

Improved activity and mental function related to proper antiasthmatic treatment in elderly patients with Alzheimer's disease

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ABSTRACT

Alzheimer's disease (AD) and bronchial asthma are common diseases in elderly patients. Untreated chronic diseases, such as chronic obstructive pulmonary disorder, diabetes, heart failure, and asthma can be associated with declining cognitive function. The objective of this study was to evaluate the influence of asthma therapy performed according to Global Initiative for Asthma (GINA) guidelines (GINA. Global strategy for asthma management and prevention. Report. Available online at www.ginasthma.com/Guidelineitem.asp??l1=2&l2=1&intId=60; last accessed Oct. 2009) on cognitive function and functional status in patients diagnosed with AD. A total of 302 participants who were diagnosed with bronchial asthma and mild or moderate AD (138 women and 164 men) with a mean age of 68.2 ± 5.1 years were included in the study. Cognitive function was assessed based on the Mini-Mental State Examination (MMSE) and the clock drawing test at the beginning of the study, after 6 months, and after 1 year. Results were compared with a control group of patients with AD but not asthma. Several patients (68.9%) had uncontrolled asthma (confirmed at the beginning of the study) and AD. After 1 year of antiasthmatic treatment, the mean MMSE score increased significantly from the baseline values of 17.2 ± 3.2 to 19.5 ± 2.1 (mean $\pm$ SD; $p < 0.05$). This change was significant compared with the control group. Significant improvement in instrumental activity was observed after 1 year of treatment in patients with asthma. Finally, 63.6% of patients met the criteria of well-controlled asthma. Adequate treatment of chronic asthma could improve some cognitive and instrumental activities. Asthma in patients with AD is commonly underdiagnosed and undertreated. (Allergy Asthma Proc 32:341–345, 2011; doi: 10.2500/aap.2011.32.3459)

Alzheimer's disease (AD) is a huge problem worldwide, especially in elderly patients. This disease currently affects more than 5 million patients in the United States and this number will increase to 16 million by 2050. Globally, an estimated 35.6 million people have dementia (mainly AD), which is expected to approach 65.7 million in 2030 and 115.4 million in 2050.^{1,2} In elderly patients with AD, some chronic diseases can worsen cognitive function, depressive symptoms, and functional status. 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} Asthma in elderly patients is a common disorder; unfortunately, it is often underdiagnosed, undertreated, and mistaken for COPD.^{6–9} Chronic uncontrolled asthma during dyspneic symptoms can lead to cerebral ischemic episodes.¹⁰ It appears that these symptoms could also influence cerebral cognitive function and

quality of life. In addition, impaired cognition may lead to worse compliance with antiasthmatic treatment. There has been some evidence that progression of AD might provide an ameliorating effect on the clinical course of asthma, probably because of alterations in the immunologic responses including eosinophilic inflammation in the airways.¹¹ It seems possible that uncontrolled asthma and impaired cognition could influence each other and lead to poor quality of life in a bidirectional fashion.

The primary objective of the present study was to examine the influence of antiasthmatic treatment according to the 2008 guidelines of the Global Initiative for Asthma (GINA) on cognitive function and functional status in patients with AD.¹⁰ The second aim was to assess whether a history of asthma is associated with shorter life expectancy after AD diagnosis.

METHODS

Patients

A total of 570 patients (261 women and 309 men) between the ages of 60 and 87 years with suspected or diagnosed bronchial asthma were initially preselected during their first visit to outpatient allergy clinics in the Polish city of Zabrze. Finally, 302 participants with bronchial asthma (138 women and 164 men), all aged

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≥60 years (mean age, 68.2 ± 5.1 years; range, 60–87 years), were included in the study. The diagnosis of asthma was confirmed by a positive history and bronchial reversibility test (increase of forced expiratory volume in 1 second [FEV₁] ≥ 12% and/or 200 mL after 30 minutes postsalbutamol $4 \times 100 \mu\text{g}$ inhalation). All patients were classified into three subgroups based on clinical criteria for controlled asthma according to GINA 2008 guidelines:¹⁰

1. Well-controlled asthma—no daytime symptoms, no limitation in the activities, no nocturnal symptoms, no use of a rescue medication reliever, normal FEV₁, and no asthma exacerbations.
2. Partly controlled asthma—limited daytime symptoms, small limitation in the activities, nocturnal symptoms once or twice per week, occasional use of a reliever, normal FEV₁, and no asthma exacerbations.
3. Uncontrolled asthma with daily daytime and nocturnal symptoms, limited in the activities, daily use of a reliever, decrease in FEV₁, and asthma exacerbations.¹⁰

In addition, 61 (20.1%) patients had stable coronary heart disease (without circulatory insufficiency, stenocardic episodes, or the use of nitroglycerin), 103 (34%) had arterial hypertension, and 29 (9.6%) had mild diabetes without the use of insulin. All of these concomitant diseases were stable and were being treated by general practitioners. Patients with stable coronary heart disease used low-dose aspirin and calcium blockers. Patients with hypertension were using angiotensin-converting enzyme inhibitors and antidiuretic drugs.

All patients received antiasthmatic therapy according to GINA 2008 guidelines.¹⁰ The control group consisted of 213 patients (112 women and 101 men) with a mean age of 67.2 ± 4.11 years that had the same type of AD but did not have bronchial asthma.

Work was performed in the Clinical Department of Internal Medicine, Dermatology, and Allergy and approved by the Institutional Review Board of the Medical University of Silesia, Zabrze, Poland.

Alzheimer's Diagnosis and Cognition Assessment

The diagnosis of Alzheimer's-type dementia 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.^{12,13} In all patients, AD was diagnosed using a combination of clinical criteria, neuropsychological testing, and conventional CT and MRI. Patients with mild AD (II–IV degrees on the Reisberg scale) were included in the study. Cognitive function was assessed

based on 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 MMSE score was standardized according to each participant's age and years of education.^{14,15} As therapy for AD, a constant dose of donepezil (mean daily dose, 8.5 ± 3.5 mg), rivastigmine (6.1 ± 1.3 mg), and/or memantine (17.5 ± 3.2 mg) was administered 6 months before and during the whole study in patients with AD. This therapy was performed in the geriatric outpatient clinic.

Functional Status

For functional status estimation, the Activities of Daily Living (ADL) and Instrumental ADL (IADL) scales were used at the beginning of the study and every 6 months. The ADL scale evaluates six basic functions: dressing, toileting, bathing, transferring, eating, and continence. A score of 0–2 indicates considerable functional handicap, 3–4 indicates mild handicap, and 5–6 indicates good functional activity.¹⁶ The IADL scale includes telephone use, shopping, transporting, budget management, responsibility for medication, cooking, laundry, and housekeeping. The maximum score that patients can obtain is 24 points.¹⁷

Control of Asthmatic Symptoms

In addition to the clinical criteria for controlled asthma, the Asthma Control Test (ACT) was used as a screening tool for asthma assessment at the beginning of the study and every 6 months thereafter. ACT is a validated, patient-completed measure of asthma control.¹⁸ There are five questions that address activity limitation, shortness of breath, nighttime symptoms, use of rescue medication, and rating of asthma control over the previous 4 weeks. The questions are scored from 1 to 5 (from worst to the best). The maximum score is 25 points, and results of >20 indicate well-controlled asthma during the previous 4 weeks.

Patients or their guardians (in cases of dementia or impaired cognition) provided written consent to participate in the study before any procedures were performed. The study design was approved by the Ethical Committee of the Coordinating Center in the Silesian University of Medicine in Katowice (Poland).

Statistical Analysis

The means and SDs were calculated for basic parameters. Data were statistically analyzed using the chi-square test to compare results of the MMSE, control of asthma, ADL, and IADL and the Spearman test was used to evaluate the correlation between MMSE, positive history of smoking, use of antiasthmatic drugs, number of asthma exacerbations, and the ACT score. A value of $p < 0.05$ was considered to statistically signif-

Table 1 Clinical characteristics of the patients with Alzheimer's disease with asthma and without asthma (control group)

Patients with Alzheimer's Disease	With Asthma (n = 302)	Without Asthma (n = 213)	p Value, Chi-Quarter
Mean age $\pm$ SD	68.2 (5.1)	67.2 (4.11)	NS*
Females (%)	45.7	52.6	<0.5
Mean MMSE score $\pm$ SD	17.2 $\pm$ 3.1	19.4 $\pm$ 0.9	<0.5
Mean clock-drawing test score $\pm$ SD	2.89 $\pm$ 0.76	2.45 $\pm$ 0.93	NS
ADL $\pm$ SD	3.2 $\pm$ 1.1	3.4 $\pm$ 0.98	NS
IADL $\pm$ SD	14.3 $\pm$ 2.5	15.8 $\pm$ 3.1	NS
Smoking (%)	11.4	23.1	<0.5

*Student's t-test, chi-quarter test in other cases.

ADL = activities of daily living; IADL = instrumental activities of daily living; MMSE = Mini-Mental State Examination questionnaire.

Table 2 Comparison of asthma therapy in participants at the start and at the end of the study

Antiasthmatic Therapy	At the Start	After 1 Year	p Value, Chi-Quarter
Percentage of participants regularly using inhaled steroids	26.1	68.5	<0.05
Percentage of participants regularly using montelukast	1.5	20.1	<0.01
Percentage of participant using SABA	67.7	84.9	<0.05
Percentage of participants regularly using LABA	11.2	42.7	<0.05
Percentage of participants using other antiasthmatic drugs	14.8	24.8	<0.05
Mean daily dose per microgram of inhaled steroids conversion to budesonide (SD)	210 $\pm$ 185 μ g	430 $\pm$ 285 μ g*	<0.05

*Value of p in chi-quarter test.

SABA = short-acting β -agonist; LABA = long-acting β -agonist.

icant. Statistica (Version 8.0 software; StatSoft, Tulsa, OK) was used.

RESULTS

Demographic and clinical characteristics of participants are shown in Table 1. At the start of the study, 208 (68.9%) patients presented with uncontrolled asthma according to GINA criteria, whereas 76 (25.2%) had partly controlled asthma, and only 18 (6%) had well-controlled asthma. Antiasthmatic treatment before and at the end of the study is presented in Table 2. Antiasthmatic treatment significantly improved the patients' conditions after 6 months: only 99 (32.8%) patients had uncontrolled asthma, 125 (41.4%) patients had partly controlled asthma, and 78 (25.8%) patients had controlled asthma. At the end of the 1-year treatment, 35 (9.7%) of the patients had uncontrolled asthma, whereas 96 (26.7%) had partly controlled asthma and 228 (63.6%) had well-controlled asthma.

The differences between the start and the end of the study were statistically significant ($p < 0.05$).

The mean MMSE score increased significantly from 17.2 ± 3.2 to 19.2 ± 1.2 ($p < 0.05$) after 6 months of antiasthmatic treatment, and the final score after 1 year was 19.5 ± 2.1 . This was comparable with the results after 6 months of treatment. However, there was no significant increase in the clock drawing score after 6 months or 1 year of treatment. In the control group, the mean MMSE was not significantly changed after 6 months and 1 year of observation (without antiasthmatic treatment). The scores at 6 months and 1 year were 19.1 ± 1.2 and 18.8 ± 2.5 ($p = 0.2$), respectively. Significant improvement in instrumental activity was observed after 1 year of treatment in patients with asthma. The results of ADL and IADL before and after the study are shown in Table 3.

ACT mean score at the beginning of the study was 13.2 ± 3.1 . It was significantly changed after treatment,

Table 3 Activities of daily living (ADL) and instrumental activities of daily living (IADL) score comparison

	With Asthma (n = 302)	Without Asthma (n = 213)	p Value, Chi-Quarter
ADL mean score			
At the start	3.2 ± 1.1	3.4 ± 0.98	NS
After 6 mo	3.4 ± 0.6	3.1 ± 0.7	NS
After 1 yr	3.3 ± 1.3	3.0 ± 1.4	NS
IADL mean score			
At the start	14.3 ± 2.5	15.8 ± 3.1	NS
After 6 mo	16.9 ± 1.9	16 ± 2.9	NS
After 1 yr	18.3 ± 2.1*	14.9 ± 4.1	<0.05

*Comparison between the start and end of the study ($p < 0.05$; value of p in chi-quarter test).

and the scores were 15.05 ± 3.1 ($p > 0.05$) and 19.7 ± 3.1 ($p < 0.05$) after 6 months and 1 year of antiasthmatic treatment, respectively. Results obtained using the MMSE were correlated with clinical criteria for controlling asthma according to ACT ($R = 0.88$; $p < 0.01$). There were no correlations between the results of the MMSE and the result of the duration of asthma, positive history of smoking, use of antiasthmatic drugs, and number of asthma exacerbations.

DISCUSSION

According to GINA 2008 guidelines,¹⁰ asthma control is particularly problematic in elderly patients, especially those with impaired cognition. There are many factors influencing this: poor cooperation between patients and doctors, low compliance with antiasthmatic therapy because of the patient's unwillingness, a focus on other concomitant chronic diseases, a lack of education about asthmatic problems, and low economic status.^{6-9,19} After 1 year of treatment and the cooperation of study patients, we tried to resolve some of the described problems. Additionally, the presence of asthma is frequently not noticed because of more prominent disturbances such as AD. Moreover, in the study population, mistaken diagnoses of COPD were frequently observed in asthmatic patients with dementia before study inclusion. Our efforts improved asthma control in many study patients.

The second problem is that depressive symptoms and impaired cognition may frequently lead to difficulties with asthma diagnosis and influence cooperation during asthma therapy.^{19,20} However, depressive symptoms were not analyzed, because they were observed in most of our patients at the beginning of the study. A few studies suggested that many asthmatic patients with symptoms of depression saw an improvement in symptoms during asthma therapy.^{19,20}

The MMSE is one of the most commonly used mental health assessments for elderly people.^{14,21-24} It is mainly used to differentiate patients with dementia

from the normal population. However, based on published data, the sensitivity of MMSE is ~55–80%, and its specificity is 60–90%.²¹ Some studies have also shown some disadvantages of MMSE, such as the overdiagnosis of psycho-organic diseases in poorly educated people.²¹⁻²⁴ Other factors (e.g., age, social status, and deterioration of senses) may bias the MMSE result.^{23,24} The increase in the MMSE score during 1 year of active antiasthmatic therapy in patients with AD has not been previously observed. This might be explained by an improvement of relationships between the patient, family, and doctor, leading to better compliance and a reduction of asthma exacerbations. However, patients with dementia did not change their status after 1 year of observation, although some cognitive functions, such as orientation, identification of objects, and reading, improved. The role of the MMSE as "only" a screening technique should not be overlooked. In some previous studies, cognition did not change during similar observations, but the analyzed groups were not homogenous and they had a better cognitive status.^{19,21} There is evidence that low cognitive function could be associated with worse survival rates in people with chronic disorders.^{25,26} It is also important that antiasthmatic therapy, including high doses of glucocorticosteroids, could influence mental functions in all patients, especially in older people.²⁷ We did not see this in the asthmatic patients in this study. Improvement of instrumental functional status after 1 year of treatment seems to be valuable in patients with AD. This is evidence that proper therapy for every chronic disease is very important to maintain a good status of patients with AD. However, we only analyzed data from patients with mild and moderate forms of this disease with good daily activity performance.

In this study, MMSE was correlated with ACT. The ACT is useful in predicting GINA-defined asthma control categories and was particularly useful in finding patients whose asthma was not controlled.¹⁷ However, we found that sometimes, the ACT was not a valuable

tool in elderly patients with dementia who had problems answering questions, even with assistance.

CONCLUSION

The problem of bronchial asthma in patients with AD is still not widely noticeable. Adequate antiasthmatic treatment in patients with mild or moderate AD provides benefits, including improvement in some cognition functions and IADL. Further observation is needed to determine the effectiveness of antiasthmatic treatment in the severe form of AD.

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