

WHAT COMORBIDITIES ACCOMPANY SARCOIDOSIS? A LARGE COHORT (N=1779) PATIENTS ANALYSIS

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ABSTRACT. *Background:* Sarcoidosis is a systemic granulomatous multiorgan disease with the most common manifestation is in the chest, although the granulomas can also involve all other organs causing variety of symptoms mimicking different diseases. *Objectives:* To evaluate the incidence of comorbidity in a large group of patients with sarcoidosis diagnosed or followed in referral center for lung diseases in Poland. *Patients and Methods:* We performed a retrospective analysis in a group of 1779 patients discharged with the final diagnosis “sarcoidosis” (ICD-10: D86) from January 2008 to October 2011. *Results:* The majority (79.2%) were diagnosed as pulmonary and/or lymph node sarcoidosis (D86.0, D86.1, D86.2). Sarcoidosis of other and combined sites (D86.8) were diagnosed in 15.8% and unspecified (D86.9) in 5.0% of patients. At least one comorbid condition was noted in 54% of the patients, most frequently arterial hypertension (22.4%), thyroid disorders (5.6%), diabetes mellitus (5.0%), COPD (4.3%) and obesity (3.3%). Using linear regression models, the associations between the number of comorbidities and age and extent of the disease were found ($p < 0.001$). Patients with multiorgan sarcoidosis were more likely to have a comorbid condition. *Conclusions:* More than half of patients with sarcoidosis have a comorbid condition, which is more likely in older patients and those with multiorgan involvement. (*Sarcoidosis Vasc Diffuse Lung Dis* 2015; 32: 115-120)

KEY WORDS: coexisting illness, comorbidity, sarcoidosis

INTRODUCTION

Sarcoidosis is a systemic granulomatous multiorgan disease of unknown etiology. The most common manifestation is in the chest, often presenting as bilateral hilar lymphadenopathy with or without

pulmonary infiltrations. Although the location of changes in the respiratory tract is most common, granulomas can also involve all other organs (1). Sarcoidosis is considered rare, but the routine use of chest radiography as a health screening tool often detects asymptomatic chest changes and increases the reported prevalence of sarcoidosis. The incidence varies by race, sex, and latitude (1-40/100,000). The disease occurs throughout the world, can affect both men and women, and all ethnicities and ages, although some predilection for middle-aged women Afro-American and Scandinavian was noted (1-4).

The natural history of the disease and its expression largely remains a mystery. Sarcoidosis can be mild and self-limited, but also can be chronic,

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progressive, and even life-threatening (when the heart or central nervous system are involved). Genetic and environmental factors possibly affect the course of the disease. Comorbid conditions may also affect the course of disease and additionally impair the quality of life. Depression, anxiety, hypothyroidism, altered sleep patterns and other comorbidities may all contribute to sarcoidosis associated fatigue and impair the quality of life (5-7).

The National TB & Lung Diseases Research Institute in Warsaw, Poland serves as the regional referral center for patients with sarcoidosis and other interstitial lung diseases. This practice provided the opportunity to describe the prevalence of various comorbid conditions from a much larger group of patients than previously reported.

The aim of this study was to evaluate the incidence of comorbidities reported at discharge in a large group of patients with sarcoidosis diagnosed or followed in the National Tuberculosis & Lung Diseases Research Institute in Warsaw.

METHODS

Using electronic medical records, we performed a retrospective analysis of patients discharged with the final diagnosis "sarcoidosis" (the International Classification of Diseases ICD-10: D86) from January 2008 to October 2011 (46 months). Descriptive statistics were reported as mean and \pm standard deviation. In order to verify correspondence hypothesis between two nominal variables (eg. the occurrence of the disease from a given category of ICD-10 and the occurrence of "multiorgan" involvement), χ^2 tests were performed and p -value less than 0.01 was regarded as significant. The "null hypothesis" was: there is no association between multiorgan sarcoidosis and the presence of comorbidities belonging to the same group (ICD10). The relation between selected factors (eg. age, extent of the disease, sex) and the dependent variable (number of comorbidities) was done using linear regression analysis. The statistical analysis were performed using STATISTICA (StatSoft, Inc. version 9.1. www.statsoft.com).

The nature of this study is a non-interventional, descriptive, retrospective analysis of de-identified data, obviating the need for approval from local Ethics Committee.

RESULTS

1779 sarcoidosis patients (52.6% men) were hospitalized in our Institute during almost four years. All were Caucasian; Mean age of the patients was 43.2 ± 12.1 years (90% were in the age range 27-64). In the majority (90%) the diagnosis of sarcoidosis was confirmed by histopathology examination. The majority of patients (79.2%) were diagnosed as pulmonary and/or lymph node sarcoidosis (D86.0, D86.1, D86.2). Sarcoidosis of other and combined sites and unspecified (D86.8, D86.9) were diagnosed in 20.8% of patients.

At least one comorbidity was noted in 54% of patients. Figure 1 presents the distribution of patients according to the numbers of reported comorbidities.

The first three diseases most frequently reported as comorbidity were: arterial hypertension (22.4%), thyroid disorders (7.0%) and diabetes mellitus (5.0%). Percentages according to the ICD-10 classification the first ten most frequently reported illnesses are presented in figure 2 and according to groups of ICD-10 diagnoses in figure 3.

Arterial hypertension, other cardiovascular diseases and diabetes are the most common in the population, also among patients with sarcoidosis. The second place with the 7% was recorded in relation to thyroid disorders, mostly hypothyroidism ($n=50$, 2.81%) and goitre ($n=49$, 2.75%), less frequently hyperthyroidism ($n=12$, 0.67%). Among the malignancies, which were only 1.9% of comorbid condi-

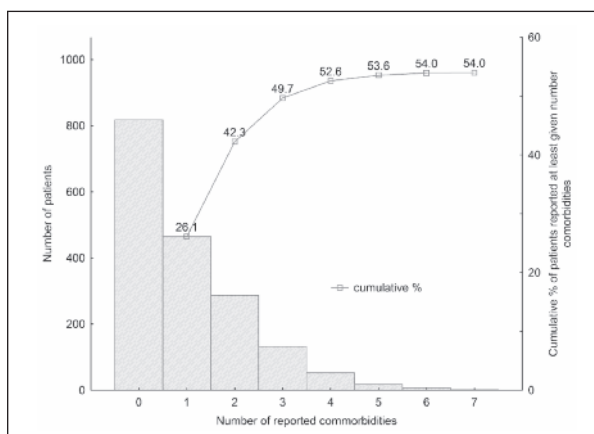


Fig. 1. Histogram of numbers reported comorbidities (line express cumulative percentage of patients reported with given less or equal number of comorbidities)

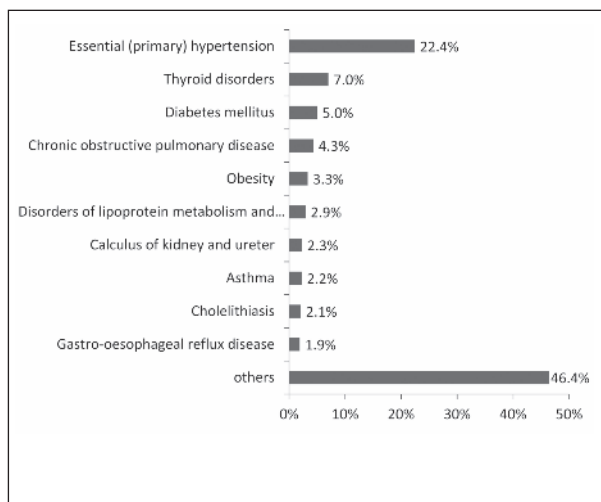


Fig. 2. The first 10 from the most prevalent diseases in sarcoidosis patients (as a % of all cases)

tions, most frequent were urinary tract cancer (n=10, 0.56%), breast cancer (n=5, 0.28%), prostate cancer (n=3, 0.17%), neoplasm of female genital organs (n=3, 0.17%) and lung cancer (n=2, 0.11%). Single

cases of lymphoma, melanoma and other less common cancers were reported. See the on-line supplementary table for details.

Subjects diagnosed as multiorgan disease (D86.8) had significantly higher numbers of reported coexisting illnesses comparing to pulmonary involvement only (respectively mean 1.52 ± 1.47 vs 0.90 ± 1.10 , $p < 0.05$). Using linear regression models, the influence of three factors: age (as a continuous predictor) and extent of the disease and sex (categorical variables) on the number of comorbidities were found. The model explained only 26% of the variance ($F_{(3,1686)} = 198.5$, $p < 0.001$). Gender effects were insignificant ($p = 0.24$). Age ($\beta = 0.48$, $p < 0.01$) was a stronger predictor than having multiorgan involvement ($\beta = 0.14$, $p < 0.01$), but adjusting for age, the extent of disease was associated with increased number of comorbidities

In order to verify the relationship between the occurrence of the disease from a given category of ICD-10 and the occurrence of “multiorgan” involvement, chi-square tests were carried out in individual groups of diseases (Table 1).

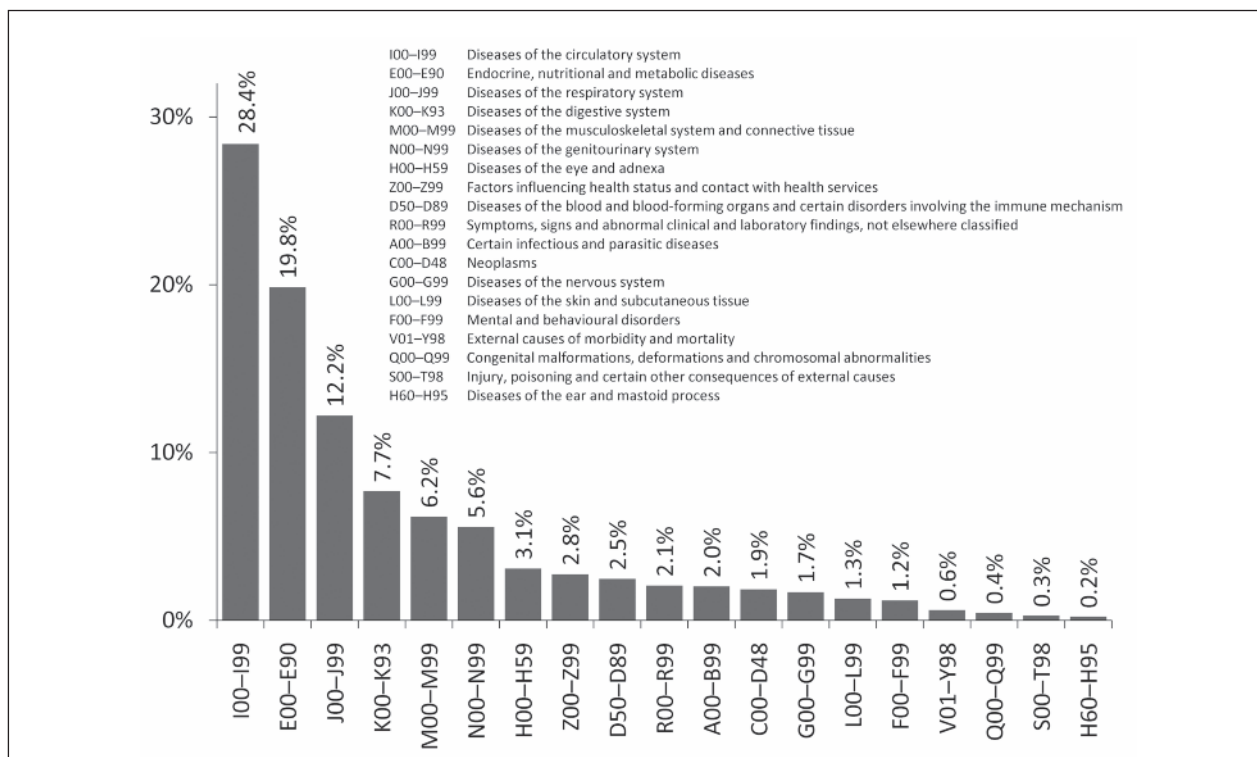


Fig. 3. Comorbidities in sarcoidosis patients according to the groups of ICD-10 classification

DISCUSSION

The present study describes the type and frequency of comorbidities in patients with sarcoidosis identified during a period of 4 years at our tertiary referral center. This investigation showed that patients with multiorgan sarcoidosis disease more frequently suffer from comorbidities. Gvozdenovic and coworkers in group of 81 biopsy proven sarcoidosis patients found higher rates of fatigue and dyspnea in

Table 1. The relationship between the occurrence of the disease from a given category of ICD-10 and the occurrence of “multiorgan” involvement. (Values of the χ^2 and the level of significance, as well as the observed direction of the dependence were based on the empirical and theoretical values; Bonferroni correction for multiple testing was applied.)

ICD-10 group	χ^2	p	Influence of the number of comorbid conditions in the “multiorgan” group
A00-B99	-	<i>p</i> =1.0	ns
C00-D48	16.87	<i>p</i> <0.01	increase
D50-D89	-	<i>p</i> =0.088	ns
E00-E90	15.16	<i>p</i> <0.01	increase
F00-F99	-	<i>p</i> =0.174	low numer of cases
G00-G99	-	<i>p</i> =0.494	ns
H00-H59	15.22	<i>p</i> <0.01	increase
H60-H95	-	<i>p</i> =0.586	low numer of cases
I00-I99	-	<i>p</i> =0.06	ns
J00-J99	13.875	<i>p</i> <0.01	increase
K00-K93	11.544	<i>p</i> <0.01	increase
L00-L99	-	<i>p</i> =1.0	low numer of cases
M00-M99	10.129	<i>p</i> <0.01	increase
N00-N99	-	<i>p</i> =0.374	ns
Q00-Q99	-	<i>p</i> =0.063	low numer of cases
R00-R96	-	<i>p</i> =0.039	ns
S00-T98	-	<i>p</i> =0.064	low numer of cases
V01-Y98	-	<i>p</i> =0.058	low numer of cases
Z00-Z99	12.258	<i>p</i> <0.01	increase

A00–B99: Certain infectious and parasitic diseases; C00–D48: Neoplasms; D50–D89: Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism; E00–E90: Endocrine, nutritional and metabolic diseases; F00–F99: Mental and behavioural disorders; G00–G99: Diseases of the nervous system; H00–H59: Diseases of the eye and adnexa; H60–H95: Diseases of the ear and mastoid process; I00–I99: Diseases of the circulatory system; J00–J99: Diseases of the respiratory system; K00–K93: Diseases of the digestive system; L00–L99: Diseases of the skin and subcutaneous tissue; M00–M99: Diseases of the musculoskeletal system and connective tissue; N00–N99: Diseases of the genitourinary system; Q00–Q99: Congenital malformations, deformations and chromosomal abnormalities; R00–R99: Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified; S00–T98: Injury, poisoning and certain other consequences of external causes; V01–Y98: External causes of morbidity and mortality; Z00–Z99: Factors influencing health status and contact with health services.

those with extrapulmonary involvement. However, patients with cardiac or other respiratory disorders were excluded from the study (8).

Cardiovascular diseases, particularly arterial hypertension (HT) was common in our group of patients. The prevalence of HT in these patients was similar to the 29% in the general population of adults in Poland (9).

Women with sarcoidosis were more likely than men to have a thyroid disease (figure 4), what corresponds with distribution for European adults and seems to be lower than in US population (NHANES survey) studies (10-12), but no prevalence data is available for adults from Poland. The 12% prevalence reported by Reynolds et all in sarcoidosis group is higher (13).

The prevalence of diabetes in our patients with sarcoidosis (5%) is similar to that reported from population-based samples of adults in Poland (14). On the one hand, it may be surprising since diabetes mellitus is known to be a side-effect of prednisone, a common treatment for sarcoidosis. On the other hand, taking into account the experience of our centre, as well following the recommendations for the treatment of sarcoidosis, we can say that the vast majority of patients observed in our institution (and included into the analysis) was not treated with glucocorticoids (less than 16% patients were discharged with such treatment – unpublished data). So health

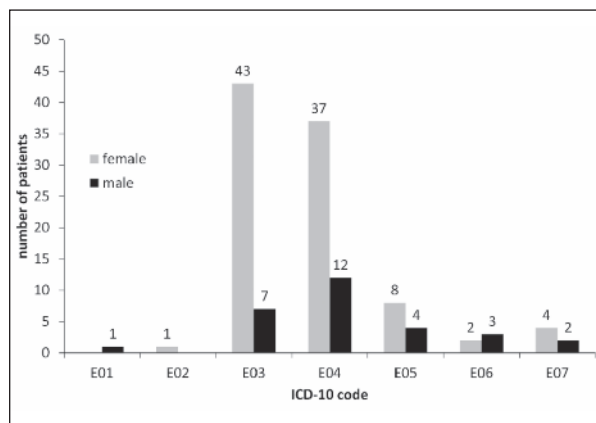


Fig. 4. Numbers of patients with reported thyroid disorders (E01 Iodine-deficiency-related thyroid disorders and allied conditions, E02 Subclinical iodine-deficiency hypothyroidism, E03 Other hypothyroidism E04 Other nontoxic goitre, E05 Thyrotoxicosis [hyperthyroidism], E06 Thyroiditis, E07 Other disorders of thyroid)

problems such as hypertension, obesity, osteoporosis, and peptic ulcer disease reported in these patients with a high probability were not derived from treatment.

It is possible that comorbid illness may influence the expression of sarcoidosis. Westney and coworkers found that 90% of 165 African-American patients with sarcoidosis had a coexisting illness, most frequently arterial hypertension (39%), diabetes mellitus (19%), anemia (19%), asthma (15%), and depression (13%). The radiographic stage of sarcoidosis was more advanced in those with anemia, depression, and age <40 years (15). Reynolds reported concurrent illness in group of 67 patients, predominantly Caucasian and female. Most often involved were gastroenterologic (36%), endocrinologic (19.4%) and cardiovascular (19.4%) systems (13).

A common clinical problem of sarcoidosis patients is depression. Chang and coworkers found clinical patterns of depression in 60% of 154 patients (6). This high prevalence of depressive symptoms is an important finding, but in other studies the rates were between 13 and 18% (13,15,16). In our group, only 21 cases (1.2%) had reported any mental/behavioral disorder (belonging to the F00–F99 category). Perhaps the difference is that patients with symptoms of mild depression are often not diagnosed as having depression (with an ICD code added to their medical record).

Sarcoidosis-associated fatigue is a common complaint (rates of 50–70%) (5,17–19). The cause of this symptom is still unknown. Sarcoidosis patients report higher fatigue scores compared with healthy controls and the symptoms may become chronic even after all signs of disease activity have disappeared (20). However, none of the physicians caring for our patients placed the R53 code for fatigue in their medical records.

The association with chronic immunologic inflammatory disease and some relationship between sarcoidosis and malignancy were also reported (13,21,22). Chronic inflammation may increase the risk for cancer, particularly cancer of the organs affected by sarcoidosis (23). Sarcoidosis related malignancy includes not only lymphomas and hematologic malignancies, but also solid tumors. In addition some antineoplastic agents (such as interferon) may contribute to the induction of new-onset or exacerbation of existing sarcoidosis. Solid tumors diag-

nosed during the course of sarcoidosis most commonly involve the cervix, liver, lung, testicles and uterus (22). The prevalence of sarcoidosis was increased at 0.58% in a cohort of 1199 patients with melanoma (24). Perhaps tumor necrosis factor-(TNF- α) increases the risk of both diseases (25,26). In our group 33 cases had reported at least one malignancy (belonging to the group C00–D48), usually in the past and successfully treated before sarcoidosis appeared, however, we failed to observe any regularities.

In the study of Spruit et al. a significant number of male sarcoidosis outpatients (46.7%) had low circulating testosterone concentrations, which was probably caused by hypogonadism (27). Systemic inflammation, or a side effect of the corticosteroid treatment may cause hypogonadism (28,29).

Further studies are needed to determine the effectiveness of diagnosis and treatment of comorbid conditions in patients with sarcoidosis, however, so far, nothing indicates that patients with sarcoidosis have a particular pattern of comorbidities. Appropriate management is mandatory especially because disease affects fairly young adults. Specialists from all medical disciplines may benefit from a multidisciplinary approach to improve knowledge of sarcoidosis.

LIMITATION OF THE STUDY

This is a retrospective, cross-sectional analysis based on the group of sarcoidosis patients seen in the National TB & Lung Diseases Research Institute in Warsaw during a 4 year period. The numbers of cases in each group reflects the actual distribution of patients in our hospital. Ideally statistical analyses would have made use of matched controls; however, this was not feasible – in “Discussion” section we presented comparison with available epidemiological data from Poland or European countries. This was a cross-sectional study of patients in various stages of the disease. Some patients may have had coexisting illnesses which were not reported in the electronic medical records. We did not perform screening tests for other illnesses, however respiratory tract and lung diseases could be detected more frequently due to the profile of the hospital. For this reason, the smokers with obstruction due to sarcoidosis could be qualified as having COPD.

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