulocytes. These cells interact with mast cells and are actively involved in immunomodulation and in the generation of the inflammatory response [13, 32]. Eosinophils play a special role in the mentioned processes. They are responsible for defense against infectious agents, development of allergic and autoimmune diseases or tissue regeneration [13]. The degranulation of eosinophils also results in the release of tissue factor, which locally activates the coagulation system [24]. It is believed that vitamin D3 deficiency may also contribute to the development of both AU and CU [33].

It should be emphasized that in 40–50% of cases the etiological factor of CU cannot be determined [10, 21], which translates into therapeutic difficulties.

DIAGNOSIS

The diagnosis of urticaria is based on anamnestic data, information from the physical examination, and the results of additional tests [2]. Acute urticaria routinely does not require diagnostic testing because it usually resolves spontaneously. The exception is when urticaria is suspected to be associated with type I hypersensitivity or a significant effect of trigger agents such as NSAIDs [1].

The occurrence of CU usually requires more extensive diagnostic evaluation to assess disease activity and control, to identify causes and triggers, and to rule out other diseases [1]. The medical history should cover a range of issues including the frequency and circumstances of urticaria onset, the nature and duration of lesions, triggers, and associated symptoms. It is important to obtain data on chronic diseases (including allergies, infections, psychiatric and psychosomatic disorders), past surgery (including implant placement, unexpected events), family history, dietary habits, hobbies, travel, exposure to stress, menstrual cycle, current medications, and response to any previous treatment for urticaria [1, 2, 11]. In addition, the Urticaria Activity Score, Urticaria Control Test and Dermatology Life Quality Index should be used to assess the severity of urticaria [1, 34]. These scales are not validated for children, but can be successfully used in clinical practice [21, 34].

Wheals, angioedema or similar changes may occur in the course of separate diseases and conditions, hence the need for careful differential diagnosis – as shown in Table 1.

The range of diagnostic work-up should be determined individually, depending on the clinical data obtained (Table 2). In the case of CU, a peripheral blood count with smear, CRP, and/or ESR are recommended among the basic tests [1, 2, 30]. If the history and physical examination do not reveal any particular abnormalities, complementary tests for the presence of autoantibodies (ASST, basophil activation test – BAT, basophil histamine release assay – BHRA), autoimmune diseases testing (celiac disease, thyroid diseases) [21, 30], and hypersensitivity reaction tests (specific IgE, SPT, provocative tests) are recommended [2] [10, 21]. It is advisable to look for possible infectious foci (parasitological examination, general examination and urine culture). In justified cases,

TABLE 1. Differential diagnosis of urticaria and angioedema [11, 21] – own modification

Type of urticaria	Disease entity/condition
Acute urticaria	
Disseminated lesions	Anaphylaxis, serum sickness like reaction (SSLR), viral rash diseases, urticaria multiforme
Local lesions	Physical urticaria, contact urticaria, insect bites
Chronic or recurrent urticaria/angioedema	Cutaneous mastocytosis, bullous pemphigoid, papular urticaria, urticarial vasculitis, bradykinin-mediated angioedema Cryopyrin-associated periodic syndrome, Schnitzler syndrome, Sweet's syndrome, Gleich syndrome, tumor necrosis factor receptor 1 associated periodic syndrome (TRAPS) Hypoproteinemic edema, head and neck tumors

TABLE 2. Recommended diagnostic tests in urticaria [1, 2, 11, 21]

Type of urticaria	Cause/accompanying factor	Test/procedure
Acute urticaria	Single episode/infection	Routinely not recommended
	Suspected allergy/anaphylaxis	Allergological diagnostics (skin prick tests, specific IgE, diagnostic elimination diets and/or oral food challenges)
Chronic spontaneous urticaria	Additional tests are required only if there are indications based on anamnesis and physical examination	Routine: complete blood count with manual smear, CRP and/or ESR Additionally Autologous serum skin test Celiac disease serology, TSH, fT4, anti-TPO, ANA, ASO, vitamin D3, C1-esterase inhibitor, C3, C4, immunoglobulin concentration Allergological diagnostics Parasitological tests, urinalysis and urine culture test Imaging tests and specialist consultations (ENT, dental, genetic) Histopathological examination of skin lesions
Chronic inducible urticaria	Cold urticaria* Delayed pressure urticaria Heat urticaria Solar urticaria * Dermographism * Vibratory angioedema Aquagenic urticaria Cholinergic urticaria Contact urticaria	Cold provocation and threshold test Pressure test and threshold test Heat provocation and threshold test UV/visible light and threshold test Elicit dermatographism and threshold test Test with vibration (e.g. Vortex test) Wet cloth at body temperature applied for 20 min Exercise and hot bath provocation Cutaneous provocation test

**Depending on anamnesis: complete blood count, CRP and/or ESR; cryoproteins in cold urticaria; other light-induced dermatoses in solar urticaria*

imaging studies (e.g., chest X-ray, abdominal ultrasound) and specialist consultations (genetic, ENT, dental) may be helpful [2]. Suspicion of urticarial vasculitis requires verification by histopathological examination of a skin biopsy [21].

Inducible urticaria are a separate group, the diagnosis of which is usually established by a characteristic clinical picture and an appropriately selected, standardized diagnostic test [2, 11].

TREATMENT AND COMPLICATIONS

The goal of urticaria treatment is to achieve symptom control by elimination of underlying causes and avoiding exposure to known eliciting factors. As in many cases it is impossible, symptomatic pharmacotherapy is used [1, 21].

First-line pharmacological treatment is based on the supply of second-generation H1-receptor blocking antihistamines [1]. If there is no clinical response, second-line treatment, based on increasing the daily dose of antihistamine, is introduced. Recommendations allow the use of four times the daily dose (including in children) [1, 17]. In the pediatric population (especially < 12 years of age) it is suggested not to exceed double the dose, as it usually does not increase the effectiveness of the treatment [21, 35]. Antihistamine treatment should be provided daily until control of symptoms is achieved. In most cases it is recommended to continue therapy for 3–6 months with periodic evaluation of the patient's condition and indications for further supply [10, 21].

A short course of oral steroid therapy may be used if a severe urticarial episode occurs (prednisolone or prednisone at 0.5–1 mg/kg bw/d for up to 10 days) [1, 4, 10]. Topical steroid preparations should not be used to treat urticaria [9]. Due to the high risk of side effects (e.g. anticholinergic, sedative, sleep disrupting effects), the use of first-generation antihistamines and the combination of several drugs in this group are not recommended [1].

TABLE 3. Selected 2nd generation H1-antihistamines for children registered in Poland

Drug	Dosage	Age registration*
Cetirizine (drops 10 mg/ml; oral solution 1 mg/ml; tablets 10 mg)	2–6 years: 2.5 mg twice a day (5 drops twice a day; 2.5 ml of a solution twice a day) 6–12 years: 5 mg twice a day (10 drops twice a day; 5 ml of a solution twice a day) Over 12 years: 10 mg once a day (20 drops once a day; 10 ml of a solution once a day)	2 years of age (6 months of age for the treatment of an anaphylactic reaction manifested by urticaria or angioedema; food allergy; atopic dermatitis)
Levocetirizine (oral solution 0.5 mg/ml; tablets 5 mg)	2–6 years: 1.25 mg twice a day (2.5 ml of a solution twice a day) Over 6 years: 5 mg once a day (10 ml of solution once a day)	2 years of age (6 months of age for the treatment of an anaphylactic reaction manifested by urticaria or angioedema; food allergy; atopic dermatitis)
Loratadine (oral solution 1 mg/ml; tablets 10 mg)	2–12 years (≤ 30 kg): 5 mg once a day (5 ml of the solution once a day) 2–12 years (> 30 kg) and over 12 years: 10 mg once a day (10 ml of solution once a day)	2 years of age
Desloratadine (oral solution 0.5 mg/ml; tablets 2.5 and 5 mg; dispersible tablets 2.5 and 5 mg)	1–5 years: 1.25 mg once a day (2.5 ml of solution once a day) 6–11 years: 2.5 mg once a day (5 ml of solution once a day) Over 12 years: 5 mg once a day (10 ml of the solution once a day)	1 year of age
Fexofenadine (tablets 30,120 and 180 mg)	6–11 years: 30 mg twice a day Over 12 years: 120 mg once a day/180 mg once a day	12 years of age (6 years of age in the treatment of seasonal allergic rhinitis)
Rupatadine (oral solution 1 mg/ml; tablets 10 mg)	2–11 years (≥ 10 kg < 25 kg): 2.5 mg once a day (2.5 ml of the solution once a day) 2–11 years (≥ 25 kg): 5 mg once a day (5 ml of the solution once a day) Over 12 years: 10 mg once a day	2 years of age
Bilastine (oral solution 2.5 mg/ml; tablets 10 mg and 20 mg, dispersible tablets 10 mg)	6–11 years (≥ 20 kg): 10 mg once a day (4 ml of the solution once a day) Over 12 years: 20 mg once a day	6 years of age

**According to ChPL (Summary of Product Characteristics)*

Second-generation antihistamines that are safe and effective in children include cetirizine, levocetirizine, loratadine, desloratadine, fexofenadine, rupatadine, and bilastine [1, 35, 36]. Currently, there is no scientific evidence regarding the superiority of a particular second-generation antihistamine over another [21]. In most European countries, cetirizine is the drug of choice for children < 6 years of age [37]. The second-generation antihistamines registered for the treatment of urticaria in children in Poland are shown in Table 3.

Omalizumab (anti-IgE antibody) and ciclosporin A are used as third-line treatment in children [1]. Omalizumab is a monoclonal anti-IgE antibody that binds to FcεRI preventing the interaction of free IgE with its receptors on mast cells and basophils. Ciclosporin is an immunomodulating drug that reduces the production of proinflammatory cytokines. It has an inhibitory effect on T lymphocytes and may inhibit the IgE-mediated release of histamine from mast cell degranulation [38]. Selected recommendations also allow the administration of leukotriene antagonists as third-line treatment [21]. The relationship between montelukast and the occurrence of neuropsychiatric events (agitation, aggressive behavior, anxiousness, depression, hallucinations, insomnia, memory impairment, suicidal ideation and behavior) is the subject of research work. The current reports, however, do not seem to confirm such an impact [39, 40].

Currently, no data are available for the pediatric population to assess the indications for other drugs, which are used in adults (mycophenolate mofetil, methotrexate, hydroxychloroquine, sulfasalazine, danazol, H2-receptor antagonists, warfarin, tranexamic acid, rituximab) [10, 30]. Table 4 shows the treatment regimen for urticaria in children.

In selected cases, therapy of patients with urticaria also includes eradication of infectious agents, treatment of possible inflammatory processes, dietary management, and psychological care [1, 4, 10].

It should be emphasized that CU significantly impairs the quality of life of patients through prolonged pain, pruritus, the presence of edema, the need for multiple hospitalizations and long-term treatment. These effects include difficulties in concentration and learning, increased school absenteeism, and sleep disturbances [3, 10].

TABLE 4. Scheme of treatment of urticaria in children according to [1, 4, 21] – own modification

Acute urticaria	Chronic urticaria
Elimination and/or limitation of exposure to the triggering agent	
Pharmacological treatment First-line treatment: 2nd generation antihistamine at standard dose Second-line treatment (in case of no improvement or intolerable symptoms – updosing 2nd generation up to four times the standard dose (consider the double dose < 12 years old) When the patient has symptoms of anaphylaxis, use the anaphylaxis treatment algorithm (adrenaline i.m.)	Pharmacological treatment First-line treatment: 2nd generation antihistamine at standard dose until the symptom control is achieved Second-line treatment (in case of no improvement or intolerable symptoms) – updosing 2nd generation up to four times the standard dose (consider the double dose < 12 years old) Third-line treatment (in specialized centers)* Omalizumab Ciclosporin
In case of severe course or suspected antihistamines resistance, up to 10 day course of oral steroid therapy (prednisone, prednisolone)	

**In Poland, omalizumab has been registered for the treatment of chronic spontaneous urticaria in children ≥ 12 years old (off label therapy ≥ 6 years old); ciclosporin – use in children only off label.*

Patients often experience anxiety, depression, and somatoform disorders, and stress factors may exacerbate skin lesions [10]. Long-term therapy with second-generation antihistamines may cause side effects (headache, drowsiness, abdominal pain), which are typically mild and usually do not affect daily activity or sleep [35]. The incidence and severity of adverse effects show a high degree of individual variability, so a particular drug may be better or worse tolerated by a patient [21]. The second-generation antihistamines present a high safety and efficacy profile, even when used in doses higher than the standard ones [35].

PROGNOSIS

Urticaria in children is a disease with a good prognosis. Acute urticaria usually occurs as a single episode in life. The diagnosis of CSU in childhood has a better prognosis than in adulthood [4]. In children, the recovery rate within 5 years after the diagnosis of CU is up to 72% [41]. High initial disease severity and the need for second- and subsequent-line drug therapy appear to be unfavorable predictors of the course of CU [4, 41].

CONCLUSIONS

Urticaria is a common pediatric disease with a good prognosis. The challenges that accompany the management of patients with urticaria arise from a number of clinical variants, causative factors, and the high proportion of idiopathic forms. Patients diagnosed with CU experience years of impaired quality of life. Correct identification of the cause of the disease and selection of appropriate treatment are key elements in achieving disease control.

DISCLOSURE

The authors declare no conflict of interest.

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