ORIGINAL ARTICLE

Annals of Agricultural and Environmental Medicine
www.aaem.pl

Adult-onset Still's disease in Poland – a nationwide population-based study

Magdalena Bogdan[1,A,C-D,F], **Aneta Nitsch-Osuch**[1,D-F], **Piotr Samel-Kowalik**[2,B-D], **Paweł Goryński**[3,B,F], **Piotr Tyszko**[4,A,D-F], **Krzysztof Kanecki**[1,A-C,E]

[1] *Department of Social Medicine and Public Health, Medical University, Warsaw, Poland*
[2] *Department of Prevention of Environmental Hazards and Allergology, Medical University, Warsaw, Poland*
[3] *National Institute of Public Health – National Institute of Hygiene, Warsaw, Poland*
[4] *Institute of Rural Health, Lublin, Poland*
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

Bogdan M, Nitsch-Osuch A, Samel-Kowalik P, Goryński P, Tyszko P, Kanecki K. Adult-onset Still's disease in Poland – a nationwide population-based study. Ann Agric Environ

Abstract

Introduction. Adult-onset Still's disease (AOSD) is a rare systemic inflammatory disorder of unknown etiology, which affects young adults and is associated with multiple organ involvement and life-threatening complications. The aim of the study was to establish the incidence and prevalence of AOSD in Poland, and factors related to this disease among hospitalized patients.

Materials and method. A retrospective, population-based study was conducted, using data from hospital discharge records compiled by the National Institute of Public Health in 2009–2018.

Results. Based on hospitalization records and census data in a group of the 1,050 patients included in the study, women were predominant (60%) and patients' mean and median ages at hospitalization were 42 (95% CI: 40.8–42.8) and 38 years, respectively. The average annual incidence rate of AOSD during the 10-year period was established at the level of 0.32/100,000 (95% CI: 0.30–0.34), and the point prevalence at the end of 2018 was 2.7/100,000. The most common comorbidities were: cardiovascular diseases (14%), diseases of the musculoskeletal system and connective tissue (14%), endocrine, nutritional and metabolic diseases (9%).

Conclusions. AOSD is a rare disease Poland with gender and territorial differences in incidence ratek, and predominance of cardiovascular diseases among comorbidities. The presented data may be useful for comparisons of the Polish population with other geographical regions. Predominance of patients from urban regions and predominance of women may suggest environmental and personal factors in AOSD development; however, further research seems to be necessary.

Key words

hospitalization, morbidity, adult Still disease, national register.

INTRODUCTION

Adult-onset Still's disease (AOSD) is a rare systemic inflammatory disorder of unknown etiology, which affects young adults and is associated with multi-visceral involvement and life-threating complications [1, 2]. In medical literature, systemic juvenile idiopathic arthritis and AOSD represent one disease continuum with different ages of onset, which are associated with a number of shared clinical, genetic and laboratory features, as well as a strikingly similar response to IL-1 and IL-6 inhibitors [3]. The diagnosis is both clinical and empirical, with inclusion and exclusion criteria based on negative immunoserological results. There are no clear-cut diagnostic, radiological or laboratory symptoms [4]. The currently applied clinical criteria for AOSD can result in misdiagnosis [5]. However, the criteria suggested by Yamaguchi are widely used in the diagnosis of the disease [6]. The 2016 EULAR/ACR/PRINTO (European League Against Rheumatism/American College of Rheumatology/Paewdiatric Rheumatology International Trials Organization) classification criteria for MAS (Macrophage Activation Syndrome) are potentially useful for the identification of patients with AOSD at high risk of a poor outcome [7]. The 2016 classification criteria for MAS in SJIA (Systematic Juvenile Idiopathic Arthritis) had a higher sensitivity but lower specificity in the identification of MAS in AOSD patients, compared with SJIA patients[8].

The etiology of AOSD is still not clear. However, auto-inflammatory disorders may develop in genetically-predisposed hosts [9]. In one study, TNFRSF1A (Tumour Necrosis Factor Receptor 1A) was associated with patients with severe AOSD, whereas causal variants were reported in the majority of patients. Significant associations between AOSD and the HLA DQB1*06:02 allele, as well as between the DRB1*1501-DQB1*06:02 haplotype and AOSD susceptibility have also been observed [10]. Additionally, in recent decades, many cases of an infection with pathogens have been reported in AOSD patients [11, 12, 13].

The incidence of AOSD has been reported at 0.16 per 100,000 in France [14], 0.22 in Japan [15], and 0.4 in northern Norway [16], where the point prevalence of AOSD was reported to have increased from 3.4/100,000 (95% CI 0.8–9.4) in 1990 to 6.9/100,000 in 2000 (95% CI 2.7–14.2) [16]. The point prevalence of AOSD in Italy has been reported at 0.1–0.34/100,000 [20]. Accordingly, the estimated crude prevalence among AOSD patients aged 16 years or older

Address for correspondence: Magdalena Bogdan, Department of Social Medicine and Public Health, Medical University, Warsaw, Poland
E-mail: mbogdan@wum.edu.pl

Received: 21.11.2020; accepted: 15.01.2021; *first published: 17.02.2021*

was established in Japan at the level of 0.73 and 1.47 per population of 100,000 males and females, respectively [15]. Some studies have shown that females are more affected and account for approximately 60–70% of the patients with AOSD [15, 17, 18, 19]. A retrospective study on the populations of Brittany and Loire in western France, conducted from 1982–1991, showed that the gender ratio was 1.06 (51.6% women and 48.4% men, reference population 1.05) [14]. However, in northern Norway, AOSD was more prevalent in males [16]. In an Italian retrospective study based on data from 15 Italian University Hospitals, male patients were reported to be predominant (116 females and 129 males), and the median age at the onset of the disease manifestations was 38.8 years (range, 16–78.6) [20]. Gender-related AOSD can also be observed, with severe complications more likely to occur in women than in men [21]. In a cross-sectional study on 18 AOSD cases diagnosed in Tunis from 1990–2014, there were 11 women and 7 men, with an average age of 27 years [22]. It was also suggested that there is no dependency on ethnic groups [14, 15, 17], although AOSD in the Italian population was reported to be significantly influenced by the ethnicity of the affected patients [23]. Asian patients were reported to have a significantly higher in-hospital mortality rate [8]. AOSD usually affects young adults; however, it has been reported that typical AOSD can develop in elderly patients with some characteristic features [24]. A study from China reported that although AOSD is a benign disease, relapses are common [25].

A lack of data on the global incidence and prevalence of AOSD suggests that there has been insufficient research in this area due to the rare nature of the disease. At present, despite the poor outcome in several patients, AOSD remains a multi-systemic disorder of unknown etiology, which is difficult to diagnose and scarcely studied. To the best of the authors' knowledge, the number of studies on AOSD is relatively low, and in Poland the epidemiology of this disease has not been fully elucidated [26, 27, 28, 29, 30].

Table 1. Annual incidence and prevalence of AOSD in selected countries per 100,000

	France [14]	Norway [16]	Italy [20]	Tunis [22]	Japan [15]
Incidence	0.16	0,4	0.14–0.40	no data	0.22
Prevalence	no data	3.4–6.9	0.1–0.34	0.18	0.73–1.47

Source: Own elaboration based on references

OBJECTIVES

The aim of the study was to describe patients in Poland at their first AOSD hospitalization in 2009–2018. A retrospective observational study was conducted to describe a cohort and identify selected factors that may be related to AOSD. This study is believed to be the first on this rare disease in Poland, based on a hospital morbidity database.

MATERIALS AND METHOD

The study was retrospective, and population-based, involving an analysis of hospital discharge records of patients diagnosed with AOSD s. Data were obtained from the National Institute of Public Health in Poland and covered the period from 2009–2018. The records of patients at their first hospitalizations for AOSD were analyzed. All hospitals in Poland, except psychiatric facilities, are legally required to send discharge data to the Institute. The data are anonymous and include information on hospitalizations with an ICD10-code diagnoses, dates of admission and discharge, date of birth, gender and place of residence. Two samples were analysed: 1) all hospitalizations for AOSD, and 2) first-time hospitalizations for AOSD. Demographic data for the general Polish population over the age of 15 were obtained from the Central Statistical Office of Poland. Incidence rates were calculated using the number of AOSD patients and corresponding census data. AOSD often requires advanced differential diagnostic procedures or hospital treatment; hospital records may therefore provide a good basis for incidence estimation. Other studies on connective tissue systemic diseases have also analyzed data from hospitalization registers [31] or data from routine clinical practice [32]. It was assumed that AOSD hospital diagnoses were based on the most current and widely-used criteria.

Ethical Issues. The programme of this non-interventional study was conducted in accordance with generally applicable law, submitted to and approved by the Bioethics Committee of the Medical University in Warsaw.

Statistical analysis. To perform the statistical analyses, Statistica [33] and WINPEPI [34] were used. Means, medians, ranges for continuous variables, counts and percentages for categorical variables were computed. 95% confidence intervals (95% CIs) were estimated by assuming that the cases followed a Poisson distribution. Prevalence and incidence rates were calculated by dividing the relevant number of disease cases by the corresponding census figures. Linear regression, time series analysis were used to assess trends. When normality assumptions were not met, no-parametric tests were applied (Mann-Whitney U test). A two-sided P value of less than 0.05 was considered to be statistically significant.

RESULTS

The study comprised 3,095 hospitalization records of AOSD patients, and the study group consisted of 1,050 first-time hospitalized AOSD patients in the analyzed period of time (Fig. 1). The long-term incidence trend appeared to be stable with periodic fluctuations. Women were predominantly affected (626 females vs. 424 males, $P<0.001$). The age range was 16–92 and patients' mean and median ages at the first-time hospitalization were 42 (95% CI: 40.8–42.8, SD: 17) and 38 years, respectively. Age distribution in the study group is presented in Figure 2. Female patients in the study group were significantly older than males (43.7 vs 39 years, $P<0.001$). Based on hospitalization records and census data, the average annual incidence rate of AOSD during the 10-year period was established at the level of 0.32/100,000 (95% CI: 0.30–0.34), and the point prevalence at the end of 2018 was 3.2/100,000. Incidence was significantly higher in urban than rural regions of Poland (0.33 vs 0.29 per 100,000, $P<0.05$). The most common patient group of comorbidities were diseases of the circulatory system (14%), diseases of the musculoskeletal system and connective tissue, other than

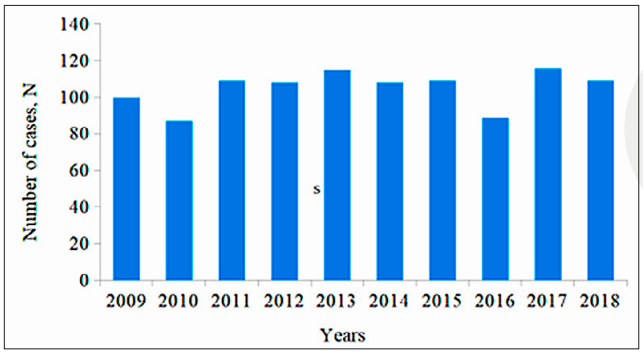

Figure 1. Year to year AOSD case number change. *Source:* Own elaboration

AOSD (14%), endocrine, nutritional and metabolic diseases (9%), diseases of blood and blood-forming organs and certain disorders involving the immune mechanism (8%), disease of the respiratory system (8%), diseases of the digestive system (7%), other diseases (below 5%). Patients with neoplasms constituted a small group – 0.5% of AOSD patients. During the study period, 20 patients died while hospitalized (11 males, 9 females; mean age 53.9, SD: 14.9, min-max: 31–80). Among them, 9 died when first-time hospitalized in the analyzed period of time.

DISCUSSION AND CONCLUSIONS

In the study, which was based on hospitalization records and census data and covered a 10-year observation period, the average annual incidence rate of AOSD was 0.32/100,000 (95% CI: 0.30–0.34), and the point prevalence was 3.2/100,000. The incidence seems to be similar to that observed in other studies [14, 15, 16], and the prevalence of AOSD is similar to that reported in other countries [15, 16, 35]. The trend of the number of first-time hospitalizations in the analyzed timeframe was not significantly increasing, and some fluctuations were observed during the study period (Fig. 1). However, significant differences in the incidence were observed between patients living in urban and rural regions of Poland. The differences may indicate an additional influence of territorial factors on the development of AOSD.

During the study period, 20 patients died while hospitalized (mean age 53.9; min-max age 31–80), which a proves relatively low hospital mortality of 2%. A large study based on a nationwide inpatient sample database and covering data on adult hospitalized patients with AOSD in the USA in 2009–2013, reported a mortality rate of 2.6%, and the age of patients who died – 62.4 years ± 3.1 [36]. An advanced age was indicated to be a significant predictive factor for the death of patients with macrophage activation syndrome in China [37]. Asian patients were also reported to have a significantly higher in-hospital mortality rate [18]. Additionally, these data may suggest the influence of territorial or race factors on the course of the disease.

In the current study, patients' mean and median ages at hospitalization were 42 (95% CI: 40.8–42.8) and 38 years, respectively. Female patients were observed to be predominant and significantly older than males. In a study from Japan, the mean age of patients was 38.1 years, and female patients tended to be older than the males [15]. However, another relatively recent study from Japan which analyzed 169 AOSD patients showed a mean age of 46 years at the disease onset [35]. In a study from the USA conducted in 2009–2015, the mean age in the AOSD cohort was 43.08 years, with the female predominance (68.9%) [19]. In a study from France, the median age at AOSD diagnosis was 36 years (range 16–75 yrs), whereby 18% of the patients were aged over 55 and 53% were females [38]. In another study from China, the mean age of all 61 patients at the time of the disease onset was 30.11±10.75 years (range 16–61). 43 of them (70.49%) were 16–35-years-old at onset [39]. A study from Japan reported a mean age of 38.1 years for the AOSD patients, and showed that female patients tended to be older than the males, with as many as 50% of the female patients at the age of 40 years or more, and only 28% of the male patients in the same age group [15]. In a study from China, the age reported in the cohort of 104 AOSD patients was 32.5±11.9 years (range 16–64 yrs) [40]. In another study from Italy, 44 of 76 patients were female [41]. In another study from China, 52.5% of the AOSD patients were female [39], and in another study in a cohort of 104 AOSD patient, the femal-to-male ratio was reported to be 3:1 [40].

In this study, the age distribution suggested it was trimodal with peaks between 20–25, 30–35, and the other between 60–65 (Fig. 2). However, a bimodal age distribution, with one peak between 15–25 and the other between 35–45 years of age was reported in another study [14]. Moreover, it was reported in other study that AOSD did not predominantly affect young adults in our study population, and elderly AOSD patients have been observed more frequently in recent years due to global population aging [21].

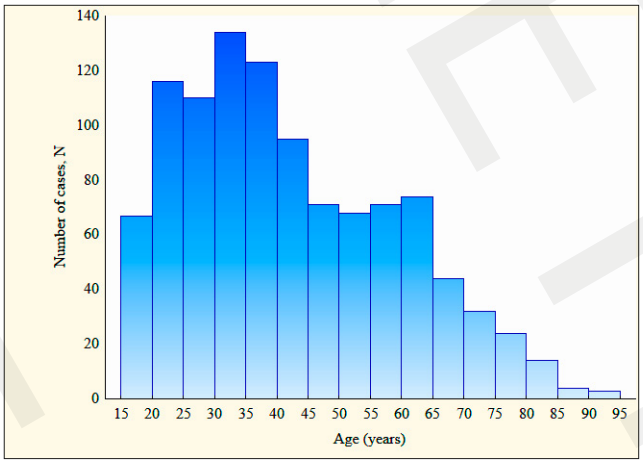

Figure 2. AOSD case number change – age reference. *Source:* Own elaboration

In the current study, the most common patient comorbidities were cardiovascular, endocrine, nutritional and metabolic diseases, diseases of the blood/blood-forming organs, and certain immune system disorders, respiratory system and digestive system disorders. In an Italian study, almost 70% of the AOSD patients presented the following comorbidities: cardiovascular diseases (61 patients), pneumopathies (17 patients), nephritis (12 patients), hepatitis 11 (patients), bowel diseases (8 patients), thyroiditis (26 patients), autoimmune diseases (8 patients), diabetes (19 patients, neoplasia (6 patients), and other diseases (4 patients) [21]. Similar to the Italian study, cardiovascular disease was also predominant in the presented study, whereas patients with neoplasms constituted a small group of 0.5% AOSD patients. Malignancy as a concomitant disease to AOSD is subject to the diagnosis

of exclusion; however, in the scientific literature there are certain reports that present patients with malignancies and AOSD-like signs and symptoms [42, 43, 44]. Besides, some cases of AOSD associated with malignancies have been observed, including solid cancer and haematological disorders [45, 46, 47].

The presented data may be useful for comparisons of the Polish population with other geographical regions. Predominance of patients from urban regions and predominance of women may suggest environmental and personal factors in AOSD development; however, further research seems to be necessary.

Advantages and limitations of the study. The study involved a nationwide survey on AOSD and provided important information on the disease epidemiology in a large cohort of Polish patients. Nevertheless, it has some limitations. Firstly, the study was retrospective, and the hospital discharge database, which was subject to analysis, did not include all variables which might be related to AOSD. Secondly, the database included discharge records from in-patient hospitalizations, but the date of the first AOSD hospitalization might not necessarily be the date of the first diagnosis. This may have resulted in the overestimation of incident cases. However, the long study period may have minimized this inaccuracy.

Despite the limitations presented above, a significant advantage of this study into AOSD is the use of the national *hospital morbidity* database where AOSD cases are obligatorily reported. Therefore, the study significantly contributes to a better understanding of the epidemiology of this rare, life-threatening disease

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