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AEROALLERGENS IN CLINICAL PRACTICE OF ALLERGY IN INDIA. AN OVERVIEW

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Abstract: Allergic diseases such as bronchial asthma, allergic rhinitis and atopic dermatitis are dramatically increasing all over the world including developing countries like India. Today, more than 30% of the population is known to suffer from one or other allergic ailment. Major causative agents implicated are pollen grains, fungal spores, dust mites, insect debris, animal epithelia, etc. Several aerobiological studies have been conducted in different parts of the country to ascertain aerial concentration and seasonality of pollen grains and fungi. Recently, an "All India Coordinated Project on Aeroallergens and Human Health" was undertaken to discover the quantitative and qualitative prevalence of aerosols at 18 different centres in the country. Predominant airborne pollen are *Holoptelea*, Poaceae, Asteraceae, *Eucalyptus*, *Casuarina*, *Putanjiva*, *Cassia*, *Quercus*, Cocos, *Pinus*, *Cedrus*, *Ailanthus*, Cheno/Amaranth, *Cyperus*, *Argemone*, *Xanthium*, *Parthenium* and others. Clinical and immunological evaluations have revealed allergenically important texa - some of them for the first time. Allergenically important pollen are *Prosopis juliflora*, *Ricinus communis*, *Morus*, *Mallotus*, *Alnus*, *Querecus*, *Cedrus*, *Argemone*, *Amaranthus*, *Chenopodium*, *Holoptelea*, *Brassica*, Cocos, *Cannabis*, *Parthenium*, *Cassia* and grasses. Further cross-reactivity of the IgE antibodies is a common phenomenon among various pollen allergens. *Ricinus communis* pollen from commonly growing weeds in India, cross-reacts with latex (*Hevea brasiliensis*), *Mercurialis annua* and also with seeds of *Ricinus communis* - all belonging to family Euphorbiaceae. *Areca catechu* cross-reacts with other members of Arecaceae such as *Phoenix sylvestris*, *Cocos nucifera* and *Borassus flabelifer*. Several reports on pollen and fruit syndrome have been analyzed. Experiments conducted by us revealed that pollutants (NO_2 and SO_2) not only affect pollen morphology but also changes their allergenic potency. Immunotherapy with recombinant proteins having similar epitopes from different allergens have been advocated, besides allergen avoidance.

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Respiratory allergy is prevalent among all populations with increasing trend all over the world. The gravity of the situation can be perceived by looking at the epidemiological data available across the globe. Epidemiological studies carried out in different countries indicate the prevalence of respiratory allergy as 15–30%. A survey conducted in Finland shows a prevalence of around 14% allergic rhinitis and 2.5% asthma [29]. In Australia, 27% of children had wheeze [46]. Among the Greek population around 9% of asthmatics have been reported [5]. A recent survey carried out in India shows that 20–30% of the population suffer from allergic rhinitis and that 15% develop asthma [4, 11]. However, a study carried over 30 years ago in Delhi reported around 10% allergic rhinitis and 1% asthma [45].

Aeroallergens play a major role in the pathogenesis of respiratory allergic diseases, particularly asthma and rhinitis. Pollen, fungi, animal danders, house dust mites,

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domestic pets, and insects are of particular importance as triggering factors. Pollen grains are well studied as important aeroallergens and a cause of pollinosis.

Knowledge about allergens has progressed, especially with recent molecular, and immunological understanding of the disease. Structure and function of allergens have been identified. These studies have provided explanations about the relationship between allergic sensitization, allergen exposure, and about clinical observations such as allergic cross-reactions. Pollen allergens may cross-react with allergens of other pollen species as well as foods. Pollen associated food allergy has also been reported. We have tried to briefly review these aspects with particular reference to pollen allergy in India

MONITORING AIRBORNE ALLERGENS

The role of the different pollen allergens varies with environment conditions, such as climatic factors, pollution and degree of exposure. Because of change in the climatic conditions, the study of variations in the diurnal and seasonal prevalence becomes very important [15]. Knowledge about diurnal, seasonal and annual fluctuation in airborne pollen in any geographical area is essential for effective diagnosis and treatment of pollen allergy.

To monitor the qualitative and quantitative prevalence of aeroallergens various gravimetric, impaction and filtration sampling devices are used [16, 21, 30].

AIRBORNE POLLEN IN DIFFERENT PARTS OF INDIA

Airborne pollen and their concentration vary in the different seasons depending upon the flowering seasons and climatic factors. Recently, an All India Coordinated Project on Aeroallergens and Human Health sponsored by the Ministry of Environment and Forests, Govt. of India, has been successfully completed by Singh and his colleagues [4]. Important pollen and fungal allergens from 18 different places have been identified, quantified and characterized for their allergenic properties. Important tree, grass, and weed pollens of the different parts of the country are summarized in Table 1.

This provides the most scientific and up-to-date information on aeroallergens in India.

Altogether, 43 types of pollen have been recorded from Northern India. The dominant types are: *Holoptelea*, Poaceae, Asteraceae, *Eucalyptus*, *Casuarina* and *Putranjiva. Cassia*, *Quercus*, *Pinus* and *Cedrus* are other important contributors in the air [4, 38].

From Central India, surveys carried out revealed that the dominant pollen types are from the Poaceae, Asteraceae, Apocynaceae, *Rosa*, *Ricinus*, *Ailanthus*, *Holoptelea*, *Cheno/Amaranth*, *Cyperus*, *Cicer*, *Argemone*, *Cocos nucifera* and *Hibiscus* [4, 38].

A recent survey in West Bengal also revealed 59 types pollen in air - their maximum concentration was recorded in May. Important dominant types are *Trema orientalis*, Asteraceae and Chenopodiaceae, *Pongamia*, *Areca catechu*, *Xanthium*, *Cocos*. At Gauhati, Poaceae, *Cheno/Amaranth*, Asteraceae, *Putranjiva*, *Mangifera* and *Eucalyptus*, are the dominant types of pollen [4, 38].

From Southern India, studies carried out revealed that *Casuarina*, *Parthenium*, *Spathodia*, *Cheno/Amaranth*, *Cocos*, *Eucalyptus*, Poaceae, *Peltophorum* and Cyperaceae are dominant pollen types [4, 38].

Pollen calendars are very useful for clinicians as well as allergic patients to establish chronological correlation between the concentration of pollen in air and seasonal allergic symptoms. The Centre for Biochemical Technology (Council for Scientific and Industrial Research) has published a book on pollen calendars of 12 different states in India [40], which provides important pollen season for grass, weeds and trees prevalent in India.

Table 1. Common allergenic plants of different seasons in India.

	Spring (Feb–April)	Autumn (Sept–Oct)	Winter (Nov–Jan)
Grasses	*Cynodon dactylon*	*Bothriochloa pertusa*	*Cynodon dactylon*
	Dicanthium annulatum	*Cenchrus ciliaris*	*Eragrostis tenella*
	Imperata cylindrica	*Hetropogon contortus*	*Phalaris minor*
	Paspalum distichum	*Pennisetum typhoides*	*Poa annua*
	Poa annua	*Sorghum vulgare*	
	Polypogon monspeliensis		
Weeds	*Cannabis sativa*	*Amaranthus spinosus*	*Ageratum conyzoides*
	Chenopodium murale	*Artemisia scoparia*	*Argemone mexicana*
	Parthenium hysterophorous	*Cassia occidentalis*	*Chenopodium album*
	Suaeda fruiticosa	*Ricinus communis*	*Asphodelous tenuifolius*
	Plantago major	*Xanthium strumarium*	*Ricinus communis*
Trees	*Ailanthus excelsa*	*Anogeissus pendula*	*Cassia siamea*
	Holoptelea integrifolia	*Eucalyptus* sp.	*Salvadora persica*
	Prosopis juliflora	*Prosopis juliflora*	*Mallotus phillipensis*
	Putranjiva roxburghii	*Cedrus deodara*	*Cedrus deodara*

Table 2. Examples of cross-reacting tree pollen allergens with different foods reported by various workers.

Plants	Foods	Evaluation Method
Ambrosia sp. (Ragweed)	Melon, banana	RAST
Grass	Swiss chard	RAST, nasal provocation test, RAST inhibition
	Tomato, peanut	RAST, skin test
Birch	Tomato, melon, water melon Apple, carrot, potato Rosaceae, hazelnuts Apple, cherry, peach, pear	Immunoblot, Immunoassay (IgE)
Birch/mugwort	Celery, carrot	SPT, RAST
Grass and birch	Kiwi fruit	
Artemisia	Rosaceae (peach, apple, chestnut)	

CLINICALLY IMPORTANT POLLEN ALLERGENS

Based on clinico-immunological studies with pollen antigens, important allergenic pollen in India have been identified. The work on pollen allergy was initiated in the 1950s by Shivpuri in Delhi. Subsequently, Kasliwal and his colleagues reported important pollen allergens of Jaipur [23]. Shivpuri and Parkash [35] observed *Prosopis juliflora* as a major cause of pollinosis with 12% patients showing a positive skin reaction. Later, important pollen allergens were identified for Delhi by Shivpuri and his colleagues. They were: *Ageratum*, *Ailanthus*, *Amaranthus*, *Anogeissus pendula*, *Artemisia*, *Cassia siamea*, *Cenchrus*, *Chenopodium*, *Cynodon*, *Ipomoea fistulosa*, *Paspalum distichum* and *Poa annua* [36, 41]. We recorded positive skin reactions in 16.9% patients to *Pinus roxburghii* from the foothills of Himalayas [41].

Pollen causing allergy are quite variable in different ecozones which makes it very important to identify pollinosis causing species from every region, and prepare extracts from them for diagnosis and immunotherapy for the benefit of allergy sufferers.

From Northern India, important allergens identified are: *Prosopis juliflora*, *Ricinus communis*, *Morus*, *Mallotus*, *Alnus*, *Quercus*, *Cedrus*, *Argemone*, *Amaranthus*, *Chenopodium*, *Holoptelea*, and grasses. From Central India the important pollen allergens are: *Argemone*, *Brassica*, *Cannabis*, *Asphoedelus*, *Parthenium*, *Cassia*, *Azadirachta*, grasses, *Alnus*, *Betula*, *Malotus*, *Trewia nudiflora*. From Eastern India, allergenically significant pollen types were found as: *Lantana*, *Cucurbita maxima*, *Cassia fistula*, *Cocos nucifera* and *Calophyllum inophyllum*. Recent studies based on clinical and immunologic parameters reported *Phoenix*, *Ricinus communis* and *Aegle marmelos* as causative agents of allergy in this region [4].

From South India *Cassia*, *Ageratum*, *Salvadora*, *Ricinus*, *Albizia lebbeck* and *Artemisia scoparia* have been reported as important aeroallergens [1, 3]. Subbarao *et al.* [43] recorded allergenicity to *Parthenium hysterophorus* pollen extracts in 34% of allergic rhinitis and 12% bronchial asthma patients from Bangalore. Agashe and Soucenadin [2] recorded high skin reactivity to *Casuarina equisetifolia* in patients from Bangalore.

Clinical studies undertaken by us recently at various medical centres under the All India Coordinated Project (AICP) on Aeroallergens and Human Health [4] sponsored by the Ministry of Environment and Forest, revealed important allergenic pollen for various regions in India. 35 pollen antigens were tested on atopic population. At Chandigarh, skin sensitivity was highest against *Rumex acetosa* and *Ailanthus excelsa* (17.6%), followed by *Trewia nudiflora* (9.7%), *Argemone mexicana* (9.5 %), and *Cedrus deodara* (9.3%). In Delhi, 12.6% of the atopic population were positive to *Amaranthus spinosus*, 8.5% to *Populus deltoides* and 7.5% to *Dodonea viscosa*, *Bauhinia vareigata*. In Calcutta, 28.8% of the patients were sensitive against *Solanum sysimbrifolium*, 21.1% to *Crotalaria juncea* and 18.2% each to *Ricinus communis* and *Ipomea fistulosa*. In Trivandrum, maximum skin reactivity was recorded to *Mallotus phillipensis* (12.1%), followed by *Prosopis juliflora* (6.3%).

Major allergens vary from place to place. It is important for clinicians to select only those pollen antigens for skin testing which are prevalent in a particular area in which the patient resides.

CROSS-REACTIVE ALLERGENS IN THE CLINICAL PRACTICE

Allergy is the result of binding between the epitopes on the proteins with the IgE. Because of evolution, certain proteins have remained conserved from the different sources. It is known that allergic patients are frequently co-sensitized against different allergen sources. Progress made in the field of allergen characterization by molecular biological techniques has now revealed that sensitization against different allergen sources can be explained as cross-reactivity of IgE antibodies with structurally and immunologically related components present in these allergen sources. The similarities among allergens may facilitate allergy diagnosis in clinical practice by using a few representative cross-reactive allergens to determine the patient's IgE reactivity profile.

Cross reactive pollen allergen. Studies carried out across the globe suggest cross-reactivity among different plants. *Lolium perenne* has bee found to be cross-reactive with *Acacia*, pineapple, *Olea europaea*, *Dactylis glomerata*, *Ligustrum vulgare*, *Cynodon dactylon* and *Pinus radiata* [7, 13, 22, 27, 31, 34]. *Platanus acerifolia* has been found to cross-react with *Corylus avellana*, *Prunus persica*, *Malus domestica*, *Arachis hypogaea*, *Zea mays*, *Cicer arietinum*, *Lactuca virosa*, *Musa* spp., and *Apium* spp. [19, 26].

Ricinus communis, commonly grown in India for its oil and abundantly present in waste land, cross-reacts with *Hevea brasiliensis*, *Mercurialis annua*, *Olea europaea*, *Betula*, *Zygophyllum fabago*, *Putranjiva roxburghii*, and *Ricinus* (seed) [8, 28, 37, 39].

Areca catechu cross-reacts with *Phoenix sylvestris*, *Cocos nucifera*, *Borassus flabelifer*, as reported from India [12]. *Cynodon dactylons* (common grass) cross-reacts with *Pennisetum clandestinum*, *Stenotaphrum secundatum*, *Eragrostis*, *Brassica napus*, *Olea europaea*, *Ligustrum vulgare*, and *Lolium perenne* [7, 10, 24, 32, 33, 42].

POLLEN - FRUIT SYNDROME

The existence of an association between sensitivity to different pollen and sensitivity to diverse edible vegetables has been described by various authors. Some studies describe a relationship between birch pollinosis and sensitization to hazelnut, apple, carrot, potato, kiwi and other vegetables or fruits [17, 20, 44]. Heiss *et al.* [20] reported association between mugwort pollinosis and sensitization to celery, carrot, spices, nuts, mustard and Leguminoseae vegetables. Enberg *et al.* [18] have reported association between ragweed pollinosis and hypersensitivity to Cucurbitaceae vegetables or fruits (e.g., watermelon, melon, cucumber) and banana. Some studies have shown association between grass pollinosis and sensitization to tomato, potato, green-pea, peanut, watermelon, melon, apple, orange and kiwi [14]. The association between pollinosis and edible vegetable sensitization may be due to the presence of lectins in edible vegetables, presence of IgE to carbohydrates of the glycoproteins (cross-reactive carbohydrate determinants); existence of common allergens between pollens and edible vegetables. Up to now three allergens have been identified as responsible for cross-reactivity in these associations: profilin, a 14 kD protein that regulates actin; Bet v 1, the 18 kD birch pollen allergen; and a 60-69 kD allergen [9, 20]. It is important to study in depth these associated sensitizations and the common allergens responsible for them in order to improve diagnostic methods and treatment of these syndromes.

POLLEN -POLLUTION AND ALLERGY

Evidence suggests that urbanization with its high levels of vehicle emissions and westernized lifestyle are linked to the rising incidence of pollen-induced respiratory allergy seen in most industrialized countries. Moreover, the increase in respiratory allergy parallels an increase in outdoor and indoor air pollution. Although the role played by outdoor pollutants in allergic sensitization of airways has yet to be elucidated, it is well established that outdoor pollution exacerbates respiratory symptoms in atopic subjects. Acute and chronic exposure to such components of air pollution as sulphur dioxide, nitrogen dioxide, ozone and respirable particulate matter (isolated or in various combinations) enhances airway responsiveness to aeroallergens in atopic subjects. Studies carried out by our group suggest that gases like SO_2 and NO_2 affects pollen grains, and these pollutants can modify the morphology of these antigen-carrying agents and alter their allergenic potential. Soluble protein content is altered significantly in experimental exposed pollen [6]. In addition, by inducing airway inflammation, which increases airway epithelial permeability, pollutants overcome the mucosal barrier and so “prime” allergen-induced responses. Lastly, air pollutants such as diesel exhaust particulates can also facilitate the immunoglobulin E response that leads to pollinosis symptoms in atopic individuals.

IMMUNOTHERAPY WITH RECOMBINANT PROTEINS

In some cases patients are co-sensitised with several unrelated pollen allergens. Based on frequent co-sensitization patterns some of the hybrid proteins have been devolved with the polymerase chain reaction. These hybrids contain all the epitopes from the different allergen in a single protein. These have been used for vaccination against pollen allergy. These molecules have shown stronger lymphoproliferative responses in cultured mononuclear cells of pollen-allergic patients than equimolar mixtures of the individual allergens. Immunization of mice with the hybrids yielded higher antibody titers than immunization with the individual allergen components or pollen extract, which suggests that the individual components of the hybrids can serve as molecular scaffolds for each other to enhance their immunogenicity. Antibodies induced with the hybrids in mice inhibited the binding of grass pollen-allergic patients’ immunoglobulin E to each of the individual allergens and grass pollen extract, and may thus represent protective antibodies. The principle of increasing the immunogenicity of antigens by engineering hybrids thereof may be applied not only for the treatment of polysensitized allergic patients but also for general vaccine development [25].

ALLERGEN AVOIDANCE

The following common precautions assist in allergen avoidance:

1. Avoid going outdoors on days when pollen are present in high concentrations in air.
2. Close all windows in evening when pollen generally settle down to minimize their concentration.
3. Air conditioning decreases indoor pollen counts.

4. Do not plant too many trees and shrubs around your house.
5. Take a bath after coming indoors and wear fresh clothes.
6. Eliminate weeds and grasses in your house garden.
7. Electronic/electrostatic precipitator can be installed.

FUTURE PRIORITIES

With the above information, the obvious question is: what next? All the possible allergens have still not been characterized. As allergen avoidance is the measure of choice for the treatment of allergies and asthma in particular, all the possible allergens are required to be characterized biochemically as well as at the molecular level. Relationship of the allergens with pathogenesis of the respiratory allergies and the increase in the prevalence are important questions which need to be studied in detail. Molecular studies with reference to the cross-reactive allergens are important for the proper diagnosis and treatment of the allergy. Allergens need to be studied up to epitope level.

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