Exposure to inorganic particles in paediatric sarcoidosis: the PEDIASARC study

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ABSTRACT

Inorganic antigens may contribute to paediatric sarcoidosis. Thirty-six patients matched with 36 healthy controls as well as a group of 21 sickle-cell disease (SCD) controls answered an environmental questionnaire. Patients' indirect exposure to inorganic particles, through coresidents' occupations, was higher than in healthy and SCD controls (median score: 2.5 (0.5–7) vs 0.5 (0–2), p=0.003 and 1 (0–2), p=0.012, respectively), especially for construction, exposures to metal dust, talc, abrasive reagents and scouring products. Wood or fossil energies heating were also linked to paediatric sarcoidosis. This study supports a link between mineral environmental exposure due to adult coresident occupations and paediatric sarcoidosis.

INTRODUCTION

Paediatric sarcoidosis is extremely rare with only three reported cohorts[1] : Danish (Caucasian), French (Afro-Caribbean) and Louisiana (Afro-American) patients. Most patients were aged 11–13 years. The disease seemed severe in children, involving multiple organs, and often persistent in adulthood.[1 2]

Granuloma formation in sarcoidosis might stem from an exaggerated inflammatory response to organic or inorganic environmental antigens in genetically predisposed patients.[3 4] Beryllium or crystalline silica have been associated with 'sarcoidosis-like' diseases.[5] This environmental factor is sustained by molecular studies involving foreign body reaction pathways such as autophagy in sarcoidosis.[6] The PEDIASARC study aims at comparing the exposure to inorganic—mineral—particles in patients with paediatric-onset sarcoidosis to controls.

METHODS

PEDIASARC was a retrospective, multicentric, case–control study from 2015 to 2019. Patients whose sarcoidosis began before the age of 16 were recruited in the French Reference network for rare lung diseases (RespiRare), without calculation of a suitable sample size. The diagnosis was confirmed by histology (91.7%) or multidisciplinary expert discussion. A control group of healthy children was matched by age ±2years and sex. In order to have a control population closer to the characteristics of the patients in terms of geographic origin, family migration experience, socioeconomic and genetic background, a second control group was recruited among patients with sickle-cell disease (SCD). Patients and controls and/or their adult representatives gave their consent and answered a detailed environmental questionnaire (online supplemental files 1,2) that evaluated inorganic exposures from birth to the age at sarcoidosis onset in both patients/controls and their coresidents. Questions targeted living habits, occupational and non-work-related environmental exposures (hobbies, housing), particularly crystalline silica, talcum, wood dust, mould, pollution or metal dust. Each phone or face-to-face interview lasted 45 min. The environmental exposure score combined a direct score measuring patients' or controls' exposures, an indirect score measuring occupational and non-work-related activities and a housing score related to in-house exposures (online supplemental figure S1). Each exposure scored 1 point. Each exposure was compared between the three groups (n, percentage). A median score and an interquartile range (IQR: 25–75) of each group were calculated for each global exposure (direct, indirect, housing) and they were compared using a Wilcoxon-Mann-Whitney test. The housing score was divided by the number of questions. The study was authorised by French legal authorities (CPP, comité de protection des personnes; CNIL, commission nationale de l'informatique et des libertés).

RESULTS

Among the 53 patients with paediatric-onset sarcoidosis of the RespiRare network, 14 could not be reached, 3 refused to participate and 36 (68%) patients—mostly from Sub-Saharan and

Table 1 Clinical features of the included patients and controls

	Patients (n=36)	Healthy controls (n=36)	SCD controls (n=21)
Gender, n (%)			
Female	24 (67%)	24 (67%)	10 (48%)
Geographic origin, n (%)			
Sub-Saharan Africa/West Indies	23 (64%)	0 (0%)	21 (100%)
North Africa	6 (17%)	0 (0%)	0 (0%)
Europe	5 (14%)	36 (100%)	0 (0%)
Asia/Middle East	2 (5%)	0 (0%)	0 (0%)
Age at diagnosis (years), median, (IQR)**	12.4 (9.53–13.15)		
Age at inclusion (years), median, (IQR)††	19.7 (15–23)	19.8 (5–38)	16.7 (3–30)
Number of coresidents, median (IQR)	3 (2.75–3)	3 (3–3)	2.7 (2–3)
Family cases, n (%)	3 (8.3%)		
Clinical features at diagnosis, n (%)			
General fatigue	17 (47%)		
Fever	13 (36%)		
Weight loss	7 (47%)		
Pulmonary localisation	34 (94%)		
Extrapulmonary localisation	34 (94%)		
Liver	21 (58%)		
Lymphadenopathies	17 (47%)		
Salivary glands	14 (39%)		
Eyes	13 (36%)		
Spleen	7 (19.4%)		
Joints	7 (19.4%)		
Skin	5 (14%)		
Stomach	5 (14%)		
Kidney	4 (11%)		
Bone marrow	2 (5.5%)		
Heart	2 (5.5%)		
Tonsils	1 (2.7%)		
Histology, n (%)			
Non-caseating granuloma	33 (91.7%)		
Treatments, n (%)			
Corticosteroids, n (%)	34 (94%)		
Oral only	12 (33%)		
Intravenous pulse only	1 (2.9%)		
Both oral and intravenous	21 (58%)		
Other drugs‡	10 (27.7%)		
No treatment	2 (5.5%)		

The explorations assessing the sarcoidosis diagnosis of the 36 included patients are provided in online supplemental table S1.
IQR: 25–75.
*Extreme values (minimal–maximal) (1–15.9).
†Extreme values (minimal–maximal) (4–36), (5–38) and (3–30), respectively.
‡Methotrexate, azathioprine, hydroxychloroquine, mycophenolate mofetil.
SCD, sickle-cell disease.

Afro-Caribbean origins—were included in the study (table 1 and online supplemental table S1). None of the patients had to be excluded because of an absence of understanding of the questionnaire. They were matched with 36 paired healthy controls—mostly from Caucasian origin. Twenty-one SCD controls could be included.

Direct exposure scores did not differ between the three groups (figure 1). Exposure to scouring powder was the only one to be higher in patients' environment as compared with healthy controls (p=0.037) (online supplemental table S2). The global indirect exposure score was significantly higher in the sarcoidosis group than in the SCD group (5.5 (1.75–9), 2.5 (1–5.25) (p=0.09), 1 (1–3) (p=0.009)), respectively for the sarcoidosis, healthy controls and SCD controls. The occupational exposure score of the patients' coresidents (whose number was similar among the three groups (table 1)), was higher than in both control groups (median scores 2.5 (0.5–7)) versus (0.5 (0–2), p=0.003 for healthy controls and 1 (0–2), p=0.012 for SCD controls), particularly exposure to abrasive material (silica), talcum, combustion or welding fumes in metal working industry. The coresidents were exposed to mineral dusts via construction works and cleaning with scouring reagents. Only the frequency of occasional do-it-yourself was found different between patients and controls regarding coresidents' non-work-related activities (online supplemental table S3) and figure 1.

The exposure score related to the current and previous housings was significantly higher for patients as compared with healthy controls (median scores: 0.069 (0.05–0.1) vs 0.05 (0.04–0.07), and 0.16 (0.11–0.16) vs 0.04 (0.025–0.065), p<0.001 for both current and previous housings) but not with SCD controls (median scores: 0.11 (0.08–0.11), p=0.3 and 0.118 (0.06–0.12), p=0.13, respectively) (figure 2 and online supplemental table S4). Wood, gas, butane, coal and fuel oil heating were more frequently reported by patients than healthy controls and SCD controls. In patients' previous housings, mould was more frequently present than in healthy controls but not in SCD controls (online supplemental table S5).

DISCUSSION

Our study is the first one supporting the fact that the adult coresidents' occupational exposure (especially crystalline silica, metal and talcum—the toxicity of which has already been put forward) could play a promoting role in the pathophysiology of paediatrics sarcoidosis, whereas direct exposures at a paediatric age would not. We found that hazardous occupations were those releasing a lot of dust, especially in construction.[7] These results are consistent with those produced in adults in the ACCESS study and the French pilot MINASARC study using also bronchoalveolar lavage (BAL) analysis of mineral dusts.[4 8] More recently, a Dutch study highlighted an increased exposure but also an increased immunoreactivity to metal and silica in adult sarcoidosis patients.[9]

As in the USA, paediatric sarcoidosis in France affects mostly black children.[1] The patients' histories often highlighted chaotic migratory trajectories, successive insalubrious homes, and parents having numerous short-contract occupations, few exposing hobbies and other extraprofessional social activities. Thus, our results could be only a characterisation of the patients' socioeconomic status, without this being an aetiological determinant for paediatric sarcoidosis. Since (1) the SCD control group allows checking social characteristics and (2) the housing score is *not* significantly different in patients and in the SCD control group, we consider that our results uncover findings specifically linked rather to paediatric sarcoidosis, than to socio-economic status.

Several studies have suggested that a genetic susceptibility could promote sarcoidosis. Moreover, Sub-Saharan Africa populations are more often affected.[3] Despite probable similar exposures within families, only 3 (8.3%) kin-related sarcoidosis were reported. This observation questions the way how environmental exposure and genetic combine. The expansion of ongoing genetic family and trio studies may undoubtedly help to answer this question.[6 10]

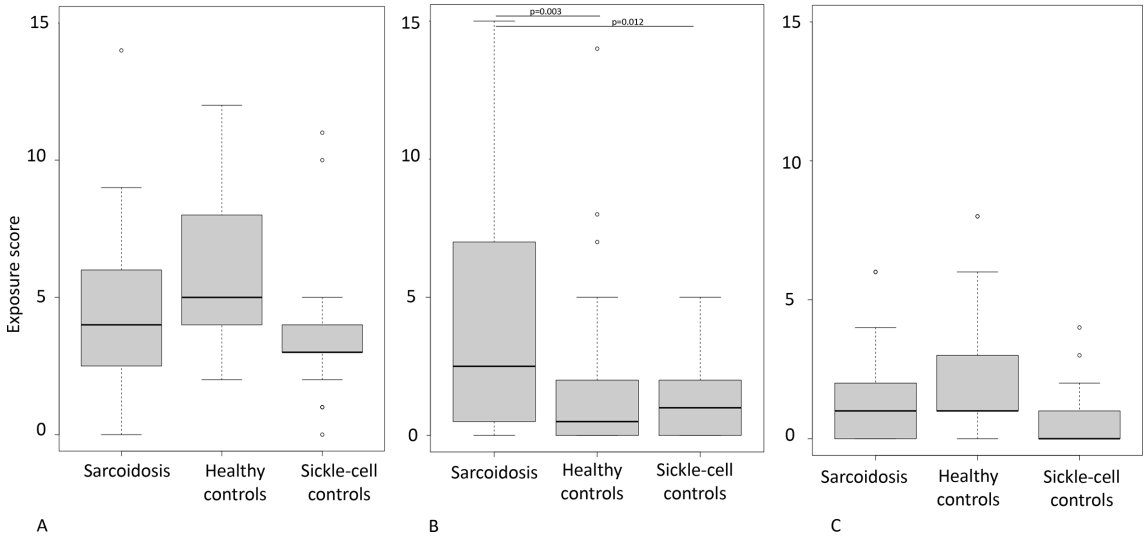

Figure 1 Exposure scores of the patients and the controls. (A) Direct exposure score, (B) indirect exposure score due to occupational activities and (C) indirect exposure score due to non-work-related activities of the patients and controls. The box represents the interquartile range (the lower line of the box represents the 1st quartile, the horizontal line within the box is the median and the upper line is the 3rd quartile), the horizontal bars at the ends are the minimum and maximum values and the isolated points represent are the extreme (exceptional) values. The theoretical maximal scores are as follows: direct exposure score = 26, indirect exposure score = 27, indirect extraprofessional exposure score = 15. The indirect exposure score due to occupational activities was higher in patients than in both control groups. No difference was found for the direct exposure score and the indirect exposure score due to non-work-related activities of the patients and controls. *p<0.05.

Despite several limitations (small population size—as in all rare diseases, retrospective design that can induce recall bias and selection bias, potential uncontrolled confounding, absence of perfect match between the SCD group and the patients regarding their number, gender and geographic origin, and the absence of testing the immunoreactivity to suspected exposure), this study supports the hypothesis that mineral environmental risk factors, through occupational exposure to inorganic particles of the patients' co-residents are linked to paediatric granulomatous disorders with sarcoidosis presentation.

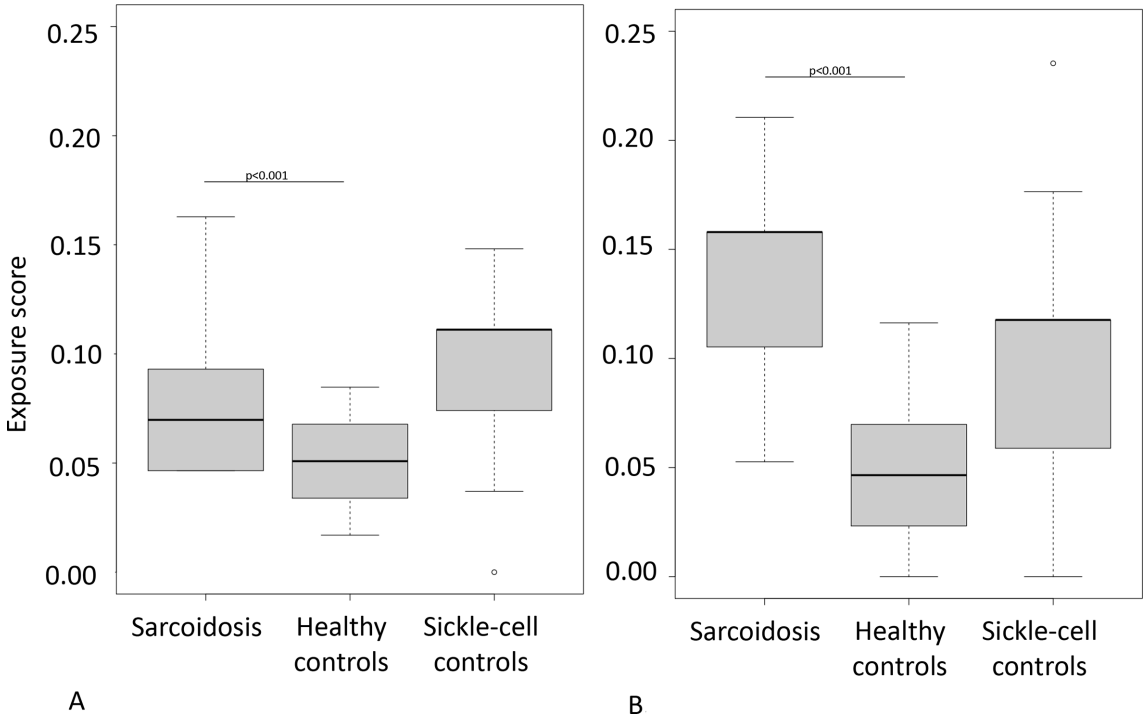

Figure 2 Housing exposure score. Exposure scores of the current (A) and previous (B) housing of the patients and controls. The housing scores were divided by the number of questions. The box represents the interquartile range (the lower line of the box represents the 1st quartile, the horizontal line within the box is the median and the upper line is the 3rd quartile), the horizontal bars at the ends are the minimum and maximum values and the isolated points represent the extreme (exceptional) values. The exposure scores were significantly higher for patients as compared with healthy controls but not with sickle-cell disease controls. *p<0.001.

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Contributors NN and CC designed the study. CC, OM, P-AR and MV designed the questionnaires. M-EM, CC, NN, MB, LS and FJ analysed and interpreted the data. M-EM, NN, P-AR, DV and CC wrote the manuscript.NN, M-EM, SC, FJ, LS, RA-T, JB, CC-A, FC-A, MC, ChD, CeD, ADe, ADo, RE, JH, VH, DI-B, KJ, SL-J, FL, UM, MM, HN, SM, J-MN, M-HO, AC, DV provided the patients' clinical data and facilitated the contacts to make the interviews with patients and SCD controls. All authors reviewed and approved the manuscript.

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