

Allergic rhinitis, bronchial asthma and other allergies in patients with Alzheimer's disease: unnoticed issue

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Abstract

Introduction: Allergic diseases are becoming more prevalent in elderly patients. Allergic diseases have been observed in patients with Alzheimer's disease (AD). The prevalence of atopic bronchial asthma, allergic rhinitis and atopic dermatitis was analyzed in such elderly Polish population.

Aim: Analysis of the presence of allergic diseases in the patients with AD in Poland, including asthma, allergic rhinoconjunctivitis and atopic dermatitis.

Material and methods: The recruitment of subjects with AD was conducted at 6 sites representative of Polish rural and urban areas, and 1060 subjects with a mean age of 69.2 ±5.1 years were screened. Medical examinations, an original questionnaire, skin prick testing for common aeroallergens and appropriate serum-specific IgE assays were performed.

Results: Probable atopy was diagnosed in 234 (22.1%) analyzed patients, including 127 women (21.5% of women) and 234 men (22.8% of men). The average prevalence associated with age and sex in this population for bronchial asthma was 2.9%, atopic dermatitis/eczema was 0.6%, seasonal allergic rhinitis was 6.6%, perennial allergic rhinitis was 11.1% and polymorphous atopic disease was 4.4%. The most frequent positive results were recorded for the following allergens: mixed grass, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae* and *Alternaria*.

Conclusions: One-fifth of diagnosed patients with AD have allergic disease requiring treatment.

Key words: allergy, dementia, IgE, bronchial asthma.

Introduction

The problem of allergic diseases is increasing in most countries. Allergic rhinitis, bronchial asthma and atopic dermatitis are global health problems that affect the quality of life of all age groups [1, 2]. The increasing incidence of allergies and the ageing of populations have led to an increased incidence of atopic diseases in older patients and also in these with concomitant Alzheimer's disease (AD). Alzheimer's disease is a huge problem all over the world especially in elderly patients. This disease currently affects more than five million patients in the U.S. and will rise to 16 million by 2050. Globally, an estimated 35.6 million people have dementia (mainly AD), which is expected to reach 65.7 million in 2030 and 115.4 million in 2050 [1, 2]. In elderly patients, some chronic

diseases can worsen cognitive function, depressive symptoms and functional status in AD. This pattern has been observed in many cases of heart failure, metabolic diseases such as diabetes, neoplastic diseases, chronic obstructive pulmonary disorder (COPD), bronchial asthma and others [3–5]. While many authors have analyzed the epidemiology, diagnostics and treatment of allergy, the occurrence and natural course of allergic disease in patients with AD has not been explored much.

Aim

This study is an analysis of the presence of allergic diseases in the patients with AD in Poland, including asthma, allergic rhinoconjunctivitis and atopic dermatitis.

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Material and methods

The recruitment of subjects was conducted at 6 sites representative of central, southern and northern Poland. The selected areas included isolated rural centers (at 3 sites) and cities (at 3 centers). A sampling stratification was performed with a key criterion of age greater than 60 years. Within each database, comparable numbers of subjects were recruited from rural and urban centers. These groups were homogeneous regarding the age and sex ratio and were consistent with the demographic structure of the Polish population over 60 years of age in 2012. All patients with a positive history of AD were chosen from the basic group. It was 1060 patients. The study was performed in 2011–2012. The permission to publish the data was obtained from all of the centers. All of the subjects and guardians signed consent to participate in the study. The study was approved by the Bioethics Committee of Medical University School of Silesia in Katowice (Poland). Screening was performed by family doctors, geriatricians, internists or allergists, with the participation of trained nurses. The diagnosis of dementia of the Alzheimer’s type was confirmed by criteria from the Diagnostic and Statistical Manual of Mental Disorder, Fourth Edition and the National Institute of Neurologic, Communicative Disorders and Stroke-AD and Related Disorder Associations [6, 7]. In all patients a diagnosis of AD was made using a combination of clinical criteria, neuropsychological testing and conventional computed tomogra-

phy (CT) and magnetic resonance imaging (MRI). Patients with a mild and moderate type of AD (II–IV degree on the Reisberg scale) were included into the study. Cognitive function was assessed on the basis of the Clock-Drawing Test and the Mini-Mental State Examination (MMSE) at the beginning of the study, after 6 months and after 1 year. The final score of MMSE was standardized according to the participant’s age and years of education [8]. Medical histories of the patients including the history of allergic diseases were analyzed. Physical examinations and additional tests were performed. Alzheimer’s disease was diagnosed by the cerebral CT. The patients with guardians completed a questionnaire about allergic diseases that was partly based on the short ECRHS II questionnaire as was shown in Table 1 [9]. Survey questions were included and concerned the type of atopic disease, its beginning and duration, and the symptoms of rhinitis, conjunctivitis, asthma, skin allergies and symptoms of hypersensitivity to the basic inhalation allergens. Next, a full medical examination was performed with a simplified otolaryngological examination (nasal rhinoscopy and a throat evaluation), dermatological evaluation and assessment of the eye. Skin prick testing with common inhalant allergens and assays of serum concentrations of total IgE and specific IgE were performed. The study was performed based on the Pharmacia CAP System FEIA (ThermoFisher, Sweden) immunoenzymatic method. The results of these assays were evaluated according to the manufacturer’s instructions [10].

Table 1. Questionnaire about allergic diseases

Questionnaire
1. General questions: assessment of cognitive function
A. How old are you?
B. Mark: female – male
C. What time is it? Please indicate within 1 h
D. An address that you give, please repeat after me and remember it (give any address, e.g., 42 Pear street, which is not recorded in the survey)
E. Please give today’s date (day–month–year)
F. What is your street address?
G. Please provide your date of birth
H. When did the Second World War begin?
I. What is the name of the president?
J. Please count backwards from 20 to 1. Mark: passed or failed
K. Please enter the address you specified earlier
L. How would you rate your wellbeing in the last year (check): very good – good – average – disappointing – bad – very bad.
2. Dermatoses
A. Have you ever suffered from allergic dermatitis? If so, how long have you been affected?
B. Did you have skin lesions in childhood (protein stain)?

Table 1. Cont.

C. Has anyone in your immediate family had similar skin lesions?
D. Are your skin changes recurrent?
E. Do you now or have you ever suffered from atopic (allergic) dermatitis?
In addition, complete a questionnaire containing criteria for the diagnosis of atopic dermatitis according to Hanifin and Rajka.
3. Diseases of the nose and conjunctiva
Perennial rhinitis and conjunctivitis
A. Have you ever had chronic allergic rhinitis and/or conjunctivitis? If so, how long have you been affected?
B. Do you often suffer from rhinorrhea or nasal blockade?
C. Do you sneeze, have a runny nose or itchy and watery eyes in response to sensitizing substances such as dust or animal dander, regardless of the season?
D. Do you use anti-allergy medications for rhinitis or conjunctivitis? If so, mark them here
Seasonal rhinitis and conjunctivitis
A. Have you ever had hay fever?
B. Do you frequently have rhinitis and/or conjunctivitis in the spring and summer season?
C. Do you get watery eyes or sneezing on contact with grass or grains, or when in a park or forest?
D. Do you use anti-allergy medications for hay fever? Mark it here
4. Asthma
A. Do you ever suffer from asthma? If so, how many years have you had asthma? When were you ill (check)? In childhood – in youth – the age – adults
B. During the past 12 months, did you experience wheezing in the chest or cough?
B1. If so, was it related to rhinitis?
B2. If so, have you had cough or wheezing without colds?
C. Were you ever awakened by a feeling of tightness or compression in the chest during the last 12 months?
D. Were you ever awakened by an attack of shortness of breath in the last 12 months?
E. Did you ever wake up coughing in the last 12 months?
F. Did you have an asthma attack in the last 12 months?
G. Have you ever used asthma medications?
5. Do you smoke?
6. Do you suffer from the following diseases:
A. Heart disease?
B. Diseases of the gastrointestinal tract?
The key to calculate the score from the survey: The questionnaire has 6 modules. Each module has an individual score as described below.
Part One. Quick test of mental ability: for each correct answer: 1 point. A normal state should be > 6 points, 4–6 points indicates moderate impairment, and 0–3 points indicates severe impairment. In the case of a result of less than 4 points, the patient does not complete the rest of the survey. In other cases, the person accompanying the patient is allowed to help the patient.
Part Two. Diagnosis of perennial rhinitis and conjunctivitis. For a positive answer to each question: 1 point. A minimum of two points confirms the diagnosis. Seasonal rhinitis and conjunctivitis: For a positive answer to each question: 1 point. A minimum of two points confirms the diagnosis.
Part Three. Diagnosis of asthma: An answer of “yes” to Question A or “no” to Question A, but affirmative answers to at least three other questions confirms the diagnosis.
Part Four. Diagnosis of skin allergic diseases An answer of “yes” to Question A or “no” to Question A, but affirmative answers to all of the other questions confirms the diagnosis.
Parts Five and Six contain descriptive questions only with positive or negative questions.

Skin prick test (SPT)

Skin prick tests were performed according to the Polish Society of Allergology [11]. First, the 10 mg/ml histamine positive control was placed, followed by the negative control, which consisted of the diluent for the other allergens (Allergopharma, Germany). A set of allergens was then applied to the skin in quantities of an approximately 0.05 ml drop in the following order: *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, cat, dog, grass/wheat, rye, hazel, alder, birch, *Artemisia*, plantain, *Alternaria*, and *Cladosporium* (50 000 BE/ml). The histamine positive control response was assessed after 10 min, and the allergen tests were assessed after 20 min. The test result was considered reliable if the wheal reaction to histamine had a diameter of at least 3 mm with associated erythema of at least 5 mm in diameter. Instances of skin bubbles larger than the negative control and with a diameter > 3 mm were considered positive. The presence of a wheal larger than the negative control and with a diameter greater than 3 mm was considered positive.

Tests were performed after the discontinuation of antihistamine drugs for at least 1 week. The patients had no symptoms of acute infection within 4 weeks and did not use antidepressants or prednisolone > 10 mg per day. Topical corticosteroid and anesthetic preparations were not used.

Serum concentration of total IgE and specific IgE (sIgE)

Ten milliliters of blood from each subject was collected in citrate and then centrifuged to yield serum for further studies. Samples were stored at 2 to -8°C, and IgE assays were performed within one week after blood collection. The determinations were made using the fluoroimmunoenzymatic Pharmacia CAP System FEIA (ThermoFisher, Sweden). The sensitivity of the method determines the concentration to below 2 kU/l. The concentrations of sIgE against allergens including *D. pteronyssinus*, *D. farinae*, cat dander, dog, grass, grain, alder, hazel, birch, *Artemisia*, plantain, *Alternaria*, and *Cladosporium*, were determined with the fluoroimmunoenzymatic Pharmacia CAP System FEIA (ThermoFisher, Sweden). Values above 0.35 kU/l were considered positive [10]. The resulting concentrations of total IgE and sIgE units are presented in kU/l as the geometric mean with one standard deviation.

Statistical analysis

The rates of allergic diseases are presented in the form of prevalence associated with gender and age. Prevalence is presented as the average percentages of all study centers with 95% confidence intervals. Odds ratios for allergy suspicion based on the selected parameters were calculated, and the data are presented with

Table 2. Characteristics of the study population

Characteristics	With probable allergy N = 234	Without probable allergy N = 826	P-value [^]
Age (mean ± SD) [years]	68.1 ±6.2	69.1 ±8.4	NS*
Female, n (%)	127 (54.3)	463 (56.1)	NS
Alzheimer's disease status, n (%):			
I°	59 (25.2)	164 (19.9)	0.03
II°	110 (47.0)	434 (52.5)	0.04
III°	60 (25.6)	225 (27.2)	NS
IV°	5 (2.1)	57 (6.9)	0.03
Education level, n (%):			
None	35 (15.0)	220 (26.6)	0.03
Basic	52 (22.2)	284 (34.4)	0.02
Average	55 (23.5)	212 (25.7)	NS
High	92 (39.3)	110 (13.3)	0.002
Family history, n (%):			
Bronchial asthma	34 (14.5)	18 (2.2)	0.003
Allergic dermatoses	45 (19.3)	31 (3.8)	0.002
Rhinitis	51 (21.8)	195 (23.6)	NS
Children of respondents	157 (67.0)	294 (35.6)	0.01

[^]χ² test with Bonferroni correction, *Student's unpaired t-test.

95% confidence intervals. The results of skin prick tests (SPT) and allergen-specific IgE (sIgE) are presented as frequencies averaged from all 16 centers with 95% confidence intervals and standardization for age and sex. To compare the SPT results and IgE levels, we used the χ^2 test. IgE values are presented as geometric means with standard deviations. After logarithmic transformation of the IgE results, the differences between groups were compared using Student's *t*-test. Multiple linear regression analysis was used to explore the relationships between total IgE and selected characteristics of the group. The statistical analyses included Bonferroni correction. *P*-value < 0.05 was considered significant.

Results

The analysis included 1060 subjects with a mean age of 69.2 ± 5.1 years (range: 60–97 years; 590 women and 470 men). Suspicion of atopy was diagnosed in 234 (22.1%) patients, including 127 women (21.5% of women) and 107 men (22.8% of men). The characteristics of the group are shown in Table 2. In the selected subgroups of patients with atopic diseases, the group of women was significantly larger than the group of men (*p* < 0.05). The average morbidity associated with age and sex in this population of people with AD and bronchial asthma (BA) was 2.9% (95% CI: 2.1–3.4), for atopic dermatitis was 0.6% (95% CI: 0.5–2.2), for perennial allergic rhinitis (PAR) was 11.1% (95% CI: 9.9–15.4), for seasonal allergic rhinitis (SAR) was 6.6% (95% CI: 4.8–8.6) and for polymorphous atopic disease was 4.4% (95% CI: 3.1–5.3). The mean duration of allergic disease was 18.8 ± 11.4 years. Suspected atopic disease prevailed in the cities compared to rural areas (*p* < 0.05).

Skin prick tests for aeroallergens in the subgroup of atopy

In 182 (77.8%) patients, at least one positive skin test to allergens was observed.

The results of the skin tests are shown in Table 2. The most frequent positive results were recorded for the following allergens: mixed grass/grain – 33.2%, *D. pteronyssinus* – 25.6% and *Alternaria* – 20.4%. Allergy associated with 2, 3 or more allergens was present in 121 (51.7%) patients. In a subgroup without allergy, 25 (3.2%) patients had one or more positive tests however without clinical symptoms.

Concentration of total and allergen-specific IgE

Patients with a positive questionnaire for allergic disease had statistically higher values of IgE (145.8 ± 62.3 kU/l) in relation to other subjects (45.2 ± 29.5 kU/l) (*p* < 0.05). There were no significant differences in IgE and AD severity. The concentrations of allergen-specific IgEs are shown in Table 3. As with the results of the

skin tests, the most frequent IgE-positive results were recorded for grass (29.1%), *D. pteronyssinus* (30.1%) and *Alternaria* (19.3%). In all analyzed patients with AD, the possibility of allergic disease occurred with the odds ratio 0.67 (95% CI: 0.55–0.73).

Discussion

The phenomenon of increasing allergy in elderly patients is new in the XXI century [12–15]. There are more and more studies of this problem especially regarding bronchial asthma. The incidence of asthma in the elderly ranged from 4% to 6%, but with significant underestimation by the authors. The problem of underdiagnosis and undertreatment of asthma in the elderly population is unquestionable and it is subject of several studies [16, 17]. A similar problem was observed also in patients with AD. Appropriate treatment of asthma leads to a cognitive improvement also in patients with mild and moderate AD [18, 19]. However there was no information about prevalence other allergic diseases in patients with cognitive impairment. Is it a problem in analyzed patients? The positive answer follows from the obtained results. The prevalence of allergic rhinitis, atopic dermatitis is significant but lower in comparison with results in healthy elderly subjects in other studies [13, 20, 21]. This differences is at a level of 5–10%. These findings are very interesting and could provide that immunomodulation in AD may function partially protective to allergy. This may be due to the balance shift in the direction of lymphocytes Th1. Typical of the elderly but also of the allergy, Th2 dominance would change in this type of patients. However, this requires precise confirmation in larger numbers of patients.

Table 3. Incidence of positive SPT and specific IgE determinations

Allergen	Percentage of positive results (95% CI)	
	SPT	sIgE
<i>D. pteronyssinus</i>	25.6 (22.4–27.8)	30.1 (28.4–33.7)
<i>D. farinae</i>	18.8 (16.8–20.4)	25.8 (20.5–27.4)
Cat	10.3 (9.5–12.7)	13.7 (11.5–16.9)
Dog	6.4 (5.0–7.8)	15.8 (13.2–17.5)
Grass	33.2 (31.2–36.7)	29.1 (26.8–32.7)
Rye	12.8 (10.2–14.5)	14.6 (11.5–15.1)
Hazel	9.4 (5.6–11.7)	9.1 (5.6–10.1)
Alder	5.9 (7.8–9.4)	5.5 (3.2–6.8)
Birch	13.9 (12.1–15.5)	16.2 (13.2–17.5)
<i>Artemisia</i>	11.4 (8.5–12.6)	13.2 (11.3–15.3)
Plantain	5.8 (3.1–10.7)	5.7 (4.1–7.4)
<i>Alternaria</i>	19.2 (17.4–22.2)	19.3 (18.2–22.7)
<i>Cladosporium</i>	10.4 (8.4–12.6)	10.7 (8.7–13.6)

Besides AD, analyzed patients with allergy confirmation had better education and more often had a positive family history of allergic diseases.

The presence of positive tests to common inhalant allergens especially to house dust mites and grass pollen are similar as in other elderly people with allergy. Additionally, similar compatibility concerns the concentration of total and specific IgE [13, 21, 22].

This leads to a conclusion that allergic diseases in patients with AD are present as in other elderly subjects. However there is a frequently significant problem with obtaining medical history and performing allergy diagnostic procedures. Therefore, it seems that allergy in patients with AD is often underdiagnosed. The limitation of this study is lack of analyzed patients with the most severe, fifth degree of AD. However, in this form of the disease, allergy has no impact on quality of life in such subjects. Another limitation of the study is the lack of assessment of quality of life in examined patients. It is a very difficult task in patients with cognitive impairment because all questionnaires of quality of life with a real influence of allergic disease are inadequate and too complicated for them. However similar assessment in elderly patients with allergy but without cognitive impairment indicates a significant deterioration in the quality of life. The treatment of allergic disease could improve not only quality of life but improve the mental function as it was demonstrated in bronchial asthma.

Conclusions

The prevalence of allergic diseases in patients with Alzheimer's diagnosis is significant but lower as compared to other elderly people. This problem may require more medical attention.

Conflict of interest

The authors declare no conflict of interest.

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