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Epidemiology of Pulmonary Aspergillosis in Hospitalized Patients in Poland During 2009–2016

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Abstract

Aspergillus is one of the most prevalent airborne fungal pathogens in the developed countries that may cause fatal invasive pulmonary aspergillosis in immunocompromised patients. The epidemiological information on aspergillosis in Poland is scarce. This retrospective, population-based study evaluated the incidence of pulmonary and other forms of aspergillosis, and also gender distribution and territorial differences in the occurrence of aspergillosis in hospitalized patients in Poland during 2009–2016. The incidence of aspergillosis was estimated on the basis of a dataset provided by hospital morbidity study carried out by the National Institute of Public Health. The data consisted of 4206 hospitalization records of 2338 patients, with some patients being hospitalized more than one time due to disease remissions. Significant gender differences were observed (1484 females *vs.* 2722 males, $p < 0.001$). No statistical differences were found for the place of residence. The average annual incidence rates for all forms of aspergillosis, invasive pulmonary aspergillosis, and other pulmonary aspergillosis were 13.8 *per* million (95% CI: 11.3–16.3), 4.0 *per* million (95% CI: 3.0–5.0), and 4.4 (CI: 3.5–5.2) *per* million, respectively. Over time, a significant increase in the rate of hospitalization were observed for all forms of aspergillosis (10.7 *per* million in 2009 *vs.* 15.7 *per* million in 2016, p for trend <0.005), invasive pulmonary aspergillosis (2.3 *per* million in 2009 *vs.* 5.0 *per* million in 2016, p for trend <0.001), and other pulmonary aspergillosis (3.6 *per* million in 2009 *vs.* 4.9 *per* million in 2016, P for trend <0.02). During the period analyzed 283 patients (12.0%) died while hospitalized and 224 of them (9.6% of all patients) died during the first-time hospitalization. We conclude that the incidence of aspergillosis is on the rise in hospitalized patients in Poland.

Keywords

Epidemiology · Hospitalized patients · Infection · Morbidity · Pulmonary aspergillosis

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1 Introduction

Fungal diseases affect a large proportion of the population, ranging in severity from mild superficial infections to life-threatening invasive diseases associated with significant morbidity and mortality. *Aspergillus* is one of the most prevalent airborne fungal pathogens in the developed countries that may cause fatal invasive aspergillosis in immunocompromised patients with neutropenia, allogeneic hematopoietic stem cell transplant, solid organ transplant, inherited or acquired immunodeficiencies, corticosteroid use, and other conditions. Invasive pulmonary aspergillosis has also been reported as a significant global health burden (Hou et al. 2017). Early recognition and diagnosis have become a major focus for the management and improvement of outcomes of this life-threatening disease (Blanchard et al. 2018). Noteworthy, the isolation of *Aspergillus* in samples from the lower respiratory tract without clinical symptoms is defined as colonization. Patients with chronic pulmonary aspergillosis (PA) have a significantly shorter survival rate than those with colonization; mortality rate 50.0% *vs.* 13.8%, respectively during the mean observation period of 28.7 ± 26.6 months (Ohba et al. 2012).

Aspergillosis-related hospitalizations remain an economic burden for hospitals in the US, with the median hospital costs exceeding $52,000 *per* patient and in-hospital crude mortality of 36.7% (Kim et al. 2011). PA often develops in smokers suffering from chronic obstructive pulmonary disease (COPD). Riera et al. (2018) have reported 1938 cases of invasive PA in a cohort of 168,000 COPD patients. Chronic invasive PA is considered a problematic pulmonary disease that complicates other respiratory disorders and is thought to affect about 240,000 people in Europe (Denning et al. 2016). Epidemiological studies on invasive aspergillosis are important, since the disease is associated with hospital readmissions within 30 days, excessive duration of hospitalization, costs, and a high mortality rate. Given nearly 40,000 annual invasive aspergillosis-related admissions in the US, the attributable aggregate excess costs may reach $600 m annually (Zilberberg et al. 2018). In Germany, invasive aspergillosis has been diagnosed in 1595 hospitalized patients in 2011–2012 (Ruhnke et al. 2015). In the UK, chronic PA affected 3600 post-tuberculosis and sarcoidosis patients in 2011 (Pegorie et al. 2017). In France, the estimated incidence of invasive aspergillosis is 1.8/100,000 inhabitants annually, based on classical high risk factors (Gangneux et al. 2016). In Belgium, the annual incidence of invasive aspergillosis and chronic aspergillosis is estimated at 6.1 and 22.7/100,000 inhabitants, respectively (Lagrou et al. 2015). In Denmark, the respective annual incidence rates are 4.4 and 3.1/100,000 inhabitants (Mortensen et al. 2015). In Norway, invasive aspergillosis is observed in 5.3/100,000 inhabitants (Nordøy et al. 2018). There are 297 cases of invasive aspergillosis and 365 people may suffer from chronic PA a year in the Czech Republic (Chrdle et al. 2015). In Greece, the annual incidence of chronic PA is 3.7/100,000 inhabitants; and invasive aspergillosis occurred in 10.4/100,000 inhabitants (Gamaletsou et al. 2016). In Spain, invasive aspergillosis has been estimated at the level of 2.7/100,000 inhabitants (Rodriguez-Tudela et al. 2015). In Portugal, the estimated prevalence of chronic PA after tuberculosis is 194 cases, whereas its prevalence for all underlying pulmonary conditions was 776 patients (Sabino et al. 2017). At least 458 cases of invasive aspergillosis occur in Romania annually in immunocompromised and cancer patients, with the prevalence of post-tuberculosis chronic PA of 8.98/100,000 (1768 cases) (Mareș et al. 2018). In India, the annual regional incidence of chronic PA varies from 27,000 to 170,000. Assuming the mortality rate from chronic PA of 15% annually, its 5-year prevalence would reach 24/100,000 inhabitants, with 290,147 cases (Agarwal et al. 2014). The incidence of invasive PA is 1.5 *per* million person-years in Taiwan (Sun et al. 2016).

Due to heterogeneity of data resources on the epidemiology of aspergillosis, it is impossible to obtain robust results and statistics. Thus, comparative analysis across countries is hardly achievable. In a US study, invasive aspergillosis has been identified on the basis of the International

Classification of Diseases (Zilberberg et al. 2018). In Norway, national registers have been used to examine the burden of fungal diseases (Nordøy et al. 2018). In Germany, statistics on the population infected with fungal disease, based on ICD10 coding, has been derived from the National Institute for Statistics (Ruhnke et al. 2015). Data on invasive PA in Taiwan have been obtained from a nationwide inpatient population study on the basis of the Taiwan National Health Insurance Research Database (Sun et al. 2016).

The information or case reports regarding aspergillosis in Poland is scarce and incomplete (Borys et al. 2017; Swoboda-Kopeć et al. 2017; Sulik-Tyszka et al. 2016; Zieliński et al. 2016; Remiszewski et al. 2002). Aspergillosis may be a life-threatening mycosis that requires hospitalization. Therefore, is study seeks to define the incidence of pulmonary and other forms of aspergillosis among hospitalized patients in Poland, based on the hospital morbidity dataset over the period of 8 years. In addition, we set out to evaluate gender distribution and regional differences in the occurrence of aspergillosis in Poland.

2 Methods

This is a retrospective, population-based study conducted with the use of hospital discharge records of patients diagnosed with Aspergillosis. The incidence of the disease was derived the Polish morbidity dataset collected by the National Institute of Public Health in Warsaw, Poland. All inpatients with ICD-10 diagnostic code of Aspergillosis, alive, rehospitalized, or dead, from all hospitals, excluding psychiatric and military hospitals, were taken into account. The data included 4206 hospitalization records of 2338 patients from 2009 to 2016. Invasive pulmonary aspergillosis was denoted by ICD10 code B44.0 and other forms of pulmonary aspergillosis by B44.1. Data were anonymized, consisted of dates of admission and discharge, birthdate, gender, and the place of residence, and were collected on a monthly basis. The incidence rates were calculated using the number of aspergillosis patients and the corresponding census data. A demographic dataset for the general Polish population were obtained from the Central Statistical Office of Poland (2018). The study took into account all forms of aspergillosis described in the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD10).

2.1 Statistical Analysis

Continuous data were expressed as means, medians, ranges and categorical data as counts and percentages. Assuming Poisson distribution of the observed disease cases, 95% confidence intervals (95%CI) were calculated. Parametric or non-parametric tests were used as appropriate. A two-tailed p-value <0.05 defined statistically significant differences. The incidence rate was calculated using the number of cases as numerator and the number of population as denominator. Linear regression was used for trend analysis. Comparison between categorical variables was performed with Fisher's exact test or χ^2 test. Commercial statistical packages of Statistica (Dell Inc 2016) and WINPEPI (Abramson 2011) were used in the study.

3 Results

In the study group of all 2338 patients, the mean age was 50.9 ± 20.9 (min–max: 0–97 years). Age distribution of the first-time hospitalized patients with aspergillosis in Poland is presented in Fig. 1. The disease was diagnosed and required hospitalizations most often in the age brackets of 50–70 years. Significant gender differences were observed among the hospitalizations (1484 females *vs.* 2722 males, $p < 0.001$) and among the patients (827 females *vs.* 1511 males, $p < 0.001$). No statistical differences were found for the place of residence in the analyzed cohort of patients.

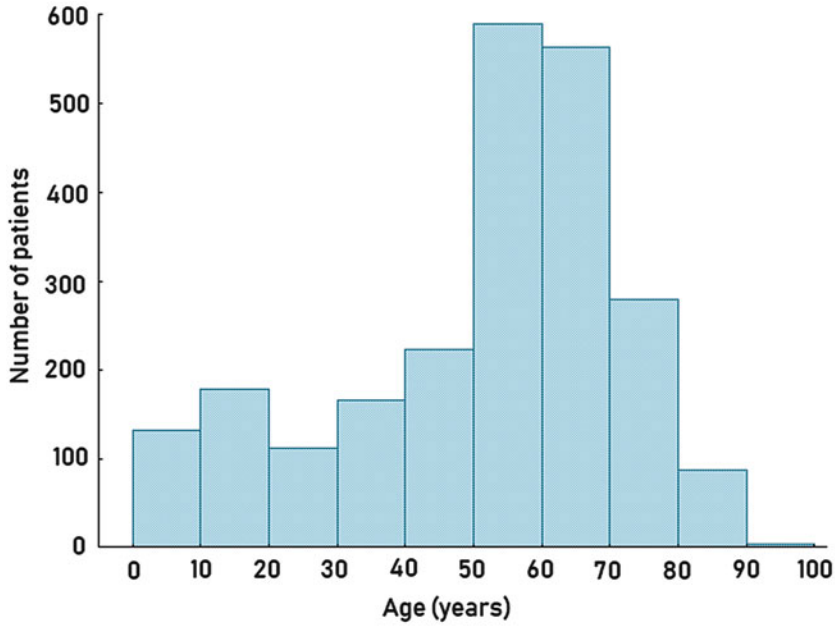

Fig. 1 Age distribution of the first-time hospitalized patients with aspergillosis in Poland

The average annual rate of hospitalizations for all forms of aspergillosis was estimated at 13.8 *per* million persons (95%CI: 11.3–16.3), for invasive pulmonary aspergillosis at 4.0 *per* million (95%CI: 3.0–5.0), and for other pulmonary aspergillosis at 4.4 *per* million (95%CI: 3.5–5.2). Over time, a significant increase in the hospitalization rate was observed for all forms of aspergillosis (10.7 *per* million in 2009 *vs.* 15.7 *per* million in 2016; p for trend <0.005), for invasive pulmonary aspergillosis (2.3 *per* million in 2009 *vs.* 5.0 *per* million in 2016; p for trend <0.001), and other pulmonary aspergillosis (3.6 *per* million in 2009 *vs.* 4.9 *per* million in 2016; p for trend <0.020).

Patients, who were diagnosed with aspergillosis for the first time, were hospitalized in the following departments: pulmonology (22.6%), tuberculosis and lung diseases (21.6%), hematology (12%), chest surgery (9.9%), and internal medicine (5.3%). The average annual incidence rate of all forms of aspergillosis, concerning the first-time hospitalized patients, was estimated at 7.6 *per* million (95%CI: 6.8–8.6). There was no significant increase in the number of patients with other forms of aspergillosis, invasive pulmonary aspergillosis, or other forms of pulmonary aspergillosis hospitalized for the first time, comparing 2009 to 2016. However, there was a slight significant increase in all the above-mentioned forms of aspergillosis combined in the time-trend analysis from 2009 to 2016 ($p < 0.05$). Fig. 2 shows the annual incidence of invasive pulmonary aspergillosis (ICD B44.0), other pulmonary aspergillosis (ICD B44.1), disseminated aspergillosis (ICD B44.7), and other forms of aspergillosis (combined number of B44.2, B44.8, and B44.9 cases).

During the study period, 283 patients (12%) died while hospitalized (96 females and 187 males; mean age: 53.0 ± 20.6 years; min-max: 0–89 years), some of them suffered from lymphoid (31 patients) or myeloid leukemia (41 patients). Two hundred and twenty four deaths occurred during the first-time hospitalization.

4 Discussion

Although epidemiological data on the incidence of invasive pulmonary aspergillosis have been reported in several European countries, the

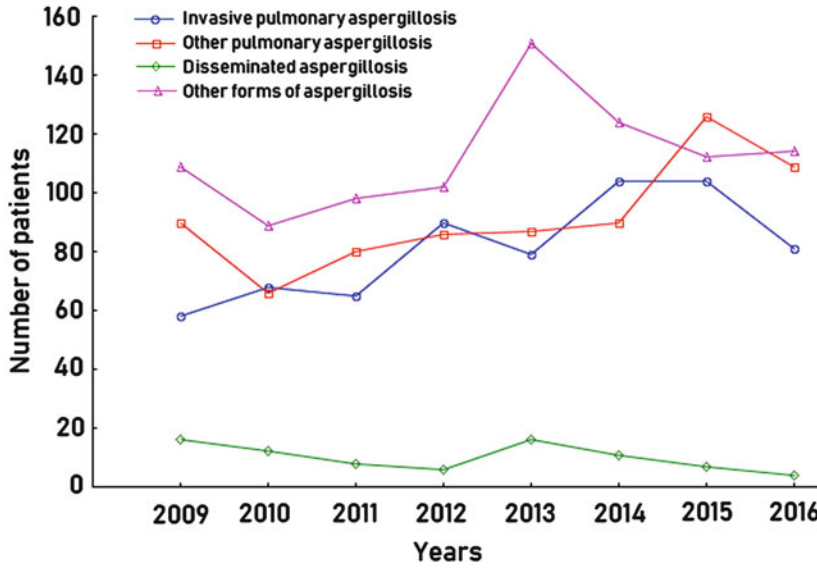

Fig. 2 First-time hospitalizations with aspergillosis *per* year in Poland in 2009–2016

present analysis is the first of its kind in Poland. Since aspergillosis with lung involvement often requires advanced diagnostic or therapeutic procedures, current analysis of hospitalization dataset may provide accurate estimates of its incidence. The average annual incidence of aspergillosis was lower in Poland than the numbers reported in other European countries (Gamaletsou et al. 2016; Gangneux et al. 2016; Mortensen et al. 2015). However, we found a significant increase in the number of hospitalizations with aspergillosis over the time of years, which, aside from the natural occurrence of this disease, might have to do with a better reporting the disease to the national register or diagnostic improvements. It has been reported that the frequency of invasive aspergillosis in the developing countries is presumably underreported (Chakrabarti et al. 2011). Furthermore, invasive pulmonary aspergillosis can be challenging to diagnose since both clinical presentation and radiographic images are often nonspecific. A definitive diagnosis from a sputum culture is time consuming, and invasive procedures such as bronchiolar lavage or tissue biopsy are not always workable due to the patient's clinical conditions, for instance, thrombocytopenia due to a coexisting hematological disorder. A recent Chinese study provided clinical and laboratory evidence for the semi-invasive properties of chronic PA (Chan et al. 2016). An increase in the incidence of invasive pulmonary aspergillosis, ranging from 0.94 to 2.06 *per* million person-years, has also been observed in a Taiwanese study ($p < 0.0001$) (Sun et al. 2016).

In this study we observed the predominance of male over female patients with aspergillosis. The proportion of male patients has been reported around 55–60% in the USA (Steinbach et al. 2012; Kim et al. 2011). Similar proportion of male patients is reported in French (62%) (Lortholary et al. 2011) studies. An underlying cause of gender differences in the occurrence of aspergillosis remains unknown. Invasive pulmonary aspergillosis develops more often in patients with some coexisting diseases, thus the gender difference might have to do with the epidemiology of those diseases. An epidemiological intensive care study shows that 31% of patients with invasive aspergillosis suffers from chronic obstructive pulmonary disease (COPD) (Taccone et al. 2015).

During the current study time, there were 283 deaths (12% of all aspergillosis-related hospitalizations) and 224 deaths (10% of the

first-time hospitalized patients with aspergillosis). This level of hospital mortality raises an assumption that patients are hospitalized in advanced disease stage. Seventy two out of the 283 patients who died had had lymphoid or myeloid leukemia. High mortality due to aspergillosis may not be directly related to the infection *per se*, but rather to accompanying comorbidities. A recent British study sets the survival rate in chronic PA at 86%, 62%, and 47% for 1-, 5-, and 10-year period, respectively (Lowes et al. 2017). It is worth noting that inhospital mortality in invasive aspergillosis amounted to 46% in intensive care patients in a retrospective cohort study based on the 2005–2008 hospital dataset (Baddley et al. 2013). Likewise, crude inhospital mortality of about 37% has been noted in a cohort of patients hospitalized with invasive aspergillosis in 2005–2006 (Kim et al. 2011). A 5-year mortality in chronic necrotizing pulmonary aspergillosis amounts to was 50% in a Japanese study (Nakamoto et al. 2013).

In this study, many patients were hospitalized more than one time for aspergillosis. It has been reported that during the first year of follow-up, there is a reasonable treatment success in about one third to half chronic PA patients (Al Shair et al. 2013; Cadranel et al. 2012). Most cases of aspergillosis were hospitalized in the pulmonology or tuberculosis wards, which strongly suggests that the lungs are the most frequent site of aspergillosis infection in Poland. Likewise, lungs are the most frequently affected tissue in another large study conducted in 960 patients with invasive aspergillosis (Steinbach et al. 2012).

This study has several limitations. Firstly, it relied on discharge records from inpatient hospitalizations, thus excluding patients who were seen on the outpatient basis. Nevertheless, most patients diagnosed with invasive pulmonary aspergillosis are hospitalized due to the very nature of infection. It has been suggested that the number of missing cases of pulmonary aspergillosis due to mild forms of infection would be too small to influence the general epidemiological trends (Sun et al. 2016). Pulmonary aspergillosis may be accompanied by multiorgan involvement, which requires advanced diagnostic procedures and treatment in the inpatient setting. Secondly, the first-time diagnosis of aspergillosis in the discharge dataset is not necessarily tantamount to the very onset of disease. This may introduce a bias concerning age of patients first-time hospitalized to aspergillosis. However, a long observation period in this study should mitigate the inaccuracy. Thirdly, validity of the diagnosis may have been limited. Patients with aspergillosis may be diagnosed on the basis of EORCT-MSG 2008 criteria (De Pauw et al. 2008). However, we were unable to fully apply these criteria to define invasive pulmonary aspergillosis since the information on clinical symptoms and culture results were unavailable in the hospital morbidity dataset. Uncertainty is intrinsic to most disease burden estimates due to limitations in the methodology and national surveillance systems.

In conclusion, we noticed an increasing trend in hospitalizations due to aspergillosis in Poland. Further research may be needed to produce more robust estimation of frequency of different forms of aspergillosis. Nevertheless, we believe that the epidemiological data on aspergillosis herein presented may be useful in comparative international studies.

Conflicts of Interest Authors declare no conflicts of interest in relation to this article.

Ethical Approval This article is a retrospective study based on the analysis of hospital discharge files. Therefore, the article does not contain any studies with human participants performed by any of the authors. A local Bioethics Committee of Warsaw Medical University in Poland has approved the study.

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