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Childhood sarcoidosis in Denmark 1979-1994: long-term follow-up of 46 children

Running headline: Follow-up of childhood sarcoidosis

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Abstract

Aim: To describe clinical features and long-term survival of childhood sarcoidosis. **Methods***:* Forty-six children, ethnic Caucasian Danes, (24 males) <16 years of age with sarcoidosis were identified in 1979-1994. In 33/46 (72%) children, diagnosis was verified by histology, in 13 by clinical and radiological findings. 37 subjects had a follow-up examination. Median age at onset of disease was 14 years (range 0.7-15.8). Clinical follow-up was median 15 years (range 3-23) after onset of disease. Median age at clinical follow-up was 28 years (range 17-30). **Results:** 36/46 children (78%) recovered completely; 30/46 (65%) showed complete clinical regression at median 0.7 years (range 0.6-5.9) after onset of disease; 2/46 (4%) recovered with organ damage (unilateral loss of vision, abnormal chest X-ray); 5/46 (11%) still have chronic active disease with multiorgan involvement and impaired lung function. Three subjects (7%) were deceased, due to central nervous system (CNS) sarcoidosis and acute myeloid leukaemia probably caused by cytostatics. **Conclusion:** In Danish children, sarcoidosis had a favourable prognosis; the majority recovered within 6 years after onset of disease. Some developed chronic active disease and impairment of pulmonary function demanding continuing medical treatment. Prognosis was not related to the age at onset of disease. Erythema nodosum was associated with a good prognosis and CNS involvement with a poor prognosis.

Key words: children; follow-up; sarcoidosis and other granulomatosis

Sarcoidosis is a disease of unknown aetiology, characterised by the formation of non-necrotizing epithelioid cell granulomas with multiorgan involvement (1). The overall incidence of sarcoidosis in Denmark is 7.2/100 000 personyears with the peak incidence occurring at ~30 years of age (2). Among Danish children the incidence rises from 0.06/100 000 personyears at ≤4 years of age to 1.02/100 000 personyears at 14-15 years of age with an overall incidence of 0.29/100 000 personyears (2, 3). The incidence declines from the Western to the Eastern part of Denmark both in adults (2) and in children (3). The regional variations in incidence rates are probably due to regional differences in diagnostic awareness although environmental and genetic differences might also be involved (2).

The natural history of sarcoidosis has been studied most extensively in adults (2, 4-6). In contrast, the natural history and prognosis of sarcoidosis has been scarcely investigated in children (3). Consequently, the objective of the present study was to describe the long-term course and prognosis of childhood sarcoidosis in Denmark, especially with respect to clinical outcome and vital prognosis.

Patients and methods

The study was approved by the Ethics Committee in the Region of Copenhagen. In Denmark all patients discharged from any hospital are registered by their diagnoses in a Nationwide Patient Registry established in 1979 and hosted by the National Board of Health. Patients with a diagnosis of sarcoidosis were drawn from this National Patient Registry in the period 1979-1994 (3). In total, 5536 patients were drawn from the registry; 81 patients were <16 years old. By reassessment of the patient records and registry information, the diagnosis of sarcoidosis could be reconfirmed in 49 (61%) patients, i.e. in one more patient than in the initial series (3).

From our series of 49 patients, three patients were excluded. A pair of monozygotic twins, who later proved to have Blau syndrome (7) and an ethnic Lebanese boy who had returned to his country and was unavailable for follow-up. The final series thus comprised 24 males and 22 females (male/female ratio 1.1), all ethnic Caucasian Danes. In 33/46 (72%) patients, the diagnosis was verified by examination of tissue biopsy specimens showing sarcoid granulomas. In 13 patients, characteristic chest X-ray findings (hilar adenopathy) associated with typical clinical features and/or laboratory findings (erythema nodosum (EN), uveitis, peripheral

lymphadenopathy, elevated serum angiotensin converting enzyme (SACE)) substantiated the diagnosis (3).

By letter, the subjects were invited to a clinical follow-up examination in November 1999; 37 subjects responded and had a clinical examination, which is referred to as "clinical follow-up". At closure of the study in September 2006, vital status on all 46 subjects was checked in the National Census Registry, which is referred to as "registry follow-up".

Clinical follow-up comprised a history, clinical examination, blood samples for biochemical analyses performed by standard laboratory methods and chest X-ray. Chest X-ray findings were scored in a blinded fashion by the authors. Blood pressure was measured with an Hg manometer. Pulmonary function tests including diffusion capacity for carbon monoxide (D_LCO) were performed on a body plethysmograph (Medical Graphics, St. Paul, Minnesota,USA).

Data analysis

The Excel program (Microsoft Corporation, Bellevue, Washington, USA) was used in analysis of the data.

Results

Duration of follow-up

Table 1 shows the duration of follow-up and the age at follow-up. Median age at onset of symptoms was 14.0 years (range 0.7-15.8); 1 patient was in the age range of 0-4 years, 10 patients were 5-11 years, and 35 were 12-15 years of age. The age at the diagnosis of sarcoidosis was slightly higher, median 14.5 years (range 3.8-16.3).

Table 1. Follow-up of children with sarcoidosis in Denmark diagnosed 1979-1994

	Clinical follow-up 1999 n = 37	Registry follow-up 2006 n = 46
Follow-up after onset of sarcoidosis (y)*	15 (3-23)	23 (4-30)
Age at follow-up (y)*	28 (17-30)	29 (18-42)

*) Median (range)

Two patients (4%) reported sarcoidosis in the family, one mother, one father, who both had recovered from the disease.

Clinical features at onset of disease

Clinical, laboratory and radiological features at the onset of disease have been described previously (3). General malaise, weight loss, fever, respiratory symptoms, lymphadenopathy, skin manifestations, ocular and central nervous system (CNS) symptoms were frequent at onset of disease, whereas arthritis was infrequent (3). The initial cardinal symptom/clinical finding at the onset of disease, which urged the patients to contact the health care system is shown in Table 2.

Table 2. Initial cardinal features at onset of disease in 46 patients with childhood sarcoidosis

Initial symptom	n
Erythema nodosum	10
Iridocyclitis	10
Peripheral lymphadenopathy	7
Skin sarcoidosis	3
Scar sarcoidosis	2
Rhinitis, sinusitis	2
Cough, exertional dyspnoea	2
Fever	2

Hypercalcaemic symptoms	2
Parotid swelling	1
Facial palsy	1
Abdominal pain	1
Diarrhoea	1
No symptoms, by incidence	2
Total	46

Treatment

The children were followed and treated in the regional departments of paediatrics all over Denmark. There were no approved common guidelines for treatment, which was at the discretion of the local doctors and it is beyond the scope of the present paper to analyse the effect of therapy. Treatment was preferably given to patients with clinically overt pulmonary involvement, with extrathoracic organ involvement (e.g. CNS involvement) and with hypercalcaemia; 23/45 (51%) of the children were treated with prednisolone for median 1.3 years (range 0.3-23). Two children were in addition treated with methotrexate (MBJ –see below) or azathioprine (JVR – see below).

Outcome at follow-up

In 30/46 (65%) subjects, there was complete clinical regression at median 0.7 years (range 0.6-5.9) after onset of symptoms. At follow-up, 36/46 (78%) of the subjects had recovered completely and appeared fit without health related problems from sarcoid disease (Table 3).

Table 3. Outcome after childhood sarcoidosis in 46 patients diagnosed 1979-1994

	n	%
Fully recovered	36	78
Recovered with sequelae	2	4
Chronic active disease with organ damage	5	11
Death from CNS sarcoidosis	2	
Death from acute myeloid leukaemia associated with treatment	1	
Total deaths	3	7

Two patients recovered with sequelae: I. A 14.6-year-old (at onset) boy recovered with unilateral loss of vision due to sarcoid uveitis, but without activity in ocular disease at follow-up. II. A 12.2-year-old (at onset) boy had persistent radiographic stage II at follow-up, but normal pulmonary function tests.

Five patients had chronic active sarcoidosis: I. A 4.3-year-old (at onset) girl (AH) had permanent impairment of lung function and active sarcoid colitis/proctitis at follow-up 18 years later. II. A 0.7-year-old (at onset) boy (MBJ) had chronic active pulmonary sarcoidosis with impaired lung function at follow-up 24 years later. III. A 15.3-year-old (at onset) boy (JTN) with pulmonary sarcoidosis stage II and neurosarcoidosis with impaired visual field, hypophyseal insufficiency and diabetes insipidus was still on treatment at follow-up 21 years later. IV. A 14.5-year-old (at onset) girl (LN) with iridocyclitis, stage I pulmonary sarcoidosis and neurosarcoidosis with diabetes insipidus still had active stage I pulmonary sarcoidosis with normal lung function tests and diabetes insipidus at follow-up 10 years later. V. A 13.3-year-old (at onset) girl (TM) with hypercalcaemia, nephrocalcinosis and stage I pulmonary sarcoidosis still had active stage III pulmonary sarcoidosis with impaired lung function at follow-up 23 years later.

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Anthropometrics

Anthropometrics were available in 31 subjects (14 men, 17 women). Mean height in men was 1.80 m (range 1.66-1.94). Height was below the age-adjusted gender specific mean height in Danes (1.82 m) in 9/14 (64%) men; two had a height below the 5th percentile (1.70 m); one had a benign course of disease without steroids and was fit and well, the other had chronic active sarcoidosis (MBV) and had been on steroids for 23 years. Mean height in women was 1.67 m (range 1.57-1.78). Height was below the age-adjusted gender specific mean height in Danes (1.69 m) in 11/17 (65%) women; one women (AH) had a height below the 5th percentile (1.59 m), she had chronic active sarcoidosis and had been on steroids for 6 years.

Mean body mass index (BMI) was 24.3. One female patient (3%) was underweight (BMI <18.5); six (19%), two men and four women were moderately overweight (BMI 25.0-29.9), and three (10%), two men and one woman were obese (BMI ≥30).

Organ involvement and course of disease

Table 4 shows the pattern of organ involvement at onset of disease and at follow-up. All children presenting with EN were fit and healthy at follow-up.

Table 4. Organ involvement in childhood sarcoidosis at onset of disease and at follow-up

	Onset of disease		Follow-up	
	(n)	(%)	(n)	
Upper respiratory tract	6/46	13	6 recovered	
Lower respiratory tract				
Abnormal chest X-ray	42/46	91	33 recovered*	1 sequela (stage II) 5 chronic active sarcoidosis** 3 deceased
Skin manifestations				
Erythema nodosum	10/46	22	10 recovered	
Scar sarcoidosis	2/46	4	2 recovered	
Sarcoid skin lesions	3/46	7	2 recovered	1 chronic active sarcoidosis
Lymph nodes				
Peripheral lymphadenopathy	11/46	24	9 recovered	1 sequela (unilateral loss of vision) 1 deceased (acute leukaemia)
Hilar lymphadenopathy	40/46	87	32 recovered	5 chronic active sarcoidosis 3 deceased
Mesenteric lymphadenopathy	1/46	2	1 recovered	
Hypercalcaemia	13/46	28	10 recovered	1 sequela (unilateral loss of vision) 1 chronic active sarcoidosis 1 deceased (acute leukaemia)
Ocular involvement				
Iridocyclitis/uveitis	13/46	28	9 recovered	1 sequela (unilateral loss of vision) 1 chronic active sarcoidosis 2 deceased
Neurosarcoidosis	5/46	11		
Peripheral neuropathy	2/46	4	1 recovered	1 deceased (acute leukaemia)
Central nervous system	3/46	7		1 chronic active sarcoidosis 2 deceased (neurosarcoidosis)

*) Two subjects with initial stage I made a complete clinical recovery with normal lung function, but had no chest X-ray at follow-up

**) Chronic active sarcoidosis indicates that the disease is in a chronic active state and may or may not involve the organ listed

Three children had sarcoid skin lesions – one boy (MBJ) with onset of sarcoidosis at 0.7 years of age still had chronic active pulmonary disease.

Thirteen children presented with uveitis/iridocyclitis; one had permanent unilateral loss of vision, but no activity in ocular disease at follow-up; one still had chronic active sarcoidosis, but no activity in ocular disease at follow-up.

The majority of children presented with mediastinal/hilar lymphadenopathy. Eleven children presented with peripheral lymphadenopathy, predominantly on the neck; 9 children recovered, one had sequela with unilateral loss of vision (see above) and one patient deceased

Of the two patients presenting with abdominal pain, a 15.6-year-old boy had a laparotomy. Mesenteric lymph nodes were enlarged, and examination of appendix vermiformis showed non-caseating epithelioid cell granulomas (3). This patient recovered completely. The other patient, a 4.3-year-old girl had sarcoid involvement of colon and rectum; at follow-up she still had chronic active sarcoidosis involving the colon and lungs (stage IV).

Two children had peripheral facial palsy and iridocyclitis, one recovered completely, the other died of acute myeloid leukaemia. Three children aged 11.2-15.3 years at onset of disease had CNS involvement, and one in addition had facial palsy. At follow-up, one patient still had chronic active sarcoidosis, two deceased.

None of the patients presented with clinically significant sarcoid associated arthritis.

Laboratory analyses at follow-up

Biochemical blood analyses at follow-up were available in 35 subjects (17 men, 18 women) (Table 5). The majority of subjects had values within the normal reference interval. All subjects had normal blood haemoglobin, blood erythrocyte counts, erythrocyte indices (mean corpuscular volume (MCV), mean corpuscular haemoglobin concentration (MCHC)), except one woman with low MCV due to iron deficiency. Blood leukocyte counts, differential counts and platelets were normal, except in one man with slight lymphopenia due to steroid treated chronic active sarcoidosis. Plasma albumin, sodium, potassium, bicarbonate, urea, creatinine and erythrocyte sedimentation rate (ESR) were normal, except in two women with slightly elevated ESR ≤25 mm/1 h, one had non-classified rheumatic disease with arthralgias, the other was healthy.

Serum soluble interleukin-2 receptor (S-sIL-2R) was measured in 28 subjects, in 24 who had recovered and in four with chronic active disease; all subjects who had recovered had normal S-sIL-2R levels, whereas all 4 subjects with active disease had elevated levels (Table 5).

Arterial blood pressure was normal, median 119/80 mm Hg in 29/30 subjects. One man was diagnosed with arterial hypertension (160/123 mg Hg) at follow-up.

Table 5. Results of some laboratory analyses at follow-up of patients who had sarcoidosis in childhood

Variable	n	Median	Range	Reference interval	Abnormal (n)
Plasma total calcium (mmol/L)	35	2.52	2.21-2.73	2.20-2.60	3 (a)
Plasma ionised calcium (mmol/L)	32	1.25	1.19-1.41	1.17-1.34	1 (b)
Plasma IgG (μmol/L)	33	73	43-95	41-99	
Plasma IgA (μmol/L)	33	12.4	4.0-23.1	4.4-22.8	2 (c)
Plasma IgM (μmol/L)	33	0.93	0.29-1.92	0.41-2.19	2 (d)
Plasma IgE (kIU/L)	29	12	2-412	0-100	2 (e)
Serum angiotensin converting enzyme (U/L)	28	48	25-130	30-115	1 (f)
Serum soluble interleukin-2 receptor (U/L)	28	469	317-1660	223-710	4 (g)

(a) 1 woman with hypercalcaemia at diagnosis, at follow-up also high ionised calcium, otherwise healthy
1 woman without hypercalcaemia at diagnosis, at follow-up normal ionised calcium, healthy
1 man without hypercalcaemia at diagnosis, at follow-up normal ionised calcium, healthy
(b) 1 woman with hypercalcaemia at diagnosis, healthy at follow-up (see reference 5)
(c) 1 man with high IgA, healthy
1 man with low IgA (TT), healthy
(d) 1 man with low IgM (TT), healthy;
1 man with low IgM (MBJ) with steroid treated chronic active pulmonary sarcoidosis
(e) 1 woman with sarcoid diabetes insipidus, no allergy (LN)
1 woman with chronic active stage III pulmonary sarcoidosis, no allergy (TM)
(f) 1 woman with chronic active stage III pulmonary sarcoidosis (TM)

(g) 1 woman with S-sIL-2R 876 U/L, SACE 113 U/L, chronic active stage I pulmonary sarcoidosis and diabetes insipidus, not on steroids (LN)
1 woman with S-sIL-2R 1112 U/L, SACE 32 U/L, chronic active stage IV pulmonary sarcoidosis and intestinal sarcoidosis, not on steroids;
1 woman (TM) with S-sIL-2R 1280 U/L, SACE 130 U/L with chronic active stage III pulmonary sarcoidosis and nephrocalcinosis, not on steroids
1 man (MBJ) with S-sIL-2R 1680 U/L, SACE 85 U/L with chronic active stage I pulmonary sarcoidosis, on steroids

Chest radiology

Table 6 shows the chest X-ray findings. At follow-up, chest X-rays were available in 39 subjects. In the 7 subjects, where chest X-rays were not taken at follow-up, radiology at diagnosis showed stage 0 in one patient, stage I in four patients and stage II in two patients. The majority (n = 31) of the 39 subjects had overall "normal" chest X-ray; however 16/31 (52%) subjects had sequelae after mediastinal/hilar lymphadenopathy in the form of mediastinal scar formation or mediastinal "fibrosis". Median time to regression of chest X-ray abnormalities in the 31 children was 2.2 years (range 0.6-5.9) and stages II-IV were seen in 4/39 (10%) patients. Mediastinal/hilar calcifications were noted in 3/39 (8%) of the subjects.

Table 6. Chest X-ray stage at diagnosis and at follow-up of patients with sarcoidosis in childhood

	Diagnosis		Follow-up	
Chest X-ray stage*	n	%	n	%
0	4	8.7	31	80
I	28	60.9	4	10
II	12	26.1	2	5
III	2	4.3	1	3
IV	0	0	1	3
Total	46		39	

*) Stage 0: normal

Stage I: mediastinal/hilar lymphadenopathy

Stage II: mediastinal/hilar lymphadenopathy and parenchymal infiltrates

Stage III: parenchymal infiltrates. Stage IV: pulmonary fibrosis

Changes in chest X-ray findings are shown in Fig. 1; 3/3 patients with stage 0, 20/24 patients with stage I, 7/10 patients with stage II and 1/2 patients with stage III at onset of disease had a normal chest X-ray at follow-up.

Lung function

Table 7 shows the results of pulmonary function tests at follow-up in 33 subjects. Thirty subjects had normal lung function, whereas three subjects with chronic active pulmonary sarcoidosis (AH, TM, MBJ) had impaired lung function.

Table 7. Pulmonary function tests at follow-up of childhood sarcoidosis

Lung function test n =33	Median (range) % of predicted	Abnormal value	n	Comment
VC	101 (45-147)	<80%	1/33	(a)
FVC	103 (50-154)	<80%	2/33	(b)
FEV_1	104 (47-139)	<80%	2/33	(b)
FEV_1/FVC	98 (81-109)	<80%	0/33	
TLC	102 (67-130)	<80%	1/31	(c)
RV/TLC	91 (61-214)	>125%	2/31	(d)
D_LCO	99 (44-134)	<80%	2/31	(e)
D_LCO/VA	98 (58-128)	<80%	2/30	(e)

VC = slow expiratory vital capacity
FVC = forced expiratory vital capacity
FEV_1 = forced expiratory volume in the first second
TLC = total lung capacity
RV = residual volume
D_LCO = diffusion capacity for carbon monoxide
VA = alveolar volume

(a) 1 woman (AH) VC 45% predicted with chronic active pulmonary sarcoidosis

(b) 2 women (AH and TM) FVC 50 and 75%, FEV_1 47 and 58%, both with chronic active pulmonary sarcoidosis

(c) 1 woman (AH) TLC 67% with chronic active pulmonary sarcoidosis

(d) 2 women (AH and TM) RV/TLC 214 and 147%, both with chronic active pulmonary sarcoidosis

(e) 1 woman (TM) D_LCO 54%, D_LCO/VA 76% and 1 man (MBJ) D_LCO 44%, D_LCO/VA 58%, both with chronic active pulmonary sarcoidosis

Sarcoidosis in the young child

In one boy (MBJ) the disease started at 8 months of age with fever and facial erythema. A skin biopsy was interpreted as panniculitis and vasculitis, but later revision disclosed granulomas. A repeat skin biopsy at 16 months of age showed epithelioid cell granulomas. Subsequently the child developed iridocyclitis, splenomegaly, hypercalcaemia and elevated SACE. Chest X-ray showed hilar lymphadenopathy (stage I). The patient has been on life-long treatment with prednisolone. In a period he was treated with methotrexate, which was discontinued due to hypogammaglobulinaemia. At 25 years of age the patient still presents with chronic active pulmonary sarcoidosis, chest X-ray stage I and pulmonary function tests showing normal spirometry values but decreased D_LCO 44% of predicted value and elevated S-sIL-2R. DNA sequencing showed no Blau syndrome associated mutations in exon 4 of the *NOD2 (CARD15)* gene.

Malignancy

One boy with onset of sarcoidosis at 14.6 years of age who had recovered from the disease was successfully operated for seminoma of the testis at the age of 19 years. One boy with onset of sarcoidosis at 11.2 years who had recovered with organ impairment, died at the age of 21 years from acute myeloid leukaemia, probably induced by former treatment with a cytostatic.

Mortality

The three deaths in our series were related to the sarcoid disease. I. A 15.3 year-old (at onset) boy with pulmonary sarcoidosis stage II, chronic iridocyclitis, and CNS sarcoidosis verified by magnetic resonance imaging died in status epilepticus at the age of 19 years. Autopsy was not performed. II. A 14.9-year-old (at onset) girl with pulmonary sarcoidosis stage II and CNS sarcoidosis with facial nerve palsy and obstructive hydrocephalus was treated with an intracerebral shunt. She died at 32 years of age from cerebral infarctions. Autopsy was not performed. III. A 11.2 year-old (at onset) boy (JVR) with iridocyclitis, facial palsy, peripheral lymphadenopathy, hypercalcaemia and pulmonary sarcoidosis stage II had active sarcoid

disease for more than 6 years causing permanent impairment of lung function. In addition to prednisolone, he was treated with azathioprine for 18 months. He died at 21 years of age from acute myeloid leukaemia, probably induced by the cytostatic therapy. Autopsy showed haemorrhagic diathesis and fungal sepsis. The mediastinal and retroperitoneal lymph nodes were adherent in large conglomerates; histologic examination showed hyalinization and fibrosis, no active sarcoid granulomas. The other organs including the brain contained no granulomas.

Discussion

The incidence, clinical picture and prognosis of sarcoidosis display marked racial differences and the majority of studies on children have presented patient series containing subjects of different ethnic origins (8, 9, 10-14). This study describes the initial clinical presentation and outcome of sarcoidosis in a racially uniform consecutive series of ethnic Danish children.

The four most frequent initial presenting symptoms were EN in 22%, iridocyclitis in 22%, peripheral lymphadenopathy in 15% and cutaneous sarcoidosis in 7% of the patients. Arthritis was not a prominent feature in this series even in children with EN. This observation is in contrast to previous series of childhood sarcoidosis having emphasized that arthritis is a common symptom in small children (15,16). However, their patients were racially heterogenous and were not examined for mutations of the *NOD2* gene. Our original series (3) comprised a pair of monozygotic twins having early onset disease with arthritis/periarthritis. They were subsequently diagnosed by genetic analysis as having Blau syndrome (7). Probably, many children previously classified as "early onset sarcoidosis" may in fact have Blau syndrome if properly investigated for *NOD2* mutations. In our series, one child had early onset sarcoidosis at 8 months of age. He developed skin sarcoidosis, iridocyclitis, and had intrathoracic involvement, but no joint symptoms and no Blau associated mutations. He was extensively investigated for autoimmune disease/vasculitis with negative result. Our conclusion is that this patient had "true" early onset sarcoidosis, which appears to be extremely rare in children below one year of age.

In general, the prognosis of childhood sarcoidosis in our series was quite good. Eighty percent of the children recovered completely without functional impairment. However, ~20% suffered from chronic active disease with organ damage or had succumbed from sarcoidosis *per se* or

from complications related to treatment of the disease. Thus the overall prognosis appears to be similar to the prognosis in adults from the Nordic Countries (6).

EN appeared to be an important prognostic marker. Children presenting with EN had a favourable prognosis compared with children without EN. Likewise children with scar sarcoidosis and peripheral lymphadenopathy had a good prognosis. Hypercalcaemia, iridocyclitis and CNS involvement were associated with a less favourable prognosis.

The majority of subjects had anthropometrics, which corresponded to the normal population. Three subjects had a height below the 5th percentile for age. One had not been treated with steroids and had recovered completely from sarcoidosis, whereas two had been on steroids for years due to chronic active disease. In the entire series, one woman was slightly underweight, she had a complete recovery from sarcoidosis and was otherwise fit and healthy. In contrast, overweight was a common finding, 19% were moderately overweight and 10% were obese. These figures are comparable to the general population.

Newly discovered arterial hypertension was found in one man at the follow-up examination. He had a normal BMI of 21 and had smoked 15 pack-years.

Hypercalcaemia was found in 28% of the children at onset of disease, four had symptomatic hypercalcaemia (17). In other studies, hypercalcaemia and hypercalciuria have been reported in 5-35% of the children (8). Hypercalciuria may occur even in the presence of normocalcaemia and may contribute to nephrolithiasis and nephrocalcinosis (16, 18). Four of our children had temporarily impaired renal function due to hypercalcaemia and one had nephrocalcinosis at the initial presentation. Renal dysfunction is most often due to hypercalcaemia, but may occasionally be elicited by granulomatous interstitial nephritis (16). In general, laboratory values at follow-up were within the normal reference intervals. Three subjects had slightly elevated plasma (P-) total calcium at follow-up, but only one of these had elevated P-ionised calcium as well. The disease activity marker SACE was elevated in one women with chronic active sarcoidosis. S-sIL-2R levels were normal in subjects who had recovered, while patients with chronic active disease had elevated levels. Consequently, we assume that S-sIL-2R is a clinically useful marker of sarcoid disease activity (19).

Involvement of the peripheral nervous system and CNS is infrequent in adult Danish sarcoidosis patients affecting approximately 1-2% (5). However, neurological involvement

appeared to be more common in children (4% had facial palcy, 7% CNS involvement) and was associated with a poor prognosis.

Like in adults (5), the most common finding in childhood sarcoidosis is an abnormal chest X-ray (8, 12, 13). In our series, more than 90% had abnormal chest X-ray at onset of disease, stage I in two thirds and stages II-III in one third of the children. At follow-up, 80% had a normal chest X-ray, although some of these subjects had slight mediastinal scarring, some with calcification of the mediastinal lymph nodes; 10% had chronic persistent stage I, and 10% had stages II-IV. This implies that 21% of the subjects presented with an abnormal chest X-ray several years after onset of the disease. However, only 9% of the subjects had impaired pulmonary function tests at follow-up.

More than half of the children had been treated with prednisolone, which may have influenced the (accelerated) the recovery. In a French study on childhood sarcoidosis, 81% of the 21 children were treated with prednisolone. However, their series contained 12 children of black race (14), in whom the disease takes a more severe course (1) and the two series are therefore not comparable.

In conclusion, in sarcoidosis in Danish children, the most frequent initial symptoms/clinical findings include EN, iridocyclitis, peripheral lymphadenopathy and cutaneous sarcoidosis. In general, childhood sarcoidosis has a favourable prognosis, which by and large is similar to the prognosis in adults. Prognosis appears not to be related to the age at onset of disease. The majority of children recover completely within 6 years after onset of disease, a few recover with persisting organ damage. Some develop chronic active disease and impairment of pulmonary function demanding continuous medical treatment. About 7% die at a young age due to sarcoidosis related complications. In general, the presence of EN is associated with a good prognosis and CNS sarcoidosis is associated with a poor prognosis.

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Fig. 1. Changes in chest X-ray findings from diagnosis of disease to follow-up in 39 patients with sarcoidosis in childhood. Figures denote number of subjects