

Vital prognosis in intrathoracic sarcoidosis with special reference to pulmonary function and radiological stage

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Vital prognosis in intrathoracic sarcoidosis with special reference to pulmonary function and radiological stage. K. Viskum, J. Vestbo. ©ERS Journals Ltd 1993.

ABSTRACT: A follow-up of 254 patients with intrathoracic sarcoidosis has been carried out after a median of 27 yrs from the diagnostic admission. All patients could be traced.

At the end of follow-up there was no excess mortality (80 deaths observed versus 65.5 expected). However, during the first 20 yrs of follow-up a slight excess mortality was seen. Thirty three out of the 80 deaths were related to sarcoidosis. No excess number of deaths from lung cancer or lymphoma was observed. Erythema nodosum was of no prognostic significance concerning survival. X-ray stage was related to survival with a significant excess mortality for stage 3. Early clearing of X-ray changes gave a favourable vital prognosis. Survival was related to lung function, and for forced expiratory volume in one second (FEV₁), FEV₁/forced vital capacity (FVC) index and total lung capacity (TLC) this relationship reached levels of statistical significance. In multivariate Cox regression models, with age and sex entered as covariates, the same parameters were found to be significant predictors of mortality. Patients with FEV₁ ≤50% predicted had an increased mortality risk of 4.2 (95% confidence interval 1.8-9.6) when compared to patients with FEV₁ >80% predicted. Likewise, patients with TLC ≤80% predicted had a mortality risk of 2.6 (1.5-4.5) when compared to patients with TLC >80% predicted.

In conclusion, a modest excess mortality was observed during the first 20 yrs of follow-up. Furthermore, both X-ray staging and lung function at the time of diagnosis influenced long-term mortality in patients with intrathoracic sarcoidosis.

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The prognosis of a disease covers a variety of aspects. In sarcoidosis, prognosis has, in particular, been related to X-ray stage [1, 2] and other objective findings, for instance erythema nodosum [1, 3], eye changes [4] and other manifestations [3]. Differences in prognosis can often be ascribed to varying definition of the disease, varying primary cause for inclusion, and ethnic differences. In addition, most investigations in sarcoidosis have been short-term studies. Very few studies have related symptoms and/or physical findings to long-term vital prognosis as compared to that of the general population [5-9]. Causes of death have been examined in a small number of studies [5, 6, 8, 10].

In the present study we report long-term survival in a previously described population [1, 8] of 254 Caucasian Danes with pulmonary sarcoidosis, followed-up after median 27 yrs.

Methods

Initial study

The study comprised 254 patients, 127 men and 127 women, who were admitted to the Department of

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Pulmonary Medicine, Bispebjerg Hospital, during the period 1956 to April 1970. On admission, they were for the first time diagnosed as suffering from sarcoidosis. The diagnosis was confirmed by biopsy in 194 cases. In 60 patients, the diagnosis was mainly based on chest X-ray findings and to some extent on symptoms (arthralgia, cough, dyspnoea, erythema nodosum and flu-like symptoms). The 60 patients without histological confirmation of the diagnosis had the same gender ratio, X-ray stage, forced expiratory volume in one second (FEV₁), vital capacity (VC), total lung capacity (TLC) and FEV₁/forced vital capacity (FVC) distribution and symptoms, as those with a histological diagnosis. They were dissimilar to the other 194 patients by having entered the study on average 2 yrs earlier (t-test, p<0.0001), and they were 4.7 yrs younger (t-test, p=0.014). Age at entry to the study ranged from 13-72 years, median 28.4 years (99, ≤24 yrs; 106, 25-44 yrs, 39, 45-59 yrs; and 10, ≥60 yrs of age). The X-ray stage at diagnosis was stage 1 for 52, stage 2 for 134, and stage 3 for 68 patients.

Pulmonary function was not a routine procedure during the first part of the inclusion period and only 222 had VC and TLC and 160 FVC and FEV₁ determined. Spirometry was performed using a Godart bell

spirometer and TLC was determined using the helium dilution technique. Retrospectively, it is not possible to see why some patients had the measurements performed and others not.

Follow-up

For this follow-up the patients were first examined in 1971 [1, 8]. The information obtained in 1971 concerning symptoms, survival and causes of death was brought up-to-date in spring 1991 by a search of the Danish register of persons. All subjects could be identified. A total of 80 patients had died since inclusion in the study. Death certificates were obtained for the 51 persons who had died since 1971. The course of the disease in these patients was substantiated by obtaining hospital records.

The 174 surviving subjects received a postal questionnaire and 166 (95%) gave a useful reply. The information given in the questionnaire was validated by obtaining the relevant information from hospital admissions. In this way some information was, in addition, obtained concerning the non-responders.

Statistical methods

Numbers of deaths in subgroups of the patient population were compared with those expected in the general population in the municipality of Copenhagen, using an observed/expected ratio (O/E); 95% confidence interval for the O/E ratio was calculated as described by BRESLOW and DAY [11]. Since information concerning time from initial examination to death was available, the multivariate Cox regression model [12, 13] was applied in order to adjust for age and, in some instances, for other variables.

Results

During follow-up 80 patients had died, 40 men and 40 women. Survival was not significantly different for men and women and not significantly different from that expected. Expected number of deaths was 65.5 (34.1 for men and 31.4 for women). The deaths were not evenly distributed during the observation years compared to the expected number. Up to 20 years from initial diagnosis there was a significant excess mortality, judged from O/E ratio's, which disappeared at later observation points as shown in figure 1.

Causes of death are listed in table 1. Sarcoidosis was, not unexpectedly, frequently listed as a primary cause of death. In addition, in a similar number of deaths, sarcoidosis was a secondary cause, the primary being well known complications to sarcoidosis. In the group of neoplastic diseases, four cases of primary bronchial carcinoma were listed, the remaining representing a broad spectrum of neoplastic diseases. None with malignant lymphoma or leukaemia were found. The number of deaths from bronchial carcinoma does not exceed the number expected (*i.e.* 3.7 deaths). Tuberculosis was the cause of death in two patients, 5 and 11 yrs after the diagnosis of sarcoidosis, respectively. The cardiovascular disease group comprises mainly ischaemic heart disease. Finally, there is a very inhomogeneous group comprising accidents, suicides, and three deaths that could not be classified.

Age at diagnosis was not associated with prognosis (age >50 yrs: 26 deaths observed, 22 deaths expected; age ≤50 yrs: 54 deaths observed, 45 deaths expected).

No difference in vital prognosis was seen between those with and those without a histological verification of the diagnosis.

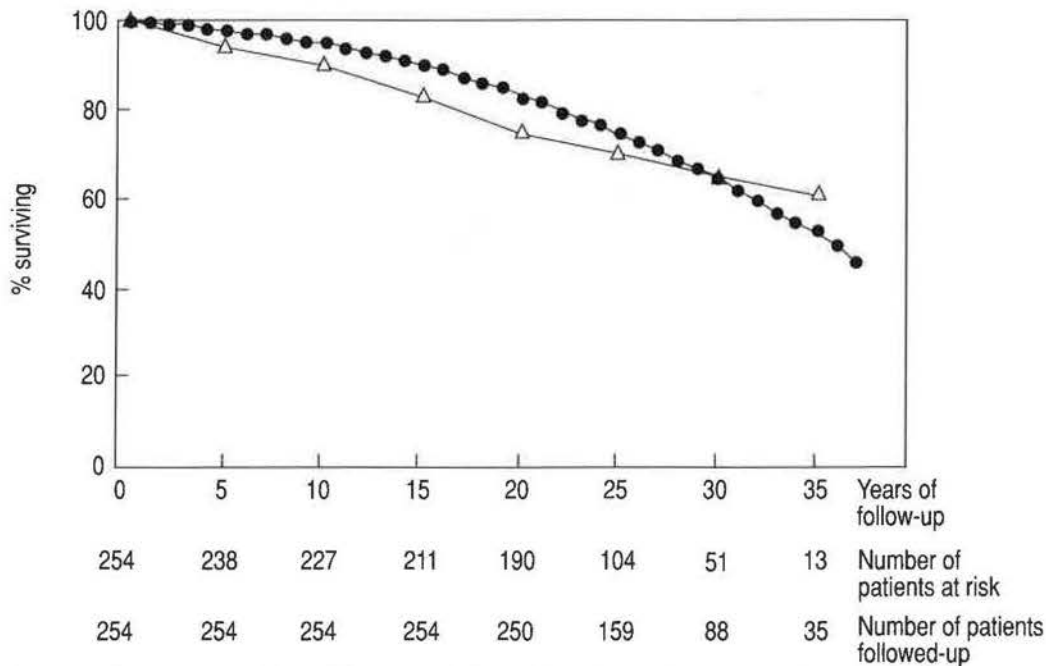


Fig. 1. — Observed and expected survival in 254 patients with intrathoracic sarcoidosis. The number of patients in study during follow-up is given below the curves. Δ: sarcoidosis patients (observed survival); ●: population of Copenhagen (expected survival).

Table 1. - Causes of death during follow-up of 254 patients with intrathoracic sarcoidosis

Cause of death	
Sarcoidosis	17
Sarcoidosis related deaths	
Cor pulmonale	4
Pneumonia	10
Chronic bronchitis	1
Nephrosclerosis	1
Tuberculosis	2
Cancer	
Cancer of the lung	4
Lymphoma	0
Others	12
Cardiovascular	18
Renal disease	1
Accidents and suicides	7
Unknown	3

Only 24 patients (9%) had erythema nodosum during the course of the disease. Of these 24 patients, 3 died during follow-up, 3.4 deaths were expected. The prognosis for these patients was better than for others within the patient population. If patients with erythema nodosum are compared with the population of Copenhagen, or if a correction for age is made, erythema nodosum is of no prognostic importance.

Steroid treatment was given to 52 of the 254 patients (20%) during the course of the disease. There was no difference in the frequency with which patients with and without a histological diagnosis were treated with steroids. The indications were the usually accepted: hypercalcaemia (7 patients), or progression in X-ray changes and/or shortness of breath (45 patients). The excess mortality was concentrated in the group treated with steroids (31 deaths observed *versus* 18 expected), whereas 49 deaths were observed *versus* 47.5 expected in the untreated group ($p < 0.0001$). When a correction for age and X-ray stage was made in a Cox multivariate regression model, there was still a significant excess death in the group treated with steroids compared to those not treated. However, when in addition a correction for FEV₁ was made, a significant excess death was no longer present. If only deaths from sarcoidosis are looked at, there was, after correction for age, X-ray stage and FEV₁, a 4 fold increase ($p < 0.05$) of deaths among those treated with steroids. The study is not prospective and no randomization to treatment had taken place.

Hypercalcaemia was not related significantly to mortality.

The observed and calculated number of deaths according to the initial X-ray stages is shown in table 2. There is a significant excess mortality for patients in stage 3. Patients whose chest X-ray was normalized at examination in 1971 compared to the X-ray at inclusion had a favourable prognosis; among these 76 patients, 7 deaths were observed *vs* 10.1 expected (O/E = 0.7, 95% confidence interval 0.6-0.9). In 32 patients with partial regression O/E was 1.4 (0.9-1.9), in 14 patients with progression O/E was 1.6 (0.9-2.7); and in 95 patients with unchanged X-ray O/E was 1.2 (1.0-1.5). Thirty seven patients had no X-ray taken in 1971.

Table 2. - Observed and expected number of deaths according to X-ray stage (254 patients)

X-ray stage	n	Observed deaths	Expected deaths	O/E ratio	95% confidence interval
1	52	6	9.2	0.7	0.3-1.6
2	134	43	34.7	1.2	0.9-1.7
3	68	31	21.6	1.4*	1.0-2.0

*: $p < 0.05$; O/E: observed/expected.

Table 3. - Observed and expected number of deaths according to lung function (254 patients)

Lung function parameter	n	Observed deaths	Expected deaths	O/E ratio	95% CI
FEV₁					
≤50% pred	30	23	13.6	1.7*	1.1-2.6
51-80% pred	78	17	14.1	1.2	0.7-1.9
>80% pred	52	8	8.3	1.0	0.5-2.0
FEV₁/FVC					
<70%	44	23	14.2	1.6*	1.1-2.4
≥70%	116	25	21.9	1.1	0.7-1.6
VC					
<80% pred	128	47	35.1	1.3	1.0-1.7
≥80% pred	94	26	22.4	1.2	0.8-1.8
TLC					
≤80% pred	35	23	13.2	1.7*	1.1-2.6
81-120% pred	171	45	38.3	1.2	0.9-1.6
>120% pred	16	5	6.1	0.8	0.3-1.9

pred: predicted; *: $p < 0.05$; O/E: observed/expected; CI: confidence interval; FEV₁: forced expiratory volume in one second; FEV₁/FVC: FEV₁/forced vital capacity ratio; VC: vital capacity; TLC: total lung capacity.

Table 4. - Mortality according to lung function and X-ray staging

	Mortality risk	95% CI
FEV₁		
≤50% pred	4.2***	1.8-9.6
51-80% pred	1.5	0.6-3.4
(when compared with FEV ₁ >80% pred)		
FEV₁/FVC		
<70%	1.9*	1.0-3.6
(when compared with FEV ₁ /FVC ≥70%)		
VC		
<80% pred	1.4	0.9-2.3
(when compared with VC ≥80% pred)		
TLC		
≤80% pred	2.6**	1.5-4.5
(when compared with TLC >80% pred)		
X-ray stage 2	2.2	0.9-5.3
X-ray stage 3	2.5*	1.1-6.2
(when compared with stage 1)		

Results of multivariate Cox regression models, with age and sex entered as covariates. *: $p < 0.05$; **: $p < 0.005$; ***: $p < 0.001$. For abbreviations see legends to table 3.

In table 3 the relationship between FEV₁, VC, FEV₁/FVC, and TLC, and observed and expected number of deaths is seen. Relative death risks for lung function parameters and X-ray staging have been calculated using multivariate Cox regression models, with age and sex entered as covariates. Results of these analyses are shown in table 4. Within the patient population a low FEV₁ and TLC were especially associated with an increased mortality risk.

Discussion

The patients in this study are selected as they have all been referred to a specialist department. This is not usual for all patients suspected of sarcoidosis. In Denmark, it is not considered necessary to bioptically verify sarcoidosis in younger persons with bilateral hilar adenopathy and no symptoms, or symptoms compatible with sarcoidosis [14], and these patients are rarely referred to hospital. Thus, the results of this study could be expected to be worse than those that would apply to the general population of patients with sarcoidosis. Very few studies have described the survival of defined populations of patients with sarcoidosis compared to that of a population of similar background [5–9]. The observation periods have generally been short. In the present study, we observed a statistically significantly lower than expected survival up to 20 yrs of observation, but the survival is not much different from that of the general population; a finding very similar to that of the previous shorter term studies. A prognostic factor is X-ray stage, which could be expected, as the frequency with which X-ray changes clear up depends entirely on stage.

Causes of deaths in most studies have been dominated by pulmonary sarcoidosis [2, 5, 6, 10]. This too is the case in the present study, but as age has influenced our patients to a higher degree than in previous studies, other causes are frequent as well. A dispute - mainly Danish - has been going on for years concerning a connection between lymphoma, lung cancer, cancer in general and sarcoidosis [15–17]. In the present study, none of the patients had ever had malignant lymphoma and only four had had lung cancer, which is not in excess of the number expected. Our findings, thus, lend no support to the alleged link between sarcoidosis, lymphoma and lung cancer [15, 16].

Few patients in this study had had erythema nodosum, probably because patients with this symptom often had stage 1 disease and, therefore, would not be admitted to hospital. Among these patients, a better prognosis *quo ad vitam* could not be confirmed. Previously, the chances for clearing of the X-ray in particular have been shown to be good.

Advanced age at diagnosis was not a predictor of a poorer survival than expected. Patients who are diagnosed at the second peak of incidence, which in Denmark is at the age of 50 yrs [7], presumably represent a population with persistent disease, and only rarely new cases. This, however, does not affect long-term prognosis.

Pulmonary function changes in sarcoidosis were first

described to be restrictive. That this is not always the case has been pointed out in several investigations showing an obstructive pattern or a combination of restriction and obstruction as in the present study [18, 19]. FEV₁ has been a marker of prognosis in studies of chronic obstructive pulmonary disease (COPD) [20, 21]; in the present study it was the best spirometric predictor of survival. Other parameters were of less influence.

Treatment with steroids was associated with a very unfavourable outcome as compared to no steroid treatment. The study was in no way designed to evaluate treatment. However, no study has ever documented the long-term value of steroid treatment for chest X-ray, spirometric changes or survival [18, 22, 23].

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