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Chapter

Aerobiology in the Clinics of Pollen Allergy

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Abstract

Diagnosis and treatment of pollen allergies is facilitated by the cooperation between the allergist and the aerobiologist. The selection of relevant allergens for in vivo diagnosis, the interpretation of results, the timing of trials, and treatments should be related to the local pollen season, abiotic variables, and the patient history. Meteorological aspects and flowering dynamics of plants condition the course of the pollen season each year. Pollen forecasting integrates weather data with long- and short-term pollen data. Crowdsourced patient symptoms are used to delineate pollen threshold loads in the forecast. Integrating aerobiological expertise warrants the success of allergy diagnostics and treatment.

Keywords: Pollen allergy, diagnostics, allergenicity, aerobiology, forecasting, pollen thresholds

1. Introduction

With the establishment of skin testing to diagnose for allergy, botanical knowledge on allergenic pollen sources became essential. The synergistic cooperation between allergists and botanists from those years shall be illustrated with an example from Ankara (Turkey), where in 1967 the botanist Kamil Karamanoglu and allergist Kemal Özkaragöz issued lists of allergenic plants, the way their pollen is carried (by wind or insects), their form of growth, and where and in which plant communities they grew [1]. Based on that knowledge, clinical trials were commenced to investigate the allergenic potential of pollen [2] based on the Thommen’s postulates [3]. Subsequently, the first Turkish pollen calendar was published for Ankara [4].

Nowadays, pollen information is issued regularly by competent monitoring intuitions as preventive measure for the allergic population in many countries. According to biogeographic peculiarities, the vegetation cover differs from region to region giving rise to varying types of pollen allergens. Which allergens to use in test batteries grounds on the knowledge of the allergenic pollen flora of the area. Immunotherapy, the only treatment that may lead to longer-lasting relief of the burden, can only be successful by considering the geographic circumstances of the patient. That means to work with relevant and good quality pollen data, have information on the course and intensity of the pollen season, and be able to interpret this information. The aerobiologists’ point of view on immunotherapy and the implementation of clinical trials has been elaborated, and standards for aerobiological tasks in clinical trials proposed [5].
This to prevent harm to patients, increase the quality and success of the trial, and to obtain comparable results (ibid).

Electronic health technology (eHealth) and mobile applications (mHealth) are, on one hand, a popular way to convey pollen information to the public. Registered users, on the other hand, provide data on their symptoms, which can be used to improve forecasting, monitor public allergy morbidity, and be part of studies on pollen allergy [6]. Pollen threshold loads for symptom development, for example, can be assessed this way along with aerobiological data [7].

In this chapter, we elaborate, firstly, on the allergist’s perspective on the choice of allergens, emphasizing the need for diagnostics without harming the patient, and when serum-specific IgE testing is adequate. We delineate limitations of allergy tests and explain why not every pollen type causes an allergic response.

Secondly, we convey the aerobiologist’s perspective on pollen forecasting, the role of pollen threshold loads obtained with crowdsourced patient symptoms, and support this with an example from Istanbul.

2. The allergists’ perspective

Skin testing has been used to diagnose allergic disorders for more than 50 years. Back in the mid-twentieth century, pricking the skin with a solution of the allergen using a lancet was the only method but today there are several test devices capable of results that are more reliable and reproducible. Skin testing continues to be the main test to confirm an IgE-mediated immunologic reaction. Not only skin testing is the best indicator of the underlying allergic pathology, but it also remains to be the most inexpensive test with rapid results making it practical in office setting.

The binding of specific IgE on tissue mast cells to the offending allergen is the unique attribute of skin testing. Alternatively, the patient can be challenged with the allergen by directly applying it to the mucous membranes, nose, bronchi, or even eyes, but the extra advantage of such procedures does not justify the risk and inconvenience. Allergen skin testing has been shown to exhibit reliable correlation with such mucosal challenges [8].

It is crucial, however, that the physician ordering or interpreting these tests be cognizant of the dynamics that can affect the outcome. Some important considerations as to when these tests are indicated and how they should be interpreted are outlined here.

2.1 Choosing the allergens with clinical relevance

Allergy testing without a clear indication or random testing for arbitrarily chosen allergens is not acceptable. The selection of allergens should be determined based on the patient’s exposure history and correlated with their symptoms. The relevant allergens should be based on the medical history, age, and the environment, geography of the patient. Knowledge on the average and the course of the pollen seasons of the patient’s geography is essential in this regard [9]. The tested allergens should be able to predict and/or confirm the clinical disease.

Most clinicians would order these tests for two main reasons: (1) the planning of avoidance of the allergen and (2) specific immunotherapy. Interdisciplinary collaboration among allergists, aerobiologists, and atmospheric scientists is important to identify the relevant allergens in the environment connecting the time of exposure to symptoms.
2.2 Allergen sensitivity without allergy

The test results should be validated by associating the exposure to allergens under natural conditions or controlled challenges with the particular allergen. There may be skin sensitivity without symptoms which may not have any validity to the current clinical problem of the patient. Routine use of arrays of skin tests or usual annual tests without a definite clinical indication is unwarranted. Nevertheless, some asymptomatic skin sensitization may be a risk factor for future organ sensitivity; hence, some clinicians would still value this coincidental sensitivity to monitor the patient for future development of clinical allergy. In a prospective trial of 15 asymptomatic patients with positive skin prick test to birch, 60% were later reported to develop true clinical allergy [10]. But we must be aware of the cascade effect in medicine which was brilliantly outlined by James Mold [11] referring to the detrimental process that once triggered proceeds to the inevitable conclusion of unnecessary tests, patient and/or physician anxiety ending up with wrong treatments, adverse effects and/or morbidity and not to mention the uneconomic medical expenses. Healthcare providers must guard against the vortex of this domino effect leading to the collision course of such preventable events. End result of such actions are infants being deprived of essential nutrients, needless anxiety for patients and caregivers, inappropriately prescribed more expensive medications possibly leading to antibiotic resistance, etc. Preventing cascade effects should be a part of the education curriculum of physicians and providers. This is not only important in the field of allergy and immunology but all specialties of medicine, especially in the technology era of healthcare services where more is unfortunately considered better.

2.3 Serum-specific IgE testing

In vitro serum IgE testing is sometimes safer than skin testing in patients with cardiovascular disease, or when severe anaphylactic reactions are expected. We also prefer to perform serum in vitro testing for patients who are unable to withhold their antihistamines or other medications interfering with tests. Another common medication that is problematic for skin testing is Omalizumab, which also interferes with many immunoassays, except the ImmunoCAP method, which usually remains accurate [12]. Skin testing on infants less than a year old may be challenging and results may not reflect true sensitivity [13]; thus, we prefer serum-specific IgE tests for infants as young as 6 to 8 weeks of age which only requires capillary blood collection [14].

On the flip side, caution is advised for commercial remote practice laboratories performing such serum tests. Some laboratories bypass the clinician and perform serum IgE tests based on the history submitted by the patients and start immunotherapy according to these ambiguous serum IgE test results. As with the skin tests, the interpretation of specific serum IgE levels require the same meticulous clinical history, physical examination, and, in some instances, challenges with natural or laboratory exposure to allergens. This, obviously, is not the typical practice of commercial laboratories [11]. The serum-specific IgE level per se may not reflect the clinical sensitivity due to the fact that clonality and affinity of the IgE antibody plays a role in translation of serum IgE production to clinically relevant allergic sensitization [15]. Thus, it is important to understand that, although an IgE-mediated immunological response is necessary to develop allergic disease, it is not sufficient.
2.4 Limitations of allergy tests

False-positive allergy test results may occur. Some tree pollens share cross-reactive carbohydrate determinants with other pollens or, for example, honey bee venom [16]. It is also not uncommon for a pollen-sensitive patient to be living in another area, not exposed to the same pollen. The co-sensitization should be differentiated from cross-sensitization when testing with extract reagents with common epitopes. Another reason for getting negative reading on allergy tests is the fact that the pathogenesis of the organ sensitization may not involve IgE-mediated pathways. Alternative immunologic pathways or non-immunologic pathways may be at play. The clinician should be in close contact and consult other specialties as well, to fully understand the scope of the organ symptoms. Also, patients who experienced an anaphylactic event may have false-negative skin test results for up to 2–3 weeks after the episode. In vitro testing serum-specific IgE levels are not affected and can be performed in the post-anaphylactic situation where testing cannot be postponed.

Serum-specific IgE test can also display false-positive or -negative levels based on the binding affinity/avidity of the offending allergen to the solid-phase system used for testing. The circulating levels of cross-reactive peptides and specific antibodies of another class, e.g. IgG or the high levels of nonspecific serum IgE levels, may also affect the readings. We do not perform IgG or IgG subclass antibody tests for food or other allergies. They have no clinical relevance. There have been reports of monitoring IgG4 during venom immunotherapy, but this is not validated [17].

2.5 Not all pollens are created equal

Most pollen types do not cause allergies and the ones that cause allergies do so in different potencies. Not all pollen types elicit an allergic response or in immunologic terms have the recognition moieties, the epitopes, that bind to specific receptors on B or T cells. Allergenicity is usually elicited by the peptidic epitopes. The glycan moieties of these glycoproteins affect the immunogenicity of these peptides. Glycans are in variable proportions in different pollens affecting allergenicity. Even when they do have these epitopes, the conformational shape of the pollen structure may limit the three-dimensional spatial alignment of the allergen to the IgE antibody binding sites. These are some of the factors that will alter the allergenicity of pollen intrinsically at the biochemical level.

Environmental factors also have effects on the allergenicity of pollen. Pollutants such as heavy metals, ozone, sulfur dioxide, nitrogen dioxide, and diesel exhaust particles may affect the allergenicity [18], by activating the immune system, referred to as the adjuvant effect [19]. Extended pollen seasons linked to climate change were recognized as factors for, not only increased pollen production but also increased allergen content of their grains [20, 21].

3. The aerobiologists’ perspective

3.1 Forecasting

We see them in newspapers, on weather apps, and on specific pollen apps: warnings on allergenic particles currently airborne in a certain region. Issuing pollen forecasts is the inherent chore of an aerobiologist. Trained technicians count meticulously
every pollen grain captured on a slide on a number of vertical or horizontal transects under a light microscope at a magnification of 400 x so to cover at least 10% of the slide’s surface to estimate the concentration of airborne pollen per cubic meter air per day [22]. This procedure, where pollen is sampled with a volumetric Hirst-type device on a weekly basis, and evaluated retrospectively, falls under the norm CSN EN 16868 [23]. Issuing warnings based on retrospective data makes forecasting essential. The longer the time series of daily or possibly bi-hourly data, the better will be the forecast. Curves of mean pollen concentrations for each pollen type help to assess the variability within years. For allergy pollen warnings, the aerobiologist uses weather forecasts, past year’s data and ideally observes the phenology of plants shedding allergic pollen [24, 25]. Models like SILAM (System for Integrated modeling of Atmospheric composition) [26] and COSMO-ART (Consortium for Small-scale Modeling Aerosols and Reactive Trace gases) [27] can provide additional information to incorporate in pollen warnings in Europe.

3.2 Pollen threshold loads

Although forecasts are useful to help patients avoid exposure when levels are high, pollen and weather data alone do not bear the information, whether or not there is an actual risk for the allergic population to suffer symptoms of allergy. It has been shown that allergy morbidity to a specific pollen type may change over the pollen season [7, 28, 29]. With the inclusion of patient’s symptom data, a dose–response relationship between exposure and symptoms can be estimated and the accuracy of pollen load thresholds determined. The focus hereby can be on the allergenic pollen type itself, for example, grasses [28, 30], ragweed [7, 31], or birch [32].

There are several ways to obtain patient symptoms, as reviewed in [33]. Practicable are, for example, questionnaire-based daily surveys for prospective clinical trials [29]. Items may include a four-point symptom scale (0 = zero; 1 = mild; 2 = moderate; and 3 = severe) related to the eyes, nose, bronchi, and medication use [ibid]. Additionally, general health is assessed on a ten-point scale [31]. Study participants may send their data to the research-coordinator daily or weekly. This way to gather symptom data is laborious but allows for the control of missing or hampered data [31]. The number of patients in exposure studies, however, is often limited in size ranging from 12 to 430 in 26 studies as reviewed in a Finnish study [34].

Another way to obtain self-reported patient data on symptoms is by means of electronic pollen diaries. Examples of crowdsourced data include the Dutch Allergieradar.nl, established in 2009 to “improve the hay fever forecasts and to decrease the amount of hay fever symptoms patients experience” [35]. The Europe-wide active pollen diary.com [36] coordinated by the Medical University of Vienna follows the same aim. Pollen data from adhering pollen monitoring networks and single stations are fed into the EAN (European Allergy Network). Registered users are encouraged to log their symptoms regularly over the hay fever period. The service is also available as an application “Pollen” that, as the website, provides personalized symptom forecasts based on previous five records [37]. The application is currently available in Austria, Germany, Switzerland, Sweden, Spain, Great Britain, and South Tyrol [38]. As emphasized in [37], the expertise of the aerobiologist is a pillar to generate personalized pollen information. The symptoms recorded translate into a 3-day allergy risk forecast for the respective region, where a sampling device is located. This personalized forecast includes, besides pollen and weather data, other risk factors for respiratory allergy like ozone, sulfur dioxide, nitrogen dioxide, and particulate matter.
3.3 The power of crowdsourced data

The development of pollendiary.com is a result of yearlong collaboration between a network of aerobiologists, data scientists, and sound management. Quality assurance is a main concern to avoid potential harm to hay fever sufferers due to inaccurate forecasts [39]. An evaluation of nine free applications showed that the accuracy of the grass pollen load forecast was 50% of six apps when compared to the actual grass pollen concentration in the location [39]. Web-based applications are an easy way to self-empower hay fever sufferers and to monitor symptom development in the allergic population. The number of hay fever morbidity data obtained between 2009 and 2019 by means of pollendiary.com across Europe was 240,000, with 190,000 logs from Germany and over 32,000 from Austria [6]. The solid number of crowdsourced data on symptoms enables the aerobiologist to provide more accurate forecasts. As a matter of fact, regional pollen concentrations alone cannot be a measure for the pollen allergenicity experienced by the population in a certain area. It is known that pollen concentrations do not exactly correlate with the allergen content in the air, as shown for ragweed in Turkey [40] or olive in Spain [41]. Pollen potency, the ratio between pollen and allergen concentrations per cubic meter, varies considerably in time and space [42, 43]. The origin of the allergen content in the air is at present not predictable as linked to ruptures of pollen that release micronic allergenic particles at varying weather conditions and altitude, resuspensions, long range transport via air currents, and the allergen content in the plants of origin [42]. Thus, the inclusion of locally experienced symptom data in pollen warnings is essential to issue the correct threshold loads for a particular region.

3.4 An example from Istanbul

The assessment of local thresholds is a pressing issue in allergology [44]. They are unique in each biogeographic area, as factors like pollen sources, their allergenicity, climate, pollution, and the genetic fingerprint at individual and population level are determining factors for symptom thresholds [33]. Crowdsourced symptom data, pollen, weather, and pollution data can be included in models that display the dose–response relationship experienced by the allergic population. Standardized pollen data as in the EAN and a uniform method for symptom data collection as in pollendiary.com allows for the calculation of threshold levels, for example, with nonlinear regression models [7, 45]. Anti-allergic medication can be an indicator for allergy morbidity. Here we show preliminary results of a study conducted with data (n = 725) from the European part of Istanbul (Figure 1).

In Istanbul anti-allergy medication use started at about 4 p/m³, and increased linearly till about 11 p/m³. Subsequently, the bending of the curve [46] suggests that the threshold for moderate medication use has been reached. Between 18 p/m³ and 30 p/m³ medication use was the most intense. After that it decreased to remain at a moderate level at >= 50 p/m³. As few as about 4 p/m³ caused morbidity that patients sought to mitigate with drugs. In Istanbul the non-linear relationship in the dose-response curve illustrates that symptoms do not necessarily aggravate at a grass pollen concentration higher than 25-30 p/m³. Longer time series of data with more users than the ones presented here would yield more solid results. Promoting the use of an electronic hay fever symptom diary should be an integral part of a public pollen information system.
4. Conclusions

Aerobiological expertise plays an integral role in the clinics of allergic disease in the qualitative forecasting of the pollen season to support the allergist in the assessment of morbidity and the timing of treatment. Cooperation between the allergist and the aerobiologist help select the most relevant allergens for in vivo diagnosis, improve the interpretation of results, and select the most appropriate immunotherapy regimen tailored for the patient.

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