ATOPIC DERMATITIS, ALLERGIC RHINITIS AND URTICARIA IN CHILDREN

Methodical elaborations for foreign students

МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
харківський національний медичний університет

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АТОПІЧНИЙ ДЕРМАТИТ, АЛЕРГІЧНИЙ РИНІТ, КРОПИВ'ЯНКА У ДІТЕЙ

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Atopic dermatitis

Atopic dermatitis (AD) is a chronic, relapsing, highly pruritic skin condition resulting from disruption of the epithelial barrier and associated immune dysregulation in the skin of genetically predisposed hosts. AD is relatively common, affecting 10-20% of children in developed countries. It is also known as eczema and atopic eczema. Onset of AD generally develops in early childhood but may occur at any age. It usually improves as the child grows older and may resolve by school age or puberty. This disease has a characteristic age-dependent distribution and is commonly associated with elevated IgE, peripheral eosinophilia and other allergic diseases.

Etiology

The causes of AD are still poorly understood. Similar to asthma and other complex, chronic disorders, AD should be viewed as a common end manifestation of many different genetic defects, resulting in impaired epidermal barrier function and immune dysregulation. On another hand the etiology of atopic dermatitis is linked to environmental agents.

The prevalence of atopic dermatitis in children with one affected parent is 60 % and rises to nearly 80% for children of two affected parents. Additionally, nearly 40 % of patients with newly diagnosed cases report a positive family history for atopic dermatitis in at least one first-degree relative. Children of parents with atopic dermatitis have an increased risk of developing atopic dermatitis by age 3 years. Much higher concordance rates for atopic dermatitis are observed in monozygotic twins (77 %) than in dizygotic twins (15 %).

Patients with loss-of-function mutations in the gene that encodes the epidermal structural protein filaggrin (FLG) have evidence a strong genetic predisposition towards the development of AD. Filaggrin deficiency causes a significant defect in the normal epidermal barrier that allows for enhanced allergen absorption through the skin, resulting in a higher incidence of dermatitis.

Environmental allergens may be trigger exacerbations of atopic dermatitis in susceptible individuals.

Triggers AD:

- stress
- allergies
- sweating
- certain soaps, cleaners or detergents
- long, hot baths or showers
- rapid changes in temperature
- low humidity
- wool or man-made fabrics or clothing
- dust or sand

- cigarette smoke
- certain foods, such as eggs, milk, fish, soy or wheat
- bacterial skin infection or colonization

Contact irritants (eg, soaps, solvents, wool clothing, mechanical irritants, detergents, preservatives, perfumes) compromise the integument, creating inflammation, irritation, and a portal of entry for further environmental insult. These surface irritants, along with the macerative effects of sweating and the drying effects of low humidity, lower the pruritic threshold. Cutaneous damage caused by scratching further lowers the pruritic threshold and subsequently causes increased itching.

Aeroallergens (eg, house dust mite, molds, pollen, dander) induce peripheral eosinophilia and elevate serum IgE levels. These early effects lead to increased histamine release from IgE-activated mast cells and elevated activity of the T-helper cell–mediated immune system. The increased release of vascular mediators (eg, bradykinin, histamine, slow-reacting substance of anaphylaxis [SRS-A]) induces vasodilation, edema, and urticaria, which in turn stimulate pruritus and inflammatory cutaneous changes.

Microbial agents (eg, S aureus, Pityrosporum yeasts, Candida organisms, Trichophyton dermatophytes) act in two different ways to promote the flares of atopic dermatitis. The microorganisms directly invade the skin, creating local injury and inflammation, and they induce a systemic allergic response to specific antigens, causing a rise in serum IgE and enhanced activity of the immune system. Anti-IgE drugs diminish pediatric atopic dermatitis severity.

Food allergy is implicated as a cause in one third to one half of children with atopic dermatitis. Food allergens may be the initial trigger for IgE autoreactivity to epithelial autoantigens in young children with atopic dermatitis. The most common food allergens in children are egg, soy, milk, wheat, fish, shellfish, and peanut, which together account for 90 % of food-induced cases of atopic dermatitis. Many clinically significant food allergies self-resolve within the first 5 years of life.

Stress may trigger atopic dermatitis at the sites of activated cutaneous nerve endings, possibly by the actions of substance P, vasoactive intestinal peptide (VIP), or via the adenyl cyclase–cyclic adenosine monophosphate (cAMP) system.

Atopic dermatitis is the result of a complex relationship between genetic predisposition and environmental exposures, including climate. Atopic dermatitis prevalence is significantly lower with higher humidity, and with increased UV exposure.

Pathophysiology

Clinically unaffected skin in patients without atopic dermatitis has decreased numbers of T-helper type 2 (Th2) cells compared with skin in patients with

atopic dermatitis. Polymorphisms of various immune pathway genes are associated with an increased risk of AD through alternations in the T-helper (Th) type 2 signaling pathway. Upregulation of interleukin (IL) 4 and IL-13 lowers FLG expression, which leads to skin barrier defects. Immune cytokines, e.g., IL-4 and IL-13, play important roles in chemokine production, skin barrier dysfunction, suppression of antimicrobial peptides, and allergic inflammation. Increased levels of interleukin (IL)-4 and IL-13 (Th2 cytokines) are seen in acute atopic dermatitis skin lesions, whereas chronic atopic dermatitis lesions show increased expression of IL-5 (Th2 cytokine) and IL-12 and interferon (IFN)-γ (Th1 cytokines). Chronic atopic dermatitis lesions also exhibit greater eosinophil infiltration compared with skin in patients without atopic dermatitis.

IL-4 enhances differentiation of T-helper cells along the Th2 pathway, and IL-13 acts as a chemoattractant for Th2 cells to infiltrate atopic dermatitis lesions. IL-13 may also directly induce IL-5 expression and eosinophil infiltration, thereby facilitating the transition from acute lesions into chronic lesions.

In addition, patients with atopic dermatitis have significantly decreased levels of skin barrier molecules compared with normal controls. Ceramide lipids in the stratum corneum, which are responsible for water retention and permeability functions, and skin barrier proteins such as filaggrin are expressed at significantly lower levels in the skin of patients with atopic dermatitis compared with the skin of patients without atopic dermatitis.

Significant evidence favors the hygiene hypothesis for the development of atopic dermatitis. An inverse relationship is recognized between helminth infections and atopic dermatitis but no other pathogens. In addition, early day care, endotoxin, unpasteurized farm milk, and animal exposure appear to be beneficial, likely because of a general increase in exposure to nonpathogenic microbes.

Clinical manifestations.

Atopic dermatitis is characterized by a chronic, relapsing dermatitis that is pruritic, begins in the first 5 years of life in 90 % of patients (but not in the first weeks of life, as seen in the autosomal dominant hyper-IgE syndrome), and usually presents in a characteristic agedependent distribution with facial, scalp, and extensor involvement in infants and young children, and predominant flexural involvement in older children and adults. Pruritus is universal and xerosis is a common feature in children with atopic dermatitis. Acute lesions are characterized by pruritic papules with erythema, excoriations and serous exudate, while chronic AD is characterized by areas of lichenification and fibrotic nodules, often accompanied by acute lesions.

Diagnostic criteria for AD have been proposed by Hanifin and Rajka (1980) and largely adopted by the American Academy of Allergy, Asthma, and Immunology. Appropriate cases must have at least 3 major characteristics and at least 3 minor characteristics.

Major clinical features of atopic dermatitis

- Pruritus
- Characteristic morphology and distribution:
- Facial and extensor involvement in infants and children; flexural involvement with lichenification in adults
- Chronic or chronic, relapsing course
- Personal or family history of atopy, including asthma, allergic rhinitis, atopic dermatitis

Minor clinical features of atopic dermatitis

- Early age of onset
- Xerosis
- Palmar hyperlinearity, ichthyosis, keratosis pilaris
- Immediate skin test reactivity, elevated serum IgE
- Cutaneous infection, including Staphylococcus aureus and Herpes simplex virus
- Nipple eczema
- Cheilitis
- Pityriasis alba
- White dermatographism, delayed blanching
- Perifollicular accentuation
- Anterior subcapsular cataracts
- Itch when sweating
- Non-specific hand or foot dermatitis
- Recurrent conjunctivitis
- Dennie-Morgan folds
- Keratoconus
- Facial erythema or pallor

Five major clinical features based on these criteria are: (1) pruritus; (2) a chronic, relapsing course; (3) typical distribution; (4) family or personal history of atopy; (5) onset before 2 years old. In addition, associated minor criteria are frequently observed in patients with AD and aid in diagnosis.

The following three classes of skin lesions are recognized:

Acute – Intensely pruritic erythematous papules and vesicles overlying erythematous skin; frequently associated with extensive excoriations and erosions accompanied by serous exudates

Subacute – Erythema, excoriation, and scaling

Chronic – Thickened plaques of skin, accentuated skin markings (lichenification), fibrotic papules (prurigo nodularis); possible coexistence of all 3 types of lesions in chronic atopic dermatitis.

The clinical manifestations of AD are determined by the age of the child.

Infants

- Infants less than one year of age often have widely distributed eczema. The skin is often dry, scaly and red with small scratch marks made by sharp baby nails.
- The cheeks of infants are often the first place to be affected by eczema.
- The napkin area is frequently spared due to the moisture retention of nappies. Just like other babies, they can develop irritant napkin dermatitis, if wet or soiled nappies are left on too long.

Toddlers and pre-schoolers

- As children begin to move around, eczema becomes more localized and thickened. Toddlers scratch vigorously and eczema may look very raw and uncomfortable.
- Eczema in this age group often affects the extensor (outer) aspects of joints, particularly the wrists, elbows, ankles and knees. It may also affect the genitals.
- As the child becomes older the pattern frequently changes to involve the flexor surfaces of the same joints (the creases) with less extensor involvement. The affected skin often becomes lichenified i.e. dry and thickened from constant scratching and rubbing,
- In some children, the extensor pattern of eczema persists into later childhood.

School-age children

- Older children tend to have the flexural pattern of eczema and it most often affects the elbow and knee creases. Other susceptible areas include the eyelids, earlobes, neck and scalp.
- They can develop recurrent acute itchy blisters on the palms, fingers and sometimes on the feet, known as pompholyx or vesicular hand/foot dermatitis.
- Many children develop a 'nummular' pattern of atopic dermatitis. This refers to small coin-like areas of eczema scattered over the body. These round patches of eczema are dry, red and itchy and may be mistaken for ringworm (a fungal infection).
- Mostly eczema improves during school years and it may completely clear up by the teens, although the barrier function of the skin is never entirely normal.

Adults

- Adults who have atopic dermatitis may present in various different ways.
- They may continue to have a diffuse pattern of eczema but the skin is often more dry and lichenified than in children.
- Commonly adults have persistent localised eczema, possibly confined to the hands, eyelids, flexures, nipples or all of these areas.
- Recurrent staphylococcal infections may be prominent.
- Atopic dermatitis is a major contributing factor to occupational irritant contact dermatitis. This most often affects hands that are frequently exposed to water, detergents and /or solvents.

• Having atopic dermatitis does not exclude contact allergic dermatitis (confirmed by patch tests) in children and adults)

• Hand dermatitis in adult atopics tends to be dry and thickened but may also be blistered.

Differential Diagnoses.

A number of diseases may present with eczematous rashes and can be misdiagnosed as AD.

Hyperimmunoglobulinemia E (Job) Syndrome

Hyper-IgE syndrome (HIES) is a rare, primary immunodeficiency distinguished by the clinical triad of atopic dermatitis, recurrent skin staphylococcal infections, and recurrent pulmonary infections. IgE level over 2000 IU/ml.

Pediatric Acrodermatitis Enteropathica

Acrodermatitis enteropathica is a rare and is contributed severe genetic disorder, of autosomal recessive inheritance, which determines the deficiency of the intestinal absorption of zinc, an essential trace element required by more than one hundred enzymes and whose role in the metabolism of nucleic acid is important. The classic clinical manifestations of acrodermatitis enteropathica are characterized by the triad eczematous and erosive dermatitis, acral and perioficial symmetrical dermatitis, alopecia and diarrhea.

Pediatric Contact Dermatitis

Contact dermatitis is inflammation of the dermis and epidermis as a result of direct contact between a substance and the surface of the skin. In fact, almost all dermatitis is the result of skin surface injury from epicutaneous exposures. Contact dermatitis is divided into two broad categories: irritant contact dermatitis and allergic contact dermatitis. Irritants cause immediate inflammation of the skin; allergens cause an inflammatory response that is delayed by days.

Common irritants that can cause contact dermatitis in children include: lotions, soaps, detergents, saliva, urine in a diaper. Common allergens that can cause contact dermatitis in children include: these are plants with oil that causes skin allergies, metals, latex, medicines, and cosmetics.

Pediatric Herpes Simplex Virus Infection

Patients with atopic eczema are susceptible to particularly severe infections with herpes simplex virus. Most cases are probably due to type 1, but eczema herpeticum due to the type 2 virus has been described. Cases of eczema herpeticum mostly represent an initial infection. Patients with eczema herpeticum may become seriously ill with a high fever, and death can occur. The cause of death may be due to some undetected immune deficiency state such as the Wiskott-Aldrich syndrome or to secondary bacterial infection, usually with a combination of group A haemolytic streptococci and Staphylococcus aureus. Severe herpes simplex infections are known to be a complication of other dermatological disorders including autosomal dominant ichthyosis vulgaris, Darier's disease, familial benign pemphigus, pemphigus foliaceous, and congenital ichthyosiform erythroderma.

Pediatric Wiskott-Aldrich Syndrome

Wiskott-Aldrich syndrome is an X-linked recessive immunodeficiency disorder characterized in one third of patients by the triad of recurrent bacterial sinopulmonary infections, eczema, and a bleeding diathesis caused by thrombocytopenia and platelet dysfunction.

Phenylketonuria (PKU)

PKU is an inherited disorder that increases the levels of a substance called phenylalanine in the blood. Phenylalanine is a building block of proteins that is obtained through the diet. If PKU is not treated, phenylalanine can build up to harmful levels in the body, causing intellectual disability and other serious health problems. The signs and symptoms of PKU vary from mild to severe. The most severe form of this disorder is known as classic PKU. Infants with classic PKU appear normal until they are a few months old. Without treatment, these children develop permanent intellectual disability. Seizures, delayed development, behavioral problems, and psychiatric disorders are also common. Untreated individuals may have a musty or mouse-like smell as a side effect of excess phenylalanine in the body. Children with classic PKU tend to have lighter skin and hair than unaffected family members and are also likely to have skin disorders such as eczema.

Scabies

Scabies is an itchy skin condition caused by a tiny burrowing mite called Sarcoptes scabiei. Intense itching occurs in the area where the mite burrows. The urge to scratch may be especially strong at night.

Staphylococcus Aureus Infection

Staphylococcus aureus is the almost-universal cause of furuncles, carbuncles, and skin abscesses and worldwide is the most commonly identified agent responsible for skin and soft tissue infections. S. aureus skin and soft tissue infections frequently begin as minor boils or abscesses and may progress to severe infections involving muscle or bone and may disseminate to the lungs or heart valves.

Diagnosis of AD.

Diagnosis of AD is based primarily on clinical data. Objective diagnostic tests to confirm the diagnosis do not currently exist. Examination of a patient with AD includes a medical history, specific skin tests and blood tests, as well as control tests, depending on the severity of the disease and the alleged factors involved.

Laboratory and instrumental studies:

• Clinical blood test (the presence of eosinophilia may be a nonspecific sign; neutrophilic leukocytosis is possible if an infectious skin process is attached).

• Skin tests with allergens (prik test) detect IgE-mediated allergic reactions; are carried out by an allergist in the absence of acute manifestations of AD in a child.

• Determining the concentration of total IgE in serum has low diagnostic value (a low level of total IgE does not indicate the absence of atopy and is not a criterion for excluding the diagnosis of AD).

The elimination diet, as well as the diagnostic introduction of the product, is prescribed by specialists (doctors, allergists, nutritionists) to confirm / exclude food allergies (especially in cases of sensitization to cereal and cow's milk proteins). The diagnostic effectiveness of the elimination diet is assessed in dynamics, usually 2–4 weeks after strict performance of dietary recommendations. Provocation by food allergens (diagnostic introduction of the product) is needed to confirm the diagnosis both in dynamics (to assess the formation of tolerance) and after the desensitization phase to allergens.

• In vitro diagnostics are carried out by an allergist and include the determination of allergen-specific IgE antibodies in blood serum, which is preferred for children. Indications for in vitro testing are also:

– with common skin manifestations of AD;

– if it is impossible to cancel the taken antihistamines, tricyclic antidepressants, antipsychotics;

– with doubtful results of skin tests or in the absence of a correlation of clinical manifestations and results of skin tests;

– with a high risk of developing anaphylactic reactions to a specific allergen during skin testing;

– infancy;

– in the absence of allergens for skin testing.

Treatment of AD.

The goal of therapy for AD should focus on improving quality of life by keeping skin healthy – repairing barrier function, minimizing pruritus, and preventing exacerbations of disease. Bathing with a gentle cleaner or body wash

Treatment of atopic dermatitis includes:

1. Avoidance of triggers, application of cleanser and moisturizer,
2. Bathing with a gentle cleaner or body wash.
3. Keeping child's fingernails short, to help prevent scratching that can cause skin irritation and infection.
4. Corticosteroid cream or ointment. Calcineurin inhibitor cream or ointment. Cream or ointment is put on the skin. This is to help ease itching and swelling.
5. Systemic anti-inflammatory treatment

Oral glucocorticosteroids are used in many European countries for treatment of AD. Well known side effects limit their use especially for long-term treatment. Short-term (up to 1 week) treatment with oral glucocortico-steroids may be an option to treat an acute flare in exceptional cases of AD. The daily dose should be adjusted to and not exceed 0.5 mg/kg bodyweight. Long-term use of oral glucocorticosteroids in AD patients is not recommended. The indication for oral steroids in children should be handled even more cautiously than in adults.

Cyclosporine. Cyclosporine may be used in children and adolescent patients showing a refractory or severe course of disease. The duration of cyclosporine therapy is guided by clinical efficacy and tolerance of the drug. Both short-term and long-term therapies may be useful in AE. An initial daily dose of 5 mg/kg/day, divided upon two single doses, is recommended. A dose reduction of 0.5–1.0 mg/kg/day every 2 weeks is recommended, once clinical efficacy is reached.

Azathioprine (AZA). The suggested dose range is 1– mg/kg bw/day. AZA should not be combined with UV therapy, and effective UV protection should be used.

Methotrexate (MTX)

6. Use of antibacterial, antiviral and antifungal drugs.

Antibacterial drugs. In up to 90 % of patients with AD, even the normal looking skin is extensively colonized by S. aureus. This bacterium is a major trigger of AD, as it leads to inflammation through the release of superantigen toxins, which enhance T-cell activation of superantigen-specific and allergen-specific T cells, expression of IgE antistaphylococcal antibodies and as it increases expression of IL-31 which leads to pruritus. A short course of systemic antibiotics, such as cephalosporin, may be considered in AD patients clinically infected with S. aureus.

Viral infections including herpes simplex, varicella zoster, molluscum contagiosum, smallpox and Coxsackie viruses occur more frequently in AD patients than in healthy individuals, with a tendency to disseminated, widespread disease. Eczema herpeticum, a disseminated herpes simplex virus infection, is a potentially serious complication of AD that requires immediate medical action. Mainstay of Eczema herpeticum therapy is a systemic treatment with aciclovir or valaciclovir, in a majority of cases administrated intravenously.

Topical or systemic antifungal therapy may be effective in some AD patients, mainly in those suffering from the ‘head and neck’ variant of AD or with demonstrated IgE sensitization to Malassezia ssp.

7. Other systemic treatment:

Immunoadsorption has been used in patients with AD and high serum IgE levels based on the assumption that a reduction in IgE might result in a reduction in disease activity.

Intravenous immunoglobulins are considered as immunomodulatory substances, but not as immunosuppressive agents.

H1R-blocking antihistamines. Traditional histamine 1 receptor (H1R)-blocking antihistamines have been used for decades, in an attempt to relieve pruritus in patients with AD.

Leukotriene antagonists. Montelukast is a cysteinyl leukotriene receptor antagonist that blocks the action of LTD4, LTC4 and LTE4. It has been used at doses of 10 mg daily (4 mg/day in children below 6 years, 5 mg/day in children below 12).

Allergen-specific immunotherapy (ASIT) has been investigated for treatment of AD, and the two relevant therapeutic regimens are subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT).

8. Phototherapy (light therapy). Light therapy may be done in the healthcare provider's office or at home. Most patients affected by AD improve during the sunny summer season, artificial UV radiation is frequently employed in the treatment of AD.

Allergic rhinitis

Allergic rhinitis (AR) is an inflammatory process of the nasal mucosa, typically IgE-mediated, elicited by environmental allergens and characterized by the presence of inflammatory cells within the mucosa and submucosa. The course of the disease involves one or more of the symptoms enumerated below, persisting for at least one hour a day for at least two consecutive days, which are reversible spontaneously or with treatment. The symptoms include nasal discharge, nasal itching, sneezing and nasal obstruction.

The disease is a serious public health problem in a number of countries. Worldwide, allergic rhinitis affects between 10 % and 30 % of the population. The prevalence of AR in children is high and still progressively increasing. It is estimated to occur in between 4.2 and 12.7 % of children aged 6–7, and 1 to 45.1 % of 13 and 14-year-olds worldwide. Allergic rhinitis has a profound negative impact on the quality of life of patients and their families. It is also a major cause of school and work absenteeism. Consequently, it is vital to ensure timely and correct diagnosis, and implement appropriate management based on the latest international or national guidelines. For many years there have been attempts to systematize various forms of AR based on a number of criteria. The current classifications of AR take into account the following criteria:

1) allergen causing symptoms (etiological classification): seasonal (SAR), perennial (PAR) and episodic (EAR)

2) duration of symptoms: intermittent (INT) and persistent (PER)

3) severity of clinical symptoms reported by the patient, including AR-related quality of life: mild, moderate or severe clinical course.

SAR develops only during specific periods of the year (corresponding to the pollination of wind-pollinated plants or mold sporulation). PAR occurs when the condition is triggered by allergens found in the patient’s environment at concentrations sufficient to induce symptoms of the disease all year round. The triggers include house dust mites, pet fur, cockroaches and mold in the Central Europe or wind-pollinated plant pollen in the tropical zone. EAR is caused by exposure to a specific airborne allergen on a sporadic and short-term basis.

INT is defined by symptom duration of less than 4 days per week or less than a month per year, and PER allergic rhinitis refers to the presence of symptoms for ≥ 4 days per week and ≥ 1 month per year.

According to the third criterion, AR is classified as either mild or moderate/severe, depending on the impact of the disease on the following quality-of-life measures: a) daily activities and sport, b) school/work attendance, c) sleep, and d) need of therapy, as reported by the patient. In mild AR, there is no impact on the quality-of-life aspects listed above. In moderate/severe AR, an adverse effect on one or more of the above items is present.

Both INT and PER AR may have a mild or moderate/severe clinical course and different forms of the disease may pass into one another (effect of evolution of the disease and/or therapy). Some patients are affected by the so-called mixed rhinitis in which AR coexists with non-allergic rhinitis (44–87 % of patients with AR). Seasonal AR may have an intermittent course.

Pathophysiology.

In allergic rhinitis, numerous infammatory cells, including mast cells, CD4-positive T cells, B cells, macrophages, and eosinophils, infltrate the nasal lining upon exposure to an inciting allergen (most commonly airborne dust mite fecal particles, cockroach residues, animal dander, moulds, and pollens). In allergic individuals, the T cells infltrating the nasal mucosa are predominantly T helper 2 in nature and release cytokines (e.g., interleukin [IL]-3, IL-4, IL-5, and IL-13) that promote IgE production by plasma cells. Crosslinking of IgE bound to mast cells by allergens, in turn, triggers the release of mediators, such as histamine and leukotrienes, that are responsible for arteriolar dilation, increased vascular permeability, itching, rhinorrhea, mucous secretion, and smooth muscle contraction in the lung. Te mediators and cytokines released during the early phase of an immune response to an inciting allergen trigger a further cellular infammatory response over the next 4–8 h (late-phase infammatory response) which results in recurrent symptoms (usually nasal congestion) that often persist.

Signs and symptoms.

Classic symptoms of allergic rhinitis:

- Rhinorrhea, nasal congestion, postnasal drainage
- Pale nasal turbinates, with or without clear nasal discharge
- Repetitive sneezing
- Itching of the palate, nose, ears, or eyes
- Snoring
- Constant clearing of the throat, cough
- Frequent sore throats
- Headaches

Allergic conjunctivitis is frequently associated with allergic rhinitis and symptoms generally include redness, tearing and itching of the eyes.

Physical examination.

The physical examination of patients with suspected allergic rhinitis should include an assessment of outward signs, the nose, ears, sinuses, posterior

oropharynx, chest and skin. Outward signs that may be suggestive of allergic rhinitis include: persistent mouth breathing, rubbing at the nose or an obvious transverse nasal crease, frequent sniffling or throat clearing, and allergic shiners (dark circles under the eyes that are due to nasal congestion).

Examination of the nose typically reveals swelling of the nasal mucosa and pale, thin secretions. An internal endoscopic examination of the nose should also be considered to assess for structural abnormalities including septal deviation, nasal ulcerations, and nasal polyps.

The sinus examination should include palpation of the sinuses for evidence of tenderness or tapping of the maxillary teeth with a tongue depressor for evidence of sensitivity. The posterior oropharynx should also be examined for signs of post nasal drip (mucous accumulation in the back of the nose and throat), and the chest and skin should be examined carefully for signs of concurrent asthma (e.g., wheezing) or dermatitis.

Diagnostic tests.

Diagnostic testing is necessary to confirm that underlying allergies cause the rhinitis. Skin-prick testing is considered the primary method for identifying specific allergic triggers of rhinitis. Skin prick testing involves placing a drop of a commercial extract of a specific allergen on the skin of the forearms or back, then pricking the skin through the drop to introduce the extract into the epidermis. Within 15–20 min, a wheal-and-fare response (an irregular blanched wheal surrounded by an area of redness) will occur if the test is positive. Testing is typically performed using the allergens relevant to the patient's environment (e.g., pollen, animal dander, moulds and house dust mites). A reasonable alternative to skin prick testing is the use of allergen-specific IgE tests (e.g., performed by immunosorbent assay—previously performed by radioallergosorbent tests [RASTs]) that provide an in vitro measure of a patient's specific IgE levels against particular allergens. Skin prick tests are generally considered to be more sensitive and cost effective than allergen-specific serum IgE tests, and have the further advantage of providing physicians and patients with immediate results.

Treatment.

The treatment goal for allergic rhinitis is relief of symptoms. Therapeutic options available to achieve this goal include avoidance measures, nasal saline irrigation, oral antihistamines, intranasal corticosteroids, combination intranasal corticosteroid/antihistamine sprays; leukotriene receptor antagonists (LTRAs), and allergen immunotherapy. Other therapies that may be useful in select patients include decongestants and oral corticosteroids.

Antihistamines. The second-generation oral anti-histamines (e.g., desloratadine, fexofenadine, loratadine, cetirizine) are the first-line pharmacological treatments recommended for all patients with allergic rhinitis.

Intranasal corticosteroids. Intranasal corticosteroids are also first-line therapeutic options for patients with mild persistent or moderate/severe symptoms and they can be used alone or in combination with oral antihistamines. The intranasal corticosteroids include fluticasone furoate (Avamys), beclomethasone (Beconase), fluticasone propionate (Flonase), triamcinolone acetonide (Nasacort), mometasone furoate (Nasonex), ciclesonide (Omnaris) and budesonide (Rhinocort).

Leukotriene receptor antagonists (LTRAs): montelukast and zafrlukast.

Allergen immunotherapy. Allergen immunotherapy involves the subcutaneous or sublingual administration of gradually increasing quantities of the patient's relevant allergens until a dose is reached that is effective in inducing immunologic tolerance to the allergen. Allergen immunotherapy is an effective treatment for allergic rhinitis, particularly for patients with intermittent (seasonal) allergic rhinitis caused by pollens, including tree, grass, ragweed pollens, house dust mites, Alternaria, cockroach, and cat and dog dander.

Other therapeutic options. Oral and intranasal decongestants (e.g., pseudoephedrine, phenylephrine) are useful for relieving nasal congestion in patients with allergic rhinitis. However, the side-effect profile associated with oral decongestants (i.e., agitation, insomnia, headache, palpitations) may limit their long-term use.

Oral corticosteroids may be effective in patients with severe allergic rhinitis that is refractory to treatment with oral antihistamines and intranasal corticosteroids.

Although not as effective as intranasal corticosteroids, intranasal sodium cromoglycate (Cromolyn) is used to reduce sneezing, rhinorrhea and nasal itching.

Surgical therapy may be helpful for select patients with rhinitis, polyposis, or chronic sinus disease that is refractory to medical treatment.

Urticaria and angioedema.

Urticaria is a common dermatologic condition that typically presents with intensely pruritic, well-circumscribed, raised wheals ranging from several millimeters to several centimeters or larger in size. Urticaria can occur with angioedema, which is localized nonpitting edema of the subcutaneous or interstitial tissue that may be painful and warm. The intense pruritus can cause significant impairment in daily functioning and disrupt sleep. Typically otherwise benign and self-limited, urticaria can be a symptom of life-threatening anaphylaxis or, rarely, indicate significant underlying disease.

Urticaria can appear on any part of the skin. The wheals can be pale to brightly erythematous in color, often with surrounding erythema. The lesions are round, polymorphic, or serpiginous, and can rapidly grow and coalesce. Angioedema presents primarily in the face, lips, mouth, upper airway, genitalia, and extremities. The onset of symptoms for urticaria or angioedema is rapid, usually occurring over minutes. Individual urticarial lesions typically resolve in one to 24 hours without treatment, although additional wheals can erupt in new crops. Angioedema may take days to resolve.

Urticaria, with or without angioedema, can be classified as acute or chronic. Urticaria that recurs within a period of less than six weeks is acute. Recurring chronic urticaria lasts longer than six weeks. Urticaria can present in persons of any age, with a lifetime prevalence of approximately 20%. Chronic urticaria has a lifetime prevalence of approximately 0.5 % to 5 %.

Etiology and pathophysiology.

Urticaria and angioedema have similar underlying pathophysiologic mechanisms: histamine and other mediators released from mast cells and basophils. If the release occurs in the dermis, it results in urticaria, whereas if the release occurs in the deeper dermis and subcutaneous tissues, it results in angioedema. IgE often mediates this release, but non-IgE and nonimmunologic mast cell activation also can occur. Proteases from aeroallergens and activation of the complement system have been proposed as examples of non-IgE triggers. There may be a serologic autoimmune component in a subset of patients with chronic urticaria, including antibodies to IgE and the high-affinity IgE receptor. However, the clinical significance of these autoantibodies is unclear. Anti-IgE antibodies can also be found in atopic dermatitis and several autoimmune diseases. There are a number of identified causes of urticarial.

Immunoglobulin E (IgE) mediated:

- Aeroallergens
- Contact allergen
- Food allergens
- Insect venom
- Medications
- Parasitic infections

Non-IgE immunologically mediated:

- Aeroallergens (proteases)
- Autoimmune disease
- Bacterial infections
- Cryoglobulinemia
- Fungal infections
- Lymphoma
- Vasculitis
- Viral infections

Nonimmunologically mediated:

- Contact allergen
- Elevation of core body temperature
- Food pseudoallergens
- Light
- Mastocytosis
- Medications (direct mast cell degranulation)
- Physical stimuli (cold, heat, pressure, vibration)
- Water

Infections are the most common cause of urticaria in children. The infectious agents commonly associated with urticaria include various viruses (e.g., rhinovirus, rotavirus, hepatitis A, Epstein-Barr, hepatitis B, herpes simplex, hepatitis C, human immunodeficiency virus), bacteria (e.g., streptococcus, mycoplasma, urinary tract infections, Helicobacter pylori), and parasites.

Medications, notably beta-lactam antibiotics, typically cause urticaria via allergic reactions, although some medications (e.g., nonsteroidal anti-inflammatory drugs, aspirin, opiates, vancomycin) can also trigger urticaria through direct mast cell degranulation.

In some patients, physical stimuli, including pressure, cold, heat, and the raising of the core body temperature (cholinergic urticaria), cause urticaria that tends to be chronic.

Systemic disease is an uncommon cause of urticaria. Illnesses that have been associated with urticaria or angioedema include systemic lupus erythematosus, rheumatoid arthritis, Hashimoto thyroiditis, mastocytosis, Sjögren syndrome, vasculitis, lymphoma, and celiac disease. Causes of acute urticaria often can be identified during the patient history, although 80 % to 90 % of chronic urticaria cases are idiopathic.

Treatment.

Treatment of acute urticaria and angioedema.

The mainstay of treatment is avoidance of identified triggers. It is also recommended that patients avoid using aspirin, and nonsteroidal anti-inflammatory drugs, as well as avoid wearing tight clothing, because these may worsen symptoms.

Second-generation H1 antihistamines are first-line medication for the treatment of acute urticaria. If symptoms are not sufficiently controlled with second-generation H1 antihistamines, H2 antihistamines such as cimetidine, famotidine, and ranitidine may be added. In severe cases, corticosteroids such as prednisone or prednisolone (0.5 to 1 mg/kg per day) may be added for three to 10 days to control symptoms.

If systemic symptoms are suggested, especially when an identified trigger is associated with anaphylaxis (e.g., insect envenomation, certain foods), it may be prudent to prescribe epinephrine autoinjectors.

Patients should follow up in two to six weeks to evaluate treatment success and tolerance.

Treatment of acute angioedema is largely the same as treatment for urticaria, although corticosteroids may be more commonly recommended. However, angioedema of the larynx and massive angioedema of the tongue are medical emergencies because of the risk of airway obstruction, and they require intramuscular epinephrine and airway management. Patients with angioedema that previously threatened airway compromise should be prescribed epinephrine autoinjectors.

Treatment of chronic urticaria

As with acute urticaria, the first step is second generation H1 antihistamines. For improved symptom control, the medication should be dosed daily, rather than on an as-needed basis. If first-line treatment is insufficient, the second step is implementation of one or more of the following additional strategies: the second-generation H1 antihistamine can be titrated up to two to four times the usual dose; a different second generation H1 antihistamine can be added; first-generation H1 antihistamines may be added at nighttime; H2 antihistamines may be added; and leukotriene receptor antagonists, such as montelukast and zafirlukast, can also be added, especially in patients with nonsteroidal anti-inflammatory drugs intolerance or cold urticaria.

If symptomatic control is still not achieved, the third step is addition and titration of high potency antihistamines as tolerated, such as hydroxyzine or the tricyclic antidepressant doxepin (possesses markedly more antihistaminic effect than diphenhydramine). The fourth step is referral to a subspecialist for use of immunomodulatory agents. There are a number of such agents, but the data on the effectiveness in chronic urticaria for most are weak at best. The two agents with the most robust data are omalizumab and cyclosporine. For controlling flare-ups in chronic urticaria, a three- to 10-day burst of corticosteroids (prednisone or prednisolone up to 1 mg per kg per day) is sometimes used; long-term use is not recommended because of adverse effects. Potent topical corticosteroids may have a benefit in localized delayed-pressure urticaria.

Once symptoms are adequately controlled, physicians should consider stepping down treatment sequentially. Empiric elimination diets are not recommended. If an underlying cause of chronic urticaria is identified, the condition should be treated or the patient referred to an appropriate subspecialist.

Prognosis

Acute urticaria is typically self-limited and resolves with proper avoidance of triggers. With chronic urticaria patients may experience repeated episodes throughout their lives.

Control questions

1. What is major clinical features of atopic dermatitis?

A. Pruritus, chronic, relapsing course, typical distribution, family or personal history of atopy.

B. Early age of onset, xerosis, palmar hyperlinearity, ichthyosis, keratosis pilaris.

C. Immediate skin test reactivity, elevated serum IgE

D. Itch when sweating, cutaneous infection, including Staphylococcus aureus and Herpes simplex virus.

E. Dennie-Morgan folds, keratoconus, facial erythema or pallor

2. At what age do the first symptoms of atopic dermatitis most often appear?

A. Before 2 years old. *C. After 3 years old.* *E. Any age.*

B. Before 5 years old. *D. After 6 months.*

3. What are the features of skin lesions in atopic dermatitis in infants?

A. *The skin is often dry, scaly and red. The cheeks are often the first place to be affected.*
B. *Eczema often affects the extensor surface of joints.*
C. *The affected skin often becomes lichenified.*
D. *Recurrent acute itchy blisters on the palms, fingers and on the feet.*
E. *AD most often affe*cts the elbow and knee creases.

4. What are the features of skin lesions in atopic dermatitis in school-age children?

A. *Flexural pattern of eczema and it most often affects the elbow and knee creases.*
B. *AD often affects the extensor aspects of joints, particularly the wrists, elbows, ankles and knees.*
C. *The predominant exudative component.*
D. *The cheeks the first place to be affected by AD.*
E. *May be limited to hand and foot eczema.*

5. Diffuse rash on the body (raised well-circumscribed areas of erythema and edema that are very pruritic) has appeared in an 8 year-old child after eating peanuts within 2 hours. General condition is not changed, temperature is normal. What is the most appropriate diagnosis?

A. *Allergic dermatitis.*
B. *Acute urticaria (hives).*
C. *Atopic dermatitis.*
D. *Food allergy.*
E. *Angioneurotic (Quincke's) edema (angioedema).*

6. A 3-month-old boy is breast-fed. There are papular rash and erythema of forehead, checks and external surface of shank, disposition to xerosis. His mother suffers from bronchial asthma, does not keep the diet. What diagnosis is the most probable?

A. *Allergic dermatitis.*
B. *Food allergy.*
C. *Atopic dermatitis.*
D. *Ichthyosis.*
E. *Exfoliative dermatitis.*

7. Cholinergic urticaria was diagnosed in a 13-year-old girl. Call the factors which can provoke exacerbation of disease the most frequently.

A. *Infectious diseases.*
B. *Physical activity.*
C. *Inhalation allergens.*
D. *Epidermal allergens.*
E. *Medicamental allergens.*

8. 11 year-old child has been suffering from moderate degree of seasonal allergic rhinitis for 4 years. What drugs for basic treatment should be used?

A. *Nasal corticosteroids.*
B. *β-2 agonists.*
C. *Mucolytics.*
D. *Decongestants.*
E. *Antibiotic.*

9. Urticaria was diagnosed in an 11-year-old boy with bronchial asthma after eating of peanuts. What is the algorithm of your actions?

A. *Inhalation of β-2 agonists.*
B. *Inhalation of corticosteroids.*
C. *Antihistamins i.m., i.v.*
D. *Antihistamins and corticosteroids i.m., i.v.*
E. *Corticosteroids and euphyllin.*

10. Infant's atopic dermatitis was diagnosed in a 2 year-old child. What investigation(s) is (are) obligatory?

A. Evaluation of blood IgE.
B. Urinalysis.
C. Evaluation of blood IgM.
D. Evaluation of glucose of blood.
E. Evaluation of blood protein level.

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