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Peculiarities of Allergy to Tree Pollen and Approaches to Diagnosis and Allergen Immunotherapy in Patients – Residents of Lviv Region

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Abstract: *The study involved 286 patients (17-58 years, 55.9% females and 44.1% males). SPT was performed with extracts "Mixture of trees" (Diater Laboratorios, Spain). The study of allergen components was made by ImmunoCAP. We evaluated the efficiency of SLIT by visual analogue scale. 98.3% patients had positive SPT to extract "Mixture of trees". N=281:191 (68.1%) individuals were positive to birch extract, 8 (2.8%) – to ash tree, 82 (29.1%) – to birch+ash tree. Ash sensitization according to SPT – 31.9%. ImmunoCAP: among patients with positive SPT to birch, true sensitization – in 147 (77%) individuals, among patients with polysensitization – 63 (76.9%). The number of patients with minor components in both groups was similar – 21.1%. The results revealed a significant decrease in the severity of symptoms in experimental group after one (83.1%) and two years (94.1%) of treatment. SLIT by combined vaccine "Spring Tree" demonstrates high efficiency for patients with sensitization to Betulacea and Oleaceae.*

Keywords: *Betulacea allergens, Oleaceae allergens, sensitization, efficiency of allergen immunotherapy.*

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I. INTRODUCTION

Pollen allergy (from Latin *pollinis* pollen) is a chronic allergic disease, caused by plant pollen, which is manifested by allergic inflammation of the respiratory mucosa with symptoms of allergic rhinitis (AR), rhinosinusitis, often combined with conjunctivitis. A severe complication of pollen allergy is bronchial asthma (BA). The disease is referred to the most common allergic diseases among both children and adults. Statistic data in different countries range within 4.8 – 36% in children and from 2 to 39% in adults [1]. The peculiarity of children population is the fact that signs of pollen allergy can be observed already during the second year of life; however, the disease often remains undiagnosed. In other sources, it is indicated that BA is detected in 80% of children with AR below 10 years of age. Underdiagnosis of pollen allergy among adults has also been addressed, since patients with mild form do not consult physicians. Thus, it is considered that the number of patients, statistically recorded, is 10 times lower than real indices of morbidity [2].

Among thousands of plants worldwide, over 60 of them produce pollen, which possesses allergenic properties, thereby, it is capable to sensitize the body [3]. One of the specific sources of allergens is tree pollen. Trees belong to the composition of many natural ecosystems, and are important elements of artificially created landscapes. They are also grown on agricultural lands in large amounts.

It is known that peculiarities of patients' sensitizing profile depend not only on endogenous factors, lifestyle, but, to a large extent, on climate and geographic conditions of living, ecological situation, associated with certain region.

Lviv region is one of the most forested regions of Ukraine. Forestland percentage constitutes 28%, while the average in Ukraine is 14.5%. Lviv is situated in the southern-western part of East European Plain, approximately 100 km to the north from Eastern Carpathians, in the region of broadleaved and coniferous woodland. Potential of wood species in Lviv is formed with beech, alder, hazelnut, birch, maple, ash tree, privet, etc. [4, 5]. According to literature data, in our region, pollination season of the above-mentioned trees started in February in the recent years, and maximal concentration of pollen was observed in March-April [6].

Components, including those of pollen allergens, can be classified by their reference to different protein families, based on their structure and functions [7]. Thus, a group of pathogenesis-related proteins PR-10 (for example, Bet v 1 and homologous allergens) is the main allergen of *Fagales* pollen and the basic cause for the

development of symptoms of allergic diseases. As it was stated above, in our region, the representatives of *Fagales* are *Betulacea* family (birch, alder tree), *Corylaceae* (hazelnut, horn-beech), *Fagaceae* (beech, oak, chestnut), *Aceraceae* (maple); among them birch, alder tree and hazelnut (in decreasing order) have the most allergic properties. In particular, Bet v 1 is a major component of a birch, specific IgE to which are found in 95% of patients with allergy to the tree pollen [8]. Presence of protein-homologues Bet v 1 is often associated with local symptoms in the form of oral allergic syndrome (OAS) during consumption of fresh fruit from *Rosaceae* family, carrots, celery and hazelnut [9-10]. There are reports about cross reactivity between pollens of birch, alder tree and hazelnut (due to presence of homologues Bet v 1: Aln g 1, Bet v 1 and Cor a 1) [11-15]. Particularly, it has been proven that identity of amino acid sequence between Aln g 1 and Bet v 1 constitutes 86.8% [16]. Amino acid sequence of isoform Cor a 1 of hazelnut is by 75.5-76.7% identical with Aln g 1 [17].

Another representative of wild and cultivated flora of Prykarpattia (Ciscarpathia) is European ash *(Fraxinus excelsior)*, referred to *Oleaceae* family. Its pollination period starts in February and, as a result, of warming, often coincides with birch flowering. According to literature review, over 30% of patients with allergy to pollen in Central Europe are sensitized to ash pollen [18, 19].

Fra e 1 – is a major allergen of ash in individuals sensitized to pollen in Northern and Central Europe. This allergen is referred to the family Ole e 1-similar proteins and has a high level of cross reactivity with other members of this family [20]. In particular, almost identical profiles of IgE-binding to Ole e 1 and its homologue Fra e 1 were observed in patients with pollen allergy to ash tree and olive. Specific IgE to Fra e 1 are present in 70-80% of individuals, sensitized to ash tree pollen [21, 22].

Panallergens (profilins, polcalcins), which initiate cross-reactions between unallied plant species, are present in pollens of *Betulacea* as well as *Oleaceae.* In particular, profilins are Bet v 2 – allergen of birch pollen, Cor a 2 – hazelnut, Fra e 2 – ash tree pollen. These actin-binding proteins can cause secondary food allergy to fruit and vegetables [23, 24]. Bet v 3 and Bet v 4 of a birch, Aln g 4 – alder and Fra e 3 – ash tree pollen are referred to calcium-binding proteins (polcalcins) [25].

Concerning other minor molecules of birch pollen – Bet v 5, Bet v 6, Bet v 7, Bet v 8 (www.allergen.org), they are potentially reactive allergens and are responsible for allergic reactions to certain foods. It should be mentioned that proteins-reductases, homologues of Bet v 6 are also present in hazelnut pollen (Cor a 6) and olive (Ole e 12) [18, 24].

Analyzing data of international investigations, it should be mentioned that allergic cross reactivity between members of *Betulacea* and *Oleaceae* families has been known since 1996 [1]. It has been revealed that a partial cross reactivity exists between pollens of a birch and an ash tree, but is not associated with Bet v 1 and Fra e 1 [9, 26]. There are also data that analogues of 1.3-beta glucanase Ole e 9 – components of olive pollen, are present in pollens of an ash tree, a birch, in tomatoes, potatoes, sweet pepper, bananas and latex [27]. It is suggested that a specific cross reactivity between an ash tree and a birch is due to a protein component Ole e 9 [28].

Thus, separate sensitization to an ash tree can occur even in the regions where birch dominates. Thus, it is necessary to diagnose sensitization to an ash tree in patients with pollen allergy in early spring and add ash tree allergens to an extract for allergen immunotherapy.

The aim of our research was to study peculiarities of sensitization to spring trees in patients of Lviv region and analyze efficacy of allergen immunotherapy with extract of spring trees (Diater Laboratorios, Spain).

II. MATHERIAL AND METHODS

The research was conducted in 2013-2016 years in Lviv regional medical center of clinical immunology and allergology. Totally, 286 patients having problems with allergic rhinitis and conjunctivitis with exacerbation of clinical symptoms in early spring were examined. The age of patients was 17-58 years, among them 55.9% – females and 44.1% – males. In the period of clinical remission, patients had skin prick-tests (SPT) with the extract "Mixture of trees" (*Alnus glutinosa*=25.00 %; *Corylus avellana*=25.00 %; *Betula verrucosa*=25.00 %; *Fraxinus excelsior*=25.00 %), as well as an extract of birch (*Betula verrucosa*) and ash tree pollen (*Fraxinus excelsior*) Diater Laboratorios, Spain. Negative and positive controls (1% histamine solution) were also produced by Diater Laboratorios, Spain. The results of SPT were estimated in 15 minutes, according to European requirements (practical manual for conduction of skin prick-tests in allergy to aeroallergens, Bousquet J, Allergy, 2012). Immunofluorescent method ImmunoCAP (Thermo Fisher Scientific, USA) was used to detect species-specific components of allergens. The material of investigation was blood serum.

Estimation of allergen immunotherapy effectiveness was conducted with 5-score *Visual analogue pain scale (VAS), Huskisson* (up): before treatment; in one year of allergen immunotherapy; in two years of therapy [2].

The research was conducted according to the 7th consideration of the principles of Helsinki declaration of human rights (2013). Having been informed, the patients consented.

III. RESULTS

The diagnosis of allergy to tree pollen was based on case history, which indicated seasonal character of clinical allergic manifestations. Symptoms of difficult nasal breathing, rhinorrhea, swelling and itching in the nasal cavity, and sneezing were present in 100% of patients. Among them, nasal symptoms were combined with conjunctivitis in 66.7%, and complaints of breathlessness were present in 10.8%. Most patients experienced intensification of clinical symptoms in early spring (the end of February – the beginning of March) and improvement of the condition at the end of May – in June. However, 21% of individuals experienced similar signs to September-October, and the symptoms were observed all year round with specific exacerbation in spring in 5.9%. Also, 10.8% of individuals complained of discomfort in the oral cavity (swelling or numbness of the tongue, lips, itching of the palate etc.) after consumption of raw apples, carrots, kiwi by the type of oral allergic syndrome (OAS). Burdened family history was recorded in 32.2% of patients, and in most cases (72%) – on the mother's side. Allergic character of rhinorrhea was confirmed in 86%, using the rhinocytology.

The next step of investigation was SPT conduction with an extract "Mixture of trees" – 281 (98.3%) patients showed a positive (> 3mm) result. Since the extract contained the same amounts of allergens *Betulacea* and *Oleaceae,* we decided to differentiate these allergens and performed SPT separately to birch and ash tree. Thus, n=281: 191 (68.1%) individuals – were positive only to birch extract, 8 (2.8%) – to ash tree, 82 (29.1%) – birch + ash tree (fig 1.).

Since we could perform component investigations of only *Betulacea* proteins on regional level, patients (according to SPT results) with monosensitization to a birch (1 group, n=191) and polysensitization (2 group, n=82) were recommended molecular complex "Spring Trees" (Bet v 1, 2, 4). The results are given in table 1.

Based on the results of investigation, it was found – among patients with positive SPT to a birch, true sensitization was confirmed in 147 (77%) individuals. Among patients with polysensitization – in 63 (76.9%) individuals. The number of patients with only minor components in both groups was similar and on average constituted 21.1%. In five (1.8%) individuals with positive SPT, no components were found.

Actually, the only important method for prevention of pollen allergy progress and severe complications is specific allergen immunotherapy with causative allergens. According to literature data, its efficacy in pollen allergy constitutes 80-90%, not only in allergic rhinitis, but also in pollen asthma [1,2].

Patients in both groups – 210 (74.7%) with true sensitization to *Betulacea* were recommended allergy immunotherapy with a mixture "Spring Trees". The feature of this vaccine is its combined composition, which contains in equal amounts allergens of *Fagales* order (*Alnus glutinosa*-25.00 %; *Corylus avellana*-25.00 %; *Betula verrucosa*-25.00 %) and family *Oleaceae* (*Fraxinus excelsior*-25.00 %). The vaccine is standardized by HEP activity, controlled for the presence of natural major components and is used for sublingual application in spray form, one puff per day. Vaccines are represented in initial vial C, containing 1/5 concentration of supporting dose and two vials D, which contain a supporting dose.

Based on data of literature review, which indicate the absence of approved resources concerning contemporary biomarkers for evaluation of allergen immunotherapy efficacy, and according to international recommendations, determination of efficacy of specific therapy was performed with 5-score visual analogue scale (VAS). The results were compared before allergen immunotherapy, after the first and the second years of therapy (table 2).

Based on SPT results, 210 patients with true sensitization to *Betulacea* were divided into two groups: the first group (147 individuals) – monosensitization to a birch + presence of Bet v 1 or Bet v 1, 2, 4 and the second group (63 individuals) – polysensitization to a birch and an ash tree + presence of Bet v1 or Bet v 1, 2, 4.

As the results of investigation showed: clinical symptoms, typical for this pathology, were observed in patients before treatment. A reliable decrease in symptom manifestations was detected in both investigated groups after conducted allergen immunotherapy ($p<0.05$). In particular, a positive effect was observed in 83.1% of individuals after the first year of treatment; in 80.6% – in the group with mono- and in 85.6% – with polysensitization.

As it is seen in the table – though a reliable decrease in clinical symptoms was in both groups, however, it was expressed, largely, in the group with combined sensitization. Among the mentioned symptoms, itching in the nasal cavity (palate) lasted the longest, though tendency to reduction of this index was observed in both groups. It should be mentioned that individuals with OAS to raw fruit and vegetables were among these patients. Thus, they were advised to avoid these products in raw form at least for the time of allergen immunotherapy. Two patients in each group (1.9%) refused treatment for personal reasons and left the investigation.

In two years of treatment, a positive clinical effect was observed in 94.1% of patients, without a significant difference in both groups: 93.8% - the first group and 94.4% - the second group. All patients noticed a considerable improvement of life quality.

Thus, conduction of allergen immunotherapy with a combined vaccine of the mixture "Spring Trees" for two years had a positive effect in patients with monosensitization to *Betulacea,* as well as polysensitization to *Betulacea* and *Oleaceae.* All patients were advised to continue therapy for one additional year to ensure a positive result of allergen immunotherapy.

IV. DISCUSSION

According to literature data, approximately 100 species of *Angiospermae* and *Gymnospermae* trees may provoke specific sensitization in susceptible individuals [28]. A taxonomic correlation exists between related tree species depending on the presence of homological molecules, which are not detected in other non-related tree species. A profile of patients' sensitization depends on local exposition of pollen, associated with prevalence of trees in certain geographic conditions. Since the most common trees in Lviv region are *Fagales* (alder, beech, birch, hazelnut, oak), diagnosis of molecules of PR-10 family (homologues Bet v 1), which are major *Fagales* allergens, in particular *Betulacea* family, and often associated with OAS, is important for our patients.

However, according to the data of the Forestry Department in Lviv region, an ash tree is common in mixed and sticky alder forest, a total area of which being 3515 ha (2014). Total forest plantation of ash trees in Ukraine occupies an area over 153.8 thousand ha and is the most common in Vinnytya (over 14 thousand ha), Sumy (912.8 thousand ha), Luhansk (12.3 thousand ha), Kirovohrad (11.9 thousand ha) and Cherkassy (11.5 thousand ha) regions [5, 29, 30]. From taxonomic point of view, an ash tree is referred to *Lamiales* order, *Oleaceae* family. All trees in this family have homologues Ole e 1 – glycosylated proteins, glycan residues of which give allergic properties.

Having reviewed scientific literature, we came across a message that ash tree pollen constituted 4% of total sensitization among patients with pollen allergy – residents of Strasbourg suburbs (Germany) [22]. The conclusion of this research stated that the role of ash tree pollen as a cause of sensitization was underestimated and, first of all, due to simultaneous pollination periods with a birch. In the East of Austria, among 5416 patients sensitive to various pollens, positive skin tests to ash tree were detected in approximately 17.6% [31]. In Cordoba (Spain), SPT with an extract of ash tree pollen was performed to 1500 patients with pollen allergy and they were positive in 59% of individuals, monosensitization was in 8% [32]. Considering prevalence of ash tree in Lviv region, peculiarities of simultaneous pollination seasons of *Betulacea* and *Oleaceae*, as well as reference of major allergens of these tree species to different taxonomic groups, we decided to conduct SPT separately with extracts of birch and ash tree allergens. It should be mentioned that previous SPT results, conducted with the extract "Tree mixture", which contained the same amount of *Betulacea* and *Oleaceae* allergens, were positive in 93.3% of patients.

Based on SPT results, 2.8% of individuals were monosensitized to an ash tree, and, thus, homologues Ole e 1. Accordingly, allergen immunotherapy with mono vaccine to an ash tree is necessary for this group of patients. Though some authors claim that allergen immunotherapy with Ole e 1 can be helpful for the treatment of patients with allergy to European ash tree.

According to SPT data, we also received 29.1% of patients with combined sensitization (ash tree + birch). It can be suggested that a relatively high (31.9%) sensitization to an ash tree is explained both by the presence of major components of an ash tree and by panallergens or minor components Ole e 9, Ole e 12, which are also present in these extracts (*Betulacea and Oleaceae)* and possess cross properties. In our opinion, an interesting explanation of high sensitization to an ash tree may be one more fact. Based on detailed anamnestic data it was revealed that 23 individuals with positive SPT to ash tree extract had been working for several years in agricultural facilities seasonally in Italy, Greece, Spain, Portugal, where olive trees are common. The patients claimed that in these regions they particularly experienced exacerbation of symptoms. Thus, it may be assumed that due to primary sensitization to Ole e 1 and other components *Oleaceae*, patients reacted to ash tree extract. Unfortunately, we could not determine a major molecule of an ash tree Fra e 1 or its homologue Ole e 1 (because of local conditions).

Thus, having patients with sensitization to trees of different taxonomic groups necessitated conduction of component investigations and, first of all, choice of effective allergen immunotherapy.

As the results of molecular investigation showed, true allergy to birch pollen was detected equally in patients with mono- (77.0%) and polysensitization (76.9%). The number of patients with only minor components was also similar in both groups and constituted, on average, 21.1%. Having considered clinical-anamnestic peculiarities of these individuals, which indicated a continuous persistence of symptoms (to September-October) or all year round, we assumed that sensitization to other aeroallergens was also present (pollen of grass, weed, house dust mite, mould fungi etc.). The presence of minor components indicated only cross reactivity with other aeroallergens. These patients required more detailed collection of anamnesis and conduction of additional investigations, including component ones.

Based on SPT results, which indicated high incidence of sensitization to an ash tree (31.9%) and, respectively, the presence of these trees in Lviv region, as well as the results of component diagnostics and detection of true allergy to a birch in 77% of individuals, it became necessary to choose a vaccine for allergen immunotherapy, which would contain *Betulacea* and *Oleaceae* components.

Thus, a combined vaccine – mixture "Spring Trees" was chosen for allergen immunotherapy. The vaccine contained a mixture of allergens *Betulacea* and *Oleaceae.*

Evaluation of therapy efficacy by VAS scale showed that a positive clinical effect was observed in both groups already after two years of treatment. However, in patients with monosensitization to a birch, a positive effect was less evident, and symptoms persisted in 19.4% of individuals. Obviously, a reaction to ash tree allergens was present due to a combined nature of the vaccine. It should be mentioned that patients with OAS manifestations continued to experience appropriate symptoms. They were recommended to avoid raw fruit and vegetables in their diets. Following two years of treatment, patients' condition, including those from the first group, significantly improved. Only 5.9% of individuals noticed slight symptoms in early spring, manifested by nasal congestion, itching in the nasal cavity and the eyes, and on sunny days – sneezing. These patients also indicated that the symptoms persisted from 6 to 14 days and this period was shorter than in the previous years.
A positive effect in 2 years after conducted therapy with a combined vaccine mixture "Spring trees" enabled us to recommend patients to prolong specific therapy for one additional year to achieve a stable effect and continuous remission.

V. CONCLUSIONS

1. Sensitization profile in patients of Lviv region was as follows: 68.1% - sensitized only to tree pollen allergens of *Fagales* order; 2.8% – only allergens of *Oleaceae* family; 23.9% – combined sensitization to spring trees.
2. True sensitization to allergens of *Betulacea* pollen constituted 77%.
3. Sensitization to an ash tree in patients of Lviv region is common and according to SPT data constituted 31.9%.
4. It is recommended to include mandatory examination for an ash tree into routine SPT-diagnostics.
5. SLIT with a combined vaccine "Spring Trees" in patients with sensitization to *Betulacea and Oleaceae* demonstrates safety and high efficacy.

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Table 1. Results of component investigations of patients with sensitization to spring trees (n=281)

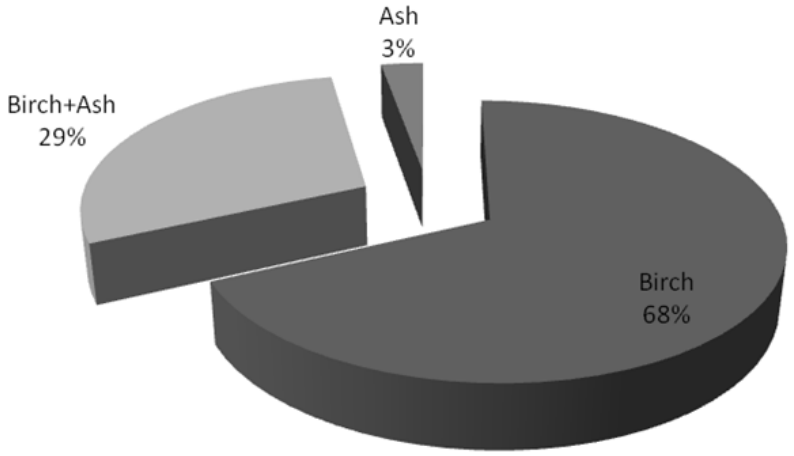
Component investigation	**1 group, n=191**	**2 group, n=82**
Bet v 1	64 (33.5%)	34 (41.5%)
Bet v 1, 2, 4	83 (43.5%)	29 (35.4%)
Bet v 2, 4	41 (21.5%)	17 (20.7%)
Not found	3 (1.5%)	2 (2.4%)

Table 2. Estimation of allergen immunotherapy efficacy by VAS scale

Sign	1 group (n=147)			2 group (n=63)		
	Before treatment	After 1 year of treatment	After 2 years of treatment	Before treatment	After 1 year of treatment	After 2 years of treatment
Difficult nasal breathing	4.21±0.36	2.34±0.17*	0.94±0.01*^	4.28±0.91	1.45±0.09*	0.55±0.02*^
Rhinorrhea	4.76±0.27	2.12±0.11*	0.85±0.02*^	4.80±1.01	1.06±0.08*	0.68±0.03*^
Sneezing	3.24±0.16	0.65±0.03*	0.3±0.01*^	3.22±0.07	0.25±0.02*	0.10±0.01*^
Swelling	2.45±0.17	1.87±0.06*	0.45±0.05*^	2.52±0.06	0.32±0.03*	0.30±0.04*
Itching in the nasal cavity (palate)	1.65±0.09	1.45±0.17	0.95±0.04*^	1.65±0.20	1.30±0.11	0.87±0.08*^
Life quality	3.35±0.08	1.15±0.08*	0.4±0.01*^	3.45±0.09	1.35±0.08*	0.20±0.01*^

Note * - $p<0.05$ – comparison with the group before treatment
^ - $p<0.05$ – comparison between groups of the 1st and 2nd years of treatment

Fig. 1. Results of skin prick-tests in patients with pollen allergy to trees



Peculiarities of Allergy to Tree Pollen and Approaches to Diagnosis and Allergen Immunotherapy in Patients – Residents of Lviv Region