



Update on Type-1 Allergy Diagnostics

Regina Treudler and Jan-Christoph Simon

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Abstract

Diagnostics in type-1 allergy rely on medical history and clinical examination. Extent and severity of signs and symptoms can be documented by standardized scores and questionnaires. Both skin prick test and intradermal test are useful for search of immunoglobulin E-mediated sensitizations but the availability of commercially available diagnostic extracts has been markedly reduced during the last years. Investigation of total and of specific serum IgE is the most important in vitro diagnostic analyte in type-1 allergy. Identification of the individual molecules to which patients are sensitized, known as molecular or component-resolved diagnostics (CRD), has recently markedly improved management of type-1 allergy to pollen, food and hymenoptera venoms. Main features of CRD are increased analytic sensitivity, detection of cross-reactivity and determination of individual sensitization profiles which allow for risk assessment and facilitate decisions for or against allergen immunotherapy. Basophil activation test as well as determination of selected biomarkers (e.g. tryptase) may also be helpful in

R. Treudler (✉) · J.-C. Simon

Department of Dermatology, Venereology and Allergology, Leipzig Interdisciplinary Allergy Centre – Comprehensive Allergy Centre, University Medicine Leipzig, Leipzig, Germany
e-mail: regina.treudler@uniklinik-leipzig.de

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some cases. If any allergy test is positive, one will have to distinguish reactions, which are clinically relevant, from those, which are not. In vivo provocation tests (e.g. nasal provocation, oral drug or food challenge) may help to clarify the relevance of a sensitization.

Keywords

Component-resolved diagnostics · Diagnostics · Provocation test · Review · Skin prick test · Type-1 allergy

1 Introduction

Type-1 (immediate type) allergy involves immunoglobulin E (IgE) mediated mast cell degranulation and release of histamine and other inflammatory mediators (see Part II, Chap. 1). Typical type-1 allergens are pollen, mites, animal dander, moulds, foods, drugs, insect venoms, etc. As a result of allergen exposure, i.e. by ingestion, inhalation, injection or direct contact, the clinical reactions may become manifest as allergic rhinitis or hay fever, allergic conjunctivitis, hives, atopic eczema, or erythema, angioedema, allergic asthma or anaphylaxis (Abbas et al. 2020). Non-IgE-mediated mechanisms may also be responsible for mast cell degranulation, which clinically is not distinguishable from IgE-mediated allergy (Redegeld et al. 2018). Both in vivo and in vitro tests are used in the diagnosis of type-1 hypersensitivity.

2 Medical History and Examination

The diagnosis of type-1 hypersensitivity relies on a thorough clinical history and physical examination. Information about the patient's history should include: signs and symptoms as well as timing with onset, allergen exposure (e.g. indoor, outdoor, professional), prior history of allergic reactions, (family) history of atopy or food allergies (Abbas et al. 2020). Scoring of clinical signs and symptoms may help to categorize the activity/severity of the disease and for therapeutic decision making (Table 1). Spirometry and measurement of fractional exhaled nitric oxide (FeNO) may be helpful for investigation of lung function, eosinophil count in nasal smear may be seen in allergic rhinoconjunctivitis (Ansotegui et al. 2020). Health related quality of life can be measured by several standardized questionnaires (Alvarado et al. 2019; Apfelbacher et al. 2016; Beyer et al. 2016; Fischer et al. 2011; Lanario et al. 2020; Muraro et al. 2018; Pariser et al. 2020; Steinke et al. 2018; Stone et al. 2020; Weller et al. 2020; Wise et al. 2018; Zuberbier et al. 2018) (Table 1). History taking should also include evaluation of possible comorbidities, e.g. psychosocial or autoimmune comorbidities in atopic dermatitis or mastocytosis in anaphylaxis (Kage et al. 2020; Treudler et al. 2018; Treudler et al. 2020; Worm et al. 2018). Once the history has been collected, one of several primary confirmatory tests for sensitization can be performed to detect allergen-specific IgE in the skin or blood.

Table 1 Instruments for measurement of activity, severity and health related quality of life in selected manifestations of type-1 allergy

Disease	Activity/severity	Health related quality of life (QOL)
Allergic rhinoconjunctivitis	Allergic rhinitis and its impact on asthma (ARIA) classification	Rhinoconjunctivitis QOL questionnaire – RQLQ
Allergic asthma	Global initiative for <i>Asthma classification (GINA)</i>	Severe asthma questionnaire – SAQ
Anaphylaxis (insect, food, drug)	Ring & Messer Scale, Müller scale, et al.	Food allergy QOL questionnaire – FAQOLQ
Urticaria	Urticaria control score – UCS Urticaria activity score – UAS7	Urticaria QoL questionnaire – UQOL
Angioedema	Angioedema control test – AECT	Angioedema QOL questionnaire – AEQOL
Atopic dermatitis (AD)	Severity scoring of AD – SCORAD Eczema activity and severity index – EASI AD control test – ADCT	Dermatology life quality index – DLQI

3 Skin Tests

Skin tests must be performed under medical supervision, with emergency equipment available for the treatment of possible anaphylaxis, especially in drug allergy. (Ansotegui et al. 2020; Aurich et al. 2017) Usually, skin tests are performed on healthy volar skin of one or both forearms. Special recommendations on how to perform allergy skin tests in drug allergy or in occupational allergy exist (Brockow et al. 2013; Brockow et al. 2015; Raulf et al. 2014; Wurpts et al. 2020). Negative and positive controls (e.g. saline and histamine hydrochloride solution) are required. Importantly, drugs can suppress skin test results, e.g. antihistamines tricyclic antidepressants, oral glucocorticosteroids >10 mg prednisolone per day (Bousquet et al. 2012; Malling 1993). It is recommended to use standardized test extracts, which, however, may show large differences between extracts from different manufacturers (Heinzerling et al. 2009; Rüeff et al. 2011). Also, the availability of commercially available diagnostic extracts, used for skin and for provocation tests, has been markedly reduced in the European Union since they have been defined as medicinal products (EU-Directives 89/342/EEC, 2001/83 EC) (Klimek et al. 2020). Accordingly, to an increasing degree native allergens have to be used (e.g. in food and drug allergy).

In *skin prick test (SPT)*, a specific allergen is introduced via a lancet into the skin and degranulation of dermal mast leads to wheal and flare reaction in sensitized people. After 15 min, the largest and perpendicular diameter of the each wheal's size is measured in millimetres (mm) with a ruler, then the largest plus perpendicular diameter/2 is calculated. The positive control should optimally show a wheal diameter ≥ 3 mm. SPT should be interpreted as being positive if the wheal diameter is 3 mm greater than the negative control and negative if the wheal diameter is less

than 3 mm with a positive simultaneous histamine control (Ansotegui et al. 2020). False-positive skin tests may result from dermographism or may be caused by ‘irritant’ reactions or a nonspecific enhancement from a nearby strong reaction (Bousquet et al. 2012). False-negative skin tests can be caused by extracts of poor potency, drugs modulating the allergic reaction, diseases attenuating the skin response, improper technique, limited local IgE production, for example, only in the nose or in the eye. (Bousquet et al. 2012).

Intradermal skin test (IDT) should be performed only if the patient’s history indicates relevant sensitization and a negative SPT result was obtained (Malling 1993). IDT is more technically demanding than SPT and carries a higher risk of adverse reactions. Allergens (usually, 0.02 mL) are injected intradermally with small needles to produce a small bleb, and the outcome measure is an increase in the size of the wheal with flare reaction at 20 min. Allergenic extract must be diluted (10–1,000-fold or more) from the concentrations used for SPT (Ansotegui et al. 2020). IDT may be helpful in drug or in insect allergy but is said to be not useful for allergy diagnosis with inhalant allergens (Bousquet et al. 2012). Interpretation of IDT results is less standardized than in SPT and there is no true consensus (Malling 1993). According to German Guidelines, IDT is regarded positive if the mean wheal diameter is ≥ 5 mm (Ruëff et al. 2011). The International Consensus Statement on Allergy and Rhinology considers IDT positive if the diameter of the resulting wheal is at least 7 mm, and at least 2 mm wider than the control (saline, glycerin solution) (Wise et al. 2018).

4 In Vitro Tests

Total IgE may be elevated in atopic disorders; however, abnormal levels may also be seen in several entities, not only in allergy (Ansotegui et al. 2020). *Allergen-specific (s)IgE antibody* is the most important analyte in the diagnosis of type I hypersensitivity reactions. The measurement of sIgE recognizing allergenic epitopes can be achieved both through the usage of single reagents (singleplex) or with a pre-defined panel more than hundred of molecules to be tested simultaneously (multiplex) (Treudler 2012; Treudler and Simon 2013). IgE is usually measured by using a fluorescence enzyme immunoassay in singleplex platforms. When comparing the singleplex and multiplex assays, concordance of results vary between allergens tested, and the sensitivity of multiplex platform is lower than that of singleplex, particularly when sIgE levels are low. Otherwise singleplex platforms are quantitative assays and multiplex are semiquantitative (Treudler 2012). Purified native or recombinant allergens, identifying the individual molecules to which patients are sensitized, can be determined by the so-called molecular or *component-resolved diagnostics (CRD)* with the following specialized features (Matricardi et al. 2016; Treudler 2012; Treudler and Simon 2013): standardization of allergen extracts by use of individual allergens, increase of analytic sensitivity by replacement/supplementation of relevant individual allergens in the test extract, detection of cross-reactions, determination of individual sensitization profiles, no cross-reacting

carbohydrate chains (CCD). An increasing number of allergens have found their way into routine diagnostics in recent years and individual IgE profiles and allergen patterns allow for closer examinations of cross-reactivity, molecules of risk and prognostically significant sensitizations. Overall, CRD has improved management of the allergic patient as it allows to some extent to discriminate between clinically significant and irrelevant sIgE results and to establish sensitization patterns with particular prognostic outcomes (Matricardi et al. 2016). Reliable detection of sIgE requires allergen reagents with a sufficient representation of all relevant allergen components. As this might not be the case in all reagents, some of them are meanwhile enriched with recombinant allergens (also known as spiking). Examples for reagents with enriched recombinant allergen components are hazel and nut mix (enriched with Cor a 1), latex (Hev b 5), or wasp (Ves v 5) (Treudler 2012; Treudler and Simon 2013). In *pollen allergies* with determination of the respective major allergens (i.e. Bet v 1: birch, Phl p 1/5: grass) clinically relevant sensitizations can be differentiated from those to cross-reacting, clinically less relevant panallergens such as profilins (i.e. Bet v 2/4, Phl p 7/12). These diagnostics allow for establishing a more precise indication for specific immunotherapy. In food allergies, sensitizations to storage (i.e. Ara h 2/peanut) or lipid transfer proteins (i.e. Pru p 3/peach) signal a high risk of anaphylaxis, while sensitizations to Bet v 1 homologues (e.g. Ara h 8/peanut) are usually associated with milder symptoms (Table 2). By determination of the major allergens Api m 1 (bee) and Ves v 1 and Ves v 5 (wasp) double sensitizations can already today be better differentiated from cross-reactivities in

Table 2 Main sensitizing plant allergen families in type-1 allergy

Family	Characteristics	Examples
Bet v 1 homologue	Major allergen of birch <i>Betula verrucosa</i> . Similar proteins are termed Bet v 1 homologues or pathogenesis-related proteins (PR) 10	rAra h 8 – Peanut rCor a 1 – Hazel rGly m 4 – Soy
Lipid transfer Proteins	Sensitizations usually in southern Europe, severe reactions, gastrointestinal sensitization	rAra h 9 – Peanut rPru p 3 – Peach rCor a 8 – Hazel
Profilins	Little clinical relevance, often responsible for cross-reactions	rBet v 2 – Birch rPhl p 12 – Grass
Storage proteins	Stable proteins represent a large proportion of proteins in nuts, seeds, legumes and cereals	rAra h 2 and 3 – Peanut rGly m 5 and 6 – Soy rTri a 19 – Wheat

hymenoptera venom allergies than previously. Further promising improvements in diagnostics are expected from additional, not yet commercially available molecules of risk. Elevation of *serum tryptase* indicates degranulation of mast cells. An acute rise in tryptase levels starts to be detected in serum within minutes of anaphylaxis. In contrast to serum histamine, which has a very short half-life, the serum tryptase level gradually reverts to normal over 6–24 h. Persistently elevated serum tryptase levels are seen in mastocytosis but may also be present in other entities like chronic kidney disease (Lee 2020).

The *Basophil activation test (BAT)* uses flow cytometry to measure the expression of activation markers on the surface of basophils that are upregulated following the cross-linking of IgE antibodies bound to the high-affinity IgE receptor (FcεRI) that result from allergen or anti-IgE stimulation. BAT can be used to support the diagnosis of various allergic conditions, such as food, drug, respiratory and insect venom allergies, and the assessment of clinical response to allergen-specific immunotherapy and other immunomodulatory treatments (Hemmings et al. 2018). There are several other analytes that may be used outside the clinical routine and/or for research purposes, e.g. allergen-specific IgG (as parameter for course of allergen-specific immunotherapy), indoor aeroallergen quantitation in surface dust, IgE-specific autoantibodies (in chronic spontaneous urticaria), eosinophil cationic protein mediators, leukotriene C4, prostaglandin D2, proteoglycans, mast cell chymase/carboxypeptidase, cathepsin, different cytokines (e.g. Interferon-gamma, Interleukin (IL)-4, IL-5, IL-13). (Ansotegui et al. 2020)

5 In Vivo Provocation Tests

In -vivo provocation tests (Table 3) are considered confirmatory tests that are available when one needs to adjudicate the correctness of discordant clinical history and results from allergen-specific IgE antibody skin or serologic tests (Hamilton 2010). Provocation tests are more difficult to perform in a reproducible manner than skin or blood tests for IgE antibodies, and they place the patient at some risk for a

Table 3 In vivo provocation tests in type-1 allergy

In vivo tests	Disease
Conjunctival/nasal provocation test, rhinomanometry	Allergic rhinoconjunctivitis
Bronchial inhalation challenge (e.g. allergen, methacholine, histamine)	
Oral food challenge (open/single or double blind/placebo controlled)	Food allergy
Physical exercise test	Exercise induced anaphylaxis
Drug provocation test (oral, subcutaneous, intravenous, open/single or double blind/placebo controlled)	Drug allergy
Physical tests (e.g. temp test, Fric test, ultraviolet light)	Chronic inducible urticaria
Sting challenge (only recommended under venom immunotherapy)	Insect allergy

reaction because they involve a direct allergen challenge. Interpretation of their results can also be difficult because they often involve subjective endpoints that can be altered by observer and patient bias (Brockow et al. 2015; Muraro et al. 2014a, b; Sampson et al. 2012; Treudler et al. 2016; Wurpts et al. 2020).

6 Conclusion

Most important diagnostics in type-1 allergy are history taking, allergy skin tests (e.g. SPT) and in vitro tests (e.g. specific IgE, tryptase, BAT). If any test is positive, one will have to distinguish reactions, which are clinically relevant, from those, which are not. Provocation tests may help to clarify the relevance of a sensitization.

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