Oleaceae Pollen Allergy and its Cross-Reactivity in the Mediterranean Area in the Context of Globalization

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ABSTRACT

Opening frontiers has led in the last two decades to a massive migration of Romanians to Spain and Italy, two countries known to have large areas planted with olives. Romania owns large areas planted with ash forests. Because of cross-reactivity between these two trees belonging to the Oleaceae family and the big allergenic potential of olive pollens, after a number of years of residence in these countries, many Romanians will present allergic respiratory symptoms of rhinitis and asthma, both in the season of olive pollination and ash pollination.

Keywords: Cross Reaction; Italy; Oleaceae; Pollen; Romania; Spain

INTRODUCTION

Oleaceae is a basal family belonging to the monophyletic order Lamiales. Oleaceae family includes about 400 tree species, which can grow spontaneous or can be planted for ornamental, medicinal or food purposes. The family is distributed on all continents except the Antarctic, from northern temperate to southern subtropical regions and from low to high elevations. Some genera are widespread and occur on more than one continent. These species are mostly entomophilus (having limited allergic relevancy), while species of Oleae, Ligustrum, Fraxinus and Syringa have clinical importance, with Oleae europaea being the most important. The olive (Olea europaea) is cultivated for its fruit and oil, species of Fraxinus are grown for timber, and Syringa, and Ligustrum are planted as ornamentals.

Olive Biology and Clinics

The Mediterranean Sea area represents the leading producer of olive oil. The most important countries in this industry are Spain, Italy, Greece, Portugal, Tunisia, Turkey, and some other European Union members. Olive orchards can reach big city suburbs; in some countries they can occupy half of the agricultural lands. In the last years, due to the agricultural policies of the European Union, there was a tendency to increase the areas planted with olive trees, especially in regions where other types of plants had been initially cultivated. The season of olive pollen (Olea europaea) begins late in April and ends in early June, reaching its maximum around the middle and end of May. Diurnal fluctuation in pollen concentration shows consistent release throughout the day and night, but with a slight peak between 2-6 PM. While primarily insect-pollinated, O. europaea pollen is very light and buoyant, and therefore, large amounts are airborne. Pollen’s density can present major diversity, depending on climate, vegetation and ground, with a certain degree of variation between East and West Mediterranean, coastal and inland regions,
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provinces situated at the same latitude (for example Cordoba versus Sicily) and from one year to another. Olive species from the inland of the continent (Cordoba region) are more vulnerable to climatic variation (frost-defrost) than the species cultivated in the coastal regions (Sicily) with more stable climatic conditions. Bloom and accordingly pollination periods are earlier in Sicily when compared to the Cordoba region. Differences have also been observed between olives which grew in the same geographical region but at a different altitude.6

Spain possessed in 2007 according to Eurostat informations 2.47 millions hectares (ha), with 350.000 ha increasing since 1991, most important regions occupied with olive orchards being Jaen, Cordoba, Seville, Ciudad Real, Toledo, Badajoz and Andaluzia.7 Italy possessed in 2007 approximately 1.2 mil ha olive orchards8 with the biggest areas in Puglia, followed by Calabria and Sicily; get together these 3 provinces cover 60% of olive oil production of Italy. In the northern Italy areas with important olive orchards are, in order, Tuscany (about 108 000 ha), Lazio (about 87 000 ha), Campania (about 81 000 ha), and Abruzzo (about 44 000 ha).8 Greece has 800.000 ha of olives, mainly in semi-mountainous and coastal areas (Crete, Peloponnese) and Portugal 379.000 ha. Tunisia has 1.69 million ha of olive groves and Turkey 815.000.7

Oleaceae pollen presents an important allergic potential, representing one of the most important causes of respiratory allergies in Mediterranean area.9 The extract of olive pollen contains at least 20 protein bands with allergenic reactivity.10,11 Olive pollen contains 12 allergens, classified from Ole e 1 to Ole e 12.12 The most frequent allergen is Ole e 1, which is reported to cause clinical symptoms in 70% of olive pollen allergic patients, thus being considered the major allergen. This allergen contributes significantly to the total allergenicity of Oleaceae pollen extract and its concentration is closely related to the allergenic reactivity of the entire pollen extract. Ole e 1 was the first allergen discovered in olive pollen. Ole e 1 is an acidic heterogeneous protein that exhibits 2 variants: a glycosylated form (20 kDa) and a nonglycosylated one (18.5 kDa) of the same 145 polypeptide chain.12,13 Its function is still unknown; at present there are 2 hypothesis: reproductive function or the control of the osmotic gradient in the hydration process.14 Besides Ole e 1, further 11 additional olive pollen allergens have been described following purification from the Olea europea pollen extract.11 Ole e 2 is a significant allergen and belongs to the profilin family. Profilin is a ubiquitos protein that controls actin polymerization in eukaryotic cells from vegetable and animal biological sources. Because of high cross-reactivity between profilins and the wide distribution they are considered pan-allergens. Ole e 2 displays high cross-reactivity, showing structural and immunological similarity with other pollen sources such as birch, ash, and grass. The prevalence of this allergen was estimated between 24 and 27% in olive allergic patients and its presence was related to the risk of developing asthma.11 Ole e 3 is a pocalcin belonging to the Cu1- binding protein subfamily. The prevalence varies between 20 and 50% in olive allergic patients, depending on the geographical area. Ole e 3 has a lower cross-reactivity than Ole e 2 with pollens from rapeseed, Bermuda grass, and birch.11 Ole e 4 shows IgE binding capacity and has no homology with any known protein. Ole e 5 is a superoxide dismutase (SOD), recognized by 39% of pollen allergic patients. It shows 90% homology with other SOD from several plant species. Ole e 5 was found in the olive fruit pulp and this could be an explanation for cross allergy between olive pollen allergy and olive fruit allergy. Ole e 6 is the smallest allergen, recognized by 50% of allergic patients and without homology with other proteins. Ole e 7 shows similarities with nonspecific lipid transfer proteins (LTP) from plant tissues. Ole e 7 was found in 47% of allergic patients and its presence was associated with an increased risk of food anaphylaxis, depending on the geographical area. Ole e 8 is a calcium-binding protein with a very low prevalence. Ole e 9 is a glycosylated -1,3-glucanase, which belongs to the pathogenesis-related (PR-2) protein family, has the highest molecular mass from olive pollen allergens and a low concentration in olive pollen. Ole e 10 is considered a major allergen, presents cross-reactivity with proteins from various pollens (Oleaceae, Graminame, Chenopodiaceae, Cupressaceae, Ambrosia and Parietaria) and is associated with severe asthma. Ole e 11 is a pectin methylesterase recently detected and Ole e 12 belongs to the family of the isoavone reductases.11 Value limits for olive pollen’s density to provoke symptoms are 162 grains/m³ (equivalent to 22.7 ng of olive pollen allergen/m³ or 0.9 ng/m³ of Ole e 1).10 The sensitization rate in the Mediterranean areas covered with important olive orchards is comparable to those for gramineae.14 Olive pollen allergy is among the first three sensitizations in Italy15 and the second in Spain as a whole, while being in the first place in the southern

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provinces, with incidences exceeding 20% for prick tests.\textsuperscript{19} Olive pollen density can reach in some Spanish provinces up to 14.000 grains/m\textsuperscript{3} (Andalusia),\textsuperscript{17} which, alongside a higher frequency of symptoms of rhinitis and asthma among the inhabitants of that region, has led to the term “special olive pollen sensitization”, causing an important consequence for public health.\textsuperscript{10} The clinical picture of Oleaceae pollen allergy is dominated by symptoms of rhinitis or rhinoconjunctivitis (nasal itching, sneezing, obstruction, discharge, tearing), followed or associated by symptoms of asthma (wheezing, cough, chest tightness, shortness of breath),\textsuperscript{10,18,19} with a higher incidence in adults.\textsuperscript{11} Allergic symptoms have been also reported after the pollination season is over.\textsuperscript{18}

**Ash Biology and Clinics**

Ash is a European native tree with a large distribution on the entire continent, from Ireland to the Russian Federation and from southern Scandinavia to southern Europe (Spain, Italy, the Balkans).\textsuperscript{20} Ash is the principal member of the Oleaceae family in Romania. Ash trees can be found in forests, riverside coppices, meadows, at altitudes ranging from those of plains, including the Danube Delta, to that of inferior mountain regions. Ash forests are called frasinetes (Fraxinetum). Fraxinetum are rather rare and don't have a specific area. In forests, ash grows mainly among other trees (oak, elm, alder, maple, and hawthorn) in areas characterized by a permanent excess of humidity. The ash pollination season is between March and May.\textsuperscript{21} Exposure to ash pollen is higher in rural areas than in urban areas\textsuperscript{22} and 50% of total daily pollen was noted at 14:00.\textsuperscript{23} Ash pollen contains 3 allergens, out of which sensitivity to Fra e 1 is found in approximately 80% of the patients tested positive at prick tests, thus being considered the major allergen. An important study made in Austria between 1997 and 1999 has diagnosed the sensitization to ash pollen in ~18% of pollen-allergic patients.\textsuperscript{20} Until now, this is the biggest study realized in Europe regarding the prevalence of ash pollen allergy.

**Privet and lilac Biology and Clinics**

The genus Ligustrum contains about thirty-five species of deciduous or evergreen shrubs native to Europe, Northern Africa, Asia, and Australia. Common privet, *L. vulgare*, is widely distributed through almost all of Europe. Privets grow along woodland edges, in floodplains, and riparian forests. Common privet is a deciduous or semi-evergreen shrub with height and spread of 3 m. Pollination season is between May and June. Despite being primarily insect-pollinated, privets are facultatively anemophilous.\textsuperscript{4} The major allergen is Lig v 1, with important cross-reactivity with Ole e 1.\textsuperscript{25} Sensitization can easily be demonstrated and skin test positivity to olive in an olive and ash-free area has been attributed to privet.\textsuperscript{24,26,27}

*Syringa vulgaris* (lilac or common lilac) is a species of flowering plant in the family Oleaceae, native to the Balkan Peninsula, where it grows on rocky hills. The major allergen is Syr v 1 which presents important cross-reactivity with Ole e 1.\textsuperscript{28} Until now, this cross-reactivity was very little studied in clinical studies.

**Cross-reactivity in the Oleaceae Family**

Cross-reactivity between the major allergens (Ole e 1, Fra e 1) of these 2 trees is important, reaching 85%-95% due to the considerable amino-acid sequence identity, and immunologic cross-reactivity.\textsuperscript{29-31} An important clinical argument for this comes from Turkey, in the region of Anatolia, a part of the country without olive trees, but with important ash forests nearby; 2 studies realised in Ankara and Eskisehir have indicated a degree of sensitization to *Olea* pollen of 60% for Ankara\textsuperscript{2} and 22% for Eskisehir.\textsuperscript{33} Arguments come also from a small study which showed 14 positive skin tests to Ole e 1, Fra e 1, Lig v 1 and Syr v 1 from 15 olive-monosensitized patients\textsuperscript{29} and from an earlier study\textsuperscript{34}. Most of the studies published until now about *Oleaceae* pollen allergy used extracts for olive, much less extracts for ash and very few privet extracts. Therefore, it is difficult to conclude with high precision about the primary sensitization in patients, especially in cases where we can find in the same region 2 or more of the species detailed before. An older article which studied the cross-reactivity between pollen extracts of four species of *Oleaceae* (olive, ash, privet, lilac) suggested that only *O. europaea* extract should be used in diagnosis in Oleaceae pollen allergy.\textsuperscript{35}

**Cross-reactivity with other Plant Species**

In the previous years, several studies have demonstrated cross-reactions between allergens from olive pollen and allergens from other plant species pollens. Ole e 1 shows partial structural similarities and various cross-reactivity with Che a 1,\textsuperscript{29,36} Phl p 11,\textsuperscript{37} Pla 1,\textsuperscript{29,38} and Sal k 5 (unpublished data). This cross-reactivity for a part of olive pollen allergens (Ole e 1,
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Ole e 2, Ole e 3, Ole e 10), demonstrated in laboratory studies, shall need confirmation in future clinical studies.

Therapeutical Aspects

Respiratory allergy to olive pollen has a specific treatment: immunotherapy. This can be administrated subcutaneous or sublingual, with natural allergenic extracts or allergoids with favorable results. Recent experimental studies that used various peptides have suggested the possibility of using some Ole e 1 peptides as a safe vaccine candidate for immunotherapy of Oleaceae pollen allergy. In the case of cross-reactivity, the best option is represented by the personalized treatment.

Romanians in the Mediterranean Area

The last decade meant for more than two million Romanians leaving their country in order to work abroad, especially in Italy and Spain, countries with big plantation of olives. A significant part of Romanians who went to work in Spain has worked or is still working in agriculture, picking olives or in constructions, an occupation with daily exposure to pollens. According to the latest official estimates, over 700,000 Romanians live and work legally in Spain; however unofficial figures indicate about more than 1 million Romanian citizens living in Spain. Areas with big Romanian communities are Madrid, Huelva, Castellon, Alcala de Henares, many of them having big areas planted with olives. Another important Romanian community lives in Italy, approximately 900,000 according to official records, with large groups living in the southern provinces (Sicily, Sardinia, Calabria, Basilicata) and northern provinces (Piedmont, Lombardy, Tuscany, Umbria, Lazio). The majority of these persons have arrived in Spain and Italy between 2000-2005, thereby being exposed for a period of time enough to be sensitized to Oleaceae pollen.

CONCLUSION

As we have shown above, the prevalence of Olea europaea pollen allergy is significant in regions where Romanians work and live, especially in the case of Spain and Italy. Because of the long time presence of Romanians in these regions, there is a high probability for a part of them to acquire over the years a sensitization at Oleaceae pollen. According to observations made for other countries, which were confronted with a massive wave of work migration, a lot of the migrants will return to their home countries after a number of years. In the situation discussed above, an important part of those who will come back will be sensitized to Oleaceae pollen. This sensitization will call for the introduction in the routine testing in Romania for Oleaceae pollen and particularly for Fraxinus excelsior pollen, because of the cross-reactivity between the main allergens presented in the pollens Fra e 1 and Ole e 1. This material is a review of English articles regarding Oleaceae pollen allergy and presents a hypothesis which shall need confirmation from a future partnership between allergists from Romania, Italy and Spain.

Competing Interests

The author declares that he has no competing financial interests.

REFERENCES

5. Bonofiglio T, Orlandi F, Ruga L, Romano B, Fornaciari M. Climate change impact on the olive pollen season in Mediterranean areas of Italy: air quality in late spring from an allergenic point of view. Environ Monit Assess 2013; 185(1):877-90.
7. Gabriella Camarsa, Stephen Gardner, Wendy Jones, Jon Eldridge, Tim Hudson, Edward Thorpe, Eamon O’Hara (AEIDL, Communications Team Coordinator). Four main olive producing countries in: LIFE among the olives Good practice in improving environmental performance in the
olive oil sector European Commission Environment Directorate-General, 10-11.


Olea europaea pollen: cross-reactivity with other Oleaceae species. Role of Ole e 1-related proteins. Allergy 2002; 57(Suppl 71):29-34.


