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Catherine Cavalin, Odile Macchi, Dominique Valeyre, Annick Clement

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## Paediatric sarcoidosis

Nadia Nathan<sup>1</sup>, Chiara Sileo<sup>2</sup>, Alain Calender<sup>3</sup>, Yves Pacheco<sup>3</sup>, Dominique Valeyre<sup>4</sup>, Annick Clement<sup>1</sup>, for the French Sarcoidosis Group (GSF) and the Silicosis Group

1. Service de Pneumologie Pédiatrique et Centre de référence des maladies respiratoires rares. AP-HP, Hôpital Trousseau ; Unité INSERM UMR-S933 ; Sorbonne Université, Paris, France.

nadia.nathan@aphp.fr; annick.clement@aphp.fr

2. Service de Radiologie Pédiatrique, AP-HP, Hôpital Trousseau, Paris, France.

chiara.sileo@aphp.fr

3. Service de Génétique, CHU Lyon ; Equipe EA7426 (PI3) Inflammation et immunité de l'épithélium respiratoire, Lyon, France alain.calender@chu-lyon.fr ; yves.pacheco@chu-

lyon.fr

4. AP-HP Service de pneumologie, Hôpital Avicenne, EA2363, Université Paris13, Bobigny, France dominique.valeyre@aphp.fr

### Corresponding author

Nadia Nathan

Paediatric Pulmonology, Hôpital Trousseau

26 avenue du Dr Arnold Netter, 75012-Paris, France

Tel : +33(1) 44 73 66 18

Fax : +33(1) 44 73 67 18

nadia.nathan@aphp.fr

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## **Summary**

Paediatric sarcoidosis is an extremely rare disease characterized by a granulomatous inflammation. The estimated incidence is 0.6 to 1.02/100,000 children, but in the absence of international registers, the disease is probably under-reported. Its pathophysiologic basis is not clearly understood but the current hypothesis is a combination of a genetic predisposition and an environmental exposure that could be either organic or mineral. Contrary to adult forms of the disease, general symptoms are often at the forefront at diagnosis. In its most frequent form, paediatric sarcoidosis is a multi-organ disorder affecting preferentially the lungs, the lymphatic system and the liver, but all organs can be affected. This review aims to provide an overview of current knowledge on sarcoidosis in children, providing a summary of the data available from cohort studies on the presentation, the management and the evolution of the disease in this specific population.

## **1. Introduction**

Sarcoidosis, also called Besnier-Boeck-Schaumann disease, was first described in the 19<sup>th</sup> century as a systemic granulomatous disorder involving predominantly the lungs and the lymphatic system (1). More than a century after, its pathogenesis remains unknown and its pathophysiology remains controversial (2,3). The current hypothesis is a multifactorial disease associating a genetic susceptibility and an environmental exposure that triggers or enhances the inflammatory and granulomatous process. Sarcoidosis is mainly an adult disease, children being affected around 10 times less frequently. Its phenotypic spectrum is wide, from a sub-clinical form with only two organs involved to a severe multi-organic disease (4,5). A pathologic confirmation after rigorous investigation for excluding alternative diagnoses, particularly immune deficiencies, is particularly indispensable in children in whom paediatric sarcoidosis remains a “diagnosis of exclusion”.

The aim of this review is to provide an overview on sarcoidosis in children, and to propose ways to improve its understanding, diagnosis and management. This work is based on the literature on paediatric sarcoidosis that is extremely limited. Most of the studies refer to Blau syndrome and “early onset sarcoidosis”, which are now recognized as specific genetic entities different from sarcoidosis. This inflammatory disorder, that is not discussed in this review is related to *NOD2/CARD15* gene mutations.

## **2. Literature information and epidemiology**

In recent decades, a maximum of 22 manuscripts per year have been published with reference (in the title or in the abstract) to paediatric sarcoidosis (compared to more than 900 for adult sarcoidosis), more than half of them being case reports, and the majority of the remaining articles not being focused on sarcoidosis. This could be due to the rarity of the disease in the paediatric population, but also to the lack of centralized management of

orphan diseases in the majority of the countries that does not help to gather these rare cases. Considering these limitations, cohort studies can be an unreachable challenge. However, in the recent years, a few studies that will be discussed reported cohorts of patients and showed that paediatric sarcoidosis can be of importance in the comprehension of sarcoidosis pathophysiology.

Only 3 retrospective limited case series have been described since 2004: 48 Danish patients (that we will further call the “DK series”), 41 French patients (the “FR series”) and 27 American patients from Louisiana (the “US-LA series”) respectively (6–8). Their main characteristics are summarized in **Table 1**. The DK series was conducted on the national registries between 1979 and 1994 and reviewed 48 patients among which 2 twins were finally diagnosed with Blau syndrome (7). A pathologic confirmation of the diagnosis was available for 33 of the 46 patients. The management and the follow-up of these children was secondarily reported until 2006 (9). The FR series reported 41 patients registered since 2008 in the national reference network for rare lung diseases. All of them had lung involvement and a histologically proven diagnosis (8). The US-LA series reported 27 patients diagnosed in a single rheumatologic department between 1992 and 2013 with paediatric sarcoidosis (22 patients), or Blau syndrome (5 patients). A histologic confirmation was obtained in 18 (67%) (6).

The incidence of sarcoidosis is difficult to assess but the DK series estimated an incidence of 0.29 per 100,000 children, and the FR series 0.4–0.8 per 100,000 children. Excluding Blau syndrome, the incidence seems to increase with age, from 0.06 in children <4 years of age to 1.02 in children aged 14-15 years, but children of all ages were affected (**Figure 1**) (7,10). However, paediatric figures are far lower than in adults as recently shown in Seine Saint Denis area (France) with an incidence of 4.9/100,000 (11). The mean age at diagnosis was 11 to 13 years-old in the 3 studies and sarcoidosis was encountered equally in

males and females. A predominance of black children was noticed in the US-LA series (n=20, 74%) and the FR series (n=36, 88%) contrasting to only 33.8% of adult patients in the same area in France, and to none of the patients of the DK series (12,13).

### **3. Pathophysiology**

Knowledge of the pathophysiology of sarcoidosis is still limited. The current hypothesis is an aberrant granulomatous and inflammatory reaction following the combination of 2 complementary factors: a genetic predisposition, and an exposure to an organic or a mineral antigen. Studies involving twins suggested that genetic background accounts for more than half of the risk factors for sarcoidosis onset, but they were limited studies and the relative contributions of both genetic and environmental aspects to sarcoidosis evolution remains to be ascertained (14).

#### 3.1 Granuloma constitution

Sarcoidosis granulomas have a typical pathologic aspect of a central follicle constituted by activated macrophages named epithelioid cells, and T CD4 lymphocytes (L) mainly of the Helper subtype (Th1). A lymphocytic ring of CD8 TL and BL surrounds the central follicle. The granuloma contains no necrotic aspects (**Figure 2**) (15). During the granuloma formation process, a Th17 (T-reg) TL influx is observed and could be locally responsible for the perpetuation of the granulomatous response despite the eventual removal of the causative agent and, at the peripheral level, could be responsible for the negative tuberculosis skin test of the patients (16).

#### 3.2 Genetics and sarcoidosis

A genetic background of sarcoidosis is supported by the observations of familial forms of sarcoidosis in 3% to 5% of the cases (17). An additional effect of a limited number of genes, such as common variants, presenting in more than 1% of the general population (single nucleotide polymorphisms, SNP) seems a more realistic model than a monogenic transmission. Recent whole genome association studies highlighted the implication of various genes or loci in the development of the disease. These genes have in common their role in regulation, activation and differentiation of TL and macrophages. Among them, the most studied are *BTNL2* (Butyrophilin Like 2), *Anxa11* (Annexine A11), *HLA-DRB1*, *CCDC88B* (Coiled-Coil Domain Containing 88B), and *XAF1* (XIAP Associated Factor 1) (18–20). *BTNL2* encodes a cofactor of the TL cluster of differentiation (CD) 86. A splice variant, rs2076530, that truncates the *BTNL2* protein, has been initially associated with an increased risk of sarcoidosis (21). However, this association seems weak with an odds ratio (OR) of 2 in the development of familial and sporadic forms of sarcoidosis (22,23). *Anxa11* plays an important role in cellular division, intra-cellular trafficking and apoptosis issues. The "C" allele of SNP rs1049550 seems associated with an increased risk of sarcoidosis, again with a limited OR around 1.5, whereas the SNP rs2573346 and rs2789679 seem to confer a protection against sarcoidosis (24). Recently, the hypertrophy and proliferation of the macrophages resulting in the granuloma formation were shown to be enhanced by the activation of the checkpoint kinase mTORC1 in macrophages in vivo (25). The role of autophagy pathways was also supported by a national study on a large cohort of paediatric and familial cases of sarcoidosis that revealed with the mean of trio analysis (one child with sarcoidosis and his two healthy parents), that numerous genes involved in autophagy seem to play a major role in the development of the disease (26).

### 3.3 Exposome and sarcoidosis

The role of environmental exposures in sarcoidosis has been reinforced in recent years. Organic exposure, mainly to mycobacteria, were first reported, followed by inorganic, mainly mineral exposures (27–30). Various studies have revealed an increased incidence of sarcoidosis after uncommon exposures to silica, aluminium, and inorganic dusts (31). This observation has been reinforced by the significant increase of sarcoidosis cases in individuals exposed to the World Trade Centre debris in 2001 (32). To date, the impact of inorganic particles on inflammatory stimuli seems accepted in sarcoidosis but needs further confirmation (33,34). This hypothesis is the basis of a national study on the exposome in the French paediatric cohort (35). A larger adult and paediatric project studying the mineral exposome in sarcoidosis and other inflammatory diseases is currently undergoing: the SILICOSIS project funded by the European Research Council (2012-2017) <http://www.sciencespo.fr/silicosis/fr>.

#### **4. Diagnosis**

In children, sarcoidosis is an exclusion diagnosis that is suggested by clinical manifestations and needs to be confirmed by the observation of a typical granuloma at the histologic examination of a biopsied tissue. Other causes of granuloma should be excluded: Blau syndrome, tuberculosis and other mycobacteria, immune deficiency such as combined immunodeficiency, eosinophilic granuloma, Crohn's disease, tumours, and rarely drug induced granulomatosis.

The investigations need to be extensive as paediatric sarcoidosis is identified as a multi-organ disorder in 70% of the US-LA patients and 85% of the FR patients, with a mean of 3.8 to 5.1 involved organs at diagnosis (6,8).

##### 4.1 Clinical presentation

In the 3 main paediatric cohorts, general signs were at the forefront (98% in the DK series, 78% in the FR series and 66% in the US-LA series). They included mainly fever (38%, 44%, 48% in the DK, FR, US-LA series respectively), but also marked fatigue, weight loss or lack of weight gain (6–8,36). The families frequently reported severe fatigue in the weeks or months preceding the diagnosis.

The most frequent presentations of sarcoidosis in children were related to lung and mediastinal disease (7,8,37). Respiratory symptoms were reported in the US-LA series in 3 of the 7 patients (43%) with a lung involvement and in 56% of the FR patients, despite all of them having lung sarcoidosis. When present, the lung manifestations were mainly dry cough, dyspnoea and chest pain. They were respectively reported by 65%, 29% and 12% of the DK patients. Extra-respiratory manifestations were often present. These should be actively sought at diagnosis: hepatomegaly and/or splenomegaly (50%, 49%, 30% in the DK, FR, US-LA series respectively); a decrease in visual acuity, an eye pain, a red eye, or any other visual anomaly that can evoke a posterior or anterior uveitis (29%, 39%, 74% respectively); peripheral lymphadenopathy (40%, 29%, 30% respectively); skin anomalies (42%, 19%, 18% respectively); or articular pain or inflammation (14%, 15%, 30% respectively). Other clinical signs were less frequently described (ENT, cardiac, neurological, gastrointestinal, parotiditis) but have to be considered at diagnosis, as well as indirect signs of haematologic involvement (pallor, ecchymosis, purpura) (6–8). Finally, an anergic tuberculin skin test for tuberculosis was usually noted.

#### 4.2 Paraclinical tests

In the reported children with lung sarcoidosis, the chest X-ray could be normal (stage 0 of the Scadding classification), as reported in 39% of the patients included in the DK, FR and US-LA series, even if respiratory signs were present (38). Hilar and mediastinal

lymphadenopathies without lung involvement (stage I) were reported in 34% of the patients. A lung infiltration without fibrosis (stages II and III) was reported in 10% and 15% respectively. No patient presented with a stage IV lung disease. High-resolution computed tomography (HRCT) revealed with greater sensibility and specificity the mediastinal and lung involvement. It highlighted features of an interstitial lung disease with peri-lymphatic nodules or micro-nodules involving pleural surfaces and fissures and peri-bronchovascular interstitium, but also ground glass opacities, alveolar consolidations and thickened septa. The irreversible parenchymal abnormalities were less common (**Figure 3**). Hilar with or without mediastinal, non-compressive and non-necrotizing, roughly symmetrical, lymphadenopathy were usually associated, similarly to adults, as reported in a recent study on 18 patients retrieved from the FR series (39). The flexible bronchoscopy with bronchoalveolar lavage (BAL) documented the lung involvement and was performed, as long as it was possible, before any corticosteroid therapy. The macroscopic aspect was normal, and in most situations, the BAL cell count was characterized by a moderate lymphocytosis, seen in 35 out of 37 FR patients, with a mean percentage of 40% ( $\pm 22$ ) and a mean CD4+/CD8+ ratio of 4 ( $\pm 4$ ). However, a normal BAL cell count does not exclude sarcoidosis diagnosis. Lung function tests (LFT) were detailed in the DK and the FR series in 8 and 37 patients respectively. A restrictive pattern with a significant decrease in FVC was documented in 20% and 65% respectively, and an airflow obstruction was seen in 37% of the cases in the DK patients (7,8). DLCO impairment was reported in 80% and 54% respectively. Interestingly, in the FR series, the lung function was more impaired in the oldest than in the youngest (<10 years-old) patients.

An abdominal ultrasound (US) or an abdominal CT scan was often useful to confirm abdominal involvement, or to guide hepatic biopsy. The abdominal US and CT-scans of 22 patients from the FR series were recently analysed (40). Eleven (50%) of them had

radiological abnormalities. Hepatomegaly was the most frequent sign, mostly homogeneous and rarely nodular, homogeneous lymph node enlargement was noted in 6 patients, and splenomegaly in 4 patients. All 11 patients had simultaneous thoracic involvement, despite a lack of any clinical respiratory signs in some of them. The authors concluded that a thoracic CT-scan should be performed in all patients with radiologic abdominal sarcoidosis. In all patients, an electrocardiogram and a cardiac US, as well as a specialized ophthalmologic examination are also considered mandatory.

Biologic blood tests are not specific. Stigmata of inflammation could be observed with a moderate increase of the sedimentation rate (median 36mm, 44mm, 46mm in the DK, FR and US-LA series respectively), an inflammatory anaemia (54% of the US-LA patients), an hypergammaglobinaemia (36% and 65% respectively in the DK and US-LA series), and an inconsistent lymphocytosis or lymphopenia (6–8). Alternatively, a non-regenerative anaemia or a thrombocytopenia is suggestive of a splenic or a bone marrow involvement (that should be confirmed by a bone marrow biopsy). Increased transaminases could be a sign of liver sarcoidosis. Serum angiotensin converting enzyme [ACE] dosage's significance was restricted to positive cases (63% of the patients included in the 3 series). Blood and urinary calcium were also tested and a mean of 16% of the patients suffered from hypercalcaemia at diagnosis (6–8). Other biologic tests were guided by the organs involved. In all cases, a DNA biobank specimen should be discussed with expert centres, in both familial cases and sporadic cases.

Pathologic examination of the biopsied organs is critical to assess the diagnosis of sarcoidosis in children. Biopsies are usually difficult and invasive in children, and corticosteroids can mask granuloma after only a few days or weeks of treatment. They should be performed, when possible, before any corticosteroids are started. In the DK series, 73% of the patients

benefited from a histologic diagnosis and peripheral lymph nodes, mediastinal lymph nodes and skin lesions were the most common biopsy sites (7). In the FR series, the accessory salivary glands, the liver and the lung were the most informative biopsy sites, but more than one organ biopsy were often needed to highlight a typical granuloma. The lung biopsies were performed by bronchial or transbronchial biopsy during a flexible bronchoscopy, but this procedure was difficult in infants and young children below the age of 6 years old because of the size of the bronchoscopes (8). Surgical lung biopsies were an alternative and were performed through video-assisted thoracoscopy or open lung biopsy with a usually good safety (41).

## **5. Therapeutic management**

The management of paediatric sarcoidosis should be overseen by multidisciplinary specialized reference centres with the aim of gathering these rare cases and improving the patients' care. The management and evolution of the DK, FR and US-LA series are summarized in **Table 2**.

In children, therapeutic abstention [no treatment] was almost never discussed as a management option, except in the rare asymptomatic cases, as reported in the DK series (7). Corticosteroids were the mainstay of the treatment in the published cases. They were given orally, starting with high doses (1-2 mg/kg/d) and/or by intravenous pulses (300 to 500 mg/m<sup>2</sup>/d for 3 days) in 50%, 97% and 89% of the patients in the DK, FR and US-FR series respectively. Corticosteroids were given for a mean duration of 15.6, 23.9 and 9 months respectively, with extreme durations of 1 month to 23 years (6-9). Besides corticosteroids, the caloric supplementation and the usual D vitamin intake was adapted, depending on the calcium dosage. Various immunosuppressive drugs were used as a second line of therapy in a highly variable proportion of patients, depending on the local prescribing preferences (4%,

36% and 85% respectively) (6,8,9). Methotrexate was the most frequently used in the 3 studies (total 22 (19%) of the overall 114 reported patients), followed by mycophenolate mofetil (7 patients), hydroxychloroquine (4 patients), infliximab (4 patients), cyclophosphamide (4 patients), ethanercept (2 patients), azathioprine (1 patient), and tacroilimus (1 patient) (6,8,9). The authors did not provide any explanations for the choice of the immunosuppressive drugs in these 3 studies. In adults, recent data on sarcoidosis treatments highlighted that low-dose methotrexate or azathioprine were the most used and that ethanercept, tacrolimus and thalidomide did not prove any efficacy (42,43). However, there is no available study evaluating these drugs in paediatric patients.

Aside from drugs, a nutritional support is frequently needed in children presenting an initial weight loss, and has to be adapted to the corticosteroid regimen. A paediatric nutritionist [dietician] can be a precious resource when managing the dietary needs depending on the age of the children and the on-going therapies. A social management plan is crucial in paediatric sarcoidosis, including adapting school time as long as fatigue is present.

## **6. Evolution and prognosis**

The follow-up management reported in the 3 main paediatric studies was not consistent and seemed adapted to each individual situation (**Table 2**). Following the patients' description at diagnosis, the DK series provided a long-term report (mean follow-up duration of 23 years (4-30)) on the follow-up of 46 patients, based on clinical evaluation and national registry data (9). At a median of 0.7 (0.6-5.9) years after diagnosis, 65% of the patients experienced a full recovery; and 78% at follow-up. Recovery with sequelae was noted in 2 additional patients (unilateral loss of vision and persistent radiographic stage II disease with normal spirometry), and 5 patients presented with active disease at follow-up. Three patients died: two from

central nervous system sarcoidosis and one from secondary acute leukemia. The same authors evaluated the quality of life of 34 adult survivors of paediatric sarcoidosis (30 who had recovered, and 4 with persistent sarcoidosis). They found no differences of the QoL scores compared to a reference Danish population and concluded that the majority of the patients had a health status that was similar to the reference population (44). The FR series was followed for 18 months for 38 (93%) patients, and for 4-5 years for 29 (70%) (8). A full recovery, defined as an asymptomatic patient on no treatment, was observed in 45% of the patients at follow-up, 14 additional patients were stable under treatment, and 41% experienced 1 to more than 10 relapses, mainly with an extra-thoracic localization. In this study, the <10 years-old group who had a lighter lung disease at diagnosis but received more steroid pulses and less immunosuppressive drugs than the >10 years-old group had a better outcome. The US-LA series reported a mean follow-up of 4 years (0.1-14) (6). At a mean follow-up of 3 months (1-9), 50% of the patients were in remission, defined as asymptomatic patients under treatment. At follow-up, 1 to 4 relapses were encountered by 40% of the patients, mainly with ocular involvement. Four (58%) patients experienced side-effects from the corticosteroids. The morbidity included iritis (n=4), joint sequelae (n=3), skin lesions (n=2), uveitis (n=1) and restrictive lung disease (n=1). One patient died after kidney transplantation for granulomatous nephritis. Prognostic factors are not yet established in children. However, the FR series raised the hypothesis that the disease extension, evaluated by the number of affected organs at diagnosis, could be associated with a higher rate of mid-term and long-term relapses (8). The age at diagnosis nor the Scadding radiological stage were not found to be associated with the disease evolution, perhaps in part because of the small number of children with stage IV disease; in contrast to adults with lung fibrosis and pulmonary hypertension factors being most associated with mortality (45).

There is no guideline in children regarding the optimal follow-up schedule. Considering the variable outcomes of the disease, a repeated clinical evaluation seems necessary life-long and emphasizes the importance of a close collaboration between paediatricians and adult pulmonologists. In the DK series, 39 patients had a radiographic evaluation at follow-up, and that found that 80% had normal chest X-rays (vs 9% at diagnosis), whilst only 1 patient that evolved toward lung fibrosis (9). In the US-LA patients, 37% had an abnormal chest X-ray at follow-up, and 68% had impaired spirometry (6). In an evaluation of 18 of the FR patients, the spirometry at follow-up was shown to be well-correlated with the lung imaging appearance and so could be used to reduce the frequency of imaging and thereby lower the irradiation exposure in children (39).

## **7. Conclusion and future research directions**

Regarding the 3 main patient series of paediatric sarcoidosis, it seems that the disease is severe and long-lasting. Children of all ages can be affected. It is a multi-organic disorder presenting with non-specific general symptoms. Despite an initial aggressive treatment, the evolution may be marked by relapses. There is a crucial need for future large international studies, and for long-term studies assessing the evolution of the disease in adult age range: these goals may be achieved by the launch of European and other international networks for rare lung diseases and by a better paediatric and adult physician cooperation.

## **8. Educational aims**

**The reader will come to appreciate:**

- **Paediatric sarcoidosis is a rare granulomatous disease of uncertain aetiology that can affect all organs, in patients of all ages.**

- **At diagnosis, fever and weight loss are often at the forefront of the symptoms, respiratory signs being inconstant despite usual thoracic involvement.**
- **In children, pathologic evidence is mandatory, highlighting a typical epithelioid non-necrotizing granuloma.**
- **Oral or pulses of intravenous corticosteroids are the mainstay of the treatment.**
- **Relapses are frequently observed, mainly extra-thoracic: even in cases of initial remission, so long-term follow-up is required.**

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**Table 1:** Characteristics at diagnosis of the patients included in the 3 main pediatric sarcoidosis series (Hoffman et al. 2004, Nathan et al. 2015, Gedalia et al. 2016 (6–8))

	DK series (7)	FR series (8)	US-LA series (6)	Total
<b>EPIDEMIOLOGY</b>				
Dates	1979-1994	2008-2014	1992-2013	
Total number of included patients, n	48	41	27	116
- Including patients with Blau syndrome, n	2	0	5	7
- Including patients with sarcoidosis, n	46	41	22	109
Pathologic confirmation of sarcoidosis, n (%)	33 (69%)	41 (100%)	18 (67%)	92 (84%)
Mean age at diagnosis, years (range)	13 (0.7-15)	11 (1.1-15.8)	11 (2-23)	12 (0.7-23)
Male/female (sex ratio)	26/22 (1.18)	19/22 (0.86)	14/13 (1.08)	59/57 (1.03)
Geographical origin of the patients				
- Afro-Caribbean and Sub-Saharan, n (%)	0 (0%)	36 (88%)	20 (74%)	56 (48%)
- Caucasian, n (%)	48 (100%)	4 (10%)	6 (22%)	56 (48%)
- Others or NA, n (%)	0 (0%)	1 (2%)	1 (4%)	4 (3%)
Familial form, n (%)	NA	5 (12%)	3 (11%)	NA
<b>CLINICAL PRESENTATION</b>				
General signs	47 (98%)	32 (78%)	18 (66%)	97 (83%)
Fever, n (%)	18 (38%)	18 (44%)	13 (48%)	49 (42%)
Respiratory symptoms, n (%)	17 (35%)	23 (56%)	3 (11%)	43 (37%)
Hepatomegaly and/or splenomegaly, n (%)	2 (50%)*	20 (49%)	8 (30%)	30 (42%)
Skin manifestations, n (%)	20 (42%)	8 (19%)	5 (18%)	33 (28%)
Eye manifestations, n (%)	14 (29%)	16 (39%)	20 (74%)	50 (43%)
Joint manifestations, n (%)	7 (14%)	6 (15%)	8 (30%)	21 (18%)
Peripheral lymphadenopathy, n (%)	19 (39%)	12 (29%)	8 (30%)	39 (34%)
<b>CHEST RADIOGRAPHY (Scadding classification)</b>				
Stage 0, n (%)	5 (10%)	18 (44%)	22 (81%)	45 (39%)
Stage 1, n (%)	34 (71%)	3 (3%)	2 (18%)	39 (34%)
Stage 2, n (%)	4 (8%)	6 (15%)	2 (18%)	12 (10%)
Stage 3, n (%)	4 (8%)	12 (29%)	1 (9%)	17 (15%)
Stage 4, n (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
<b>BIOLOGICAL SIGNS</b>				
Median sedimentation rate, mm	36	44	46	NA
Elevated serum angiotensin converting enzyme, n (%)	11 (55%)**	24 (60%)***	20 (74%)	55 (63%)
Hypercalcemia, n (%)	10 (30%)****	3 (7%)	3 (12%)	16 (16%)

Abbreviations: DK: Danish; FR: French; US-LA: Louisiana; NA: not available  
 \* data available in 4 patients; \*\* data available in 20 patients; \*\*\* data available in 40 patients; \*\*\*\* data available in 33 patients

**Table 2:** Management and evolution of the patients included in the 3 main pediatric sarcoidosis series (Milman et al. 2008, Nathan et al. 2015, Gedalia et al. 2016 (6,8,9))

	<b>DK series (9)</b>	<b>FR series ((8)</b>	<b>US-LA series (6)</b>	<b>Total</b>
Total number of included patients, n	46	41	27	114
Including Blau syndrome patients, n	0	0	5	5
Number of sarcoidosis, n	46	41	22	109
<b>TREATMENTS</b>				
Corticosteroids, n (%)	23 (50%)	40 (97%)	24 (89%)	87 (76%)
Oral, n (%)	NA	37 (90%)	NA	NA
Intravenous pulses, n (%)	NA	22 (54%)	NA	NA
Immunosuppressive drugs, n (%)	2 (4%)	15 (36%)	23 (85%)	40 (35%)
Methotrexate, n (%)	1 (2%)	7 (17%)	14 (51%)	22 (19%)
Mycophenolate mofetil, n (%)	0 (0%)	5 (12%)	2 (7%)	7 (6%)
Hydroxychloroquine, n (%)	0 (0%)	4 (10%)	0 (0%)	4 (3%)
Infliximab, n (%)	0 (0%)	2 (5%)	2 (7%)	4 (3%)
Cyclophosphamide, n (%)	1 (2%)	1 (2%)	2 (7%)	4 (3%)
Ethanercept, n (%)	0 (0%)	0 (0%)	2 (7%)	2 (2%)
Azathioprine, n (%)	0 (0%)	1 (2%)	0 (0%)	1 (1%)
Tacrolimus, n (%)	0 (0%)	0 (0%)	1 (4%)	1 (1%)
<b>EVOLUTION</b>				
Mean length of follow-up, years (range)	23 (4-30)	5 (0.4-15.2)	4 (0.1-14)	11 (0.1-30)
Time point of the follow-up evaluation	At follow-up	At 1.5 years* / 4-5 years**	At 1-9 months	NA
Remission (with or without treatments), n (%)	36 (78%)	20 (53%) / 17 (58%)	13 (50%)	NA
Recovery with sequels, n (%)	2 (4%)	NA	11 (41%)	NA
Active disease	5 (11%)	18 (47%) / 12 (41%)	NA	NA
Decease	3 (6%)	0 (0%) / 0 (0%)	1 (4%)	NA

Abbreviations: DK: Danish; FR: French; US-LA: Louisiana; NA: not available

\* data available for 38 patients; \*\* data available for 29 patients

## **Legends to figures**

**Figure 1:** Age at sarcoidosis diagnosis of the children included in the Danish experience (DK series (7)) and the French experience (FR series (8)).

The Danish cohort is composed of 46 patients with sarcoidosis (after exclusion of 2 patients with Blau syndrome) of European origin aged 8 months to 15 years (median age 13 years) at diagnosis. The French cohort includes 41 patients, mainly Afro-Caribbean and Sub-Saharan children aged 13 months to 15.75 years at diagnosis (median age 11.8). In both cohorts, the majority of the patients are teenagers, but it seems important to notice that 20 to 30% of the patients are below 10 years of age at diagnosis.

**Figure 2:** Sarcoidosis granuloma (10).

A central follicle is observed, constituted by T lymphocytes, mainly CD4, and epithelioid cells that are activated macrophages. A T CD8 and B lymphocyte ring is surrounding the central follicle.

**Figure 3:** Chest high resolution computed tomography (HRCT) in pulmonary paediatric sarcoidosis.

HRCT obtained in a 12-year-old boy (a), in a 6-year-old boy (b), in a 13-year-old boy (c) and in a 7-year-old boy (d). HRCT showed a peri-lymphatic distribution of nodules and micronodules involving the pleural surfaces, fissures and peri-brochovascular interstitium, ground glass areas of attenuation and alveolar consolidations. Bronchiectasis, bronchiolectasis and nonseptal parenchymal bands are also shown (d).

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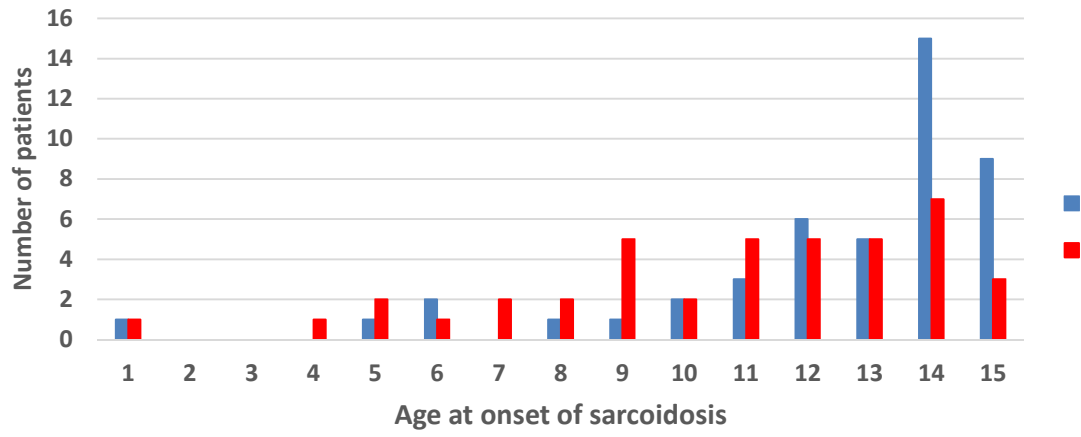
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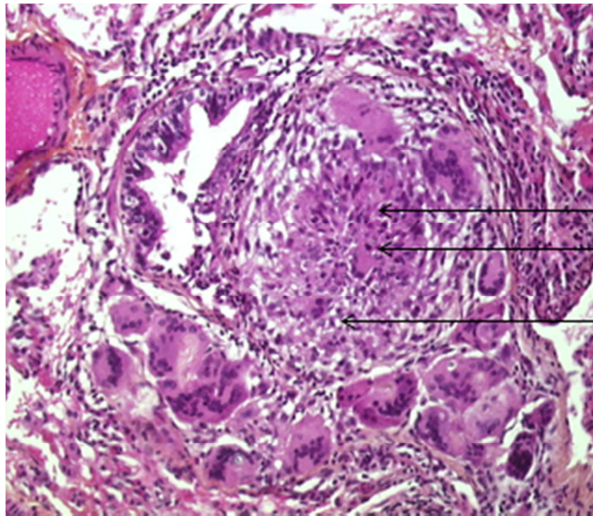
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**Figure 1**



**Figure 2**



Central follicle  
Epithelioid cells  
Lymphocytes ring

**Figure 3**

