Clinical and molecular profiles in patients allergic to amaranthaceae

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Recent studies have shown that patients monosensitized to Amaranthaceae pollen present a mismatch between the air pollen concentration and their clinical symptoms [1]. The wide range of flowering months (May - October) for Amaranthaceae species could justify the long symptomatic period of most patients [2]. This botanical family is more likely to adapt to climate change than others are. Therefore, a better understanding of its behavior is becoming interesting due to a likely increasing number of sensitizations and allergic respiratory symptoms in the near future.

Nowadays, there are few studies about the allergenic and clinical relevance of the different Amaranthaceae species, with only *Salsola kali (S. kali), Salsola oppositifolia (S. oppositifolia) and Chenopodium album (C. album)* pollen available for the diagnosis and treatment of patients.

S. kali pollen is a complex allergen source containing numerous Sal k 1 [3,4] isoforms and other allergens with a variable cross-reactivity [5-9]. Currently, only one recombinant

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Sal k 1 isoform is available for molecular diagnosis, which results insufficient for the complete evaluation of this pollen hypersensitivity.

The aim of our study was to establish different clinical profiles of patients with relevant symptoms to Amaranthaceae pollen and correlate them with their molecular sensitization profiles.

This study was approved by The Ethics Committee of Aragón (CEICA), in Spain. All patients signed an informed consent to participate.

Fifty patients sensitized to *S. kali* with symptoms compatible with respiratory allergy during the pollination period of Amaranthaceae species from Zaragoza (Aragón, Spain) were included. Blood samples were drawn and sera used for the *in vitro* study. Subjective assessments of symptoms were performed using a Visual Analog Scale (VAS) from April to October 2018, both included.

SDS-PAGE (Online supplement, figure 1), Immunoblotting and ELISA were performed for qualitative and quantitative studies of *S. kali* allergens, respectively. Recognition of allergens was performed by Immunodetection while indirect ELISA assays were used for (previously identified allergens) specific IgE (sIgE) quantification.

PSPP statistical program was used to distribute patients into clusters and mean symptom curves were obtained for each group (Online supplement, figure 2). These mean curves were graphically confronted with the flowering curves of different species of Amaranthaceae obtained in a previous study [2] and three associations (clusters) were obtained (Figure 1). Statistical analysis methods are given in the online supplement (File 1).

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Therefore, the fifty patients were classified into these 3 groups according to this statistical association, observing specific differences in terms of intensity and temporality of the symptoms for each of the clusters (Online supplement, figure 3).

Group 1, formed by 13 patients correlated with *S. kali* flowering season (R=0.92; PSPP program was also used to calculate these correlations), presented symptoms of low intensity and a peak between the end of July and the beginning of August. The mean global VAS was 4.46 ±1.42. All of them had allergic rhinitis, associated with conjunctivitis in 77% and asthma in 54%. 92% in this group recognized Sal k 1, 23% Sal k 4 (profilin), 15% Sal k 5 (Ole e 1-like), 15% Sal k 6. However, the panallergen Sal k 7 (polcalcin) was not recognized by any patient. In this group, one of the patients who recognized Sal k 4 (profilin) was negative for Sal k 1.

Group 2, formed by 10 patients correlated with *S. kali* and *Bassia scoparia (B. scoparia)* flowering together (R=0.86), presented two medium intensity symptom peaks: the first one between late July and early August, and a second one by late August. The mean global VAS was 4.66±1.97. All them had allergic rhinitis, associated with conjunctivitis in 80% and asthma in 30%. 90% of the patients in this group recognized Sal k 1, 10% Sal k 5, 10% Sal k 6, 20% Sal k 7 but none of them did to Sal k 4. In this group, a patient who recognized Sal k 6 was negative for Sal k 1.

Group 3, formed by 27 patients, presented higher intensity symptomatology throughout the spring-summer season in Spain. All patients´ symptoms were correlated (R=0.74) with the sensitization to *Amaranthus muricatus (A. muricatus), S. kali and B. scoparia* flowering. The mean global VAS was 5.43 ±1.83. All patients in this group had allergic

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rhinitis, associated with conjunctivitis in 59% and asthma in 56%. 89% in this group recognized Sal k 1, 11% Sal k 4, 11% Sal k 5, 7% Sal k 6 and 7% Sal k 7.

For all groups, only 33% of the patients who recognized Sal k 5 (Ole e 1-like) also recognized Ole e 1. All asthmatic patients were well controlled. No other prevalent sensitization was observed in patients with asthma in this case.

Figures showing scores, each group analysis and all *S. kali* studied allergens are given in the online supplement (Tables 1 and 2).

No significant differences were observed in the clinical presentation and values of Sal k 1 ($p=0.168$), Sal k 4 ($p=0.592$), Sal k 5 ($p=0.474$), Sal k 6 ($p=0.662$) and Sal k 7 ($p=0.643$) among the three groups. No significant differences in VAS symptoms values were observed either. Likewise, Sal k 1 and Sal k 5 were predominant in group 1 and Sal k 1 and Sal k 6 in group 3. However, the absence of relevant allergens such as panallergens, Sal k 4 and Sal k 7, in some of the groups could be of interest for further studies. Besides, other unknown allergens could be responsible for these discrepancies because different patterns of bands around 40 kDa are visible in the immunoblotting (Online supplement, figure 3). This 40 kDa molecular mass is the one reported for Sal k 1 and Sal k 6 allergens.

On the contrary, significant differences were observed in the values of *S. kali s*IgE ($p<0.05$), with lower values in group 1 (6.25±3.72 kU/L) compared to group 2 (38.10±1.56 kU/L) and 3 (29.53±16.42 kU/L), which implies that total *S. kali* extract IgE levels correlate with symptoms´ intensity. The lack of significant differences among allergen components could imply the existence of other still unknown allergens that could be responsible for these differences in clinical presentation.

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To our knowledge, this is the first paper studying the relationship between molecular profile of sensitized patients to Amaranthaceae, the allergic symptoms and the seasonality produced by *S. kali* pollen.

Our results reveal the existence of different sensitization profiles that may help to include other relevant allergens in the diagnosis and treatment of Amaranthaceae allergy although further studies are needed to confirm these findings.

In conclusion, *S. kali* pollen is more complex than what we have analyzed in the past, due to the presence of different species and the large number of isoforms of certain allergens. Significant differences are observed in the complete extract of *S. kali* but not among the rest of the studied allergens. This could imply the existence of other still unknown allergens that could be responsible for these differences in clinical presentation.

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Conflict of interest

None.

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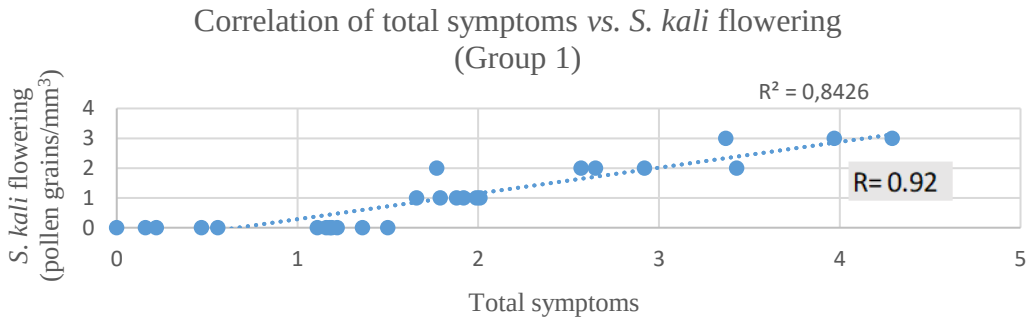
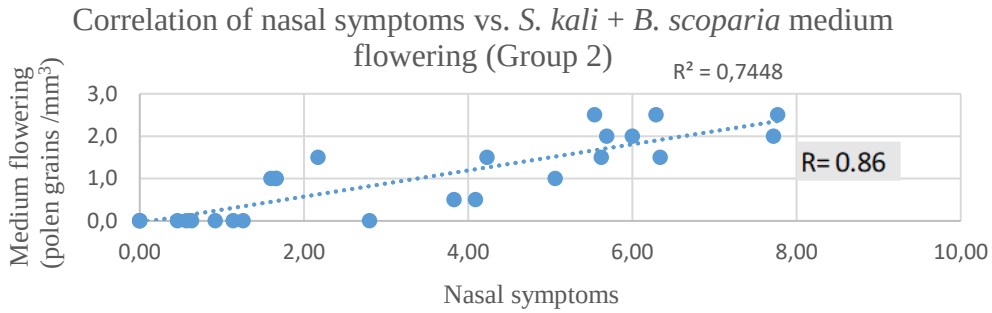
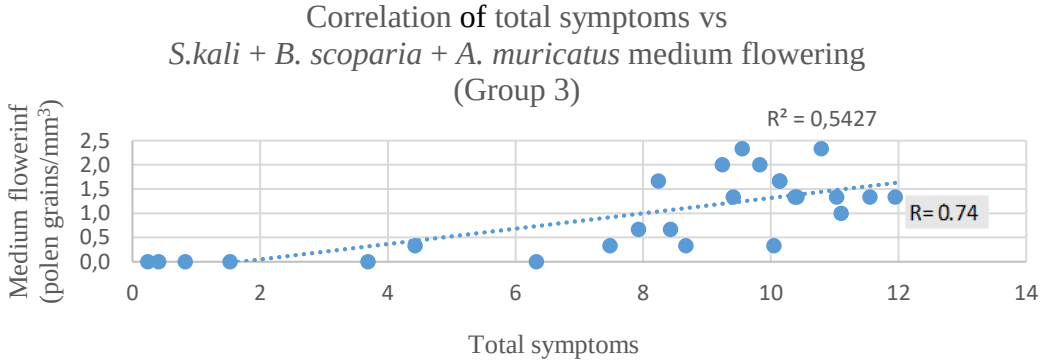
Figure. Symptoms-flowering correlation analysis of the three groups. Symptoms Score was evaluated using TSS4 questionnaire.







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