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Childhood sarcoidosis: long-term follow-up

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ABSTRACT: The aim of the present study was to describe clinical features and long-term survival in childhood sarcoidosis.

In total, 46 ethnic Caucasian Danish children (aged <16 yrs, 24 males) with sarcoidosis were identified in 1979–1994. In 33 (72%) children, diagnosis was verified by histology and, in the remaining 13, by clinical and radiological findings. In total, 37 subjects had a follow-up examination. Median (range) age at onset of disease was 14 (0.7–15.8) yrs and median (range) clinical follow-up was 15 (3–23) yrs after onset of disease. The median (range) age at clinical follow-up was 28 (17–30) yrs.

At follow-up: 36 (78%) children recovered completely; 30 (65%) showed complete clinical regression at a median (range) 0.7 (0.6–5.9) yrs after onset of disease; two (4%) recovered with organ damage (unilateral loss of vision, abnormal chest radiograph); five (11%) still had chronic active disease with multiorgan involvement and impaired lung function; and three (7%) were deceased, due to central nervous system sarcoidosis and acute myeloid leukaemia probably caused by cytostatics.

In Danish children, sarcoidosis had a favourable prognosis; the majority recovered <6 yrs after onset of disease. Some developed chronic active disease and impairment of pulmonary function, demanding continuous medical treatment. Prognosis was not related to the age at onset of disease. Erythema nodosum was associated with a good prognosis, and central nervous system involvement with a poor prognosis.

KEYWORDS: Children, follow-up, granulomatosis, sarcoidosis

Sarcoidosis is a disease of unknown aetiology, characterised by the formation of non-necrotising epithelioid cell granulomas with multiorgan involvement [1]. The overall incidence of sarcoidosis in Denmark is 7.2/100,000 person-yrs, with the peak incidence occurring at ~30 yrs of age [2]. Among Danish children, the incidence rises from 0.06/100,000 person-yrs at age ⩽4 yrs to 1.02/100,000 person-yrs at age 14–15 yrs with an overall incidence of 0.29/100,000 person-yrs [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, patients discharged from any hospital are registered according to their diagnoses in a Nationwide Patient Registry, established in 1979 and hosted by the National Board of Health. Patients with a diagnosis of sarcoidosis in the period 1979–1994 were drawn from this National Patient Registry [3]. In total, 5,536 patients were drawn from the Registry; 81 patients were aged <16 yrs. 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 the present 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 young male 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 (72%) patients, the diagnosis was verified by examination of tissue biopsy specimens showing sarcoid granulomas. In 13 patients, characteristic chest radiograph

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findings (hilar adenopathy) associated with typical clinical features and/or laboratory findings (erythema nodosum (EN), uveitis, peripheral lymphadenopathy and elevated serum angiotensin-converting enzyme (SACE)) substantiated the diagnosis [3].

The subjects were invited by letter to a clinical follow-up examination in November, 1999. In total, 37 subjects responded and had a clinical examination, which is herein 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 herein 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 radiograph. Chest radiograph findings were scored in a blinded fashion by the present authors. Blood pressure was measured with a mercury manometer. Pulmonary function tests, including diffusing capacity of the lung for carbon monoxide ($D_{L,CO}$), were performed using a body plethysmograph (Medical Graphics, St Paul, MN, USA).

RESULTS

Duration of follow-up

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

Two (4%) patients reported sarcoidosis in the family, one mother and 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 and 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 for which the patients contacted the healthcare system is shown in table 2.

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 study 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 (51%) out of 45 (data were not available for one patient) of the children were treated with prednisolone for median (range) 1.3 (0.3–23) yrs. Two children were additionally treated with methotrexate (patient 1) or azathioprine (patient 2).

Outcome at follow-up

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

Five patients had chronic active sarcoidosis as follows. 1) A 4.3-yr-old (at onset) female (patient 3) had permanent impairment of lung function and active sarcoid colitis/proctitis at follow-up 18 yrs later. 2) A 0.7-yr-old (at onset) male (patient 1) had chronic active pulmonary sarcoidosis with impaired lung function at follow-up 24 yrs later. 3) A 15.3-yr-old (at onset) male (patient 4) with pulmonary sarcoidosis stage II and neurosarcoidosis, with impaired visual field, hypophyseal insufficiency and diabetes insipidus, was still on treatment at follow-up 21 yrs later. 4) A 14.5-yr-old (at onset) female (patient 5) 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 yrs later. 5) A 13.3-yr-old (at onset) female (patient 6) with hypercalcaemia, nephrocalcinosis and stage I pulmonary sarcoidosis still had active stage III pulmonary sarcoidosis with impaired lung function at follow-up 23 yrs later.

Anthropometrics

Anthropometrics were available in 31 subjects (14 males, 17 females). The mean (range) height in males was 1.80 (1.66–1.94) m. This height was below the age-adjusted sex-specific mean height in Danes (1.82 m) in nine (64%) males and two had a height below the 5th percentile (1.70 m). Of these, one had a benign course of disease without steroids and was fit and well and the other had chronic active sarcoidosis (patient 7) and had been on steroids for 23 yrs. The mean (range) height in females was 1.67 (1.57–1.78) m. This height was below the age-adjusted sex-specific mean height in Danes (1.69 m) in 11 (65%) females. Of these, one (patient 3) had a height below the 5th percentile (1.59 m), had chronic active sarcoidosis and had been on steroids for 6 yrs.

TABLE 1 Follow-up of children with sarcoidosis diagnosed in 1979–1994 in Denmark

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

Data are presented as median (range), unless otherwise stated.

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

Initial symptom	Subjects n
Erythema nodosum	10
Iridocyclitis	10
Peripheral lymphadenopathy	7
Skin sarcoidosis	3
Scar sarcoidosis	2
Rhinitis and/or sinusitis	2
Cough and/or 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

TABLE 3 Outcome after childhood sarcoidosis in 46 patients diagnosed in 1979–1994

	Subjects
Fully recovered	36 (78)
Recovered with sequelae	2 (4)
Chronic active disease with organ damage	5 (11)
Deaths	3 (7)
From central nervous system sarcoidosis	2
From acute myeloid leukaemia associated with treatment	1

Data are presented as n or n (%). Two patients recovered with sequelae: 1) a 14.6-yr-old (at onset) male recovered with unilateral loss of vision due to sarcoid uveitis, but without activity in ocular disease at follow-up; and 2) a 12.2-yr-old (at onset) male had persistent radiographic stage II at follow-up, but normal pulmonary function tests.

Mean body mass index (BMI) was 24.3 $kg \cdot m^{-2}$. One (3%) female patient was underweight (BMI <18.5 $kg \cdot m^{-2}$); six (19%), two males and four females were moderately overweight (BMI 25.0–29.9 $kg \cdot m^{-2}$), and three (10%), two males and one female were obese (BMI $\geqslant 30$ $kg \cdot m^{-2}$).

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.

Three children had sarcoid skin lesions and one male (patient 1) with onset of sarcoidosis at 0.7 yrs of age still had chronic active pulmonary disease.

In total, 13 children presented with uveitis/iridocyclitis. One had permanent unilateral loss of vision, but no activity in ocular disease at follow-up and one still had chronic active sarcoidosis, but no activity in ocular disease at follow-up.

The majority of children presented with mediastinal/hilar lymphadenopathy: 11 children presented with peripheral lymphadenopathy, predominantly on the neck. Of these, nine children recovered, one had sequela with unilateral loss of vision (table 4) and one patient was deceased.

Of the two patients presenting with abdominal pain, a 15.6-yr-old male had had a laparotomy. Mesenteric lymph nodes were enlarged and examination of appendix vermiformis showed noncaseating epithelioid cell granulomas [3]. This patient recovered completely. The second patient, a 4.3-yr-old female, had sarcoid involvement of colon and rectum and at follow-up she still had chronic active sarcoidosis involving the colon and lungs (stage IV).

Two children had peripheral facial palsy and iridocyclitis, of which, one recovered completely, and the other died of acute myeloid leukaemia. Three children aged 11.2–15.3 yrs at onset of disease had CNS involvement and one, in addition, had facial palsy. At follow-up, one patient still had chronic active sarcoidosis and two were 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 males, 18 females; table 5). The majority of subjects had values within the normal reference interval. All subjects had normal blood haemoglobin, blood erythrocyte counts and erythrocyte indices (mean corpuscular volume (MCV) and mean corpuscular haemoglobin concentration), except in one female with low MCV due to iron deficiency. Blood leukocyte counts, differential counts and platelets were normal, except in one male with slight lymphopaenia due to steroid treated chronic active sarcoidosis. Plasma albumin, sodium, potassium, bicarbonate, urea, creatinine and erythrocyte sedimentation rate (ESR) were normal, except in two females with slightly elevated ESR ($\leqslant 25$ $mm \cdot h^{-1}$). Of these, one had nonclassified rheumatic disease with arthralgias and 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 four subjects with active disease had elevated levels (table 5).

Arterial blood pressure was normal, with a median of 119/80 mmHg in 29 out of 30 subjects. One male was diagnosed with arterial hypertension (160/123 mmHg) at follow-up.

Chest radiology

Table 6 shows the chest radiograph findings. At follow-up, chest radiographs were available in 39 subjects. In the seven subjects where chest radiographs 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 of the 39 subjects (n=31) had overall ''normal'' chest radiographs; however, 16 (52%) of the 31 subjects had sequelae after mediastinal/hilar lymphadenopathy in the form of mediastinal

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

	Onset of disease	Follow-up	
		Recovered	Disease if not recovered
Upper respiratory tract	6 (13)	6	
Lower respiratory tract			
Abnormal chest radiograph	42 (91)	33[#]	1 sequela (stage II) 5 chronic active sarcoidosis[¶] 3 deceased
Skin manifestations			
Erythema nodosum	10 (22)	10	
Scar sarcoidosis	2 (4)	2	
Sarcoid skin lesions	3 (7)	2	1 chronic active sarcoidosis
Lymph nodes			
Peripheral lymphadenopathy	11 (24)	9	1 sequela (unilateral loss of vision) 1 deceased (acute leukaemia)
Hilar lymphadenopathy	40 (87)	32	5 chronic active sarcoidosis 3 deceased
Mesenteric lymphadenopathy	1 (2)	1	
Hypercalcaemia	13 (28)	10	1 sequela (unilateral loss of vision) 1 chronic active sarcoidosis 1 deceased (acute leukaemia)
Ocular involvement			
Iridocyclitis/uveitis	13 (28)	9	1 sequela (unilateral loss of vision) 1 chronic active sarcoidosis 2 deceased
Neurosarcoidosis	5 (11)		
Peripheral neuropathy	2 (4)	1	1 deceased (acute leukaemia)
Central nervous system	3 (7)		1 chronic active sarcoidosis 2 deceased (neurosarcoidosis)

Data are presented as n (%) or n. [#]: two subjects with initial stage I made a complete clinical recovery with normal lung function, but had no chest radiograph 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.

TABLE 5 Results of laboratory analyses at follow-up of patients who had sarcoidosis in childhood

Variable	Subjects n	Median (range)	Reference interval	Abnormal n
Plasma total calcium mmol·L^{-1}	35	2.52 (2.21–2.73)	2.20–2.60	3[#]
Plasma ionised calcium mmol·L^{-1}	32	1.25 (1.19–1.41)	1.17–1.34	1[¶]
Plasma IgG μmol·L^{-1}	33	73 (43–95)	41–99	
Plasma IgA μmol·L^{-1}	33	12.4 (4.0–23.1)	4.4–22.8	2[+]
Plasma IgM μmol·L^{-1}	33	0.93 (0.29–1.92)	0.41–2.19	2[§]
Plasma IgE kIU·L^{-1}	29	12 (2–412)	0–100	2[f]
SACE U·L^{-1}	28	48 (25–130)	30–115	1[##]
Serum soluble interleukin-2 receptor U·L^{-1}	28	469 (317–1660)	223–710	4[¶¶]

Ig: immunoglobulin; SACE: serum angiotensin-converting enzyme. [#]: one female with hypercalcaemia at diagnosis also had high ionised calcium at follow-up and was otherwise healthy, one female and one male without hypercalcaemia at diagnosis had normal ionised calcium at follow-up and were healthy; [¶]: one female with hypercalcaemia at diagnosis was healthy at follow-up; [+]: one male with high IgA and healthy, one male with low IgA (patient 8) and healthy; [§]: one male with low IgM (patient 8) and healthy, one male with low IgM (patient 1) with steroid-treated chronic active pulmonary sarcoidosis; [f]: one female with sarcoid diabetes insipidus and no allergy (patient 5), one female with chronic active stage III pulmonary sarcoidosis and no allergy (patient 6); [##]: one female with chronic active stage III pulmonary sarcoidosis (patient 6); [¶¶]: one female with serum soluble interleukin-2 receptor (S-sIL-2R) 876 U·L^{-1}, SACE 113 U·L^{-1}, chronic active stage I pulmonary sarcoidosis and diabetes insipidus and not on steroids (patient 5), one female with S-sIL-2R 1112 U·L^{-1}, SACE 32 U·L^{-1}, chronic active stage IV pulmonary sarcoidosis and intestinal sarcoidosis and was not on steroids, one female (patient 6) with S-sIL-2R 1280 U·L^{-1}, SACE 130 U·L^{-1} with chronic active stage III pulmonary sarcoidosis and nephrocalcinosis and not on steroids, one male (patient 1) with S-sIL-2R 1680 U·L^{-1}, SACE 85 U·L^{-1} with chronic active stage I pulmonary sarcoidosis and on steroids.

scar formation or mediastinal fibrosis. Median time to regression of chest radiograph abnormalities in the 31 children was 2.2 (0.6–5.9) yrs and stages II–IV were seen in four (10%) of the 39 patients. Mediastinal/hilar calcifications were noted in three (8%) of the subjects.

Changes in chest radiograph findings are shown in figure 1; three out of three patients with stage 0, 20 out of 24 patients with stage I, seven out of 10 patients with stage II and one out of two patients with stage III at onset of disease had a normal chest radiograph at follow-up.

Lung function

Table 7 shows the results of pulmonary function tests at follow-up in 33 subjects. In total, 30 subjects had normal lung function, whereas three subjects with chronic active pulmonary sarcoidosis (patients 1, 3 and 6) had impaired lung function.

Sarcoidosis in the young child

In one male (patient 1) 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 radiograph showed hilar lymphadenopathy (stage I). The patient had been on life-long treatment with prednisolone. At one point, he was treated with methotrexate, which was discontinued due to hypo-γ-globulinaemia. At 25 yrs of age, the patient still presented with chronic active pulmonary sarcoidosis, chest radiograph stage I and pulmonary function tests showing normal spirometry values but decreased $D_{L,CO}$ 44% of predicted value and elevated S-sIL-2R. DNA sequencing showed no Blau syndrome-associated mutations in the exon 4 of the *NOD2* (*CARD15*) gene.

Malignancy

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

TABLE 6 Chest radiograph stage at diagnosis and at follow-up of patients with sarcoidosis in childhood

Chest radiograph stage#	Diagnosis	Follow-up
0	4 (9)	31 (80)
I	28 (61)	4 (10)
II	12 (26)	2 (5)
III	2 (4)	1 (3)
IV	0	1 (3)
Total n	46	39

Data are presented as n (%). Stage 0 can be described as normal; stage I as presenting mediastinal/hilar lymphadenopathy; stage II as mediastinal/hilar lymphadenopathy and parenchymal infiltrates; stage III as parenchymal infiltrates; stage IV as pulmonary fibrosis.

Mortality

The three deaths in the present study were related to the sarcoid disease as follows. 1) A 15.3-yr-old (at onset) male with pulmonary sarcoidosis stage II, chronic iridocyclitis and CNS sarcoidosis verified by magnetic resonance imaging, died aged 19 yrs in status epilepticus. An autopsy was not performed. 2) A 14.9-yr-old (at onset) female with pulmonary sarcoidosis stage II and CNS sarcoidosis with facial nerve palsy and obstructive hydrocephalus was treated with an intracerebral shunt and died aged 32 yrs from cerebral infarctions. An autopsy was not performed. 3) A 11.2-yr-old (at onset) male (patient 2) with iridocyclitis, facial palsy, peripheral lymphadenopathy, hypercalcaemia, pulmonary sarcoidosis stage II and active sarcoid disease for >6 yrs causing permanent impairment of lung function was treated with azathioprine for 18 months in addition to prednisolone. He died aged 21 yrs from acute myeloid leukaemia, probably induced by the cytostatic therapy. An autopsy showed haemorrhagic diathesis and fungal sepsis. The mediastinal and retroperitoneal lymph nodes were adherent in large conglomerates; histological examination showed hyalinisation and fibrosis with 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]. The present study describes the initial clinical presentation and outcome of sarcoidosis in a racially uniform consecutive series of 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 the series, even in children with EN. This observation is in contrast to previous series of childhood sarcoidosis, which emphasised that arthritis is a common symptom in small children with the disease [15, 16]. However, those patients were racially heterogenous and were not examined for mutations of the *NOD2* gene. The present authors' 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]. It is possible that many children previously classified as ''early onset sarcoidosis'' may in fact have Blau syndrome if properly investigated for *NOD2* mutations. In the present 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 results. The present authors concluded that the patient had ''true'' early onset sarcoidosis, which appears to be extremely rare in children aged <1 yr.

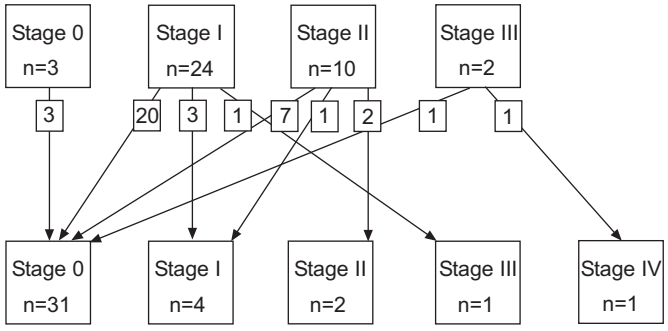

FIGURE 1. Changes in chest radiograph findings from diagnosis of disease to follow-up in 39 patients with sarcoidosis in childhood.

In general, the prognosis of childhood sarcoidosis in the present group of patients was quite good. In total, 80% of the subjects 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. Similarly, 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 that corresponded to the normal population. Three subjects had a height below the 5th percentile for age. Of these, 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 group of patients, one female was slightly underweight, 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 male at the follow-up examination. He had a normal BMI of 21 $kg \cdot m^{-2}$ and had smoked for 15 pack-yrs.

Hypercalcaemia was found in 28% of the children at onset of disease, four of which had symptomatic hypercalcaemia [17]. In another study [8], hypercalcaemia and hypercalciuria have been reported in 5–35% of the children. Hypercalciuria may occur even in the presence of normocalcaemia and may contribute to nephrolithiasis and nephrocalcinosis [16, 18]. Four of the children in the present study 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

TABLE 7 Pulmonary function tests at follow-up of childhood sarcoidosis

Lung function test	Abnormal value %	Median (range) % pred	Abnormal n/N
VC	<80	101 (45–147)	1/33[#]
FVC	<80	103 (50–154)	2/33[¶]
FEV_1	<80	104 (47–139)	2/33[¶]
FEV_1/FVC	<80	98 (81–109)	0/33
TLC	<80	102 (67–130)	1/31[+]
RV/TLC	>125	91 (61–214)	2/31[§]
***D*L,CO**	<80	99 (44–134)	2/31[f]
***D*L,CO/VA**	<80	98 (58–128)	2/30[f]

% pred: % predicted; n: number of subjects who presented abnormal pulmonary function tests; N: total number of subjects tested; VC: vital capacity; FVC: forced vital capacity; FEV_1: forced expiratory volume in one second; TLC: total lung capacity; RV: residual volume; $D_{L,CO}$: diffusing capacity of the lung for carbon monoxide; VA: alveolar volume. [#]: one female (patient 3) had VC 45% pred with chronic active pulmonary sarcoidosis; [¶]: two females (patients 3 and 6) had FVC 50 and 75%, and FEV_1 47 and 58%, respectively, both with chronic active pulmonary sarcoidosis; [+]: one female (patient 3) had TLC 67% with chronic active pulmonary sarcoidosis; [§]: two females (patients 3 and 6) had RV/TLC 214 and 147%, respectively, both with chronic active pulmonary sarcoidosis; [f]: one female (patient 6) had $D_{L,CO}$ 54% and $D_{L,CO}$/VA 76%, and one male (patient 1) had $D_{L,CO}$ 44% and $D_{L,CO}$/VA 58%, both with chronic active pulmonary sarcoidosis.

SACE was elevated in one female 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, the present authors 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 ~1–2% [5]. However, neurological involvement appeared to be more common in children (4% had facial palsy, 7% had CNS involvement) and was associated with a poor prognosis.

As in adults [5], the most common finding in childhood sarcoidosis is an abnormal chest radiograph [8, 12, 13]. In the present series, >90% had abnormal chest radiograph at onset of disease, stage I in two thirds and stages II–III in one third of the subjects. At follow-up: 80% had a normal chest radiograph, 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 radiograph 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 (*i.e.* accelerated) the recovery. In a previous study on childhood sarcoidosis [14], 81% of the 21 children were treated with prednisolone. However, their group of patients contained 12 children of black ethnicity, in whom the disease takes a more severe course [1]. Therefore, the two studies are not comparable.

The present authors conclude that the most frequent initial symptoms/clinical findings in sarcoidosis of Danish children include iridocyclitis, peripheral lymphadenopathy and cutaneous sarcoidosis. In general, childhood sarcoidosis has a favourable prognosis, which 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 yrs after onset of disease, but a few recover with persisting organ damage. Some develop chronic active disease and impairment of pulmonary function demanding continuous medical treatment. Approximately 7% die at a young age due to sarcoidosis-related complications. In general, the presence of erythema nodosum is associated with a good prognosis, and central nervous system sarcoidosis is associated with a poor prognosis.

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