

**DIFFERENCES IN THE SENSITISATION
TO RAGWEED POLLEN AND OCCURRENCE
OF LATE SUMMER ALLERGIC SYMPTOMS
BETWEEN NATIVE AND IMMIGRANT WORKERS
OF THE NUCLEAR POWER PLANT
OF HUNGARY**

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ABSTRACT

Regular medical screening including allergic symptoms of workers of the Nuclear Power Plant in Paks, Hungary, offered a unique opportunity to study the influence of the environmental factors on the development of allergy. The city Paks has been one the areas of the country most heavily exposed to ragweed pollen allergens. The occurrence and extent of sensitisation assessed by skin prick test to common allergens and prevalence of seasonal and perennial allergic symptoms were compared among 880 workers (695 immigrants, 185 natives) with self-reported allergic symptoms. The percentage of sensitised people against common allergens (ragweed, grass, *D. pteronyssinus*) was almost the same in the natives and immigrants. When, however, the strength of sensitivity to ragweed was determined by quantitative skin prick test and specific IgE

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determination, significantly ($P < 0.0001$) more immigrants (69%) than native workers (20%) exhibited high sensitivity to ragweed and the titres of specific IgE antibodies was also significantly ($p < 0.0001$) higher in the former group. Similar differences were found in the occurrence and type of allergic symptoms. Seasonal symptoms alone occurred in 69% and 38% of the immigrant and native workers ($p < 0.0001$). This difference was mostly due to those with late summer symptoms characteristic to ragweed allergy. These symptoms occurred in 57% of the immigrant workers, much more frequently ($p < 0.0001$) than in the natives (18%). Our findings indicate that the length of exposure to an inhalant allergen does affect the extent of sensitisation to ragweed allergen and markedly influences the clinical symptoms that develop in the ragweed allergic patients upon allergen exposure. It can be assumed that the natives who have been living with ragweed pollen for a long time (that is were exposed to natural immunotherapy), developed a natural tolerance to it.

Key Words: Allergy; Ragweed; Grass; *D. pteronyssinus*; Nuclear plant; Native; Immigrant

1. INTRODUCTION

Although not conclusively proven, it is reasonable to assume that the increasing prevalence of atopic diseases over the past decades is largely a consequence of changes in the environment. The escalation has been linked to exposure to high aeroallergen concentration [1], air pollution, and other factors connected with the Western lifestyle [2–5]. The powerful influence of environmental factors has also been demonstrated by migrant studies [6, 7].

We conducted a screening questionnaire and interview survey about the occurrence of rhinitis and/or asthma symptoms among adults who were registered with the general medical service in the Nuclear Power Plant of Hungary. The factory was built from the seventies and was opened at the eighties. It has been supported by a qualified medical care center. The plant was built in a region of Hungary where ragweed was most widespread. The majority of the workers were immigrants who had moved to the region because of the new workplace. There has been no considerable fluctuation among the workers in the last years. All employees must take part in medical screening yearly. This situation has offered a unique opportunity to monitor the population and to study the effect of migration on development of allergic diseases. The findings related to the subject's symptoms, atopic state, and correlation with immigration are presented here.

2. MATERIALS AND METHODS

2.1. Subjects Tested, Survey by Questionnaire

The study group consisted of 2851 subjects, 97% of all workers (aged 18–65 years) registered at the general medical practice of the Nuclear Power Plant. Subjects were divided into two groups, natives and in-migrants. They were considered *natives* if they were born and/or lived in the region since their childhood for a minimum of 10 years. Workers born outside the area of the city, mostly in parts of Hungary where ragweed has been less widespread, who moved in the city for working in the plant were considered as *immigrants*. Among all the workers 2245 people (77%) were immigrants and 573 subjects (23%) were natives.

The workers were asked to fill out a screening questionnaire designed to identify those with rhinitis and/or asthma symptoms.

Subjects were interviewed about their current nasal and bronchial symptoms, allergic disease, demographic characteristics, medical history, type of bedding and pet ownership.

If any answer was “yes” subjects were then asked “Have you had these symptoms in the past 12 months? For how many years have you had these symptoms and Are these symptoms perennial or seasonal – if seasonal, in which months?”

Subjects were defined to have *rhinitis* if they reported that they had had trouble with sneezing or a running or blocked nose for two or more years. Subjects were defined to have *asthma* if they gave a combination of three or more positive responses to the questionnaire, their respiratory symptoms were described as current in the preceding 12 months and were present for two or more years.

880 out of 2851 workers reported on allergic symptoms in the questionnaire. In this group 695 (79%) subjects (455 males, 240 females, $43 \pm 9,5$ years) were immigrants, the number of native subjects was 185 (21%) (124 males, 61 females, $36 \pm 10,8$ years).

In the case of these individuals a new, more detailed questionnaire was completed by a physician. In the medical interview the subjects were also asked about their airways (nasal and bronchial) symptoms in the past 12 months, history and characteristic of rhinitis and/or asthma, including provoking factors; disability; use of medical services; drug treatment; and genetic background. There was no significant difference in the frequency of familiar occurrence of allergic diseases between the immigrants and natives. The Hungarian population is genetically homogenous and no differences were found between Hungarian and the other Caucasian populations in several investigations. The effects of environmental factors in the surrounding of the Power Plant were continuously strictly controlled according to the international prescriptions. The degree of pollen exposure monitoring by

pollen trap was the same in the group of immigrants and natives over the period of the study in Paks.

2.2. Allergy Skin Prick Test

Allergy skin prick test (SPT) materials included 7 allergens (ALK, Denmark, Copenhagen);- House dust, *D. pteronyssinus*, cat dander, mixed tree pollens, mixed grass pollens, mixed weed pollens and ragweed-pollen alone. At the present analyses, the SPT reactivity to ragweed allergen were compared between immigrants and natives, as on the basis of a local pollen determination ragweed pollen proved to be the most frequent pollen in this region [9]. Because of high cross-reactivity between ragweed and other late fallen pollens the latest were not compared in the two study groups. Reactivity to grass mix and to *D. pteronyssinus* were used as controls as the exposure to these were the same in the areas being evaluated. The skin prick tests were performed on the volar side of the forearm. The reaction was read after 15 minutes by three physicians. Wheal diameter was the indicator used to evaluate SPT, and diameters greater than 3 mm were accepted as positive [8]. The test was taken to be invalid in subjects who failed to respond to the histamine control.

2.3. Quantification of The Skin Prick Test Results

For obtaining estimation about skin reactivity to RWA of a patient, skin prick testing was performed by titration. The aqueous extract of RWA was applied in three different concentrations (10^3 , 10^4 , and 10^5 biological units [BU]/ml). The results were evaluated after 15 minutes. The diameters of wheals were determined and compared to the histamine reference. The lowest concentration which gave rise to a histamine-equivalent positive reaction was considered as the measure of skin reactivity, and was expressed in arbitrary skin reactivity units (SRU). Skin reactivity was designated as 1 SRU if 10^5 BU/ml RWA produced a wheal with a diameter equal to the histamine control at a given patient, while 10^3 and 10^4 BU/ml RWA induced less or no reaction. Skin reactivity was designated as 10 or 100 SRU if a histamine-equivalent positive reaction was obtained already with 10^4 and 10^3 BU/ml RWA, respectively.

2.4. Specific IgE Estimation

The amount of RW-specific IgE antibodies was estimated by IgE Quick Test^R (Dexall Biomedical, Gaithersburg, MD). It could be tested in 439

subjects (99 natives, 340 immigrants. The level of specific IgE in the serum samples tested was expressed as a score from 1 to 4.

2.5. Statistical Analysis

Similarities and differences in the clinical presentation and in the skin test reactivity were examined among subjects with seasonal, perennial and seasonal + perennial symptoms. The significance of differences between variables was assessed by the χ^2 -square test for categorical variables and the Mann-Whitney U test for continuously distributed variables.

3. RESULTS

3.1. Clinical Presentation

Table 1 shows the types of clinical presentation of allergic airway diseases in the group of 880 workers with self-reported allergic symptoms. The median age of the onset of seasonal rhinitis/asthma was 30.2 years. The median age at the onset of perennial, and seasonal-perennial symptoms did not differ significantly from that at the onset of seasonal symptoms.

Rhinitis was the most common presenting symptom. The majority of subjects reported seasonal symptoms, the prevalence of late-summer symptoms was the highest. Asthma alone or in combination with rhinitis occurred significantly ($p = 0.013$) more frequently in the seasonal alone group (109/551, 19.8%) than in perennial alone group (21/181, 11.5%).

Table 1. Types of Symptoms in Workers of the Nuclear Power Plant (Paks, Hungary) with Self-Reported Allergic Symptoms

Type of Symptoms	Seasonal Alone				Perennial Alone	Seasonal + Perennial
	Early summer (n = 28)	Late summer (n = 430)	Early and late summer (n = 93)	Total (n = 551)	(n = 182)	(n = 147)
Age at onset of symptoms, mean $\pm$ SD	29.16 $\pm$ 11.5	31.6 $\pm$ 10.1	28.2 $\pm$ 11.7	30.9 $\pm$ 10.2	31.9 $\pm$ 10.6	31.0 $\pm$ 9.4
Symptoms	Number (%) of subjects					
Rhinitis	24 (86)	345 (80)	73 (78)	442 (80)	161 (88)	117 (80)
Asthma	1 (4)	9 (2)	2 (3)	12 (2)	11 (6)	18 (12)
Both	3 (10)	76 (18)	18 (19)	97 (18)	10 (5)	12 (8)
Total	28 (100)	430 (100)	93 (100)	551 (100)	182 (100)	147 (100)

3.2. Significant Difference Between Immigrants and Natives in the Skin Reactivity to Ragweed Allergen and Serum Level of Ragweed-Specific IgE

The frequencies of subjects with positive skin prick test and positive specific IgE test to three different common allergens (ragweed, grass and *D. pteronyssinus*) were compared among the in-migrant and native workers in the factory. The occurrence of positive skin prick tests or positive IgE tests was almost the same in the two groups. (Table 2). When, however, the skin reactivity to ragweed and the amounts of IgE antibodies were compared, marked differences were observed between the immigrant and native workers.

We have found that significantly more subjects were highly sensitive to ragweed allergen among immigrants than among the natives (Fig. 1A). 69% and 20% of the subjects of the two groups had a high (100 SRU) skin reactivity to ragweed allergen ($p < 0.0001$). In contrast the majority (51%) of the natives but only 9% of the immigrants showed low (1 SRU) skin reactivity. Similar differences between immigrants and natives were obtained in the serum concentration of ragweed specific IgE (Fig. 1B); the majority (80%) of the immigrants had high serum concentration (score 3 or 4) of IgE antibodies while most (63%) native workers had low concentration (score 1 or 2) ragweed specific IgE antibodies ($p < 0.0001$).

3.3. Effect of Immigration on the Frequency and Type of Allergic Symptoms

As the majority (77%) of the workers of the Nuclear Power Plant and 79% of those with complains of rhinitis and/or asthma have moved in this region only since the starting of the factory, the effect of immigration on the prevalence of different symptoms patterns could be examined (Table 3).

The age at the onset of symptoms was higher among the immigrants than at the natives, the difference was the most pronounced in those with seasonal symptoms alone or in combination with perennial symptoms.

Table 2. Frequency of Positive Skin Prick Test and Positive Specific IgE Test Among Immigrant and Native Workers with Self-Reported Allergic Symptoms

	<i>D. pteronyssinus</i> Percentage of Subjects Positive to		Grass Percentage of Subjects Positive to		Ragweed Percentage of Subjects Positive to	
	Skin Prick Test	Specific IgE Antibodies	Skin Prick Test	Specific IgE Antibodies	Skin Prick Test	Specific IgE Antibodies
Immigrants	9	2	10	7	73	51
Natives	12	3	13	9	69	56

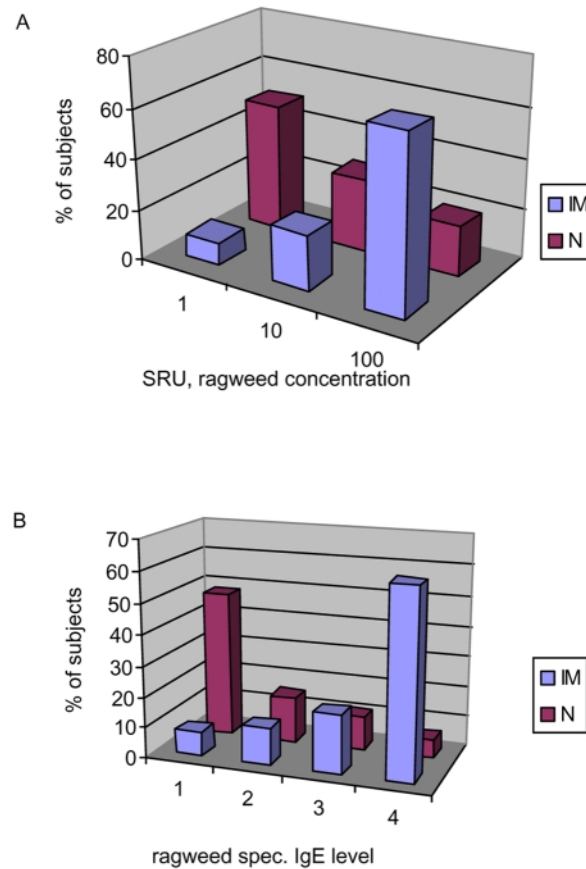


Figure 1. Skin reactivity expressed in skin reactivity units (SRU, see Materials and Methods) (A) and serum concentration of IgE antibodies (scored 1 to 4) (B) in the groups of immigrant (IM) and natives (N) workers with self-reported symptoms. The differences between the two groups are highly significant ($p < 0.0001$) for both skin reactivity and IgE concentrations.

Then the frequency of the seasonal and the perennial symptoms was compared in the groups of immigrant and native workers (Table 3). Seasonal symptoms occurred very frequently (481/695, 69%) among the immigrant workers while the perennial symptoms alone were relatively rare (10/195, 16%). By contrast, almost 40% of the native workers complained on perennial symptoms alone while the frequency of seasonal symptoms alone was relatively low (38%). The difference among the two groups was highly significant ($p < 0.0001$).

A highly significant ($p < 0.0001$) difference between the two groups was also observed in the distribution of the early and late summer symptoms within the groups with seasonal symptoms alone: 395/695

Table 3. Relationship Between Immigration and Seasonal Occurrence of Clinical Symptoms in 880 Workers of the Nuclear Power Plant (Paks, Hungary) with Self-Reported Allergic Symptoms

	Seasonal Alone			Perennial Alone	Seasonal + Perennial
	Early summer (n = 28)	Late summer (n = 430)	Early and late summer (n = 93)	Total (n = 551)	(n = 182) (n = 147)
Age at Onset of Symptoms, Mean $\pm$ S.D.					
Immigrants	30.7 $\pm$ 11.3	32.4 $\pm$ 10.6	28.1 $\pm$ 12.0	31.8 $\pm$ 11.1	32.7 $\pm$ 9.7 32.8 $\pm$ 7.3
Natives	25.2 $\pm$ 8.9	26.7 $\pm$ 9.3	28.8 $\pm$ 11.7	26.5 $\pm$ 12.4	29.7 $\pm$ 8.5 26.3 $\pm$ 9.1
p value*	n.s.	0.0022	n.s.	0.0003	0.038 < 0.0001
Number (%) of Subjects with Symptoms					
Immigrants	21 (3)	395 (57)	65 (9)	481 (69)	110 (16) 104 (15)
Natives	7 (4)	35 (19)	28 (15)	70 (38)	72 (39) 43 (23)

Difference between the immigrant and native workers in the frequency of seasonal, perennial, and seasonal + perennial symptoms, χ^2 test, $p < 0.0001$. Difference between the immigrant and native workers in the frequency of early summer, late summer and early + late summer symptoms, χ^2 test, $p < 0.0001$.

*two sample t-test.

n.s. not significant.

(57%), and 35/195 (18%) of the immigrant and native workers with rhinitis and/or asthma symptoms, respectively had late summer symptoms alone. The reason of this difference was the significantly higher frequency of late summer rhinitis among the immigrants (324/695, 47%), than among natives (21/185, 11%) while the occurrence of late summer asthma alone or in combination with rhinitis was similar in the two groups (8% and 10%, respectively).

3.4. Relationship Between Migration and Onset of Late Summer Symptoms

Since the seventies the ragweed pollen count has increased dramatically and at the time of the starting of the factory it had become the dominant pollen in this region [9]. A significant correlation was found between the time of immigration and the changes in the incidence of the immigrants' late summer symptoms (Fig. 2). Large-scale immigration began in 1975, peaked in 1979 and thereafter, except a second peak in 1985, gradually decreased to almost 0 in 1993. The curve of incidence of late summer symptoms in immigrants followed the curve of in-migration with an approximately 5 years delay: the first significant increase in the symptoms was noted in 1980 and a peak in the frequency of symptoms was observed in 1988–89 followed again by a gradual decrease. In contrast no regular changes in the incidence of late summer symptoms were observed among the native workers.

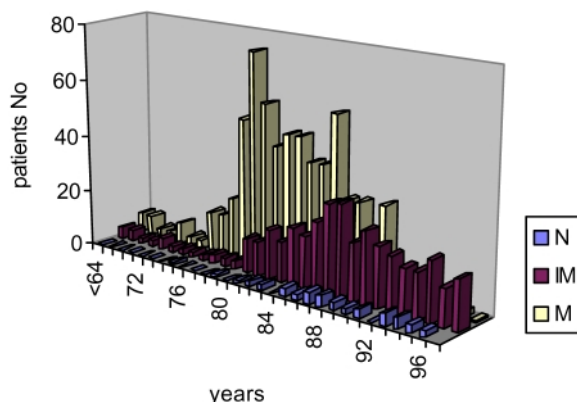


Figure 2. Correlation between migration (M) and changes in the incidence of late summer symptoms among the immigrant (IM) and native (N) workers of the Paks Nuclear Power Plant in Hungary.

4. DISCUSSION

Construction and introduction of a new factory supported with a good medical monitoring system (which attracted thousands of people to move and work there) offered an unique possibility to study the allergic diseases that developed in the region.

In this study group of 880 workers with the symptoms of self-reported rhinitis and/or asthma at the Nuclear Power Plant, the majority (49%) of subjects reported late-summer symptoms which are mostly due to exposition to ragweed pollen in our country [9]. At the comparison of workers who were born in the region and those who migrated in it turned out that while less than one-fifth (19%) of the natives showed late summer symptoms, while more than half (57%) of the immigrants suffered from these symptoms.

These dramatic differences in the frequency and type of allergic symptoms between the immigrant and native workers were most probably due to the markedly stronger sensitisation of the immigrants to ragweed allergen. Both skin reactivity and serum concentration of ragweed-specific antibodies were significantly higher with the immigrant workers than in case of natives (Fig. 2). Skin reactivity was defined as the development of a histamine-equivalent skin reaction to different dilutions of ragweed allergen administrated by skin prick test. It was quantified according to a method used in our previous work as arbitrary skin reactivity units [10]. Skin reactivity to allergens strongly correlates to the in vitro and in vivo mediator release, like histamine release from basophil leukocytes [11, 12] in vitro, histamine release into skin chambers during allergen incubation in vivo [11, 13], or bronchial sensitivity [13]. Norman et al. [11] have demonstrated a good correlation between patients' allergic sensitivities in terms of clinical symptoms score and quantitative intradermal skin sensitivity.

Several factors may influence the development of allergic diseases. In addition to genetic propensity, the likelihood of sensitisation is affected by the time for, and the conditions under which exposure to allergens takes places [14–16, 6, 7]. In the present study there was no significant difference between immigrants and natives in the genetical background, in the degree of pollen exposure over the duration of time being studied and the effects of environmental factors were strictly controlled according to the international prescription in the Nuclear Power Plant. The most probable explanation for the markedly different extent of sensitisation to ragweed allergen of immigrants and natives can be found in the history of growth of ragweed plant in Hungary. Ragweed reached Hungary from south 90 years ago. It spread unequally in the country in the following decades [9, 17] and by 1945 appeared only in south-western part of Hungary (Southern Transdanubia) where Paks is located. At the time of the patients' birth (from 1940) the area of Paks was mildly infected by ragweed but the northern and the eastern parts of the country (where most immigrants were born) were still ragweed-free. From 1960 ragweed could be found in continuously increasing quantities in the area of Paks mostly due to the process of the construction of the nuclear power plant. It seems reasonable to suppose that the natives, living with a ragweed pollen concentration that increased slowly from initially low to high concentration levels in this environment, may have developed a tolerance to it. Thus a gradual exposure to pollen may have an immunotherapeutic effect.

By 1990 Ambrosia was widespread in Hungary, it is present in significant amounts even in the areas from which the immigrants came and nowadays the majority of pollen sensitive patients is sensitive to ragweed.

It is well known that immunotherapy may affect the progression of allergic diseases. Allergic rhinitis constitutes the main indication for immunotherapy [18] and many controlled studies report on the satisfying clinical efficacy of immunotherapy in patients with rhinitis. Immunotherapy has been reported to reduce both the degree of the skin test reactivity [19–22] and the seasonal specific IgE level [23–25].

In contrast to native workers the immigrants had not previously encountered ragweed pollen [26–28, 17], and in the seventies, at the beginning of their massive influx the region had already been severely infected by ragweed. Thus the majority of immigrants were first confronted in Paks with ragweed pollen in a massive dosage in their adult age. Within 5 years a large number of the immigrant workers acquired symptomatic ragweed allergy and the prevalence of disease had already been high among them since 1980 (Fig. 2).

Similar to our present findings, Barbee et al. examined the longitudinal changes in allergen skin test reactivity in Tucson [1] and concluded that the high overall prevalence of reactivity in this population was due to the high concentrations of aeroallergens in the Tucson environment and recent immigrants accounted for most of the increased prevalence.

In conclusion, we have demonstrated in high numbers of patients that the type of exposure to an inhalant allergen, ragweed pollen not only affects the rate of sensitisation but markedly influences the clinical consequences of the exposure as well. The onset of symptoms showed correlation with the time as well as with the degree of exposure.

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