PEDIATRIC SARCOIDOSIS: RETROSPECTIVE ANALYSIS OF BIOPSY-PROVEN PATIENTS

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ABSTRACT:

Objectives:

To describe the phenotype, disease course, and treatment of a large cohort of children with sarcoidosis.

Methods:

Patients with biopsies consistent with sarcoidosis, performed between 2010 and 2020, were included. Patients' notes were reviewed retrospectively. Children with disease onset before five years were compared with older children. Regression analysis was performed to determine predictors of treatment outcome.

Results:

Forty-eight children with a mean age at diagnosis of 9.5 years and male to female ratio of 0.71 were identified. 72% were of Afro-Caribbean descent. 94% had multiorgan disease with an average of 4.8 organs involved, most commonly lymph nodes (65%), skin (63%), and eyes (60%). Laboratory findings of note were raised serum calcium in 23% and ACE in 76% of patients. 6 of 14 patients tested had mutations in NOD2. 81% of patients received systemic steroids, 90% conventional disease-modifying antirheumatic drugs (cDMARDs), and in 25%, a biologic (mostly anti-TNF) was added. Although most patients could wean off steroids (58%), most remained on long-term DMARDs (85%). Children before the age of five presented more often with splenomegaly (p=0.001), spleen involvement (p=0.003), and higher CRP (p=0.003).

Weight loss was more common in adolescents (p=0.006). Kidney (p=0.004), eye (p=0.005), and liver involvement (p=-0.028) were more common in black ethnicity. Regression analysis identified no single factor associated with positive treatment outcomes.

Conclusion:

Multiorgan involvement, response to steroids, and chronic course are hallmarks of pediatric sarcoidosis. The phenotype significantly varies for age and ethnicity. Where cDMARDs were not efficacious addition of an anti-TNF was beneficial.

INTRODUCTION:

Multiorgan idiopathic granulomatous inflammation in children, also called pediatric sarcoidosis, may manifest with multiple phenotypes in childhood and represent a spectrum of diseases rather than separate disease entities. Most described in the literature are early-onset sarcoidosis and its genetically defined counterpart, Blau syndrome, associated with NOD2 mutations.[1-4] Adult presentation of proven Blau syndrome has recently been reported in a Japanese cohort.[5] The early-onset disease classically includes recurrent uveitis, granulomatous dermatitis, and symmetrical, boggy arthritis.[5,6] However, Rose et al. reported additional organ involvement beyond the typical triad in 52% of the patients.[1]

Later onset sarcoidosis is seen in older children, although there is no precise age group for this presentation, and little has been published. The phenotype seems less systemic, but, in contrast to the adult presentation, multiorgan involvement is common, including liver, spleen, lymph nodes, interstitia of the lungs, eye, and adnexal structures, including lachrymal glands, and extra-ocular glands such as the parotids. It may also involve the kidneys and display systemic features. Presentation is mostly insidious and may lead to multiorgan inflammation and dysfunction, especially eye inflammation complicated by long-term damage (mostly granulomatous uveitis and dacryoadenitis) and interstitial lung disease.[7-10]

There is little evidence to support treatment choices in children beyond corticosteroids when a steroid-sparing agent is needed. Gedalia et al. reported the safety and efficacy of methotrexate (10-15 mg/m^2) in 7 children with steroid-sparing effect.[11] Most

evidence has been published for Blau syndrome and supports using DMARDs such as methotrexate, anti-TNF, and anti-interleukin-1.[1,12,13]

Research into the treatment of adult sarcoidosis has mainly focused on managing the most common manifestation in adults, sarcoidosis-related interstitial lung disease, and has identified DMARDs such as methotrexate, azathioprine, and mycophenolate mofetil (MMF) as medications of interest. Furthermore, recent studies reported the efficacy and safety of anti-TNF therapy in managing sarcoidosis-related interstitial lung disease when patients had an incomplete response to conventional DMARDs.[14-17] There is also evidence supporting anti-TNF therapy in the management of refractory uveitis.[18] More recently, JAK inhibitors have been identified as medications of interest.[19]

Sarcoidosis is postulated to be a multifactorial disease caused by chronic antigenic stimulation. The immunopathogenesis of sarcoidosis encompasses a complex interaction between the host, genetic factors, and postulated environmental and infectious triggers, which result in granuloma development.

Little has been published about the presentation and response to treatment in patients with pediatric sarcoidosis outside of Blau syndrome. Our study reports a retrospective cohort of patients with biopsy-proven pediatric sarcoidosis. We describe the phenotype of these children, their treatment, and disease outcome on treatment.

METHODS

Patients

Patients were identified by screening the electronic health record for all biopsies performed or reviewed at two large UK centers, one for pediatric rheumatology and one for adolescent rheumatology, between 2010 and 2020. Four patients moved to the young adult clinic when they turned 18 but remained at the same center. The diagnosis of sarcoidosis was made by a pediatric rheumatologist meeting the following criteria derived from an adult guideline in the absence of pediatric criteria: a compatible clinical and radiological finding, histological evidence of non-caseating granulomata, and exclusion of other diseases with granulomatous inflammation and malignancy.[20] Biopsies with granulomatous inflammation suggestive of Crohn's disease, mycobacterial infection, other infections, or granulomatous inflammation in the context of immunodeficiency were excluded from our study.

Variables:

A retrospective chart review was conducted to collect demographic data (age at diagnosis, gender, ethnicity) and clinical variables (including site of biopsy, systemic features at presentation (fever, weight loss), and site of organ involvement throughout the study period). No defined criteria for organ involvement in pediatric sarcoidosis exist. The organ involvement definitions used in this cohort were adapted from the WASOG Sarcoidosis Organ Assessment Instrument for adults.[21] Definitions for organ

involvement are detailed in Table 1S in the supplementary material. Laboratory variables collected included histopathology reports, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), antinuclear antibodies (ANA), extractable nuclear antigen (ENA), angiotensin-converting enzyme (ACE), amylase, lipase, alanine transaminase (ALT), bilirubin, creatinine, renal and urinary markers, lung function parameters and, in some cases, NOD2 genetic testing performed by Sanger sequencing method). Further recorded were medications used (systemic corticosteroids, conventional disease-modifying antirheumatic drugs (cDMARDs), biologics, and eye drops) and outcome measures (improvement in clinical features, normalization of laboratory variables, reduction of abnormalities in radiological findings, and reduction in medication use). Definition of treatment response applied is detailed in Table 2S (suppl. material).

Systemic features were recorded at presentation only, whereas all other parameters were observed throughout the study period between 2010 and 2020. The follow-up interval varied depending on time of study entry and discharge from pediatric/adolescent services. The mean follow-up time for patients was 4.9 years ranging from 4 months to 14 years.

Statistics:

Statistical analysis was performed using the Statistical Package for the Social Sciences software (SPSS; Version 26.0, SPSS UK Ltd, Chertsey, United Kingdom). Data were log-transformed for normalization purposes as needed. Differences

between age groups for characteristics and clinical parameters in children with sarcoidosis were assessed using one-way variance (ANOVA) analysis with Tukey's post hoc test for continuous variables or Fisher's exact analysis for categorical variables. P values for Tukey's multiple comparison test were adjusted to limit the family error rate in the alpha value. Logistic regression analyses were conducted to identify the predictors associated with treatment response, improvement in clinical features, normalization of laboratory values, reduction in abnormal radiology, and reduction in medication. To compare the proportion of organ involvement between groups based on ethnicity and age, data were analyzed using a χ^2 test. A P value <0.05 was considered statistically significant.

Ethics

Study approval was granted by the Great Ormond Street Hospital Biomedical Research Centre (R&D number 19CB46) on 1/12/2019. This approval was issued based on the project documentation submitted to date. The study was registered as a Case Note Review with access to previously collected, non-identifiable information/data under GAfREC 2018 and, as a result, was exempt from NHS REC approval.

RESULTS:

A total of 48 children with biopsy-proven sarcoidosis were included in the study. General characteristics showed that the patients were aged between 1 to 15 years, with a mean (SD) age of 9.5 (4.2) years at diagnosis (Table 1). The proportion of females to males was 58% versus 42%, and most patients were of black ethnicity: 72% vs. 15% for Asian, 11% for Caucasian, and 2% for other ethnicities. The mean body mass index (BMI) was between the 75th to 91st centile, with 33% of children classified as obese.(Table 4S, suppl. material) Biopsies were taken from 15 different sites with lymph node and skin most frequent (each 31%), followed by liver and kidney (15% and 10%, respectively). (Figure 1b) Symptom onset to diagnosis ranged from 1 month to 9 years with a mean of 21 months.(Table 5S, suppl. Material)

Systemic features were recorded at presentation only, whereas all other parameters were observed throughout the study period of 10 years. Analysis of general symptoms showed that 46% of patients presented with fever, 39% with weight loss, and 72% with lymphadenopathy (Table 1). A high proportion of the patients had raised ESR (74%) and ACE (76%), and a considerable proportion had raised CRP (33%) and hypercalcemia (23%). Furthermore, NOD2 testing was performed on a total of 14 patients. This analysis showed that two patients had 'Blau' Syndrome, while four patients had mutations of unclear significance (common NOD2 variant p.(Pro268er), novel variant p.(Cys706Tyr), known variant p.(Ala725Gly), novel variant p.(Val592Met)). No gain of function mutation was identified. Of 43 patients tested, 16% had a positive antinuclear antibody titer (ANA) (≥ 1:160), while no extractable nuclear

antigen antibodies were detected (ENA). Comorbidity of note was two patients with sickle cell disease and a further two with sickle cell trait.

Forty-five out of 48 children (94%) presented or developed multiorgan involvement with an average of 4.8 organs involved (Figure 1a, Table 1). Most affected were lymph nodes (65%), skin (63%), eyes (60%), followed by liver (46%), pancreas (38%), and kidneys (35%). Musculoskeletal involvement was present in 27% (arthritis) and 8% (tenosynovitis). The lungs were involved in 33%, with interstitial changes most frequently observed.(Table 5S suppl. material) Only four patients developed some level of fibrosis or scarring. Two patients had significant pulmonary hypertension at presentation that resolved with treatment. In 28% of these cases, lung disease developed later on in the disease course. The average age of onset of lung disease was 9.7 years. Skin appearances were variable, with maculopapular eruptions most common and five cases of erythema nodosum. (Table 5S in suppl material) In 25 of the 28 patients with eye involvement, this was present at time of diagnosis at an average age of 8.5 years. Bilateral uveitis and panuveitis were the most common diagnoses (86%). (Table 5S suppl. material) Complications were cataract, synechiae, subretinal fibrosis, corneal opacity, retinal detachment, glaucoma, and ocular hypertension. Vision loss occurred in 6 of 28 patients, with one being registered blind.

Medication for sarcoidosis was used in 92% of patients, with 81% receiving systemic steroids (Figure 2a, Table 1). Patients were usually started on an oral dose of prednisolone of 1mg/kg daily (46%) or had a course of intravenous methylprednisolone of 30mg/kg for three consecutive days (maximum dose of 1g)

(51%) prior to starting the oral dose. cDMARDs were given in 90%, of which methotrexate was most common (58%). Methotrexate was usually commenced at a weekly dose of 15mg per meter of body surface area and a maximum total dose of 25mg. No comparison was made between different cDMARDs. Treatment of 12 (25%) patients was, due to disease progression, escalated to include a biologic, of which 11 patients received an anti-TNF agent (adalimumab, infliximab (usually 6mg/kg in 4-8 weekly intervals), etanercept). In three patients, second-line treatment with an Il-1 blocker (anakinra, canakinumab), Il-6 blocker (tocilizumab, sarilumab), or anti-CD20 (rituximab) was used. One patient received a JAK inhibitor (baricitinib) as first-line target therapy.

Four patients did not receive medication. In two cases, this was advised but declined by the family, one patient was being observed with skin disease only, and one patient has only recently been diagnosed and has not started treatment.

81% of patients improved with treatment. All had a good response to steroids, and most responded to MTX. An improvement in clinical features was observed in 77%, abnormal radiology in 88%, and medication in 63%; normalization of laboratory values was achieved in 68%. (Table 1) Most patients could wean off steroids (58%), but the majority remained on long-term DMARDS (85%).(Figure 2b) Length of systemic steroid therapy varied greatly. 18 of 39 patients who received systemic steroids had courses for less than one year (mean of 6.2 months), whilst 19 patients were treated between 1 and 11 years with a mean of 3.9 years. (Table 5S suppl. material) cDMARDS were discontinued in only three patients, of which two continued on a

biologic monotherapy, and one stopped against medical advice. (Figure 2b and Table 5S in suppl. material) Median length of DMARD therapy was 5.5 years ranging from 3 months to 11 years. Of the 11 patients who received an anti-TNF blocker, to date, 80% have achieved inactive disease without the need for systemic steroids, and 70% were still taking it at last follow-up. (Figure 2b and Table 5S in suppl. material) At the last recorded clinic visit, 34% of the cohort took systemic steroids, 81% cDMARDS, and 21% a biologic. Eight patients were treated with a cDMARD as well as a biologic (Figure 2b and Table 5S in suppl. material).

Characteristics and clinical parameters in children with sarcoidosis were compared between three age groups (chosen a priori) based on the time of diagnosis (<5 years, 5-11 years, and ≥12 years).(Table 1, Figure 3, Table 4S suppl. material) The incidence of weight loss at diagnosis was shown to be higher in adolescents (≥12 years) compared to the other two age groups (P= 0.006), whereas the incidence of spleen involvement (P= 0.003) and splenomegaly (P= 0.001) were significantly higher in children with early-onset disease than children aged 5 to 11 years and adolescents. Moreover, there was a trend toward a higher incidence of hepatomegaly (P= 0.057) and skin involvement (P= 0.076) in the youngest children compared to those > 12 years, albeit this failed to reach statistical significance. In addition, the incidence of raised CRP is higher in the youngest age group (71%) versus 25% and 32% in children in the middle and oldest group, respectively; however, this failed to reach statistical significance (P=0.097). The use of methotrexate was higher (P= 0.028) in children with

early-onset disease (88%) compared to those children who were aged 5 to 11 years at diagnosis (70%) or adolescents (37%).

Univariate analysis was conducted to compare the proportion of organ involvement between groups based on ethnicity and age. The significant differences are shown in Figure 4.

The odds ratio for splenic involvement varies by age. Compared to the oldest age group (≥12 years), the < 5-year-olds had an odds ratio of 11.1 (95% CI 1.1 to 112.0, p=0.041).

None of the White or Asian children had apparent renal involvement, compared to 34% (95% CI 20 to 49%, p=0.1172) of children from Black ethnic backgrounds. None of the White children had apparent liver or ocular involvement, compared to 56% (95% CI 41 to 71%, p=0.0179) for liver and 68% (95% CI 53 to 82%, p=0.0037) for ocular involvement of children from Black and Asian ethnic backgrounds.

Logistic regression analysis showed that neither gender, ethnicity, use of steroids, cDMARDs, or biologics are independently associated with treatment response, normalization of laboratory values, and improvement in clinical features, medication, and abnormal radiology (Table 3S a), b) and c) in suppl. material).

DISCUSSION:

This study suggests that non-caseating granulomatous inflammation on biopsy, multiorgan involvement, response to steroids, and chronic course are hallmarks of

pediatric sarcoidosis and that pediatric sarcoidosis is a spectrum of disease displaying different phenotypes depending on age and ethnicity.

In support of this, Rose and al reported that 52% of the patients in the international Blau syndrome registry had additional organ involvement to the typical triad of Blau syndrome.[1] This suggests that children with early-onset disease presented with a similar phenotype and course of disease to Blau syndrome compared to those with later-onset pediatric sarcoidosis. However, these young patients seem to display more systemic inflammation, as shown in this cohort (higher CRP p=0.04 and more splenomegaly p=0.002) along with skin disease and hepatomegaly. We had very few patients with Blau syndrome as these rarely undergo tissue biopsy when the diagnosis is confirmed genetically.

These data suggest that patients may have different phenotypes, mostly depending on their age. While younger patients have a phenotype closer to early-onset sarcoidosis with the most systemic features, older patients experience more chest involvement with interstitial lung disease (ILD), mediastinal lymphadenopathy, and weight loss. More patients in this cohort have skin disease, lymphadenopathy, and uveitis than the pediatric studies published to date, which might represent a tertiary center bias.[7,22,23] Table 2 summarizes the data from these three published pediatric studies with the data from this cohort. A recent adult study reporting a tertiary center experience of cutaneous sarcoidosis also identified multiorgan involvement as described in this study.[24] A recent adult review described all the organ involvement reported to date. There is great variability in association between organ involvement

and presentations, as shown in this study.[25] As described in adult sarcoidosis[26], this study shows that patients are predominantly of Afro-Caribbean background. This is confirmed in two of the published cohorts of pediatric sarcoidosis.[7,23] Black children in this study appear to have a characteristic phenotype that has also been observed in adults. Black adult patients tend to have skin, eye, liver, and bone marrow involvements and extra-thoracic lymphadenopathy.[27] A recent study including 1237 adult patients with sarcoidosis identified five distinct phenotypes based on organ involvement. These phenotypes overlap with the phenotypes described in this article. Some patients have erythema nodosum, joint involvement, and hilar lymph nodes, and other patients have hepatosplenic involvement, peripheral lymph nodes, and bone involvement. The five different phenotypes are interestingly associated with gender, ethnicity, and environmental exposure. The two most common phenotypes are observed in non-Caucasian patients like in this study.[28]

This study also suggests pediatric sarcoidosis is a chronic disease that responds well to corticosteroids as a first line of treatment, DMARDs, particularly methotrexate, and anti-TNF treatment (when response to cDMARDs is partial). Most of the patients in this study had to continue immunosuppression to maintain clinical remission. This is supported by the pediatric[7,23,29] and adult literature[30,31] on sarcoidosis. It implies that patients with pediatric sarcoidosis will need long-term management and will have to transition to adult care.[32] These data confirmed that anti-TNF inhibition is an effective option as a steroid-sparing agent for patients with pediatric sarcoidosis refractory to cDMARDs. This is supported in published adult studies and reviews.[16-18,33,34] Of note,

there is a recruitment bias in our study as only patients with uveitis could access anti-TNF treatment due to commissioning policies in the UK. One patient in this study received a JAK inhibitor (JAKI) with efficacy. JAK inhibitors appear to be a class of medication of interest in managing pediatric sarcoidosis due to Th1 and Th17 involvement. A recent review and several case reports have reported the efficacy of tofacitinib in adults with cutaneous and multiorgan sarcoidosis.[19,33,35-37] Two clinical trials are ongoing in adults (ClinicalTrials.gov Identifiers: NCT03793439, NCT03910543).

ACE alone was not an informative biomarker of sarcoidosis. Further studies are needed to identify biomarkers for diagnostic criteria and monitor disease activity in children based on adult data. Several biomarkers and their associations have been reported in adults, such as ACE, soluble IL-2 receptor (soluble CD25), chitotriosidase (CTO), and KL-6.[38-45] In particular, the association of ACE / CTO appears to be a promising biomarker of disease activity in three recent studies.[41,43,44] Looking at prognostic biomarkers, KL-6 seems to have the best sensitivity, while CTO has the best specificity.[42]

This study has several limitations. Firstly, its retrospective design. Secondly, we excluded most patients with CNS disease and more minor or atypical histopathology findings by only including biopsy-proven sarcoidosis. Thirdly, despite being the largest cohort reported, the small sample size limits the capacity to detect signals. Despite a complex statistical analysis, we could not identify any predictor of outcome. Sarcoidosis is a complex disease; therefore, larger studies are needed to better

understand it. Lastly, there are no defined criteria for classifying organ involvement in children, so we used criteria adapted from adults.[21] This is an area of need for further research in children. In this study, we mainly used ECG and ECHO to screen for cardiac sarcoidosis due to the lack of pediatric recommendations in the field when adults would do a more detailed work-up, including PET-CT or cardiac MRI.[46] This would also require further research to improve our understanding of cardiac involvement in children.

Our study provides information about BMI, suggesting that obesity might play a role in childhood sarcoidosis like in adults.[47] Further studies in the pediatric population are needed.

Furthermore, this study lacks information on triggers such as house renovations and exposure to dust as we did not collect environmental exposure data. Sarcoidosis is well known to be associated with environmental triggers in adults.[48] A recently published French retrospective, multicenter case-control study showed that indirect exposure to inorganic particles through coresidents' occupations was higher in patients with pediatric sarcoidosis than in the two control- groups. [49] In this study, one child who already had uveitis developed severe interstitial lung disease following exposure to the environmental contamination of the Grenfell tower fire.[50] A similar presentation had been reported in adult patients following 9/11.[51]

CONCLUSION:

This study represents the largest pediatric cohort of biopsy-proven sarcoidosis to date. It identified the presence of general symptoms and signs as more frequent in children than in adults. As in adult studies, sarcoidosis was more common in black ethnicity. While respiratory involvement is a hallmark of adult onset-sarcoidosis, children tend to have mostly lymphadenopathy, skin involvement, and ocular sarcoidosis. Uveitis appears to be associated with the most severe/frequent morbidity observed in children. Phenotype depends greatly on age and ethnicity. Patients have a good response to corticosteroids as a first line of treatment. Methotrexate is particularly effective as it is in adults. We report that anti-TNF therapies are efficacious when response to cDMARDs is partial. Visual outcome is preserved by anti-TNF treatment. This study shows the need for long-term DMARDs or biologics.

Further research with an international cohort study is needed to increase the knowledge and understanding of this condition, collect data on environmental triggers, facilitate clinical trials, and tailor care pathways in children with sarcoidosis.

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DATA AVAILABILITY STATEMENT: The data underlying this article will be shared upon reasonable request to the corresponding author.

Table 1: Characteristics and clinical parameters in children with sarcoidosis stratified by age at diagnosis

Figure 1a: Organ involvement and biopsy sites in children with sarcoidosis in %

Figure 1b: Biopsy sites in children with sarcoidosis in %

Figure 2 a) and b): Medication used in children with sarcoidosis in % a) during the study period and b) recorded at last clinic visit

Figure 3: Organ involvement stratified by age at diagnosis (n)

Figure 4: Comparison of proportion of organ involvement in which there was a significant difference between groups based on ethnicity and age

Table 2: Comparison of the GOSH/UCLH cohort with previously published cohorts of pediatric sarcoidosis

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Table 1. Characteristics and clinical parameters in children with sarcoidosis stratified by age at diagnosis

	Paediatric patients (*n*=48)	**Children < 5 years (*n*=8)**	**Children 5-11 years (*n*=20)**	**Children ≥12 years (*n*=20)**	***P*[1]**
Age at diagnosis (years)	9.5 (4.2)	3.1 (1.1)[a]	8.1 (2.2)[b]	13.6 (1.1)[c]	<0.001
Male gender	20 (42)	6 (75)	8 (40)	6 (30)	0.105
Ethnicity					
Black	33 (72)	7 (88)	12 (60)	14 (78)	0.453
Asian	7 (15)	0 (0)	5 (25)	2 (11)	
Caucasian	5 (11)	1 (13)	3 (15)	1 (6)	
Other	1 (2)	0 (0)	0 (0)	1 (6)	
Fever	21 (46)	5 (63)	6 (33)	10 (50)	0.307
Weight loss	18 (39)	2 (25)	3 (17)	13 (65)	0.006
Lymphadenopathy	34 (72)	7 (88)	13 (68)	14 (70)	0.755
Glandular enlargement	20 (43)	2 (25)	9 (47)	9 (45)	0.627
Parotids	16 (34)	2 (25)	7 (37)	7 (35)	0.922
Serositis	3 (6)	0 (0)	0 (0)	3 (15)	0.201
Nephrocalcinosis on USS	3 (6)	0 (0)	1 (5)	2 (10)	1.000
Abnormal renal function	16 (33)	3 (38)	5 (25)	8 (40)	0.655
Raised tubulointerstitial markers	8 (35)	1 (25)	4 (36)	3 (38)	1.000
Proteinuria	5 (17)	1 (17)	1 (9)	3 (25)	0.817
Hepatomegaly	12 (25)	4 (50)	6 (30)	2 (10)	0.057
Liver function abnormalities	16 (34)	1 (14)	10 (50)	5 (25)	0.167
Splenomegaly	14 (30)	6 (86)	2 (11)	6 (30)	0.001
Abnormal lung function	10 (21)	1 (14)	4 (20)	5 (25)	1.000
Arthritis	13 (27)	2 (25)	7 (35)	4 (20)	0.694
Tenosynovitis	5 (10)	0 (0)	4 (20)	1 (5)	0.241
Hearing loss	4 (8)	0 (0)	2 (10)	2 (10)	1.000
Comorbidity	21 (44)	1 (13)	9 (45)	11 (55)	0.126
Organ involvement	4.8 (2.1)	5.9 (2.6)	4.6 (2.2)	4.5 (1.9)	0.624
Multi-organ involvement (≥2 organs)	45 (94)	7 (88)	19 (95)	19 (95)	0.561
Organs involved					
Eyes	29 (60)	6 (75)	13 (65)	10 (50)	0.497
Liver	22 (46)	4 (40)	11 (55)	7 (35)	0.474
Kidneys	17 (35)	3 (38)	5 (25)	9 (45)	0.478

Pancreas	18 (38)	5 (63)	5 (25)	8 (40)	0.167
Joints	13 (27)	2 (25)	7 (35)	4 (20)	0.694
Salivary glands	16 (33)	2 (25)	7 (35)	7 (35)	1.000
Thyroid glands	1 (2)	0 (0)	0 (0)	0 (0)	1.000
Bone	3 (6)	1 (13)	1 (5)	1 (5)	0.561
Gut	2 (4)	0 (0)	0 (0)	2 (10)	0.645
Lymph node	31 (65)	7 (88)	13 (65)	11 (55)	0.315
Brain	3 (6)	0 (0)	2 (10)	1 (5)	1.000
Ears	4 (8)	0 (0)	2 (10)	2 (10)	1.000
Lungs	16 (33)	3 (38)	3 (30)	7 (35)	1.000
Heart	4 (8)	0 (0)	1 (5)	3 (15)	0.502
Spleen	15 (31)	6 (75)	2 (10)	7 (35)	0.003
Tendons	4 (8)	0 (0)	3 (15)	1 (5)	0.502
Skin	30 (63)	7 (88)	14 (70)	9 (45)	0.100
Pharyngeal	1 (2)	1 (13)	0 (0)	0 (0)	0.167
Associated immunodeficiency	0 (0)	0 (0)	0 (0)	0 (0)	-
Medication use	43 (90)	7 (88)	18 (90)	18 (90)	1.000
Corticosteroid use	42 (88)	7 (88)	18 (90)	17 (85)	1.000
Route of corticosteroid administration					
Systemic	39 (81)	7 (88)	17 (85)	15 (75)	0.704
Intravenous	20 (42)	5 (63)	9 (45)	6 (30)	0.337
Oral	38 (79)	7 (88)	16 (80)	15 (75)	0.900
Eye drops	18 (38)	4 (50)	7 (35)	7 (35)	0.790
Intra-articular	1 (2)	0 (0)	0 (0)	1 (5)	1.000
cDMARDs use	41 (85)	7 (88)	18 (90)	16 (80)	
Methotrexate	28 (58)	7 (88)	14 (70)	7 (35)	0.019
Azathioprine	13 (27)	3 (38)	4 (20)	6 (30)	0.694
Mycophenolate mofetil	13 (27)	1 (13)	6 (30)	6 (30)	0.756
HCQ	4 (8)	0 (0)	2 (10)	2 (10)	1.000
Cyclophosphamide	5 (10)	2 (25)	3 (15)	0 (0)	0.083
Biologics use	12 (25)	2 (25)	7 (35)	3 (15)	0.407
Anti-TNF	11 (23)	2 (25)	6 (30)	3 (0)	0.538
IL-1	2 (4)	1 (13)	1 (5)	0 (0)	0.309
Other	3 (6)	0 (0)	3 (15)	0 (0)	0.200
Raised ESR	34 (74)	6 (86)	15 (75)	13 (68)	0.741
Raised CRP	16 (33)	5 (71)	5 (25)	6 (32)	0.097
Hypercalcaemia	11 (23)	3 (43)	5 (26)	3 (16)	0.415
Raised ACE	34 (76)	7 (88)	12 (67)	15 (79)	0.540

Raised serum amyloid	13 (72)	3 (75)	5 (56)	5 (100)	0.275
Raised creatinine	14 (33)	0 (0)	7 (39)	7 (39)	0.146
NOD2	2 (14)				
Treatment response	35 (81)	6 (86)	14 (82)	15 (79)	1.000
Reduction in clinical features	34 (77)	6 (86)	14 (78)	14 (74)	1.000
Normalisation of lab values	26 (68)	5 (83)	12 (75)	9 (56)	0.460
Reduction of abnormal radiology	28 (88)	6 (100)	12 (100)	10 (71)	0.084
Reduction in medication	22 (63)	4 (57)	7 (54)	11 (73)	0.593

Data expressed as *n* (%) apart from age at diagnosis and organ involvement in numbers which are expressed as mean (standard deviation).

[1]Differences between age groups were assessed using an independent t-test for continuous variables. Data were log-transformed for normalisation purposes. Categorical variables were assessed using Fisher's exact analysis. A *P* value of <0.05 represents significance. Values within a row with different superscript letters (a, b, c) denote significant differences by *Tukey post hoc* test.

Abbreviations: USS, ultrasound scan; HCQ, hydroxychloroquine; DMARD, disease-modifying anti-rheumatic drugs; ESR, erythrocyte sedimentation rate; CRP, c-reactive protein; ACE, angiotensin-converting enzyme; NOD2, nucleotide-binding oligomerisation domain-containing protein 2.

Table 2: Comparison of the GOSH/UCLH cohort with previously published cohorts of pediatric sarcoidosis

	Danish cohort[22]	French cohort[7]	US cohort[23]	GOSH/UCLH cohort
Dates	1979-1994	2008-2014	1992-2013	2010-2020
Total patients included, n	48	41	27	48
Including patients with Blau syndrome, n	2	0	5	2
Including patients with sarcoidosis, n	46	41	22	46
Pathologic confirmation of sarcoidosis, n (%)	33 (69%)	41 (100%)	18 (67%)	48 (100%)
Mean age at diagnosis in years (range)	13 (0.7-15)	11 (1.1-15.8)	11 (2-23)	9.5 (1-15)
Male/female ratio	26/22 (1.18)	19/22 (0.86)	14/13 (1.08)	20/28 (0.71)
Afro-Caribbean and Sub-Saharan origin, n (%)	0 (0%)	36 (88%)	20 (74%)	33 (72%)
Caucasian origin, n (%)	48 (100%)	4 (10%)	6 (22%)	5 (11%)
Others or NA origin, n (%)	0 (0%)	1 (2%)	1 (4%)	10 (21%)
General signs	47 (98%)	32 (78%)	18 (66%)	26 (62%)
Fever, n (%)	18 (38%)	18 (44%)	13 (48%)	24 (50%)
Peripheral lymphadenopathy, n (%)	19 (39%)	12 (29%)	8 (30%)	34 (74%)
Respiratory symptoms, n (%)	17 (35%)	23 (56%)	3 (11%)	11 (23%)
Hepatomegaly and/or splenomegaly, n (%)	2 (50%)	20 (49%)	8 (30%)	20 (42%)
Skin manifestations, n (%)	20 (42%)	8 (19%)	5(18%)	30 (63%)
Eye manifestations, n (%)	14 (29%)	16 (39%)	20 (74%)	28 (60%)
Joint manifestations, n (%)	7 (14%)	6 (15%)	8 (30%)	13 (27%)

Median sedimentation rate at presentation, mm	36	44	46	44
Elevated serum angiotensin converting enzyme, n (%)	11 (55%)	24 (60%)	20 (74%)	34 (76%)
Hypercalcaemia, n (%)	10 (30%)	3 (7%)	3 (12%)	11 (24%)

Adapted from Nathan N, Sileo C, Calender A, Pacheco Y, Rosental PA, Cavalin C, et al. Paediatric sarcoidosis. Paediatr Respir Rev. 2019;29:53-9 [8]

Figure 1a: Organ involvement in children with sarcoidosis observed during the study period

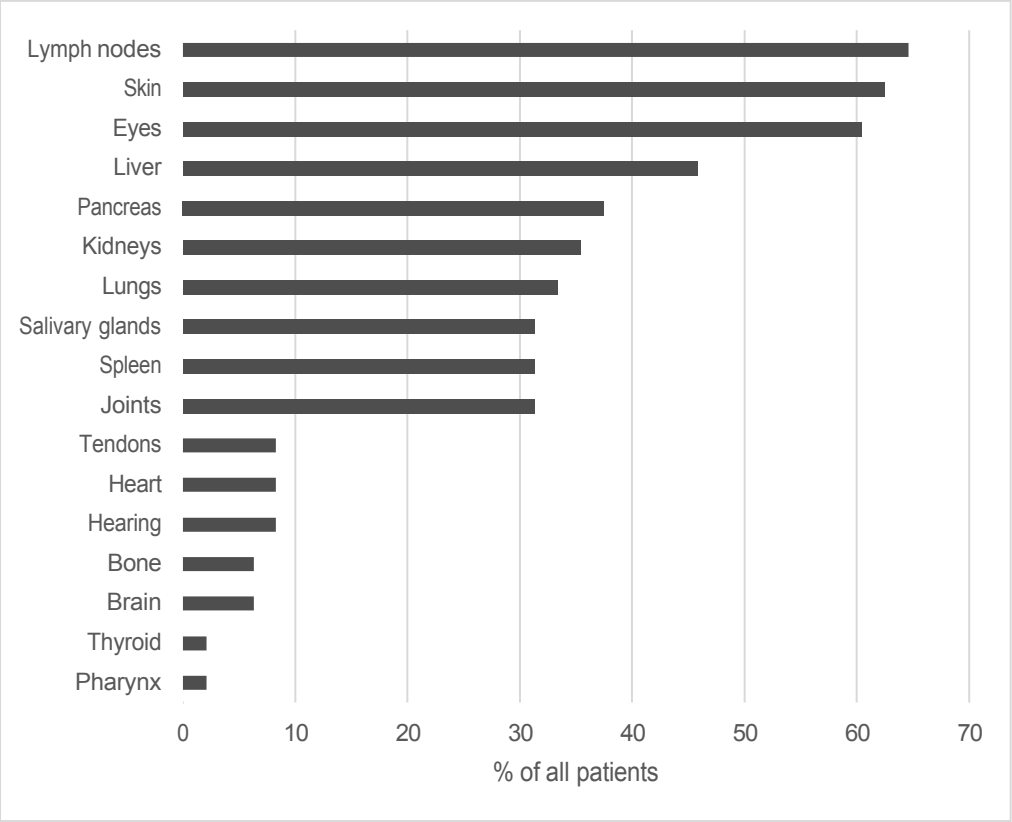


Figure 1b: Biopsy sites in children with sarcoidosis

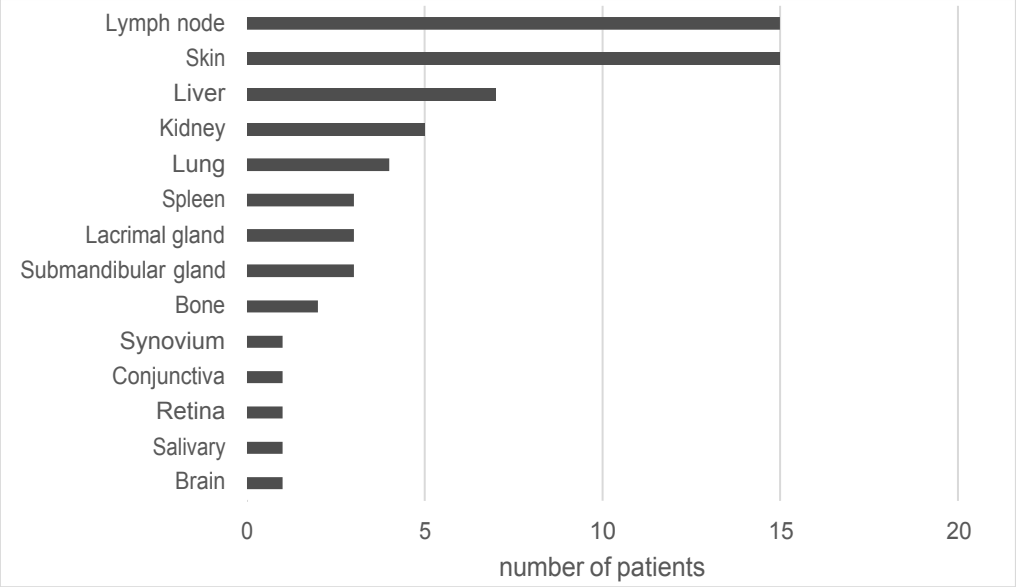
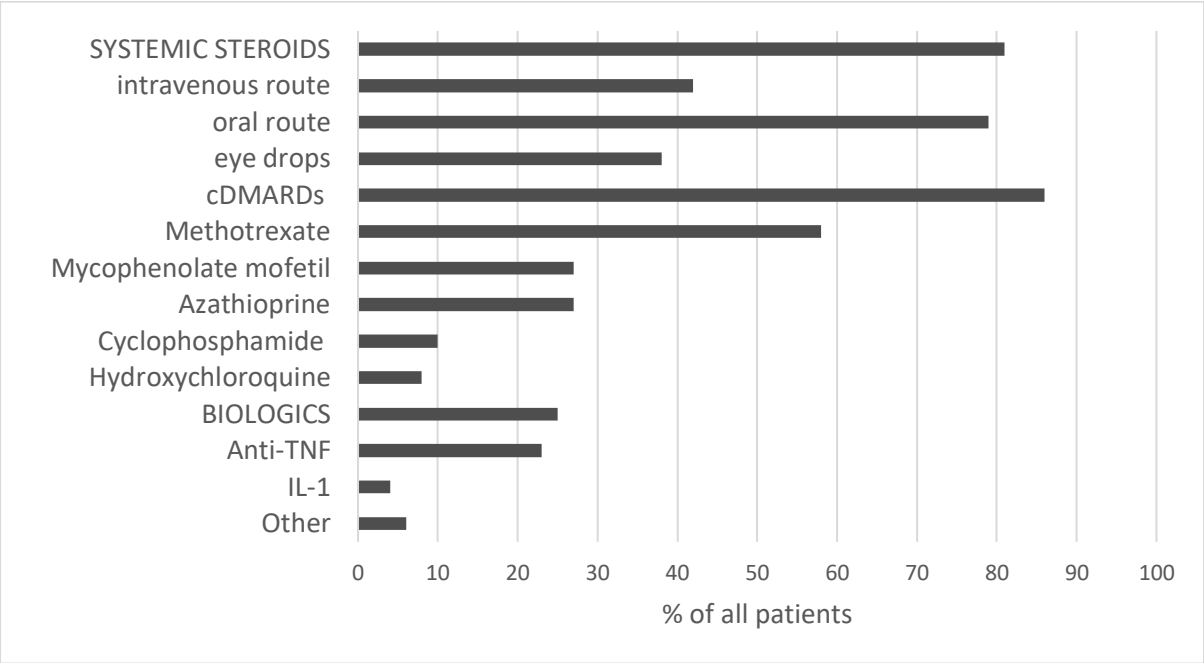
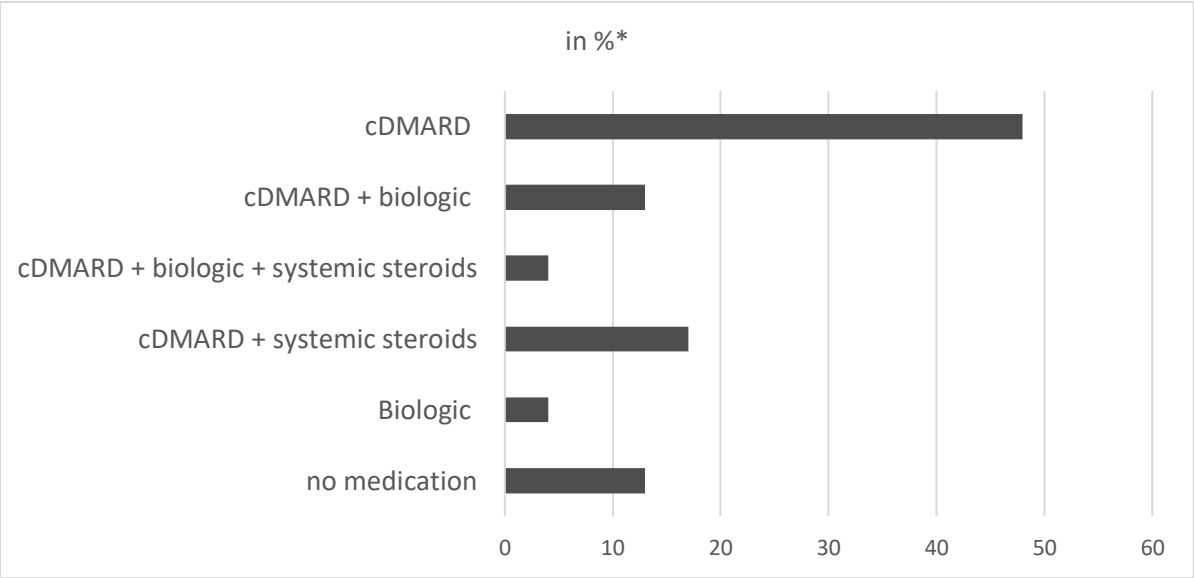


Figure 2: a) Medication used in children with sarcoidosis during the study period; b) medication recorded at last clinic visit





Abbreviations: cDMARD, conventional disease-modifying antirheumatic drugs; anti-TNF, anti-tumour necrosis factor; IL-1, anti-interleukin-1.

*n=47 as information for one patient not available

Figure 3: Fever, weight loss at presentation and organ involvement during the study period stratified by age at diagnosis in %

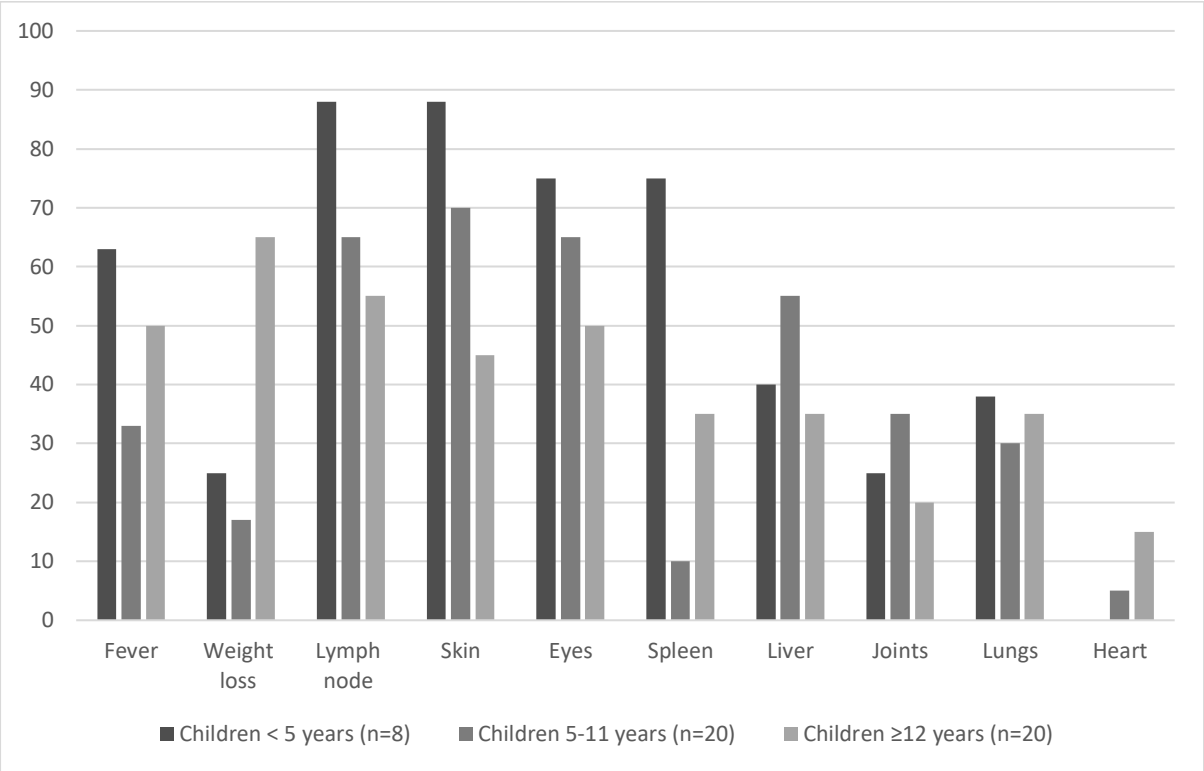


Figure 4: Comparison of proportion of organ involvement in which there was a significant difference between groups based on ethnicity and age.