CHAPTER 16

Sarcoidosis in children

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Sarcoidosis is relatively uncommon among children. Its diagnosis is based on a combination of suggestive clinical features, with histologically documented noncaseating granuloma, in the absence of other known causes of granuloma formation.

Epidemiology

The incidence and prevalence of sarcoidosis are reported to be influenced by age, race and geographical localisation. The disease shows a peak between the ages of 20–40 yrs. Although the youngest reported patients were infants aged 2 and 3 months, most of the cases reported in children have occurred in pre-adolescents and adolescents [1, 2]. From the national patient registry of patients with sarcoidosis in Denmark during the period 1979–1994, 48 patients with a confirmed diagnosis were aged $\leq$15 yrs [3]. The calculated incidence was 0.29 cases per 100,000 person-yrs in those aged $\leq$15 yrs. In children aged $\leq$4 yrs, the incidence was 0.06 cases per 100,000 person-yrs, increasing gradually to 1.02 cases per 100,000 person-yrs in children aged 14–15 yrs. It is important to point out that the age-specific incidence and prevalence of paediatric sarcoidosis remain uncertain since it is, without doubt, an underdiagnosed condition. Indeed, the disease can be asymptomatic, particularly in its earliest stages, and, in most countries, children do not undergo routine chest radiography.

Marked racial differences in the incidence and prevalence of sarcoidosis have been reported by many authors. For example, in the USA, the prevalence of adult sarcoidosis is approximately three times higher in Blacks than in Caucasians [4]. Various reports in the literature also indicate that race and ethnicity affect both the pattern of organ involvement and disease severity. In a follow-up study conducted in 21 children with pulmonary sarcoidosis, 12 were Black [5]. In addition, the number of organs involved was greater in the Black than in the Caucasian children.

From all of the reports in various populations of adult patients with sarcoidosis, the wide variations in incidence and prevalence suggest the influence of genetic factors on disease susceptibility. A genetic influence is further supported by familial cases of sarcoidosis [6, 7]. To date, linkage studies in familial sarcoidosis have shown that some areas of the genome are linked to sarcoidosis, with the strongest linkage reported for the major histocompatibility complex genes [8]. Currently, no data are available on familial cases of sarcoidosis involving paediatric patients. As for adults, gene polymorphisms of inflammatory mediators may be associated with expression of the disease in children. The pro-inflammatory genes of interest most probably include the tumour necrosis

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factor-α gene [9]. Other polymorphisms of potential relevance are polymorphisms of angiotensin-converting enzyme (ACE), with reported associations of genotypes influencing serum ACE levels and specific manifestations of the disease in adult patients [10].

Disease expression

Clinical manifestations in sarcoidosis are the consequences of local tissue infiltration with sarcoid granulomas. Therefore, disease expression depends on the organ or system involved, and a variety of symptoms and physical findings can be observed. As indicated above, sarcoidosis in children is not detected by abnormal routine chest radiographs, and children are not found to be asymptomatic at the time of diagnosis. The modes of presentation include nonspecific constitutional symptoms, alone or associated with symptoms related to specific organ involvement [11–14]. In the recent report of 48 children with sarcoidosis in Denmark [3], the most common nonspecific symptoms were fatigue, weight loss and fever. Clinical findings mainly include respiratory manifestations, lymphadenopathy, skin lesions, and ocular and central nervous system abnormalities. Disease expression seems to be influenced by age, with skin, eye and joint manifestations being more frequently observed on initial presentation in younger children.

Lung involvement

The respiratory symptoms most commonly observed include cough and dyspnoea. Physical examination results can be normal, or may document the presence of crackles and rhonchi. As for adults, chest radiographic descriptions range stages 0–IV. The most common radiographic findings in children are hilar lymph node enlargement, with or without lung changes. In the recent Danish report, chest imaging results were normal in 10% of cases (stage 0); 71% of the patients exhibited hilar lymphadenopathy (stage I), 8.3% parenchymal involvement (stage II), and only one parenchymal involvement alone (stage III). None of the 48 children showed evidence of irreversible pulmonary fibrosis [3].

The lung function abnormalities observed in children are mainly characterised by reductions in vital capacity (VC) and functional residual capacity [5]. Decreases in dynamic lung compliance and the transfer factor of the lung for carbon monoxide ($T_{L,CO}$) are also reported. Abnormalities in arterial blood gas levels are not frequently observed [15].

Extrathoracic involvement

Peripheral lymphadenopathy is one of the most common physical findings in children with sarcoidosis. Nineteen (40%) of the 48 paediatric patients in the Danish study exhibited peripheral lymphadenopathy, and this localisation contributed to the diagnosis in 15 patients by showing the typical epithelioid cell granulomas without necrosis [3]. The spleen can also be involved, frequently with splenomegaly.

Ocular symptoms are common, and may be the initial manifestation of the disease [14, 16, 17]. In the report of 21 children with sarcoidosis, uveitis was the presenting symptom in nine cases [5]. In the Danish report, 29% of the patients showed eye involvement. Anterior segment diseases are the most frequent, with chronic granulomatous uveitis,

acute iritis and conjunctival granulomas. Posterior segment diseases are less common (periphlebitis and chorioretinal granuloma).

Skin lesions are observed in approximately a quarter of patients [18, 19]. Many types of lesion are found, including purplish papules, plaques, subcutaneous nodules and hypopigmented lesions. Lupus pernio and erythema nodosum are not frequently observed in children.

Liver involvement is usually mild, with mainly an asymptomatic increase in hepatic enzyme levels. In rare cases, hepatomegaly can be documented. In children, needle biopsy of the liver can be proposed for disease diagnosis, even without any signs of liver involvement [5].

Neurosarcoidosis is seldom recognised in children. BAUMANN and ROBERTSON [20] recently reported 29 cases, in patients aged between 3 months and 18 yrs, with 48% aged <13 yrs. Seizures were the most common symptom. A total of 21% showed hypothalamic dysfunction. Five children presented with headache, four with motor signs and three with papilloedema. Twenty-four per cent showed mass lesions on imaging. This study tends to indicate that neurosarcoidosis shows different characteristics in children compared with adults. The authors concluded that children are more likely to have seizures, probably because of space-occupying lesions, and less likely to show cranial nerve palsies.

Cystic bone lesions are rare in children and often associated with skin lesions. Joint pains are reported in ~20% of patients, with acute polyarthritis or chronic arthropathy observed in ~5–10%. Granulomas are rarely found in joint tissue in the case of transient arthralgia [19].

Cardiac involvement is uncommon in children. It is mainly recognised by use of a conventional electrocardiogram. Information on heart disease in the paediatric group is very limited, and cardiac investigations should be performed in all children with sarcoidosis. In young adults, the main manifestations are arrhythmia, conduction abnormalities and congestive heart failure [21].

Other organ involvement reported in children includes the kidney, which may result in nephrocalcinosis and renal failure, the parotid gland with uveoparotid fever, the tonsils, and the pituitary gland with diabetes insipidus [11, 12].

Diagnostic approach

The diagnosis of sarcoidosis is currently based on a combination of suggestive clinical features, with histologically documented noncaseating granuloma, in the absence of other known causes of granuloma formation. Several laboratory investigations, such as bronchoalveolar lavage (BAL), blood tests (ACE) and gallium scanning, can provide additional evidence of sarcoidosis, but tissue biopsy is required for diagnosis.

Biopsy

The site for biopsy is dependent on the manifestations of the disease. In adult patients, transbronchial lung biopsy is the recommended procedure in most cases. However, this procedure can only be proposed in older children in specialised centres. In other situations, possible sites of biopsy mainly include visible skin lesions, superficial lymph nodes, minor salivary glands and the liver. Needle aspiration of the liver represents an interesting option in children in whom no other sites can be proposed [5]. In very extreme situations, surgical lung biopsy may be indicated.

The basic histopathological lesion is the noncaseating epithelioid cell granuloma. The

granuloma consists of highly differentiated mononuclear phagocytes (epithelioid cells and giant cells) and lymphocytes. The central portion of the granuloma consists of predominantly CD4+ lymphocytes, whereas CD8+ lymphocytes are present in the peripheral zone. The sarcoid granuloma may develop fibrotic changes that usually begin at the periphery and travel centrally. Granulomas may occasionally exhibit focal coagulative necrosis. Sarcoid granulomas are of a similar nature in any organ.

Other investigations

It is important to perform BAL in all children suspected of having sarcoidosis. Lung involvement is characterised by a predominant increase in the absolute and relative numbers of lymphocytes [4]. However, other lung disease may demonstrate lymphocytic alveolitis similar to that in sarcoidosis. The CD4:CD8 ratio has been reported by several groups to be increased in sarcoidosis [22, 23]. However, neither the number of lymphocytes nor the CD4:CD8 ratio in BAL fluid is a specific feature of any pulmonary disorder. A combination of results, an elevated total cell count, predominantly lymphocytes, together with a nearly normal percentage of eosinophils and polymorphonuclear neutrophils, and the lack of plasma cells, may help in distinguishing sarcoidosis from extrinsic allergic alveolitis, pulmonary fibrosis and bacterial infection.

Among the biological markers commonly measured are ACE and lysozyme levels, calcium metabolism parameters and biochemical liver function [24, 25]. Serum ACE levels are elevated in 40–90% of patients. The sources of this circulating enzyme most probably include the epithelioid cells and macrophages at the site of inflammation, and may reflect the total body granuloma burden. The levels of ACE at diagnosis have no prognostic significance, and are not different between patients who deteriorate and those who improve. Calcium metabolism can be deregulated in patients with sarcoidosis. This is mainly explained by granuloma production of the active form of vitamin D. Consequently, hypercalcaemia and hypercalcinuria can be observed, and, in some situations, may impair renal function. In the Danish study, hypercalcaemia was observed in almost 30% of the children.

Among other investigations, gallium scanning has been used in several paediatric groups. However, as for adult patients, it is of limited clinical utility in children with sarcoidosis [4]. Anergy to tuberculin is classic in sarcoidosis, and may provide additional support for the diagnosis. In adults, a growing number of biochemical parameters in serum and BAL fluid are currently being proposed for the management of patients, such as levels of soluble interleukin-2 receptor, which seems to be a better predictor of pulmonary severity than ACE level. These parameters need to be studied in children.

Patient management and prognosis

Once the diagnosis is confirmed, the type and number of organs involved need to be assessed, together with the severity of the different lesions [26, 27]. This is critical for therapeutic discussions [28–30]. As for adult patients, the clinical findings that require corticosteroid therapy remain controversial. In children with mild disease, such as anterior uveitis or skin lesions, topical steroid may be all that is necessary. In children with more severe forms of the disease, oral and/or systemic forms of steroids are employed. Systemic therapy is clearly indicated for eye disease not responding to topical therapy, cardiac disease, neurological disease and hypercalcaemia. For lung sarcoidosis,

most paediatric physicians feel that progressive symptomatic disease with altered pulmonary function should be treated.

Depending on disease severity, the steroid treatment is oral steroid either alone or in combination with intravenous pulse methylprednisolone therapy. Oral prednisone is generally started at a dose of 2 mg·kg body weight^{-1}·day^{-1}, and slowly tapered over 2–3 months to the lowest dose. The gradual tapering is guided by disease status. In severe situations, steroid pulses are started using 300 mg·m^{-2} methylprednisolone daily for 3 days, repeated once every 4–6 weeks [31]. The duration of steroid treatment in children with sarcoidosis has not been established, and it is most unlikely that there will a consensus in the near future as randomised prospective trials cannot be performed in the paediatric population. From several reports in the literature, 18 months may be reasonable treatment duration. In any case, patients need to be monitored for relapse after reduction or discontinuation of therapy. Alternative drugs alone or in association with steroids can be proposed in children, based on reports on management of adult sarcoidosis. These include mainly cytotoxic agents and the antimalarial drugs chloroquine and hydroxychloroquine. To date, reports in children with these medications are very limited [32–34].

At present, the management of sarcoidosis remains empirical. This is because the course of the disease is difficult to predict in an individual patient. In addition, there is ample evidence that many adults experience spontaneous remission within 6 months after diagnosis. The degree of uncertainty surrounding the treatment of sarcoidosis is even greater in children than in adults since few paediatric studies have been published and long-term data from adults may not be relevant to children. For pulmonary disease, events related to lung growth may influence the course of sarcoidosis. MARCILLE *et al.* [35] analysed data from 19 patients diagnosed with sarcoidosis in childhood and followed for a mean of 21 yrs. Pulmonary function test results remained abnormal in 68% of the patients. Although the adults included in this study may not be representative of the population of patients with a diagnosis of sarcoidosis during childhood, the findings suggest that the long-term outcome of sarcoidosis may be different in children and adults.

In the study of 21 children with pulmonary sarcoidosis, four were initially managed without specific medication [5]. All four exhibited mild symptoms and normal pulmonary function test results. During follow-up, repeated pulmonary function testing results remained normal. The initial BAL fluid contained an increased population of lymphocytes, and, 1–2 yrs after the diagnosis, BAL fluid analysis showed persistently high percentages of lymphocytes, with an increased CD4+:CD8+ ratio. In 17 children, glucocorticoid treatment was initiated based on clinical presentation and symptoms, sites and types of extrapulmonary disease, and results of pulmonary function tests. On initial evaluation, all 17 children had alterations in VC, dynamic lung compliance and/or $T_{L,CO}$, and 11 showed chest radiographic abnormalities. All children underwent repeated physical evaluations, during which the presence, nature and severity of symptoms were noted. After 6 months, chest radiography results had returned to normal in 10 of the 11 children with initial abnormalities. Improvements were seen in VC and $T_{L,CO}$. By contrast, no significant modifications in BAL fluid results were recorded. After 12 and 18 months, pulmonary function test results were unchanged compared to the 6-month evaluation, and all 17 children yielded normal chest radiographs. No further significant improvements were seen in pulmonary function test results during the 3–4 yrs of follow-up. Interestingly, BAL studies showed a persistent increase in the proportion of lymphocytes throughout follow-up.

Based on these results, the following management of children with pulmonary sarcoidosis can be proposed. BAL should be performed at the initial evaluation to document alveolitis; however, nothing seems to be gained from repeating this

investigation during follow-up in the absence of specific indications. Once the decision to initiate glucocorticoid therapy is made, treatment efficacy should be evaluated based on clinical manifestations, chest radiographs and pulmonary function test results. The treatment can be stopped even if the pulmonary function test results remain abnormal, but the child should then be carefully monitored for relapse.

Based on the small number of reports on sarcoidosis in children, it is not easy to give valuable information on prognosis. It is felt from the experience of paediatric physicians that the overall prognosis is generally good, with rapid improvement upon corticosteroid treatment. Very young children seem to experience more severe forms of the disease. In adults, it has been recently suggested that the number of polymorphonuclear neutrophils in BAL fluid may be useful in distinguishing patients with a more favourable outcome from those showing a more severe course. There are currently no data available in children to support this hypothesis.

Conclusion

Sarcoidosis is an example of a difficult diagnosis in children, as it is based on a combination of suggestive clinical features in the absence of other known causes of granuloma formation. Appropriate anti-inflammatory treatment has not been well defined in terms of molecules, doses and durations, especially in children. In addition, valuable markers of disease activity and severity are still lacking. Although sarcoidosis is thought to have a good prognosis in children, much of the current understanding and management is based on empirical information and data drawn from adult patient reports. This implies that prospective studies are urgently needed in the paediatric population. Also, a genetic predisposition is strongly suggested, with recent associations reported with the major histocompatibility complex genes in adult patients in sarcoidosis. Search for genetic influences should be developed in children.

Summary

Sarcoidosis is a chronic inflammatory disease in which granulomatous lesions can develop in many organs. It is a rare disease in children, affecting mainly adolescents. Its diagnosis is based on a combination of suggestive clinical features, with histologically documented noncaseating granuloma, in the absence of other known causes of granuloma formation. Information on genetic predisposition are lacking in children. The clinical expression of the disease is dominated by the involvement of the lung, eyes, skin, lymph nodes and liver. Management of paediatric patients remains empirical, due to the absence of validated criteria of disease activity and severity. Most children with sarcoidosis receive corticosteroids, a reasonable treatment duration being 18 months. The prognosis is clinically good, but long-term persistence of lung function abnormalities and alveolitis on bronchoalveolar lavage is frequently observed.

Keywords: Children, granulomatous disorder, lung, sarcoidosis.

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