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Diagnostic methods in allergic eye diseases

Metody diagnostyczne w alergicznych chorobach oczu

Allergic eye diseases are a group of inflammatory disorders, usually co-existing with the allergic disease manifested in other organs, the primary cause of which are immunological phenomena of hypersensitivity characterized by eosinophils in tissues of ocular conjunctiva [1, 2, 21, 24]. These disorders include: SAC — *seasonal allergic conjunctivitis* and *perennial allergic conjunctivitis*, VKC — *vernal keratononjunctivitis*, *atopic keratoconjunctivitis* and GPC — *giant papillary conjunctivitis*.

Tentative clinical diagnosis in allergic ocular disorders is usually made on the basis of clinical symptoms (Table I). Allergic conjunctivitis is an IgE-dependent disease resulting from hypersensitivity and it follows Type I immunological reaction described by Gell and Coombs in which allergens reaching the surface of conjunctiva cause degranulation of sensitized local mast cells, release of inflammatory mediators and cytokines, migration and activation of other cells resulting from allergic inflammation. Manifestation of clinical symptoms such as watering, itching and redness of conjunctiva may develop shortly after a contact with allergen, due to a great number of blood vessels. Ocular signs of both acute – seasonal allergic conjunctivitis (SAC) and perennial allergic conjunctivitis (PAC) are usually mild and cornea is almost never affected by the disease [2]. GPC affects tarsal portion of the upper eyelid and develops mainly in atopic adults and adolescents wearing contact lenses; GPC is caused by the combination of immunological reaction of type I and IV and other unknown factors [2, 21]. VKC and AKC are the most severe atopic eye diseases due to persistency of symptoms, probability of corneal disorders and threat to vision. In both disorders immunological mechanisms of type I and IV are involved, as well as mechanisms related to the activation of lymphocytes T and genetic and environmental factors.

Taking into account differentiated pathomechanism of allergic eye diseases and the possibility of permanent damage to vision in misdiagnosed and ineffectively treat-

Table 1.
The classification of ocular diseases according to clinical symptoms (Hignorani 1997: 21)

Disease	Timing	Age group	Prevalence	Keratopathy	Sight threatening	Course
Seasonal allergic conjunctivitis (SAC)	Seasonal	Majority children and young adults	Very common	No	No	Mild, non-progressive, often resolves
Seasonal allergic conjunctivitis (PAC)	Perennial	Adult	Common	Common	No	Not seroius, non-progressive
Acute allergic conjunctivitis (AAC)	Single episode	Fairly common	Common	No	No	Spontaneous resolution within 24 hours
Vernal keratoconjunctivitis (VKC)	Seasonal, perennial if severe	Children	Uncommon	Yes	Yes	Serious, but usually resolves in 2-10 years, with good outcome if well managed. Occasionally-metamorphoses into AKC
Atopic keratoconjunctivitis (AKC)	Perennial	Adults	Rare	Yes	Yes	Serious and progressive, vision often reduced

ed cases, it seems advisable that every patient suspected of underlying allergic cause of eye disorders should be individually evaluated using detailed case history, ocular examination and additional specialist immunological tests.

Medical history regarding ocular signs includes onset, duration of first signs, severity, number of exacerbations (requiring specialist consultation), seasonal occurrence, effect of environmental factors (airborne allergens, industrial pollution) and response to treatment [21].

In the majority of patients suffering from allergic ocular diseases first symptoms appear under 30, and the most characteristic are itching, eye redness and sticky mucous discharge [21]. Seasonal symptoms occur in SAC— seasonal allergic conjunctivitis with exacerbation of symptoms in spring and summer (grass pollination) and in autumn (peak of weed pollination), and also in VKC — intensification of symptoms in spring and summer. Severity of symptoms may vary during the day, according to the amount of pollen in the atmosphere, humidity and air temperature. Perennial appearance of symptoms often suggests hypersensitivity to allergens of house dust mites, animal fur or spores of moulds or may be due to persistent course of the disease (e.g. AKC).

Medical history should also include a question about the setting of symptoms that in patients with SAC are more pronounced in outdoor environment and are alleviated in air-conditioned rooms. However, exacerbation of symptoms in indoor environment may suggest relationship to high concentration of allergens of house dust mites or presence of pets at home.

You should also consider possible effect of occupational allergens and other non-specific irritants such as cigarette smoke and wind, and in some cases a relation of ocular symptoms to food allergens [8]. Non-specific triggers such as cosmetics, soap, shampoo and topical drugs (ointments, creams, powders) should be also analysed. In patients wearing contact lenses it is necessary to collect information about the type of lenses (daily, monthly) and hygienic and maintenance habits.

Medical history of symptoms from other organs is also important, especially seasonal or perennial coexistence of allergic rhinitis of nasal mucosa that is demonstrated by watery nasal discharge, nasal itching, paroxysmal sneezing or nasal congestion. In such patients rhinophonia is observed, as well as nasal breathing, widening of nasal dorsum, Dennie–Morgan suborbital folds (due to rubbing the itching areas of eyes and nose), facial grimaces with twitching the nose and "allergic salut" — a characteristic rubbing the nose with dorsum of hand.

Symptoms of atopic dermatitis may be also observed, urticaria and/or angioedema or contact dermatitis [15]. In their past history patients often mention protein allergy in early childhood and symptoms of intolerance to cow's milk and/or other foods, as well as diarrhoea, constipation, intestinal colic, flatulence and necessity to follow elimination diet. Their skin is often covered with eczematous or papulous changes, dry, scaling and itching, typically localized on cheeks, behind ears, on upper eyelids and in joint fossae of extremities.

Episodes of dry cough, dyspnea with panting on exertion, wheezing or paroxysmal dyspnoea may suggest the symptoms of bronchial asthma.

Suspected coexistence or presence of another allergic disease, especially in cases of difficult diagnosis or moderate response to treatment may require additional consultation by a specialist in otolaryngology, dermatology or lung diseases.

The ocular examination may detect symptoms suggesting ocular allergy: itching and watering, photophobia, blepharospasm, thickening or cicatrical ciliary blepharitis, oedema and/or redness of palpebral folds, periorbital oedema, inflammatory and desquamating lesions in the area of eyebrows and lashes, inflammation and oedema of palpebral and orbital conjunctiva, conjunctival papillae and also corneal lesions: losses, erosion, ulceration, corneal plaques and scars [21]. After preliminary examination the following score analysis of exacerbation of local ocular signs and clinical symptoms is carried out to evaluate the effectiveness of applied treatment. The score is usually presented on a scale from 0 to 4 [3, 25]. In each case the ocular examination including also assessment of visual acuity using Snellen tables, the assessment of the dilatation of pupils and the examination of the fundus of the eye should be performed.

In ocular allergies symptoms from the organ of vision may be not characteristic or very similar to those found in other diseases, therefore differential diagnosis is necessary. In **the differential diagnosis** the following diseases should be considered [14, 20, 23]:

- glaucoma,
- inflammatory conjunctivitis (viral, bacterial, Chlamydial),
- inflammatory corneitis,
- superior and inferior ciliary blepharitis,
- dry conjunctivitis and corneitis,
- foreign body in the conjunctival sac,
- cicatrical pemphigoid,
- iritis,
- scleritis,
- conjunctival granuloma accompanying sarcoidosis,
- cancerous lesions within conjunctiva.

LABORATORY INVESTIGATIONS

A basic test applied in **the diagnosis of allergy** is SPT — *skin prick test*, a simple and safe test used to diagnose IgE-dependent allergy. Immediate reaction to the subepidermal administration of the allergen solution is observed and the resulting blister is an indirect marker of the amount of allergen-specific IgE antibodies bound by mastocytes present in the skin. Diagnostic sets for skin tests usually contain solutions of inhaled allergens: house dust mites (*D. pteronyssinus*), flour dust mites (*D. farinae*), feather, animal fur (cat, dog), moulds (*Cladosporium*, *Alternaria*, *Penicyllium*), plant pollen (grass, trees, shrubs and weeds) and in some cases following the information from a case history-also food allergens: cow's milk, the white and yolk of hen's egg, soya, corn, fish, tomato, nuts, citric fruits, cacao.

Some researchers notice a small number of positive skin tests in patients with ocular allergy because allergens responsible for sensitization of mastocytes in skin may differ from factors causing allergic reaction in the eye [12, 21], for example Bremond-Gignac et al. found a positive result of SPT only in 20% of studied patients. In the case of a 10-year old patient with SAC described by them in their study total skin anergy was observed — no reaction to administered allergens and control solutions of histamine and codeine at increased serum levels of specific IgE in relation to allergens from trees and moulds [12]. In such cases, when discrepancy between case history and SPT results is observed, and when patients present considerable skin demographism or diffuse skin lesions making SPT test impossible in infants, small children and the elderly with reduced skin reactivity and in non-cooperative patients, it is possible to evaluate the concentration of allergen specific IgE *in vitro* using radioimmunological (RAST, CAP-FEIA) or immunoenzymatic (CAP-EIA) assay. In these tests a high correlation with present clinical symptoms of allergic disease is usually observed [30], but negative result of SPT, level of total IgE and allergen specific IgE does not exclude atopic background of the disease in every case.

In order to identify a sensitizing allergen provocation tests with suspected allergen may be helpful. To diagnose ocular allergy [9, 10], allergic inflammation of the nasal mucous membrane, or even bronchial asthma [32], **a conjunctival provocation test** has been used for a long time. This test is specific, safe and may be repeated on condition that patients are properly selected (asymptomatic patients, beyond pollination season) and the test is carried out by experienced staff [3]. The conjunctival provocation test consists in the administration of 10–25 μl (1drop) of allergen solution to the inferior conjunctival sac of one eye or bilaterally. The type of allergen used for the provocative test is chosen using data from the case history and results of skin prick tests. The initial concentration of allergen is the highest dilution of this allergen producing positive result in the skin test. For example Alberson et al. [3] applied the initial concentration of allergen 19 AU/25 μl, that was obtained after 7-fold dilution of standard solution for provocative tests (100,000 AU/m l). Prior to the test or simultaneously a solution of allergen solvent (buffered solution of saline or solution of human albumin) is instilled into the other eye as a negative control. Increasing concentrations of allergen are administered every 10 minutes until ocular symptoms appear. When the result of test is positive itching and redness of conjunctiva are observed (Abelson et al., [3]), and their intensity is scored usually after 3 and 10 minutes, and after 6 hours to assess the early and late phase of allergic reaction. At present a provocation conjunctival test is applied for the diagnosis of eye diseases only occasionally — most often in cases of chronic and severe perennial conjunctivitis and for research purposes — mainly for the objective evaluation of the effectiveness of drugs.

To make a diagnosis of ocular allergy it may be necessary to test **a tissue sample** obtained from conjunctival biopsy or more often using less invasive method: conjunctival scrapings or cellular sample collected using the impression cytology method. The collected tissue material is usually tested histopatologically for epithelial conjunctival cells and cellular contents of the infiltrate within epithelium and basic layer of con-

junctiva. The following factors are evaluated: goblet cells, metaplasia of conjunctival epithelial cells, presence of adhesion molecules (ICAM-1) [16], number and degree of activation of mastocytes [28], and of eosinophils, immunological phenotype of lymphocytes [26], and also intracellular cytokines or mRNA transctypes for studied cytokines or cellular ability to release mediators and cytokines in *in vitro* cultures.

Material from conjunctival biopsy — fixed in 4% formaldehyde and frozen in liquid nitrogen is analysed on prepared sections from freezer microtome. Specimens are usually marked immunohistochemically using streptavidine-biotyne method with monoclonal antibodies [6].

Conjunctival scapings are obtained under local anaesthesia (e.g. 2% oxybuprocaine) from the upper tarsal conjunctiva using Kimura spatula or Cytobrush-S [36]. Tissue material is placed on microscope glass, dried and stained with commercial dye hematoxiline-eosine. Cells found in the visual field are evaluated under the light microscope usually using magnifaction 100x [10, 17].

Impression cytology — is an easy to use non-invasive method of obtaining tissue material, that supplies important diagnostic findings in a short time. It is helpful for a differential diagnosis of allergic or inflammatory conjunctivitis and also the dry eye syndrome [18].

In impression cytology circles of nitrocellulose filter paper (Milipore HAWP 304, Bedford, USA) are placed on inferior orbital conjunctiva or superior tarsal conjunctiva (after inverting tarsal conjunctiva. Conjunctival cellular material is evaluated under the light microscope following previous fixing and staining using PAS method. Possible deficiency of goblet cells and squamous metaplasia of conjunctival epitheliumis analysed [4], symptoms that are found in the majority of patients with AKC [19] or features characteristic of allergic conjunctivitis: change in the shape of cellular nuclei, fragmentation of conjunctival epithelium, increased number of lymphocytes, eosinophils, basophils and increased number of goblet cells and their hypertrophy [18, 31].

Many authors consider the impression cytology useful in the diagnosis of allergic conjunctivitis, because the presence of eosinophil infiltrates is a characteristic feature of the disease [1, 17]. Assessment using impression cytology is non-specific for allergic conjunctivitis and may give false-positive results, because it deals only with conjunctival epithelium and in a smaller degree with cells from lacrimal fluid or submucous layer of conjunctiva [17]. The reliability of obtained results may be increased by combining the analysis of eosinophils and the determination of markers of granulation in these cells (such as main basic protein or eosinophil basic protein), however, negative result does not exclude allergic background of the disease [21].

Eosinophilic infiltrates in conjunctival scrapings or more often in the basic layer of conjunctiva are found in 45% of patients with SAC, 25% with PAC, 25% with AKC and over 60% with VAC [21]. It has been demonstrated that eosinophilic basic proteins, especially major basic protein (MBP) and eosinophilic cationic protein ECP are responsible for the cytotoxic effect and the damage to corneal epithelium in patients with AKC and in some cases of VAC [7]. Cellular infiltrate consisting mainly of

eosinophils and lymphocytes T CD4+ is a characteristic feature of both AKC and VAC. In AKC a predominant population of conjunctival lymphocytes T CD4+ are cells of cytokin with profile IL-2 and IFN-gamma [26, 27]. It is thought that VAC is connected rather with non-specific proliferation and activation of lymphocytes T with profile Th2, releasing IL-3, IL-4, IL-5, while the IgE-dependent response found in 50% of patients with VAC is not a characteristic feature and is probably secondary [10].

Tear evaluation may provide additional information about the pathomechanism of allergic disease, exacerbation and type of inflammatory response reaction, involvement and degree of activation of particular cells in allergic eye diseases. Tears may be collected directly into capillary test-tubes or by soaking them up into standardized strips of blotting paper during Schirmer test. Blotting-paper strips may be placed in the inferior canthus of conjunctiva or lateral corner of the eye for 5 minutes, then lacrimal fluid is extracted by PBS solution containing 10% bovine serum albumin (BSA) [4]. To diagnose ocular allergy it is necessary to determine total IgE, allergen specific IgE and carry out the analysis of cellular composition, inflammatory mediators and cytokines in tears of patients.

IgE present in tears are probably produced locally by lymphocytes B and plasmocytes found/localized in conjunctiva [22]. Determining the level of total IgE in tears seems to be the most sensitive test in the diagnosis of allergic eye diseases [11, 29]. Concentrations above the normal limit that is 6–16 IU/ml are found in 98% of patients with SAC, 100% with PAC, 60–100% with VAC and over 80% with AKC [21]. However, it should be remembered that increased level of IgE in tears may be found also in other atopic diseases with no ocular symptoms in the course of disease, therefore this parameter may be only suggestive of allergic background of the disease [11].

In some particular cases it may be useful for the diagnosis to determine allergen specific IgE (asIgE) in tears. It has been demonstrated that asIgE found in tears are directed against the same allergens as those found in serum [22, 33] and asIgE concentration in tears correlated with the severity of ocular allergic symptoms (in SAC and VAC) in a provocation conjunctival test with allergen [22, 23]. The asIgE in tears is found only in 50% of patients with SAC, and therefore determining asIgE concentration is not a specific parameter for ocular allergy and is not a routine test [4, 21].

In order to study the pathomechanism of allergic reactions in the eye and to evaluate the effectiveness of administered drugs the determination of concentration of inflammatory mediators derived from mast cell is carried out: from histamine, tryptase [13], from eosinophils: (eosinophilic cationic protein, eosinophilic neurotoxin), or lymphocytes T (soluble fragment of receptor for IL-2), that indirectly indicate the degree of activation of these cells. The increased level of histamine-mediator responsible for symptoms of itching and eye redness was detected in VAC and other allergic eye diseases [2, 25, 34, 35]. However, histamine is a mediator undergoing fast biodegradation and measurement of its concentration in tears is difficult as far as the method is concerned. Therefore histamine concentration in lacrimal fluid cannot be treated as a suitable marker of allergic inflammation and is rather used for exploration and

research as an indicator of mastocyte activation [35]. It seems that tryptase is a more specific marker of activation and of degranulation of mast cells — it is found in higher concentration in granulation of mastocytes (histamine is also released by basophiles in peripheral blood), and the determination of this mediator is possible for a long time after the degranulation of mast cell. However, in the study by Leonardi et al. only increased concentration of ECP — marker of eosinophil activation-detected both in serum and tears of patients correlated well with the severity of clinical course in VAC, AKC and SAC [24, 25].

In tears it is also possible to determine the level of other inflammatory mediators, e.g. prostaglandins (PGD2) or leucotriens (LTC_4), concentration of cytokins (IL-2, IL-4, IL-5, GM-CSF, TNF-α), as well as soluble fragments of adhesive molecules (sICAM-1, sVCAM-1, sE-selectine). These tests are not performed as routine and are mainly used for research [24, 25, 26, 27, 30]. It seems that extending the range of diagnostic methods presented in this study may contribute to a better knowledge of factors causing symptoms in allergic eye diseases and observed immunological phenomena that are not fully explained yet. Such attitude followed by more effective methods may result in reducing continuously increasing number of new cases of allergic eye diseases and eliminating permanent damage to the organ of vision that may be due to misdiagnosis or improper treatment.

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STRESZCZENIE

Alergiczne choroby oczu stanowią grupę zapalnych schorzeń, u których podłoża leżą immunologiczne zjawiska nadwrażliwości, zwykle współwystępujących z chorobą alergiczną o innej manifestacji narządowej i charakteryzujących się obecnością granulocytów kwasochłonnych w tkankach spojówki oka. Wstępne rozpoznanie w alergii oka stawia się zwykle na podstawie miejscowych objawów klinicznych, lecz podkreślono rolę wywiadu alergicznego osobniczego i/lub rodzinnego oraz lekarskiego badania przedmiotowego. W artykule omówiono znaczenie diagnostyczne alergicznych testów skórnych, oznaczeń surowiczych stężeń alergenowo swoistych IgE, a także badań histologicznych i immunologicznych: zeskrobin spojówkowych, cytologii impresyjnej, testu prowokacji spojówkowej a alergenem oraz oznaczeń poziomu mediatorów zapalnych i cytokin.