

Paget disease of bone among hospitalized patients in Poland

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A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of article

Kanecki K, Nitsch-Osuch A, Goryński P, Bogdan M, Tarka P, Tyszko P Z. Paget disease of bone among hospitalized patients in Poland. *Ann Agric Environ Med.* 2018; 25(1): 182–185. doi: 10.26444/aaem/81080

Abstract

Introduction. Paget's disease (PDB) is a focal disorder of bone remodeling that occurs commonly in older people with decreasing prevalence reported in European countries. This disease is most often asymptomatic, but it can cause a variety of medical complications resulting in considerable morbidity and reduced quality of life. There is little information regarding the epidemiology of PDB in Poland. To the best of the authors' knowledge, this is the first large epidemiological analysis of this disease in Poland.

Objective. The aim of this study was to analyze factors that may be related to the PDB epidemiology among hospitalized patients in Poland.

Materials and method. The analysis was conducted on the basis of population-based administrative data, taken from a Polish hospital morbidity study carried out by the National Institute of Public Health between January 2008 – December 2014.

Results. Analyzed data covered 662 hospitalization records. The final study sample comprised 94 (41.8%) male and 131 (58.2%) female patients with first-time hospitalizations for PDB, with a significant predominance of females ($P < 0.02$), and the predominance of patients living in urban (73%) than in rural areas (27%), $P < 0.001$. The average age of the sample was 56.8 years (CI: 54.3–59.3; SD 18.8; range 1–93 years). The number of PDB cases hospitalized in Poland significantly decreased during the analyzed period of time.

Conclusions: PDB is a rare disease with decreasing trends observed among hospitalized patients in Poland. The study results may suggest the existence of environmental risk factors for the development of PDB.

Key words

Paget's disease of bone, hospitalization, rural population, urban population, risk factors.

INTRODUCTION

Paget's disease of bone (PDB) is a focal disorder of bone remodeling that occurs commonly in older people. PDB is the second most common metabolic bone disease after osteoporosis. The disease is characterized by focal areas of abnormal bone remodeling which can lead to bone deformity, osteoarthritis, bone pain, pathologic fractures, deafness and nerve compression syndromes [1]. PDB is most often asymptomatic, but it can cause a variety of medical complications resulting in considerable morbidity and reduced quality of life [2]. In a recent systematic review, bone pain was the most common complaint occurring in about 40% of cases, followed by deformity (20%), pathological fracture (10%), and deafness (6%) [3]. PDB is widely observed in nations with a large Anglo Saxon population [1, 4]. The majority of PDB patients remain asymptomatic and do not require treatment [5, 6]. Some asymptomatic patients may benefit from treatment, especially when the disease is quite active or when the bones involved are close to vital organs or bones in which the progression of the disease

may lead to complications [5–7]. Patients with significant symptoms should also be treated [5, 8]. Second-generation bisphosphonates are widely regarded as the treatment of this disease [9].

Epidemiology. The prevalence rate of PDB in New Zealand is believed to be among the highest in the world [4]. In the United Kingdom, PDB was reported to be a rare disease in subjects under 50 years of age, but it increased in prevalence progressively thereafter to affect 5.8% of women and 6.9% of men aged over 85. The overall prevalence in those above the age of 55 in the UK was about 2% [1]. The prevalence of Paget's disease in elderly French women is similar to that recently reported in the UK [10]. PDB in Italy has an estimated prevalence rate ranging from 0.7% (radiological studies) – 2.4% (bone scan study) [11]. Prevalence of PDB in Spain amounts to at least 1% in individuals older than 55, with remarkable geographical variations and age-related differences [12]. In non-European countries, the PDB prevalence is lower than in European countries and varies widely. The total prevalence was 6.8 per 1,000 patients, and the incidence density for PDB at 50.3 per 10,000 person-years in Recife in South America [13]. In the USA, approximately 1–2% of the population are affected by PDB, with the north-eastern region showing the highest prevalence [14]. The

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Received: 19.07.2017; accepted: 08.12.2017; first published: 12.02.2018

prevalence rate of PDB was reported to be low in Japan (0.00028%) [15] and is believed to be a rare disease in Asia [16, 17].

Genetic, environmental and other factors related to PDB.

The cause of PDB is unknown, but genetic factors, particularly SQSTM1 mutations, and a substantial gene-environment interaction may be related to PDB [18]. Until now, SQSTM1 is the only PDB-causing gene identified. However, PDB patients without SQSTM1 mutations seem to have susceptibility to genetic polymorphisms in regions containing CaSR, ESR1, TNFRSF11B (OPG), TNFRSF11A (RANK), CSF1 (M-CSF), OPTN, TM7SF4 (DC-STAMP), VCP, NUP205, RIN3, PML, and GOLGA6A genes, which results in an increased risk of developing PDB [19].

Genetic factors seem to be important. Mutations in SQSTM1 occur in 25–50% of familial PD. Genotype-phenotype relationships are present, as PD develops at an earlier age and is more extensive and severe in those with SQSTM1 mutations. These findings are more pronounced in those with truncating mutations [20].

Age and gender are the principal factors that have previously been related to the prevalence of PDB which increases substantially with age [12, 21–24]. Patients were diagnosed with Paget's disease of bone for the first time at the mean age of 69.6 years [22]. The disease was higher in frequency in people who were in the older decades of life with the highest prevalence of 2.32 + 0.54% in the 65–74-year-old age group [14]. It has been reported that the rate of PDB may increase significantly in those over 80 years of age [25]. Men were reported to be more frequently affected [21, 25–26]. Urban vs. rural residence may also be related to the prevalence of PDB, with more cases in urban centres of population [22]. PDB is reported to be significantly associated with wood-fired heating in childhood and/or adolescence [27]. The prevalence of PDB in archeological population groups was studied through the examination of skeletons available from central Europe, and these studies showed prevalence in central Europe (0.03%) [28].

PDB trends in recent years. Prevalence of Paget's disease in New Zealand has declined over the past two decades, indicating that there are important environmental determinants in its development [4]. No secular trend for decreasing prevalence of PDB in Italy was observed [23]. Previous studies indicated a reduction in the prevalence of Paget disease [29–30]. Another large study in England and Wales estimated that the prevalence of this disorder was 0.3% in subjects over 55 years of age [1]. In addition, a decrease in the prevalence of Paget's disease has been noticed in some European countries over a 20-year period, reaching an overall rate of 0.3% [21]. Moreover, the annual incidence of new cases of PDB has declined significantly in USA over the past 20 years [22]. A recent study demonstrated that the incidence of PDB in Spain had remained stable over the past 24 years in one region, substantial changes had been observed in the other region, although the severity of the disease had declined [31]. It was reported that the secular trend of Paget's disease present later in life and in a milder form may be related to important environmental determinants. Given the secular trend and limitations to life expectancy, it is predicted that Paget's disease will become increasingly rare [25].

OBJECTIVES

Most epidemiological studies on PDB have been performed in the UK and in other populations of British descent, such as those in the USA, Australia, and New Zealand. In contrast, few data are available about the epidemiology and characteristics of PDB in other European populations. Despite the impact of the disease on the population, only limited information about the epidemiology of PDB in Poland is available. The purpose of this study was to analyze factors that may be related to the PDB epidemiology among hospitalized patients in Poland.

MATERIALS AND METHOD

The analysis was performed using population-based administrative data collected between January 2008 – December 2014 by the National Institute of Public Health, as a part of the Polish Hospital Morbidity Study. Data on all inpatients discharged (living or deceased) from all hospitals, excluding psychiatric and military hospitals, are reported to the Institute, usually on a monthly basis. The database contains information from hospital documentation about each hospitalization, including the ICD-10 codes of the admission diagnosis and comorbidities, dates of admission and discharge, and the patient's birth date, gender, and place of residence. The database does not contain patients' names. Two analytic samples were considered in the current study: 1) all hospitalizations for PDB, and 2) first-time hospitalization for PDB. In addition to data from the hospital morbidity study, demographic data for the general Polish population were obtained from the Polish Central Statistical Office [32]. Incidence and prevalence rates were calculated using the number of PDB patients and corresponding census data. One study used a large primary care record-linkage resource, the General Practice Research Database (GPRD), to evaluate the incidence, clinical presentation, and natural history of Paget's disease of bone in England and Wales [1]. In another study, PDB prevalence was estimated on the basis of inpatient data in Italy [23] and Spain [12]. In Poland, a good alternative for an analysis of PDB epidemiology may be the database of the National Institute of Public Health.

Statistical analysis. All statistical analyses were performed using a licensed version of Statistica Software Dell Inc. (2016). Dell Statistica (data analysis software system), version 13. software.dell.com.) and WINPEPI programmes [33]. The results of descriptive analyses were expressed as means, medians and ranges for continuous variables, as well as counts and percentages for categorical data. 95% CIs were calculated assuming Poisson distributions of the observed cases. Nonparametric tests were used as appropriate when normality assumptions were not met. The chi-squared test was used to determine whether there was a significant difference between the frequencies. The linear regression analysis was used for trend analysis. A *P*-value of <0.05 was considered to be statistically significant.

RESULTS

Analyzed data covered 662 hospitalization records. The final study sample comprised 94 (41.8%) male and 131 (58.2%) female patients with first-time hospitalizations for PDB, with a significant predominance of females ($P < 0.02$), and a predominance of patients living in more urban (73%) than rural areas (27%), $P < 0.001$. The average age of the sample was 56.8 years (CI: 54.3–59.3; SD 18.8; range 1–93 years). The incidence of Paget's disease is difficult to estimate because most patients are asymptomatic. Based on hospitalization registers, the average incidence of PDB among hospitalized patients may be estimated at 0.8 / million per year (95%CI: 0.6–1). The actual incidence is probably at least several times higher since PDB is largely asymptomatic. The number of newly-diagnosed cases of PDB in Poland per year across the study period by gender is presented in Figure 1, and by place of residence in Figure 2. The number of first-time hospitalizations of PDB patients decreased significantly in the analyzed period of time ($P < 0.05$).

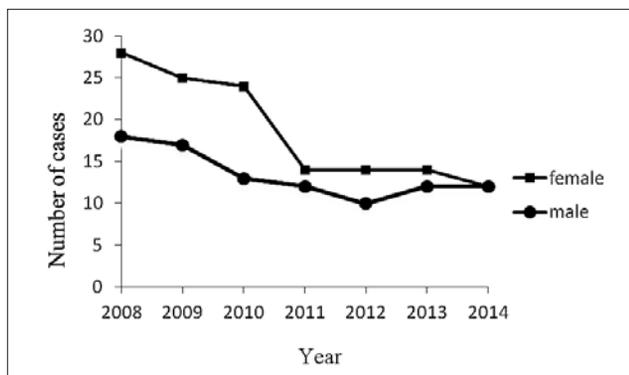


Figure 1. Number of cases of Paget's disease of bone by gender per year in Poland, 2008–2014

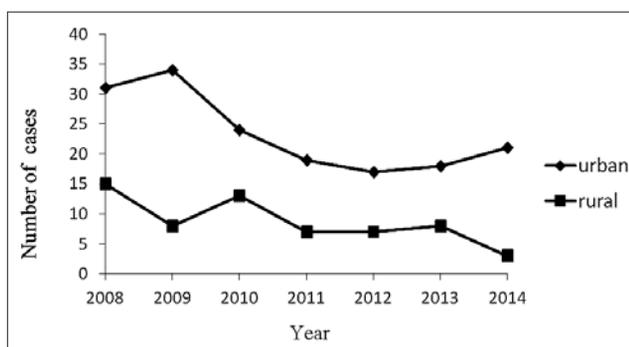


Figure 2. Number of cases of Paget's disease of bone by place of residence per year in Poland, 2008–2014

DISCUSSION

Although epidemiologic data on the PDB epidemiology have been reported in several European countries, there is no comprehensive analysis of the PDB epidemiology and factors related to this disease in Poland. Because PDB may be asymptomatic, it is difficult to assess the PDB incidence, but it is expected that the analysis of hospitalization data from a 7-year period of time may provide approximate information on the incidence of PDB in patients requiring hospitalization.

On the basis of the data obtained from a national inpatient discharge database, the average annual incidence of PDB in Poland may be estimated at 0.8 per million, which may be lower than the incidence reported in other European countries. The reason may be related to the fact that PDB is often asymptomatic and is frequently discovered incidentally when an elevated serum alkaline phosphatase is found in a routine laboratory test, or discovered radiographically in an x-ray performed for unrelated reasons. PDB can be diagnosed in outpatient care, but hospitalization may be considered necessary when the following symptoms appear: bone fractures or deformities, bone changes deteriorating quickly, unspecified pain, deafness, elevated calcium levels, heart failure, paraplegia or spinal stenosis.

PDB affects mainly elderly people, who may be hospitalized more often than those who are younger. A recent population-based study from Olmsted County, Minnesota, USA, found that 58% of the patients had symptoms at diagnosis [34]. On the basis of this information, it can be assumed that the PDB incidence rate is several times higher than the incidence calculated in this study.

The number of hospitalization cases in PDB patients in Poland decreased significantly in 2008–2014. The decline in both the prevalence and the severity of PDB has been documented in other countries in the recent past [21, 35, 36]. The incidence and prevalence rates of PDB vary widely between populations, but both have decreased in most regions in recent years [37]. At present, the reasons for these changes remain unclear, but they are likely to be due to an interaction between genetic factors and environmental triggers which may differ in different regions [37]. Additionally, the geographical distribution of PDB has been shown to differ not only between different countries, but also within the same country. Areas of remarkably high prevalence have been described in the northeast of the USA, and territories of Spain and Italy [14, 38, 39]. The average age of people with PDB ranged from 50–60 years and it is similar to data from other European countries. It was reported in another study that there was a secular trend of Paget's disease presenting later in life and in a milder form, which might be related to environmental determinants [25]. In this study, PDB was more significantly observed in females than males. This observation may be associated with an increased risk of PDB in females, or the existence of environmental or other unknown factors that increase the risk of PDB in females.

Data from this study suggest that an unknown environmental factor may be related to the higher PDB incidence in urban than rural areas. While environmental pollution affects mainly urban areas, its progressive reduction can decrease the frequency of PDB occurrence in Poland in both genders, as observed in the presented study and illustrated in Figure 1. In another study, more PDB cases were also observed in urban than rural areas [22]. Other environmental triggers suggested to be implicated include less exposure to zoonoses due to emigration from rural to urban areas, and fewer infections due to public health measures and vaccination programmes [37]. PDB appeared to be more prevalent in rural than in urban areas of Italy, and a significant association with animal contacts was shown, providing further support for the role of infective agents [11]. Additionally, animal-related factors may be important in the etiology of PDB and may interact with SQSTM1 mutations, thus influencing the disease severity [40]. It was reported that

the decreasing incidence of Paget's disease, which could be attributed to measles vaccination, supports an etiologic role of the virus [41]. However, RNA of the measles virus was not found in the bone marrow and bone cell cultures isolated from patients with Paget's disease in New Zealand [42].

CONCLUSIONS

The epidemiology of PD appears to have been changing recently, with several groups in different parts of the world reporting a marked reduction in the prevalence and incidence of PBD. PDB is rarely seen in Poland, with a decreasing incidence in recent years. These findings seem most likely to be caused by changes in the exposure to unknown environmental factors, or the existence of a genetic predisposition, or both. However, while significant progress has been made in the identification of the genetic mutations associated with PDB, further research is needed to determine the environmental factors involved.

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