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## Sensitization to *Quercus ilex* Pollen Is Clinically Relevant in Patients With Seasonal Pollen Allergy

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Holm oak, *Quercus ilex*, is the most abundant tree in the Iberian Peninsula, and its pollen is one of the most abundant types recovered from Madrid pollen collectors during spring. Former reports dating from 1995 estimated the prevalence of sensitization to this pollen in 2 Spanish populations of patients with allergic respiratory conditions at between 3.5% and 14%, with less than 1% of patients being monosensitized [1,2]. After these reports, this pollen was considered clinically irrelevant and therefore not routinely included in the allergen screening panel of patients with allergic respiratory conditions. However, holm oak belongs to the order Fagales, which includes species such as birch, alder, hazel, and hornbeam and whose pollens are potent triggers of spring pollinosis in central Europe [3]. Likewise, the presence of a homolog of Bet v 1, namely Que i 1, was recently described by our group as the main PR10 sensitizer in Madrid (Spain), a birch-free area [4]. In that paper, we also reported a frequency of sensitization to *Q. ilex* pollen of 59% in a pediatric population, that is, far higher than previously published [1,2,5]. With these results in mind, we sought to determine the current prevalence in adults and children in Madrid and to assess the clinical relevance of this sensitization by means of nasal provocation tests.

Patients (148 adults, age  $\geq 16$  years; and 100 children, age 2-15 years) suspected of allergic respiratory disease (rhinitis, conjunctivitis, and/or asthma) who were treated at the Allergy Department of La Paz University Hospital were prospectively included (adult patients between October 2021 and March 2022 and pediatric patients between October 2023 and March 2023). Skin prick tests (SPTs) were performed with a commercial *Q. ilex* pollen extract (Roxall), considering a wheal  $\geq 3$  mm to be a positive result [6]. Nasal provocation testing (NPT) was performed in a subgroup of 10 patients (aged 14-46 years, 50% male, and 50% with asthma). All 10 patients were polysensitized

**Table.** Nasal Provocation Test Results of 10 Patients and 3 Negative Individuals Tested.<sup>a</sup>

Patient	Age	Total IgE, kU/L	Q ilex SPT, mm	Q alba IgE, kU/L	Positive dilution, 0.5-0.125 mg/mL	Acoustic rhinometry, %	Lebel scale
1	36	169	7×6	4.64	0.3	-48	6
2	46	26.9	4×4	0.39	0.3	-27	4
3	20	1337	5×5	0.87	0.3	-30	3
4	24	212	10×10	0.54	0.125	-47	8
5	38	565	8×7	3.30	0.250	-33	9
6	27	1424	12×10	24.6	0.125	-35	7
7	40	418	12×10	17.1	0.250	-43	5
8	25	75.10	5×5	0.23	0.125	-27	9
9	16	927	5×5	55.50	0.125	-58	11
10	14	518	13×6	24.50	0.250	-40	7
11	30	13.4	<3	0.01	Negative	Negative	0
12	28	ND	<3	ND	Negative	Negative	0
13	39	28.40	<3	ND	Negative	Negative	0
14	26	ND	<3	ND	Negative	Negative	0

Abbreviation: ND, not determined

<sup>a</sup>The results were assessed using the subjective Lebel symptom scale (0-11) and acoustic rhinometry. Positivity was defined as an increase of  $\geq 3$  points in the Lebel score and a decrease of 2-6 cm<sup>3</sup>  $\geq 27\%$  bilaterally in acoustic rhinometry.

to other pollens. A healthy nonsensitized patient and 3 patients sensitized to other pollens were included as negative controls (Table). NPT was performed with a lyophilized extract of *Q ilex* (Roxall) serially diluted in saline solution at 0.5 mg/mL, 0.250 mg/mL, and 0.125 mg/mL. The diluted extract was applied bilaterally using a nebulizer (0.07 mL/spray). First, 2 puffs of 0.9% saline were administered as a negative control. If negative, 2 puffs of successively increasing concentrations were applied at 15-minute intervals until the test was positive or all dilutions had been applied. A nasal examination was performed using anterior rhinoscopy before the test started. The test results were assessed using the Lebel symptom scale [7], a subjective technique, and acoustic rhinometry, an objective technique. Positivity criteria were established according to the EAACI 2018 Nasal Provocation Position Paper [8]. Patients were observed for 1 hour after the test was complete and instructed on what to do in case of a delayed reaction. We verified that there were no contraindications or medications that could affect the test result. The local ethics committee approved the study (PI-2243). Written informed consent was obtained from all patients, their parents, or their legal representatives when required.

SPT was more frequently positive for *Q ilex* pollen in children (56/100, 56.0%) than in adults (34/148, 22.9%). This difference was statistically significant ( $\chi^2$  test,  $P=1.118 \times 10^{-7}$ ). All nasal provocation test results were positive (100%, Table).

Interestingly, sensitization to *Q ilex* pollen is much less frequent in adults than in children. Since sensitization profiles often remain stable from childhood to adulthood [9], these differences could reflect a tendency toward increased frequency of sensitization to this pollen, as these children are the adults of the future. However, we cannot ignore the influence of

duration of exposure to pollen, which could be more intense in children, leading to higher rates of sensitization, particularly in Madrid, where *Q ilex* pollen is one of the largest contributors to the total pollen count [10].

The current frequency of sensitization in adults (22.9%) is higher than published in 1995 in a population from the same area (14%) [1]. One possible explanation is the rising amount of this pollen in the environment and the increase in the length of the pollen season owing to global warming and higher levels of CO<sub>2</sub> in the atmosphere [11]. Irrespective of methodology, the differences between the present study and that of Subiza et al [1] and between children and adults point to an increase in sensitization to *Q ilex* pollen in our population.

Of particular interest, sensitization to *Q ilex* is commonly associated with polysensitization, as previously reported [1], and we cannot account for the absence of patients monosensitized to *Quercus* pollen. This phenomenon requires more in-depth investigation, not only to elucidate the mechanism involved in the origin of sensitization, but also to establish a correlation with other non-taxonomically related pollen species, particularly in an area where the pollen counts of birch are extremely low [12]. Moreover, we did not observe a relationship between the severity of the response in NPT and the wheal size in SPT. Indeed, the severity of symptoms upon natural exposure to an allergen does not depend solely on specific IgE reactivity. Symptom burden is affected by host and environmental factors, including immunological parameters and concomitant exposure to other coseasonal pollens. Regardless of these considerations, the whole spectrum of pollen sensitizations should be taken into account in order to prescribe the best immunotherapy and determine whether it was effective [13].

In summary, to our knowledge, this is the first study to objectively report the clinical relevance of *Q. ilex* pollen through positive NPT findings. We report a prevalence of sensitization of 22.9% and 56.0% among pollen-allergic adult and pediatric patients, respectively. These results mean that this pollen should be considered a relevant sensitizer during spring. Likewise, we confirmed an increase in the frequency of sensitization to *Q. ilex* pollen over recent years in Madrid. Nevertheless, further studies including populations from other areas are needed to properly establish the allergenic relevance of *Q. ilex* pollen.

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#### Conflicts of Interest

The authors declare that they have no conflicts of interest.

#### Previous Presentation

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