Respiratory Medicine (2009) **103**, 913–918

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/rmed

Health-related quality of life in adult survivors of childhood sarcoidosis

Nils Milman [a,*], **Claus Bo Svendsen** [b], **Anne Lisbeth Hoffmann** [c]

[a] *The Heart Centre, Division of Lung Transplantation, Rigshospitalet, University of Copenhagen, Denmark*
[b] *Statens Serum Institut, Department of Bacteriology, Mycology and Parasitology, Artillerivej 5, Building 43/112, DK-2300 Copenhagen S, Denmark*
[c] *Department of Paediatrics, Næstved Hospital, Næstved, Denmark*

Received 26 July 2008; accepted 5 December 2008
Available online 19 January 2009

KEYWORDS
Children;
Follow-up;
Quality of life;
Sarcoidosis;
SF-36

Summary
Aim: To describe health-related quality of life (hrQOL) in adult subjects who had sarcoidosis in childhood.
Methods: Forty-six children (24 boys), all ethnic Danes ≤15 years of age with sarcoidosis were recorded in Denmark in 1979–1994. Three patients were deceased prior to this study. At follow-up, the 43 surviving adult subjects were invited to complete the short-form health survey questionnaire SF-36, being completed by 34 subjects (14 men). SF-36 scores were compared with the scores in the Danish reference population.
Results: At follow-up, 30/34 patients had recovered from sarcoidosis and 4/34 patients had persistent chronic active disease with impaired lung function. SF-36 scores in all domains were similar to scores in the reference population; the four patients with chronic active disease had lower scores in three domains. In the entire series, physical component summary (PCS) score and mental component summary (MCS) score was similar to the reference population.
Conclusion: Childhood sarcoidosis has a favourable prognosis concerning health status in adulthood. The majority of adult subjects had a health status that was indistinguishable from a healthy reference population.

The overall incidence of sarcoidosis in Denmark is 7.2/100,000 person-years with the peak incidence occurring at ~30 years of age.[1] Among Danish children, the incidence rises from 0.06/100,000 person-years at ≤4 years of age to 1.02/100,000 person-years at 14–15 years of age with an overall incidence of 0.29/100,000 person-years.[1,2] The natural history of sarcoidosis has been studied most extensively in adults.[1,3–5] A number of studies have

* Corresponding author. Tel.: +45 20 10 35 77; fax: +45 35 45 26 48.
E-mail addresses: nils.mil@dadlnet.dk (N. Milman), clv@ssi.dk, clausbo@dadlnet.dk (C.B. Svendsen), alho@regionsjaelland.dk (A.L. Hoffmann).

0954-6111/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.rmed.2008.12.007

assessed the quality of life (QOL) in adults with sarcoidosis using different approaches and questionnaires.[6–11]

Few papers have reported the natural history and prognosis of sarcoidosis in children, including a Danish study.[2,12] To our knowledge, there exist no studies, which have assessed the health-related quality of life (hrQOL) in adulthood following sarcoidosis in childhood.

The objectives of the present study were to describe the impact of childhood sarcoidosis on the hrQOL at follow-up in adulthood using a standardised questionnaire, and to evaluate the relation to clinical outcome of the disease. Hence, this work represents cross-sectionally obtained information adding to the work previously published by two of the authors.[2,12]

Material and methods

Study subjects and design

The study was approved by the Regional Ethics Committee and the recruitment of the patients has been described in detail previously.[2,12] Patients with a diagnosis of sarcoidosis ($n = 5536$) were drawn from the Danish National Patient Registry in the period 1979–1994[2]; 81 patients were $\leq$15 years old and by retrospective chart review, three patients were excluded: a pair of monozygotic twins who by genetic analysis proved to have Blau syndrome[13] and a Lebanese boy who was unavailable at follow-up. The diagnosis of sarcoidosis could be reconfirmed in 46 patients as previously described.[2,12] The series thus comprised 46 patients (24 males), all ethnic Caucasian Danes.[12]

Three patients were deceased before this hrQOL study was initiated: I. A 15 year-old (at onset) boy with pulmonary sarcoidosis stage II, chronic iridocyclitis, and central nervous system (CNS) sarcoidosis died in status epilepticus at 19 years of age. II. A 15-year-old (at onset) girl with pulmonary sarcoidosis stage II and CNS sarcoidosis with obstructive hydrocephalus died at 32 years of age from cerebral infarctions. III. An 11 year-old (at onset) boy with pulmonary sarcoidosis stage II, iridocyclitis, facial palsy, peripheral lymphadenitis and hypercalcaemia was treated with azathioprine for 2 years. He died at 21 years of age from acute myeloid leukaemia.

Methods

By letter, the 43 surviving subjects were invited to a clinical follow-up examination in November 1999.[12] The letter contained the Danish version of the Medical Outcomes Study 36-Item short-form health survey questionnaire (SF-36).[14,15] At the follow-up visit, 34 subjects had completed the questionnaire, which was checked by the examiner. The evaluation of hrQOL was thus performed in a cross-sectional manner.

SF-36 is a generic, standardised health questionnaire consisting of 36 questions that measure 8 dimensions (subscales) of health status: physical functioning (PF); limitations in usual role activities due to physical problems, role limitation physical (RP); bodily pain (BP); general health perception (GH); energy and vitality (VT); social functioning (SF); limitations in usual role activities due to emotional problems, role limitation emotional (RE); and mental health (MH). In addition there are two summary scores concerning physical and mental health: physical component summary score (PCS) and mental component summary score (MCS). Subscale scores are transformed to a range from 0 to 100, with a score of 100 indicating the highest rating of health, i.e., each individual receives a percentile score that can be compared to ''standardised'' scores obtained in a control series of approximately 6000 randomly selected Danish men and women representing the reference population.[14]

Clinical follow-up comprised pulmonary function tests and chest X-ray. Pulmonary function tests including diffusion capacity for carbon monoxide (D_LCO) were performed on a body plethysmograph (Medical Graphics Corp., St. Paul, Minnesota, USA). Chest X-ray findings were scored in a blinded fashion by the authors (data presented elsewhere[12]).

Vital status was checked in the Danish Census Registry in September 2006, where all 43 subjects included in the study were alive.

Analysis

Differences between non-parametric data were analysed using Mann-Whitney's *U* test and between categorical data using Pearson's Chi-square test or Fisher's exact test as appropriate. Internal consistency reliability coefficients of SF-36 data were assessed using Cronbach's alpha test. Comparison between patient SF-36 data and control SF-36 data was assessed by a two-sided Student's *t*-test for unpaired data with a correction for inequality of group size and variance (Welch–Satterthwaite equation). We chose a significance level of $p < 0.05$. All analyses were performed using the SPSS 15.0 data package and Microsoft Excel 2003.

Results

Clinical presentation of sarcoidosis

Clinical, laboratory and radiological features at the onset of disease have been described previously.[2] Table 1 (adapted from Milman and Hoffmann[12]) shows the initial presenting features in the 34 subjects (14 men) who completed the SF-36 and the 9 subjects (7 men) who did not. There were significant differences between the groups in the symptom ''dry cough'' and in chest X-ray disease stage ($p = 0.04$ and $p = 0.01$).

Follow-up

Table 2 shows the age at onset of disease, the duration from onset to follow-up and the age at follow-up in the 34 subjects who completed the SF-36 and the 9 subjects who did not. There was a significant difference in the age of onset of disease ($p = 0.03$).

Course of childhood sarcoidosis

Among the 34 subjects who completed the SF-36, 28 subjects were healthy and had normal lung function and chest X-ray. Two men aged 25 and 35 years had recovered

Table 1 Initial cardinal features at onset of disease and chest X-ray stage in children with sarcoidosis, who at follow-up in adulthood completed/not completed SF-36.

Initial symptom	+SF-36 ($n = 34$)	−SF-36 ($n = 9$)	p-value[a]
Erythema nodosum	9	1	NS
Iridocyclitis	8		NS
Peripheral lymphadenopathy	7		NS
Skin sarcoidosis	3		NS
Scar sarcoidosis	1	1	NS
Rhinitis, sinusitis	1	1	NS
Cough		2	0.04
Exertional dyspnoea		1	NS
Fever	1	1	NS
Hypercalcaemic symptoms	1	1	NS
Parotid swelling	1		NS
Abdominal pain		1	NS
Diarrhoea	1		NS
No symptoms, by incidence	1	1	NS
Chest X-ray stage			
0	1	3	0.01
I	21		
II	11		
III	1	6	

[a] Fisher's exact test (two-sided).

with sequelae, one with chest X-ray infiltrates and one with permanently impaired unilateral vision; both had normal lung function and appeared otherwise fit and healthy. Four subjects aged 18—36 years (one man) had chronic active pulmonary disease with impaired lung function; in addition, one woman had central nervous system (CNS) affection with diabetes insipidus and one woman had chronic intestinal sarcoid disease.

Through the census registry and various health registries we obtained information of vital status and general health in the 9 subjects who did not complete SF-36. Seven subjects were in perfect health. One man aged 36 years had allergic bronchial asthma and one man aged 36 years had chronic active CNS sarcoidosis with hypophyseal insufficiency and diabetes insipidus. This was not significantly different from the patients having completed the SF-36 (χ^2 test; $p = 0.75$).

Table 2 Follow-up of children with sarcoidosis who in adulthood completed/did not complete the SF-36 questionnaire.

	Clinical follow-up	Registry follow-up	p-value[b]
	+SF-36 $n = 34$	−SF-36 $n = 9$	
Age at onset of symptoms (y)[a]	14 (1—16)	15 (13—16)	0.03
Follow-up after onset of sarcoidosis (y)[a]	16 (7—23)	17 (10—21)	0.69
Age at follow-up (y)[a]	28 (18—37)	30 (23—35)	0.14

[a] Median (range).
[b] Mann-Whitney's U test.

SF-36

All 34 subjects completed the SF-36 reliably. This was confirmed by the high Cronbach's alpha coefficients for internal consistency concerning both physical and mental components as shown in Table 3.

The SF-36 scores are shown in Table 4 and Fig. 1. The SF-36 scores in adult subjects with childhood sarcoidosis aged 18—37 years were compared with the scores in a reference population of healthy Danes aged 16—44 years.[15] Subjects with childhood sarcoidosis had significantly higher scores concerning role limitation physical (RP) (men, $p = 0.01$), role limitation emotional (RE) (men, $p = 0.02$) and bodily pain (BP) (women, $p = 0.02$) than reference subjects. There were no consistent differences in the scores of the other SF-36 components.

SF-36 in relation to outcome of sarcoid disease

The SF-36 scores in the two men with sequelae from sarcoidosis did not deviate significantly from the scores in the 28 completely healthy subjects (data not shown). However, in the four subjects with chronic active disease the scores of the categories energy and vitality (VT), mental health (MH) and mental component summary score (MCS) were significantly lower compared with the other 30 patients (Fig. 1; p-values ranging from 0.005 to 0.016).

SF-36 relation to paraclinical variables

In the entire series, we found no association between SF-36 scores and chest X-ray stage, pulmonary function tests or tobacco smoking. Fourteen patients were treated (3 were still in treatment) with prednisolone for median 17 months (range 3—276). There was no association between prednisolone treatment treated as a binary variable (treatment vs. non-treatment) and SF-36 scores.

Table 3 Internal consistency reliability coefficients (Cronbach's alpha) of SF-36 questionnaire completed in adulthood by subjects with childhood sarcoidosis.

Sarcoidosis ($n = 34$)	Dimension of health status							
	PF	RP	BP	GH	VT	SF	RE	MH
Cronbach's alpha	0.86	0.94	0.97	0.91	0.92	0.95	0.88	0.91

PF = physical functioning; RP = role limitation physical; BP = bodily pain; GH = general health perception; VT = energy and vitality; SF = social functioning; RE = role limitation emotional; MH = mental health.

Table 4 SF-36 scores (*mean ± SD*) in adult subjects aged 17–36 years with childhood sarcoidosis and in healthy Danes aged 16–44 years.

Gender	SF-36 Component	Patients	Danish Reference[a]	*p*-value[b]
Male	PF	96 ± 6	96 ± 11	NS
	RP	98 ± 7	93 ± 19	0.01
	BP	83 ± 28	85 ± 19	NS
	GH	81 ± 16	81 ± 16	NS
	VT	75 ± 19	73 ± 17	NS
	SF	92 ± 16	94 ± 13	NS
	RE	98 ± 9	92 ± 21	0.02
	MH	87 ± 12	84 ± 13	NS
	MCS	56 ± 6	54 ± 7	NS
	PCS	54 ± 5	54 ± 6	NS
	n	*14*	*1084*	
Female	PF	96 ± 8	94 ± 12	NS
	RP	93 ± 20	89 ± 26	NS
	BP	89 ± 19	79 ± 22	0.02
	GH	78 ± 26	81 ± 17	NS
	VT	70 ± 19	69 ± 18	NS
	SF	90 ± 15	92 ± 15	NS
	RE	85 ± 30	88 ± 26	NS
	MH	78 ± 18	80 ± 15	NS
	MCS	50 ± 11	53 ± 8	NS
	PCS	55 ± 7	53 ± 7	NS
	n	*20 (18 for MCS/PCS)*	*1150*	
All	PF	96 ± 7	95 ± 11	NS
	RP	95 ± 16	92 ± 23	NS
	BP	86 ± 23	82 ± 21	NS
	GH	79 ± 22	81 ± 17	NS
	VT	72 ± 19	72 ± 18	NS
	SF	91 ± 15	93 ± 14	NS
	RE	90 ± 24	91 ± 23	NS
	MH	81 ± 16	81 ± 14	NS
	MCS	53 ± 10	54 ± 8	NS
	PCS	55 ± 6	54 ± 6	NS
	n	*34 (32 for MCS/PCS)*	*2234*	

PF = physical functioning; RP = role limitation physical; BP = bodily pain; GH = general health perception; VT = energy and vitality; SF = social functioning; RE = role limitation emotional; MH = mental health; PCS = physical component summary; MCS = mental component summary.
NS = not significant.
[a] Values calculated from the Danish reference material.[14]
[b] Student's *t*-test, using Welch–Satterthwaite approximation for unequal variances.

Discussion

The overall prognosis of childhood sarcoidosis in Danes is reasonably good with a recovery rate of 83% (38/46), a chronic morbidity rate of 11% (5/46) and a mortality rate of 7% (3/46). Most patients recover within 6 years of disease onset.[12]

This study describes the health status outcome of childhood sarcoidosis in a consecutive series of ethnic Danish patients. The 9 subjects who did not complete SF-36 appeared to be comparable with the 34 subjects who completed the questionnaire concerning presentation of disease, age and outcome of disease. The results show that adult subjects having survived childhood sarcoidosis have a health status fully comparable to the reference population of healthy Danes matched for gender and age. This was evident for both the physical and mental subscales as well as physical (PCS) and mental component summary scores (MCS). Surprisingly, survivors of childhood sarcoidosis even sporadically showed significantly higher scores concerning role limitation physical (RP) (men), role limitation emotional (RE) (men) and bodily pain (BP) (women) than the reference population (Table 4). This might reflect a purely statistical coincidence due to the relatively small sample size or it could be that having a chronic disease in childhood in some cases improves the persons' coping abilities.

In adult patients with sarcoidosis, symptomatic patients appear to have a poorer health status than those without symptoms.[7] In the present series, subjects who had recovered from childhood sarcoidosis with slight sequelae had similar health status as those who had recovered completely. However, patients with persistent chronic active disease since childhood had a poorer health status, especially concerning the energy/vitality and mental components than those subjects who had recovered completely, showing that the lack of energy associated with active disease has a marked effect on health status (Fig. 1).

We did not find any significant association between health status and a number of paraclinical variables (chest X-ray, lung function, prednisolone treatment, etc.), probably because most subjects were in good health without clinically significant symptoms, e.g., only four subjects had impaired lung function (data not shown, but are presented in detail in Ref. 12).

A few studies of hrQOL have used SF-36 in adult patients with interstitial lung disease including sarcoidosis[6] and in patients with only sarcoidosis.[8] In the series with interstitial lung disease, median physical component summary (PCS) score was 32 and median mental component summary (MCS) score 53.[6] Validation of PCS and MCS scores with physiologic variables showed significant correlations with pulmonary function tests (FEV_1, FVC, D_LCO), 6-minute walking distance and Medical Research Council dyspnoea score.[6]

In adult patients with sarcoidosis (79% African-American), there were decrements in all domains of SF-36 compared to healthy persons, the most significant being in physical functioning (PF), energy and vitality (VT), role limitation physical (RP) and emotional (RE).[9] PCS score in sarcoidosis patients was 34 ± 12 (mean ± SD) vs. 45 ± 10 in control subjects ($p < 0.001$) and MCS score 45 ± 12 vs. 51 ± 10 in controls ($p < 0.001$).[8] Compared to our data, the PCS and MCS scores from adult patients with sarcoidosis were both significantly lower ($p < 0.001$ for both PCS and MCS). Cox et al. found significant correlations between PCS and/or MCS scores and pulmonary function tests (FEV_1, FVC) and dyspnoea score.[8] Patients on oral corticosteroids

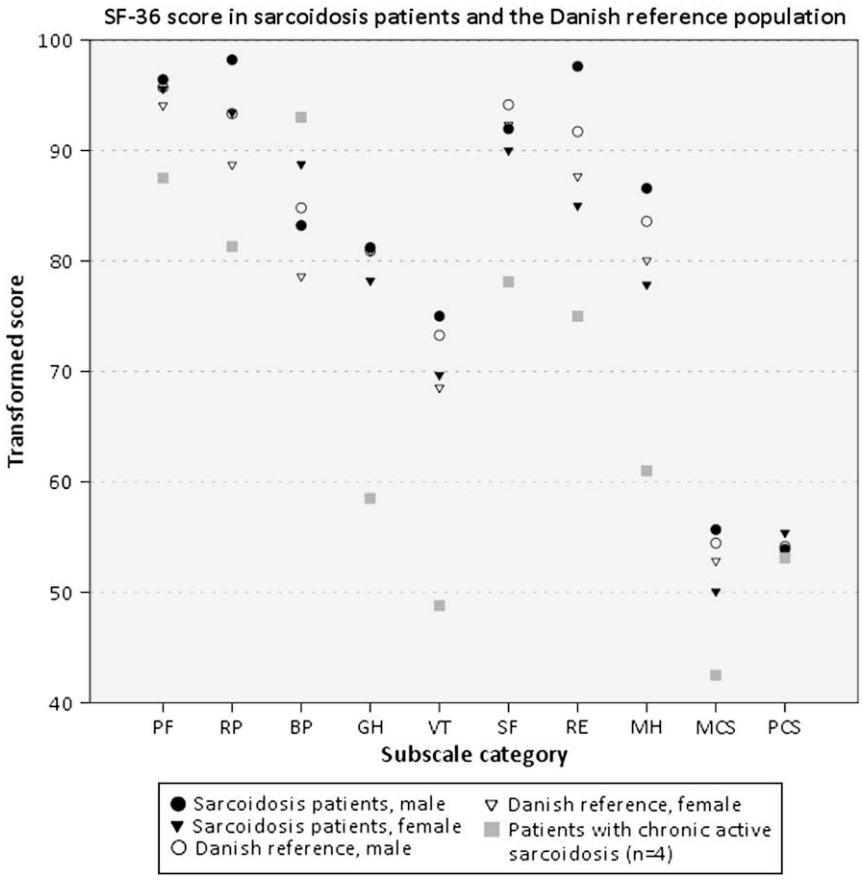

Figure 1 SF-36 scores in adult survivors of childhood sarcoidosis aged 18—37 years and in healthy Danes aged 16—44 years. Scores from ($n = 4$) patients with chronic active sarcoidosis are also included. These differ significantly from the patients without chronic disease in the categories Vitality (VT), Mental Health (MH) and Mental Component Summary (MCS).

had significantly lower PCS score than untreated patients.[8] We could not reproduce the effect of prednisolone treatment in the present series, though 51% of the children had been treated with prednisolone for median (range) 1.3 (0.3—23) years.[12]

In conclusion, childhood sarcoidosis in Danes has a relatively favourable prognosis concerning both survival and health status in adulthood. Most (65%) of our patients recovered completely within median (range) 0.7 (0.6—5.9) years after disease onset. However, there was a mortality rate of 7% that might reflect the fact that sarcoidosis among children is relatively rare and can present with diffuse, extrapulmonary symptoms making it prone to be overlooked by clinicians giving an unintentional doctor's delay in obtaining the diagnosis and hence supplying adequate treatment. The hrQOL in subjects who have survived childhood sarcoidosis is as good as in a healthy reference population.

Conflict of interest statement

None of the authors have any financial involvement in any organisation with a direct financial interest in the subject discussed in the submitted manuscript. None of the authors have conflicts of interest regarding this manuscript.

Acknowledgements

The study was supported by *Dronning Louises Børnehospitals Forskningsfond*.

References

1. Byg KE, Milman N, Hansen S. Sarcoidosis in Denmark 1980—1994. A registry-based incidence study comprising 5536 patients. *Sarcoidosis Vasc Diffuse Lung Dis* 2003 Mar;**20**(1):46—52.
2. Hoffmann AL, Milman N, Byg KE. Childhood sarcoidosis in Denmark 1979—1994: incidence, clinical features and laboratory results at presentation in 48 children. *Acta Paediatr* 2004 Jan;**93**(1):30—6.
3. Milman N, Selroos O. Pulmonary sarcoidosis in the Nordic countries 1950—1982. II. Course and prognosis. *Sarcoidosis* 1990 Sep;**7**(2):113—8.
4. Milman N, Selroos O. Pulmonary sarcoidosis in the Nordic countries 1950—1982. Epidemiology and clinical picture. *Sarcoidosis* 1990 Mar;**7**(1):50—7.
5. Scadding JG, Mitchell DN. *Sarcoidosis*. 2nd ed. London: Chapman and Hall; 1985.
6. Chang JA, Curtis JR, Patrick DL, Raghu G. Assessment of health-related quality of life in patients with interstitial lung disease. *Chest* 1999 Nov;**116**(5):1175—82.
7. de Vries J, Drent M. Quality of life and health status in sarcoidosis: a review. *Semin Respir Crit Care Med* 2007 Feb;**28**(1):121—7.

8. Cox CE, Donohue JF, Brown CD, Kataria YP, Judson MA. Health-related quality of life of persons with sarcoidosis. *Chest* 2004 Mar;**125**(3):997—1004.
9. Cox CE, Donohue JF, Brown CD, Kataria YP, Judson MA. The Sarcoidosis Health Questionnaire: a new measure of health-related quality of life. *Am J Respir Crit Care Med* 2003 Aug 1; **168**(3):323—9.
10. Michielsen HJ, Peros-Golubicic T, Drent M, de Vries J. Relationship between symptoms and quality of life in a sarcoidosis population. *Respiration* 2007;**74**(4):401—5.
11. Wirnsberger RM, de Vries J, Breteler MH, Van Heck GL, Wouters EF, Drent M. Evaluation of quality of life in sarcoidosis patients. *Respir Med* 1998 May;**92**(5):750—6.
12. Milman N, Hoffmann AL. Childhood sarcoidosis: long-term follow-up. *Eur Respir J* 2008 Mar;**31**(3):592—8.
13. Milman N, Andersen CB, Hansen A, et al. Favourable effect of TNF-alpha inhibitor (infliximab) on Blau syndrome in monozygotic twins with a de novo CARD15 mutation. *APMIS* 2006 Dec;**114**(12):912—9.
14. Bjorner JB, Damsgaard MT, Watt T, Bech P, Rasmussen NK, Kristensen TS, et al. *Danish manual to SF-36. A questionnaire about health status*. Copenhagen: LIF; 1997.
15. Ware Jr JE, Snow KK, Gandek B. *Sf-36 health survey. Manual and interpretation guide*. Boston: The Health Institute, New England Medical Center; 1993.