

# Prevalence of a Family History of Atopic Disease Among 3 Generations of Atopic Respiratory Patients in Tirana, Albania

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## ■ Abstract

*Background and objective:* Having relatives with allergic disease is associated with an increased risk of such disease, but children without a significant genetic predisposition account for much of the increase in asthma prevalence. The aim of this study was to investigate whether the prevalence of a reported family history of allergy has increased among atopic respiratory patients diagnosed in Outpatient Service No. 3 in Tirana in recent decades.

*Methods:* We evaluated the records of 693 atopic respiratory patients sensitized to mites (n = 480) or pollen (n = 218) or both (n = 5) to detect reports of allergic disease among their close relatives. Patients were classified in 3 groups: those born in 1959 or earlier, those born between 1960 and 1979, and those born between 1980 and 2003. The  $\chi^2$  test was used for statistical comparisons.

*Results:* The prevalence of a family history of allergy among those born before 1960 (42.7%) was nearly 2-fold greater than the prevalence among those born between 1960 and 1979 (25.3%) or between 1980 and 2003 (23.1%) ( $P < .001$ ).

*Conclusions:* Younger generations of atopic respiratory patients report a family history of allergic disease about half as frequently as older ones. It is possible that massive introduction of antibiotics such as penicillin and streptomycin in the late 1960s and early 1970s for use against respiratory or gastrointestinal infections has increased survival for a considerable number of young children, switching the gene thesaurus of successive adult populations to an allergy-predisposing genotype.

**Key words:** Atopic diseases. Family history. Generations. Survival rate.

## ■ Resumen

*Antecedentes y objetivo:* La existencia de familiares con enfermedad alérgica se asocia a un mayor riesgo de padecer dicha enfermedad. No obstante, el aumento en la prevalencia del asma se da mayoritariamente en niños sin una predisposición genética significativa. El objetivo de este estudio fue investigar si la prevalencia de enfermedad alérgica en la familia ha aumentado entre los pacientes respiratorios atópicos, diagnosticados en las consultas del ambulatorio n.º 3 de Tirana en décadas recientes.

*Métodos:* Estudiamos la historia clínica de 693 pacientes atópicos con sintomatología respiratoria sensibilizados a los ácaros (n = 480) o al polen (n = 218), o a ambos (n = 5), para detectar información sobre la presencia de enfermedad alérgica entre los familiares más cercanos. Clasificamos a los pacientes en tres grupos: los nacidos en 1959 o antes; los nacidos entre 1960 y 1979, y los nacidos entre 1980 y 2003. Utilizamos la prueba  $\chi^2$  para efectuar comparaciones estadísticas.

*Resultados:* La prevalencia de antecedentes familiares de alergia entre los nacidos antes de 1960 (42,7%) fue casi dos veces superior a la presencia de esta enfermedad entre los nacidos de 1960 a 1979 (25,3%) o de 1980 a 2003 (23,1%) ( $P < 0,001$ ).

*Conclusiones:* Las generaciones más jóvenes de pacientes con síntomas respiratorios atópicos informaron de la presencia de antecedentes familiares de alergia con casi la mitad de la frecuencia que las generaciones de más edad. Es posible que la introducción masiva de antibióticos como la penicilina y la estreptomina a finales de los 60 y a principios de los 70 para combatir infecciones gastrointestinales o respiratorias haya incrementado la supervivencia de un número considerable de niños pequeños, cambiando el repertorio de genes de poblaciones adultas posteriores a un genotipo que predispone a padecer alergias.

**Palabras clave:** Atopia. Antecedentes familiares. Generaciones. Tasa de supervivencia.

## Introduction

The prevalence of asthma and hay fever in children and adults has increased during the past 3 decades, especially in industrialized countries [1-3]. Despite the general rise in prevalence of such atopic diseases, there are wide variations between countries [2,4,5]. According to a report of the steering committee of the International Study of Asthma and Allergies in Childhood, the prevalence of wheezing or bronchial hyperreactivity in European children aged 13 to 14 years varied from 32.2% in the United Kingdom to only 2.6% in Albania [2,6]. The European Community Respiratory Health Survey has also detected similar variations between European countries among adults aged 20 to 44 years [4].

Although having relatives with allergic disease is associated with an increased risk of such disease for an individual, recent findings suggest that young subjects without significant genetic predisposition account for much of the increase in prevalence [3,5,7,8]. Similarly, the Multicenter Allergy Study, a cohort study of German children, found that most of the asthmatic subpopulation of 5-year-olds had non-atopic parents [9].

In this context, it might be supposed that even though the prevalence of respiratory atopic diseases in the Albanian population is still low, it is possible that in the past it might have been much lower. In order to explore the trend in atopic disease, we conducted a study in atopic respiratory patients, sensitized to mites and/or pollens. The aim of study was to evaluate the prevalence of a family history for atopic diseases among their close relatives based on the patients' reports. According to previously described data, we expected a lower prevalence of family atopic history among younger patients than among older ones [7-9]. This index could serve as an indirect demonstration that a latent rising trend of atopy prevalence in families without a previous genetic predisposition may have begun in Albania even prior to the end of political isolation.

## Materials and Methods

This was a retrospective study of patients examined at Outpatient Service No. 3 in Tirana between January 1999 and October 2004. The inclusion criteria for subjects were the presence of asthma and/or hay fever as well as sensitization to house dust mite and/or pollen diagnosed by means of skin prick tests or specific immunoglobulin (Ig) E (both Allergopharma, Reinbeck, Germany). All patients who fulfilled these criteria were included in this survey. A skin prick test was accepted as positive when the wheal diameter was 5 mm for at least 1 allergen (excluding the cases with dermographisms). A radioallergosorbent test was considered positive when the level of specific IgE for an aeroallergen was more than 0.35 IU/mL.

The reports of 693 atopic respiratory patients (353 females, 340 males; mean [SD] age 47.1 [11.2] years old), sensitized to mites (n = 480) or pollens (n = 218) or both (n = 5) were examined to identify mentions of allergic symptoms among the patients' close relatives (parents, grandparents, siblings, aunts, uncles, and close cousins). Because the relatives named varied widely between subjects, and because information concerning health problems also differed widely, we also carried out the between-generations comparison focusing

only on the rate of reported atopic symptoms in the patients' parents. Patients were classified in 3 groups: born in 1959 or earlier; born between 1960 and 1979, and born between 1980 and 2003. The year 1960 was chosen as a time when Albania was politically and economically isolated from other European countries, when Germany was divided into 2 parts, and when Europe had 2 different political and social systems. The impact of this separation on trends in respiratory allergy is well documented [10]. The year 1980 was chosen because the political and economic isolation of Albania was still complete before that time and also because it was halfway through the study period. Results are reported as frequencies and percentages in each generational group and for the population overall. To compare the prevalence of family history of atopic disease between generational groups we used the  $\chi^2$  test for independent samples. The odds ratio was used to indicate the relative frequency of family history of atopy in the oldest generation (considered the generation of reference) compared to the frequency in the other ones. Statistical significance was set at  $P < .05$ . The program used for statistical analysis was PEPI version 4.0 (JH Abramson & PM Gahlinger, Sagebrush Press, Salt Lake City, Utah, USA).

## Results

In the total study population of patients suffering from asthma (n = 330), hay fever (162), or both diseases (n = 325) a family history of atopic symptoms was reported in 214 cases (30.9%). The table shows the prevalence of each characteristic or disease in each of the 3 generations. Family atopic symptoms were about half as frequent in patients born between 1960 and 1979 (25.1%) and between 1980 and 2003 (23.3%) as they were in patients born before 1959 (42.7%) ( $P < .001$ ; odds ratio, 2.31; 95% confidence interval, 1.63-3.26). The difference between the prevalence of a parental history of atopy was significantly higher in the older generation than in the other 2 generations ( $P < .003$ ). In 71% of cases a mother was reported as being predisposed to allergic symptoms and in 31% a father was mentioned. The difference in gender distribution between the older generation (more females) and the other 2 generations (more males) was significant ( $P < .01$ ). The youngest generation studied had significantly more mite-sensitized individuals and consequently fewer pollen-sensitized individuals than the 2 older generations ( $P < .01$ ). The prevalence of hay fever or asthma did not differ significantly between the study groups.

## Discussion

This study was carried out to explore the trend in the prevalence of atopic dermatitis in subjects living in Tirana in recent decades. Reported data from international cross-sectional surveys conducted in several European countries (Albania included) provided comparative data [4,6]. These surveys revealed a rising atopy prevalence in industrialized countries in recent decades, but a lower prevalence in Eastern Europe. The prevalence of atopic dermatitis in Albania was the lowest among the European countries surveyed.

Table. Patient Characteristics Regarding Year of Birth, Sex, Disease, Sensitization, and Family Atopy by Generations<sup>a</sup>

	Generations		
	Born 1930-1959 (n=246)	Born 1960-1979 (n=267)	Born 1980-2003 (n=180)
Female	154 (62.6)	122 (45.7)	77 (42.8)
Male	92 (37.4)	145 (54.3)	103 (57.2)
Asthma	68 (27.6)	82 (30.7)	180 (31.1)
Hay fever	59 (24)	69 (25.8)	34 (18.9)
Asthma and hay fever	119 (48.4)	116 (43.4)	90 (50)
Mite sensitization	162 (65.9)	166 (62.2)	152 (84.4)
Pollen sensitization	91 (37)	97 (36.3)	30 (16.7)
Family history of atopy	105 (42.7)	67 (25.1)	42 (23.3)
Parental history of atopy	51 (20.7)	35 (13.1)	19 (10.6)

<sup>a</sup>Data represent numbers and percentages of subjects.

To explore the recent trend for these diseases we retrospectively evaluated a family history of atopic symptoms as reported by 693 atopic respiratory patients, sensitized to house dust mite or pollen. Based on those reports, the prevalence of such a family history has nearly halved among subjects born in the 1960s or later compared with subjects born before 1960. Moreover, the prevalence of a family history of atopic symptoms tended to be lower in subjects born after 1979 than in subjects born between 1960 and 1979, although the difference was not significant. This trend was confirmed when atopy predispositions of all remembered close relatives were included in subject reports as well as when only parental predispositions were analyzed. Indirectly, these results suggest that families previously considered to be at low risk of developing asthma or atopy account for a large part of the increase in the prevalence of atopy [5,7-9].

Similar results are also shown in several longitudinal studies conducted in Germany and Great Britain [3,8,9]. An increased prevalence of atopy in other countries of Western Europe has also been described, whereas in Eastern European countries the prevalence is lower [2-4]. The lower prevalence is attributed to similarities between the current Eastern European lifestyle and many respects of that prevailing in Western Europe after World War II through the 1950s, including the presence of a large number of siblings in the home, a low standard of hygiene, infrequent pet ownership, etc [2,4,10].

In this context, the high incidence of childhood infections in this period, reflected in the high infant mortality rate, may be at least a part of the reason for the low prevalence of allergic diseases in Albania [2,11,12]. However, our study demonstrates that Albania was experiencing a similar trend at the same time it was occurring in Western Europe, even if its expression was very limited. It seems that although environmental and living conditions in Albania suppressed a more marked increase in the prevalence of atopic diseases, a smaller increase in atopic disease predisposition nevertheless occurred in the 1960s and 1970s, mostly in children from families without an atopic history. Our data suggest that a newly introduced factor, or several factors, may have had a decisive impact for a certain time on the prevalence of atopy. It, or they, may remain influential now.

In our opinion, the initial massive introduction of antibiotics such as penicillin and streptomycin in the treatment of respiratory or gastroenteric infections in late 1960s and early 1970s could have had an impact and explain the trend in Albania. This hypothesis seems plausible to us, as prior to the middle of the 1960s the use of  $\beta$ -lactam antibiotics was nearly a luxury for Albanian citizens, whereas later there was massive abuse of both the aforementioned antibiotics, particularly at the beginning of the 1970s. These antibiotics were used for every kind of infection, even in all neonates in order to assure a higher chance of survival.

The exposure to antibiotics as an inducer of atopic response is accepted by many authors [13-15]. It is postulated that antibiotic-induced growth inhibition of enteric flora can suppress the education of children's T helper ( $T_H$ ) type 1 cell immunity, leading to the induction of a  $T_H2$  allergic inflammatory predisposition [12,16,17]. In addition, even though the hygienic situation has not been optimal in Albania, the massive exposure to antibiotics probably increased the chance of survival for a subpopulation of young children with some immune deficiencies toward some common infections. In this context, Nascimento-Carvalho et al [18] reported that children of lower socioeconomic status have serious lower respiratory tract disease and malnutrition more often, while they also have higher rates of hospitalization and death. Children with higher socioeconomic status, whose parents could assure more suitable antibiotic therapy, have more frequent allergic respiratory diseases or more frequent antibiotic use [18]. In other words, the use of antibiotics may enable children to survive serious respiratory and gastrointestinal infections even if they have inappropriate natural immune responses, including deficient production of specific IgG or IgA against a wide spectrum of pathogenic microorganisms.

Arguing against this theory, Varner [17] has supposed that  $T_H2$  immune responses promote parity, provide the infant protection against some infections and the inflammation induced by common pathogens in the first years of life until the immune system matures, in addition to the protect they afford young adults exposed to viral respiratory pathogens. Although this scenario is true in some cases, the most appropriate immune response against most common respiratory and gastrointestinal

infections is likely to show a predominantly  $T_H1$  cytokine profile similar to the initial situation during breast feeding [19,20]. Prior to the antibiotic era, individuals lacking this response had less chance of survival and consequently less chance of having their own offspring. In contrast, the massive introduction of antibiotics has promoted parity against these infections and may have enabled the switch of the gene thesaurus for a proportion of successive adult populations to a more frequent allergy-predisposing genotype, due to the increased survival of individuals who express a predominantly  $T_H2$  cytokine profile and consequently a specific IgE response. Unfortunately, for obvious reasons we could not conduct a controlled study regarding the impact of antibiotic use on the prevalence of atopy among Albanians in order to test this hypothesis.

A possible confounding factor affecting differences in the prevalence of a family history of atopic disease between generations in this survey might be the timing of this study 14 years after the end of political isolation and the initial Westernization of Albania. In our opinion, Albanian teenagers currently demonstrate a looser relationship to their own relatives than older ones did. Thus, they may be less informed, at least about the health of their cousins. Consequently, although the real prevalence rate of a family history of atopy might have been higher than reported from the included probands, the reports for atopy rates for parents offer some confirmation that the generational trend we identify really exists because such reports are more reliable than those for other relatives.

Thus, these data indicate that a limited rising trend in the prevalence of atopic disease might have begun even in a developing country such as Albania in the late 1960s or early 1970s. However, the level of expression of this phenomenon was much lower than in the rest of Europe [4,6]. To clarify the impact of potential factors regarding this trend, further studies focused on the genetic mosaic of generations are necessary in the near future, because these data can only partially explain the prevalence increase of atopic predisposition among Albanians in the last few decades. It should be considered that the oldest atopic individuals will be available only for a limited time.

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