The puzzling clinical spectrum and course of juvenile sarcoidosis

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Background: **Juvenile sarcoidosis is a rare, chronic, multisystem, granulomatous disease of obscure etiology which is seen in childhood and adulthood. The disease in childhood has a course different from that in adulthood.**

Data sources: **PubMed database was searched using terms sarcoidosis, children or childhood sarcoidosis or juvenile sarcoidosis in combination with one of the following terms: epidemiology, clinical manifestations, genetics, diagnosis, treatment, and prognosis. We also retrieved the terms such as early onset sarcoidosis and Blau syndrome. Furthermore, e-medicine and European Respiratory Society monographs for sarcoidosis were reviewed.**

Results: **Sarcoidosis in childhood presents with two age dependent, distinct forms. In younger children it is clinically evident before the age of four years and characterized by the triad of rash, arthritis and uveitis. In their older counterparts, the juvenile late onset sarcoidosis involves several organs and its clinical appearance resembles the adult type of the disease, with the respiratory system being most frequently affected (hilar lymphadenopathy, pulmonary infiltrations). Steroid is the main agent of treatment whereas methotrexate is also used for beneficial steroid sparing effects. New, novel therapies may change the outcome of the disease especially in difficult morbid cases.**

Conclusions: **Sarcoidosis in childhood is recognized as a systemic disease affecting various organs and having diverse clinical course depending on the age of onset.**

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Key words: **corticosteroids; early onset sarcoidosis; juvenile sarcoidosis; late onset sarcoidosis; methotrexate**

Review article

Introduction

Since Hutchinson's first description of the skin manifestations of sarcoidosis in 1885 and subsequent reports of the histopathologic pattern of the lesion and appearance of the term "sarkoid" in 1899, several investigators have greatly contributed to the current understanding of the disease although many aspects have not been elucidated.[1]

Juvenile sarcoidosis (JS) is a chronic, multisystem, granulomatous disease of obscure etiology occurring rarely throughout childhood.[2-4] Clinical manifestations vary according to the organs involved. Two age dependent, distinct types of the disease have been recognized in children.[3,4] In the youngsters the clinical triad of rash, arthritis and uveitis predominates. In their older counterparts, usually beyond the age of four years, a multisystemic disease with frequent involvement of the respiratory system is the mainstay of this entity. The demonstration of a non-caseating epithelioid granuloma on a tissue biopsy specimen in the presence of compatible clinical, laboratory and radiologic findings is required for a definite clinical diagnosis. Therapeutically, corticosteroids remain the cornerstone of treatment while oral methotrexate is a safe steroid sparing agent. There is little experience in children with other novel therapies.[3,4]

The present review will underscore the peculiar and broad clinical spectrum of JS, discuss its epidemiology, etiology, and pathogenesis, and pose some related problems because there is insufficient information for a consistent therapy to be formulated.

Epidemiology

The exact prevalence as well as the incidence of sarcoidosis remains speculative due to the high

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frequency of cases with a subclinical asymptomatic course.[2,3,5] Danish scientists have reported an annual incidence of 2-3 cases per million of childhood population,[5] whereas in more recent reports the incidence is calculated to be 0.06 children per 100 000 persons-years <4 years of age and to increase gradually with age to 1.02 children aged 14-15 years.[6] Most reported cases of sarcoidosis occurred at the age of 13-15 years.[7]

There is no clear gender predominance in childhood sarcoidosis. However, studies in adults have reported a slightly higher incidence in women.[7] Marked racial differences do exist in prevalence. In the USA, the prevalence of sarcoidosis is estimated to be 5 per 100 000 in Caucasians and 40 per 100 000 in African Americans.[2,4] Of interest, outside the USA, sarcoidosis mainly occurs in the predominant race of the country. [7] Geographic distribution of cases reveals a higher incidence in certain parts of the world, which are for example Sweden in Europe and the South Atlantic and Gulf States in the USA.[2-4] It is of note that within the USA the great preponderance of cases has been reported from the Southeastern States suggesting the endemicity of childhood sarcoidosis.

Etiology and immunopathogenesis

The ACCESS study[8] revealed that siblings of patients with sarcoidosis exhibit an increased risk of involvement. The genetic etiology hypothesis is supported by the findings that link sarcoidosis to the major histocompatibility complex (MHC) along with familial aggregation of cases.[9] Several genetic studies exploring the contribution of human leucocyte antigen (HLA) phenotypes have been published demonstrating that certain phenotypes showed the strongest linkage for sarcoidosis. In 1977 Brewerton et al[10] reported an association between class I HLA-B8 antigens and sarcoidosis. More recently, Rossman et al[11] and Iannuzzi et al[12] suggested that HLA class II antigens encoded by HLA-DRB1 and DQB1 alleles are also associated with sarcoidosis. It seems that genetic diversity may at least partly account for the clinical heterogeneity of the disease and it may predict the clinical course. Interestingly, in patients with LÖfgren's syndrome who are DRB 1*03 positive, the disease tends to resolve within two years whereas negative patients have a non-resolving disease.[13]

In the USA, familial clustering of cases is more commonly observed in African Americans. Chromosome 5 has been suggested as potentially harboring candidate genes.[7] On the other hand, the association between sarcoidosis and celiac disease, an autoimmune inflammatory disorder induced by the antigenic properties of gluten, supports the view of defective antigenic processing by the immune system.[14] The underlying pathogenetic mechanisms of JS are poorly understood. It has been suggested that the disease occurs mainly when a genetically predisposed host is exposed to a persistent, poorly degradable environmental antigenic stimulus. Nevertheless, an infectious causative agent although pursued has failed to be definitely recognized so far.[5,15] It seems that *Mycobacterium tuberculosis* and other atypical species may be associated with the pathogenesis of the disease.[7] Furthermore, Song et al[16] reported circulating IgG directed to mkatG protein of *Mycobacterium tuberculosis* catalase-peroxidase protein in 50% of patients with sarcoidosis. Other infectious agents have also been implicated. Among them, *propionibacterium acnes*, *spirochetes* and herpes viruses have been associated as potential organisms.[17,18] It was assumed that the presence of certain antigens in the mononuclear phagocytes drives to tissue granuloma formation rather than to active infection of the host.

Seemingly, the macrophage initiates the inflammatory process by presenting an undefined, so far, antigen to the CD4 lymphocytes.[2] Then, cytokines (IL-2, IL-6, IFN-γ) release follows, resulting in B cell stimulation and hyperglobulinemia, activation of fibroblasts and increase of the $CD4^+/CD8^+$ ratio of involved sites.[2-4] Of note, the pathology of granuloma, the hallmark of the disease, although not specific, consists of epithelioid cells, giant cells, $CD4^+$ T cells in the center and $CD8^+$ T lymphocytes and B lymphocytes at their periphery.[8] It has been postulated that $CD4^+$ lymphocytes, along with other immunoregulatory cells, perpetuate the inflammatory response, releasing cytokines, adhesion molecules and growth factors.[7] This persistent antigenic stimulation may be responsible for the continuity of the pathogenic process.

Clinical manifestations

It has become widely recognized that patients with sarcoidosis are prone to be manifested clinically in a manner related to their age at the onset of the disease. In children, during their first four-year period of life, florid manifestations seem to constitute a separate entity. In older children sarcoidosis presents as a multisystem disorder often accompanied by non-specific, constitutional symptoms at the onset of the disease. It is therefore difficult to compare the clinical appearances and outcome of patients in these two age-related groups. Thus, instructive reasons impose these two forms of the disease to be discussed separately.

Early onset juvenile sarcoidosis begins prior to the fourth birthday, frequently in the first year of life.[3] It is characterized by the clinical triad of rash, arthritis and uveitis.[7] It should be emphasized that the components of rash and/or arthritis are present at the onset of the

disease while uveitis and various systemic manifestations are added as the disease evolves.[3] Obviously, this form of sarcoidosis resembles systemic juvenile idiopathic arthritis (JIA) and meticulous consideration should be taken to distinguish between them. While analyzing the constituents of this form of sarcoidosis, we should remember that the rash of JIA is pink, macular and vanishing as opposed to papular or plaque like with scaling of sarcoidosis. Likewise the arthritis of sarcoidosis affects the synovium producing a painless boggy appearance although destructive polyarthritis has also been described.

Pulmonary involvement is variable in extent and characteristic,[19] affecting either the gross anatomy as can be evaluated by imaging modalities or compromising the functional parameters. It occurs in only 22% of children of this age group.[20] Racial differences do exist and Caucasians are predominantly affected.[21] The prognosis of this entity, despite treatment, is guarded as it leads to a protracted course with severe morbidity and residual impairments.[22]

Researchers suggest the term "juvenile systemic granulomatosis, familial or sporadic" to name this distinct form of the disease.[23,24] It was accepted later that a familial type of autosomal dominant granulomatous disease of childhood (ADGDC), formerly named Blau syndrome (granulomatous arthriris, iritis and rash), represents part of the same disease spectrum. This was supported by histological evidence of granulomatous visceral involvement in patients diagnosed with Blau syndrome.[25-28] A susceptibility locus of ADGDC was linked to the pericentromeric region of chromosome 16.[29] A more recent study[30] showed that the Blau syndrome gene is not a major risk for sarcoidosis. Later, "pediatric granulomatous arthritis" refers to both early onset sarcoidosis and Blau syndrome.[31] Although mutations in the *CARD15* gene are not increased in ethnic Danes with sarcoidosis compared to healthy control subjects,[32] Kanazawa et al[33] found that the majority of cases of early onset sarcoidosis and Blau syndrome share the common genetic etiology of *CARD15* mutation causing constitutive NF-κB activation.[34] More specifically, missense mutations of the *Nod2* were found in 9 of the 10 tested patients with early onset sarcoidosis in Japan.[33] It was also shown that *Nod2* genotyping may help to some extent predict the disease progression in patients with either Blau syndrome or early onset sarcoidosis.[35]

Late onset sarcoidosis presents as a rather multisystem disorder. Many different areas of involvement have been defined, and almost 75% of children are present at onset.[20] The lung is the most commonly involved organ. The predominant symptom is a mild, dry, chronic cough and approximately 60% of patients have an abnormal chest-X-ray at the time of initial presentation. It is characterized by bilateral hilar or paratracheal lymphadenopathy with or without parenchymal lung involvement.

Severity scoring systems have limited their applicability as they do not incorporate extrapulmonary sites of organ involvement. A stage evaluation based on chest X-ray findings is in clinical use, i.e., stage 1 is defined by isolated hilar lymphadenopathy, stage 2, when adenopathy is associated with pulmonary infiltration while the latter finding alone has been considered as stage 3 and stage 4, when a recognizable pattern of pulmonary fibrosis is readily seen.[2,4,6] Half of the patients are expected to show evidence of restrictive lung disease (reduction in forced expiratory vital capacity, total lung capacity, functional residual capacity) later in the course of the disease.[2,5] More recently, a scoring system that incorporates demographic data as well as data of pulmonary function and organ involvement has been introduced by Wasfi et al.[36]

Eye is the second most commonly affected organ, especially in older children (20%-30%).[2, 37] Clinically, eye redness, blurred vision, photophobia and ocular pain are indicative symptoms. Ophthalmic sarcoidosis is manifested as uveitis with anterior segment involvement in the majority (84%) of cases.[37] Conjunctival granulomas are the second most frequent ocular manifestation of the disease. They may appear as tiny pale yellow nodules.[7] Iris nodules, conjunctival granuloma, lacrimal gland involvement and unilateral proptosis are occasionally seen.[37] Cataracts or glaucoma secondary to treatment may be seen, and permanent visual loss may be casued by drugs.

Enlargement of peripheral lymph node is a clinical sign of the involvement of the reticuloendothelial system. Lymph nodes are firm, non tender, freely movable and represent the accessible site for tissue biopsy. Half of pediatric patients may also have hepatosplenomegaly.[2]

Skin disease is usually characterized by purplish red macules or plaques, skin nodules, erythema nodosum, and hypo- or hyper-pigmented areas.[2,3,38] Slight scaling is accompanied with the rash that begins peripherally and turns to be generalized.[37] In a study, erythema nodosum was observed in 31% of children.[7] It should be pointed out that erythema nodosum with the constellation of fever, arthralgias and hilar lymphadenopathy is highly suggestive of Löfgren's syndrome, a fundamental predictor of sarcoidosis.

Musculoskeletal involvement presents as joint effusions or arthralgias. These features especially in the young child should be differentiated from JIA, based on specific clinical features of sarcoid joints which are not

tender nor restrictive. Multiple joints of the upper and lower extremities are involved without predilection.[7] The tendon sheaths of dorsal wrist surface are usually affected.[2,3,5,39,40] Myositis with muscle granulomata has also been reported but it is rarely encountered both in adults and children.[3]

Although it has been stated that kidneys are affected in 6% of children, creatinine clearance determination showed that renal function was compromised in a higher percentage of 60%.[2,25] In case of renal involvement urine analysis revealed proteinuria, hematuria, leucocyturia and concentration defect. Renal participation attributed either to granuloma formation or to nephrocalcinosis resulted from concomitant hypercalciuria, even in the absence of hypercalcemia.[2,3,41,42] The epithelioid cells in sarcoid granuloma are transformed, and fixed macrophages retain the ability to produce 1-α hydroxylase, the enzyme catalyzing the final step in 1, 25 $(OH)_2$ vitamin D synthesis.[5] Vitamin D overproduction from its precursors in the skin is accelerated by sunlight exposure and results in deranged calcium metabolism in 3%-5% of children with active disease. The excess circulating vitamin D causes increased intestinal absorption of calcium along with enhanced bone resorption. As a result, hypercalcemia occurs and is not controlled by the usual feedback mechanisms.[3] Cases of hypercalcemic crisis induced by sunlight exposure in summer have been reported.[5] But there are a limited number of patients with various types of urogenital tract involvement.[43,44]

The cardiovascular system may also be affected with potentially devastating consequences. Generally cardiac structures may be involved.[45] Most often these changes affect the conduction system and the myocardium. A valvular dysfunction mainly presents as mitral insufficiency and is usually the result of a granulomatous infiltration of the corresponding papillary muscle or a change in the ventricular architecture. Granuloma infiltration of the conductive pathway of the heart may lead to arrhythmias and sudden death.[5] Being extremely rare, vasculitis can affect small to large caliber vessels adjacent to diseased tissues, mimicking hypersensitivity vasculitis, polyarthritis nodosa, microscopic polyangiitis or Takayasu's arteritis.[2,46,47]

As far as the central nervous system (CNS) is concerned, any part may be affected by sarcoidosis.[43] The incidence of clinical involvement of the nervous system in a sarcoidosis population is estimated to be 5%-15% among adults.[48] However, the incidence of subclinical sarcoidosis may be much higher. Necropsy studies suggest that ante mortem diagnosis is made in only 50% of patients with the involvement of the nervous system.[48] Cranial neuropathies are among the most common manifestations, and peripheral transient seventh nerve palsy is frequently seen. Meningeal signs with cerebrospinal fluid lymphocytosis, peripheral neuritis, papilledema and intracranial mass like lesions occur rarely. Hypothalamic infiltration has been considered as a prerequisite of diabetes insipidus and growth hormone deficiency.[20,49,50] Baumann et al[51] reported 29 children with neurosarcoidosis aged from 3 months to 18 years. Their commonly seen symptoms were seizures attributed probably to space-occupying lesions. This type of presentation differentiates children from adults in whom cranial nerve involvement predominates.

Parotid gland enlargement has also been reported especially in younger children. It may be part of Heerfordt's syndrome which consists of anterior uveitis, parotitis and Bell's palsy.[2] It has been found by isotopic studies, using 67-Ga citrate that pathological uptake is detected in exocrine glands such as lacrimal, sublingual and parotids even in cases where clinical evidence of impairment is lacking.[19,52]

Patients with sarcoidosis of the liver and spleen[53] are usually asymptomatic although function tests can be abnormal in one third of patients with increased alkaline phosphatase.

Diagnosis

Sarcoidosis is a protean disease because its various clinical manifestations resemble other disease entities.[3,54] This diversity may cause diagnostic delays. Indeed, a lapse period of 6 or 7 months after onset of symptoms was reported until a definite diagnosis was established.[20]

Demonstration of a typical non-caseating epitheliod granuloma from an easily accessible organ in association with compatible clinical and radiographic findings is reasonable to suffice for the diagnosis. Erythema nodosum lesions are an exception for the procedure as they lack granuloma formation.[55] Peripheral enlarged lymph nodes are easily accessible organs for biopsy. Otherwise, potential biopsy sites include lacrimal or parotid glands, mediastinal lymph nodes, and the lung or liver, when these organs are already involved. It should be kept in mind that there is no pathognomonic diagnostic procedure or unique histologic features to differentiate them from other granulomas. Epithelioid cell granuloma may also be found in tuberculosis, leprosy, syphilis, fungal infections, berylliosis, malignancies, Behcet disease, Sjögren syndrome and histiocytosis.[5]

Elevated erythrocyte sedimentation rate (ESR), anemia, leucopenia, eosinophilia and pathergy skin tests may provide diagnostic clues.[7] Immunological

abnormalities include hypergammaglobulinemia and impaired delayed hypersensitivity on skin test.[7] Serum angiotensin converting enzyme (SACE) should be measured when a diagnosis of sarcoidosis is considered. However, it should be remembered that SACE is elevated in a number of conditions, namely miliary tuberculosis, leprosy, Gaucher disease, primary biliary cirrhosis, diabetes mellitus, lymphoma and pulmonary neoplasms.[20] Elevated levels of SACE are of unknown origin, although they seem to originate from sarcoid granulomas. Age-related variations in normal SACE levels should be taken into account as values of 40%-50% higher than in adults have been observed in children younger than 15 years.[5,56] In adult patients with sarcoidosis, however, SACE levels generally have not been a useful guide to predict the clinical course and the response to therapy because SACE measurements do not necessarily correlate with symptoms and they do not assist in determining prognosis.

In the potential markers of sarcoidosis activity, chitotriosidase has been proposed by Brunner et al.[57] Chitotriosidase is involved in the defense against pathogens containing chitin. Likewise increased values are obtained in bronchoalveolar lavage.[58] In 2007, an increase in enzyme activity was observed in juvenile sarcoidosis. Chitotriosidase activity was found to be correlated with SACE and lung CT score for sarcoidosis, indicating that this enzyme could be a potential marker of disease severity.[59] Chitotriosidase and chemokine CCL18[60] in the plasma of patients with sarcoidosis were found to be interrelated closely, suggesting a common cellular origin. Most recently, it was shown that tryptase and mast cells may be involved in the immunopathogenesis of sarcoidosis. Higher serum concentrations of this enzyme were initially reported in patients with progressive sarcoidosis complicated by significant worsening of lung function. Later, significantly increased serum concentrations of tryptase were also observed in patients with sarcoidosis.[61]

Imaging techniques can contribute considerably to the diagnosis by revealing lung involvement and extrapulmonary manifestations of the disease. Chest X-ray may show intrathoracic lymphadenopathy involving the right paratracheal area and both hila.[62] It is detected in 95% of cases. High-resolution CT of the chest may be helpful in delineating the distribution of parenchymal lung lesions, seen as nodules with somewhat poorly defined borders and sizes, hilar adenopathy, and airway involvement with a reticulonodular pattern indicating fibrosis with central and appealing predominance.

Gallium 67 is a radioisotope that accumulates in malignant tumors and inflammatory processes.[63] Gallium 67 is taken up in granulomatous tissue, probably by activated macrophages. The reported sensitivity of Gallium 67 scanning in detecting pulmonary sarcoidosis ranges from 60% to 90%. Some combinations of different patterns of Gallium 67 distribution are characteristic of sarcoidosis. The image produced by Gallium 67 uptake of the right paratracheal and bilateral hilar lymph nodes was classified as a "lambda" pattern. The image produced by the Gallium 67 uptake of the lacrimal and parotid glands was classified as a "panda" pattern. The "lambda" pattern was seen in 72% of patients with sarcoidosis, and the "panda" pattern in 79%. Both patterns were seen simultaneously in 62%.

Positron emission tomography (PET) using 18-fluorodeoxyglycose (FDG) has not been widely used clinically.[64] FDG uptake is not specific as it mimics malignancy and metastases. PET can not, therefore, be used as a diagnostic tool but it is a contributory imaging modality for the determination of the extent of the disease and the response to treatment. Novel imaging techniques have been explored such as PET using L-[3-(18)F] fluoro-alpha-methyltyrosine (FMT), which is more specific for malignancy than 18-FDG-PET. Combined use of both FMT and 18-FDG-PET could successfully discriminate sarcoidosis from malignancy.[65]

Lung involvement, in the sense of lymphocytic alveolitis, appreciated on imaging or functional grounds, can be asserted with bronchoalveolar lavage. An increased rate of lymphocytes and an elevated ratio of $CD4^+/CD8^+$ are observed in sarcoidosis. However, other lung diseases may also demonstrate lymphocytic alveolitis similar to that of sarcoidosis. An elevated total cell count, predominantly lymphocytes, together with a nearly normal percentage of eosinophils and neutrophils and the absence of plasma cells may help in distinguishing sarcoidosis from extrinsic allergic alveolitis, pulmonary fibrosis and bacterial infection.[66]

The diagnosis of JS is greatly supported by the presence of a non-caseating epithelioid cell granuloma on tissue biopsy. As it was mentioned earlier, the more accessible sites are preferred in children. More invasive procedures such as transbronchial lung biopsy and endobronchial multiple biopsies offer a diagnostic yield of more than 60%. Lately, endobronchial ultrasound guided biopsy yielded a lower risk of complications and higher diagnostic validity. The Kveim-Siltzbach skin test is of historic significance. It has been renounced as a non-standardized, potentially hazardous procedure.

The differential diagnosis of sarcoidosis is extremely broad and includes juvenile idiopathic arthritis, lymphoma and interstitial lung disease. Certain infectious entities attributed to mycobacteria and fungi should also be ruled out when granulomatous lesions are found on lung biopsy. In case of hepatic granulomas, cat scratch disease and granulomatous hepatitis should also be excluded. Hypercalcemia caused by primary

or secondary hyperparathyroidism has to be taken into account. Early onset sarcoidosis is often misdiagnosed as systemic onset juvenile rheumatoid arthritis.[67] Acute sarcoid myopathy should be differentiated from idiopathic polymyositis.[5]

Sarcoidosis should always be taken into account in children with fever of unknown origin. Finally, the diagnosis of JS has also to be considered in children with bone pain and osseous lesions in whom infectious and neoplastic diseases have been excluded.[2]

Treatment

Treatment may not be indicated in patients with hilar lymphadenopathy alone without evidence of parenchymal lung inflammation shown by chest X-ray.[68] However, it is necessary in patients with lung disease, extrapulmonary involvement (heart, kidneys, CNS), uveitis, hypercalcemia, hepatosplenomegaly, marked lymphdenopathy or sarcoid hepatitis.[3,5,15]

Corticosteroids remain the current treatment of choice. They act by inhibiting the release of inflammatory cytokines (IL-1, IL-2) and therefore blocking granuloma formation.[2,69] Improvement is anticipated within 6 months of steroid treatment by control of symptoms, resolution of radiologic abnormalities, and normalization of lung functional capacity. However, no studies have demonstrated a favorable long-term outcome in pulmonary fibrosis and lung function tests.[5] Inhaled corticosteroids have been tried as an alternative regimen, when initial lung disease remission has been achieved.[70] Treatment consists of oral prednisolone, initially 1 mg/kg per 24 hours for 4-8 weeks as induction treatment. This treatment is continued until a significant improvement is observed. Afterwards, the dose of steroids should be tapered. The lower dose that controls the activity of the disease is often in the range of 10-15 mg per day.[71]

It is of great interest to note that certain patients are resistant to steroid treatment at high doses for prolonged periods with serious consequences. For that reason, various steroid sparing agents have been advocated. Methotrexate has been proven to be effective in treating chronic inflammatory diseases such as JIA.[72,73] Low-dose oral methotrexate is safe and effective in treating various sarcoid manifestations, i.e., skin disease, musculoskeletal complications, progressive pulmonary disease and neurosarcoidosis. It is of paramount importance to monitor closely blood and hepatic toxicity. Use of folic or folinic acid helps to minimize these effects. Liver biopsy after 5 years of treatment or a cumulative dose of 1-1.5 g is contemplated.[15,73-75]

Additional drugs with anti-inflammatory and anti-fibrotic properties have been used such as cytotoxic agents (azathioprine, calcium chelating medications, chlorambucil, cyclophosphamide) and anti-malarials like hydroxychloroquine or melatonin, thalidomide, and pentoxyphylline. Thalidomide has also been successfully used for the management of early onset sarcoidosis.[76] Future treatment may include the use of cytokines and their antagonists as they play a crucial role in the pathogenesis of the disease. Infliximab, a human-mouse chimeric anti-tumor necrosis factor alpha antibody has already been used in adults.[77] Furthermore, a favorable effect of infliximab has been described in monozygotic twins with Blau syndrome and a de novo *CARD15* mutation.[78]

Prognosis

The prognosis of sarcoidosis in children is unclear as the disease is rare and the number of the reported cases is small. Generally the prognosis is poorer in the African-American adult population. Prognosis is guarded in early onset disease where 80%-100% of patients suffer from chronic debilitating sequelae.[21,22] However, spontaneous improvement is expected in a number of patients. In Danish children who had a long-term follow-up, sarcoidosis had a favorable prognosis as the majority recovered less than 6 years after the onset of the disease.[79] An automatic resolution rate of chest-X-ray (CXR) abnormalities over time was estimated to be as high as 75%. Hilar lymphadenopathy in combination with acute or subacute onset (fever, arthralgia, erythema nodosum) is associated with a remission rate of 80%-90%. On the contrary, CXR stages 3, 4 have a remission rate of 10%-20% and 0% respectively.[19,80] Hypercalcemia, cutaneous sarcoid lesions and generalized lymphadenopathy are associated with poorer prognosis.[5] Mortality rate has been estimated to be about 1%-5%.[15]

Conclusion

Sarcoidosis is recognized as a systemic disease of unknown etiology with various organ involvement and diverse clinical course. Clinical spectrum on initial presentation varies and depends considerably on the age of the affected patients. Early onset disease is combined with guarded prognosis. The use of steroids is the main step of treatment, whereas methotrexate results in beneficial steroid sparing effects. Novel therapies may change disease outcome especially in difficult morbid cases.

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References

1 Lazarus A. Sarcoidosis: epidemiology, etiology, pathogenesis, and genetics. Dis Mon 2009;55:649-660.
2 Shetty AK, Gedalia A. Sarcoidosis: a pediatric perspective. Clin Pediatr (Phila) 1998;37:707-717.
3 Cimaz R, Ansell BM. Sarcoidosis in the pediatric age. Clin Exp Rheumatol 2002;20:231-237.
4 Pattishall EN, Kendig EL Jr. Sarcoidosis in children. Pediatr Pulmonol 1996;22:195-203.
5 Milman N, Hoffmann AL, Byg KE. Sarcoidosis in children. Epidemiology in Danes, clinical features, diagnosis, treatment and prognosis. Acta Paediatr 1998;87:871-878.
6 Hoffmann AL, Milman N, Byg KE. Childhood sarcoidosis in Denmark 1979-1994: incidence, clinical features and laboratory results at presentation in 48 children. Acta Paediatr 2004;93:30-36.
7 Shetty AK, Gedalia A. Childhood sarcoidosis: a rare but fascinating disorder. Pediatr Rheumatol Online 2008;6:6.
8 Rybicki BA, Iannuzzi MC, Frederick MM, Thompson BW, Rossman MD, Bresnitz EA, et al. Familial aggregation of sarcoidosis. A case-control etiologic study of sarcoidosis (ACCESS). Am J Respir Crit Care Med 2001;164:2085-2091.
9 Grutters JC, Sato H, Welsh KI, du Bois RM. The importance of sarcoidosis genotype to lung phenotype. Am J Respir Cell Mol Biol 2003;29(3 Suppl):S59-62.
10 Brewerton DA. Discovery: HLA and disease. Curr Opin Rheumatol 2003;15:369-373.
11 Rossman MD, Thompson B, Frederick M, Iannuzzi MC, Rybicki BA, Pander JP, et al. HLA and environmental interactions in sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 2008;25:125-132.
12 Iannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. N Engl J Med 2007;357:2153-2165.
13 Grunewald J, Brynedal B, Darlington P, Nisell M, Cederlund K, Hillert J, et al. Different HLA-DRB1 allele distributions in distinct clinical subgroups of sarcoidosis patients. Respir Res 2010;11:25.
14 Hwang E, McBride R, Neugut AI, Green PH. Sarcoidosis in patients with celiac disease. Dig Dis Sci 2008;53:977-981.
15 Statement on sarcoidosis. Joint Statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) adopted by the ATS Board of Directors and by the ERS Executive Committee, February 1999. Am J Respir Crit Care Med 1999;160:736-755.
16 Song Z, Marzilli L, Greenlee BM, Chen ES, Silver RF, Askin FB, et al. Mycobacterial catalase-peroxidase is a tissue antigen and target of the adaptive immune response in systemic sarcoidosis. J Exp Med 2005;201:755-767.
17 Ishihara M, Ohno S, Ono H, Isogai E, Kimura K, Isogai H, et al. Seroprevalence of anti-Borrelia antibodies among patients with confirmed sarcoidosis in a region of Japan where Lyme borreliosis is endemic. Graefes Arch Clin Exp Ophthalmol 1998;236:280-284.
18 Hiramatsu J, Kataoka M, Nakata Y, Okazaki K, Tada S, Tanimoto M, et al. Propionibacterium acnes DNA detected in bronchoalveolar lavage cells from patients with sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 2003;20:197-203.
19 Tsagris VA, Liapi-Adamidou G. Sarcoidosis in infancy: a case with pulmonary involvement as a cardinal manifestation. Eur J Pediatr 1999;158:258-260.
20 Pattishall EN, Strope GL, Spinola SM, Denny FW. Childhood sarcoidosis. J Pediatr 1986;108:169-177.
21 Hetherington S. Sarcoidosis in young children. Am J Dis Child 1982;136:13-15.
22 Fink CW, Cimaz R. Early onset sarcoidosis: not a benign disease. J Rheumatol 1997;24:174-177.
23 Miller JJ 3rd. Early-onset "sarcoidosis" and "familial granulomatous arthritis (arteritis)": the same disease. J Pediatr 1986;109:387-388.
24 Rose CD, Eichenfield AH, Goldsmith DP, Athreya BH. Early onset sarcoidosis with aortitis—"juvenile systemic granulomatosis?". J Rheumatol 1990;17:102-106.
25 Blau EB. Familial granulomatous arthritis, iritis, and rash. J Pediatr 1985;107:689-693.
26 Blau EB. Autosomal dominant granulomatous disease of childhood: the naming of things. J Pediatr 1998;133:322-323.
27 Ting SS, Ziegler J, Fischer E. Familial granulomatous arthritis (Blau syndrome) with granulomatous renal lesions. J Pediatr 1998;133:450-452.
28 Saini SK, Rose CD. Liver involvement in familial granulomatous arthritis (Blau syndrome). J Rheumatol 1996;23:396-399.
29 Tromp G, Kuivaniemi H, Raphael S, Ala-Kokko L, Christiano A, Considine E, et al. Genetic linkage of familial granulomatous inflammatory arthritis, skin rash, and uveitis to chromosome 16. Am J Hum Genet 1996;59:1097-1107.
30 Rybicki BA, Maliarik MJ, Bock CH, Elston RC, Baughman RP, Kimani AP, et al. The Blau syndrome gene is not a major risk factor for sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 1999;16:203-208.
31 Rosé CD, Wouters CH, Meiorin S, Doyle TM, Davey MP, Rosenbaum JT, et al. Pediatric granulomatous arthritis: an international registry. Arthritis Rheum 2006;54:3337-3344.
32 Milman N, Nielsen OH, Hviid TV, Fenger K. *CARD15* single nucleotide polymorphisms 8, 12 and 13 are not increased in ethnic Danes with sarcoidosis. Respiration 2007;74:76-79.
33 Kanazawa N, Okafuji I, Kambe N, Nishikomori R, Nakata-Hizume M, Nagai S, et al. Early-onset sarcoidosis and *CARD15* mutations with constitutive nuclear factor-kappaB activation: common genetic etiology with Blau syndrome. Blood 2005;105:1195-1197.
34 Kambe N, Nishikomori R, Kanazawa N. The cytosolic pattern-recognition receptor Nod2 and inflammatory granulomatous disorders. J Dermatol Sci 2005;39:71-80.
35 Okafuji I, Nishikomori R, Kanazawa N, Kambe N, Fujisawa A, Yamazaki S, et al. Role of the *NOD2* genotype in the clinical phenotype of Blau syndrome and early-onset sarcoidosis. Arthritis Rheum 2009;60:242-250.
36 Wasfi YS, Rose CS, Murphy JR, Silveira LJ, Grutters JC, Inoue Y, et al. A new tool to assess sarcoidosis severity. Chest 2006;129:1234-1245.
37 Kataria S, Trevathan GE, Holland JE, Kataria YP. Ocular presentation of sarcoidosis in children. Clin Pediatr (Phila) 1983;22:793-797.
38 Clark SK. Sarcoidosis in children. Pediatr Dermatol 1987;4:291-299.
39 Mallory SB, Paller AS, Ginsburg BC, McCrossin ID, Abernathy R. Sarcoidosis in children: differentiation from juvenile rheumatoid arthritis. Pediatr Dermatol 1987;4:313-319.
40 Sahn EE, Hampton MT, Garen PD, Warrick J, Smith D, Silver RM. Preschool sarcoidosis masquerading as juvenile rheumatoid arthritis: two case reports and a review of the

literature. Pediatr Dermatol 1990;7:208-213.
41 Coutant R, Leroy B, Niaudet P, Loirat C, Dommergues JP, André JL, et al. Renal granulomatous sarcoidosis in childhood: a report of 11 cases and a review of the literature. Eur J Pediatr 1999;158:154-159.
42 Dimitriades C, Shetty AK, Vehaskari M, Craver RD, Gedalia A. Membranous nephropathy associated with childhood sarcoidosis. Pediatr Nephrol 1999;13:444-447.
43 Weinberg A, Ginsburg CM. Epididymal sarcoidosis in a prepubertal child. Am J Dis Child 1982;136:71-72.
44 Evans SS, Fisher RG, Scott MA, Kennedy BG, Brock JW 3rd, Wilson GJ. Sarcoidosis presenting as bilateral testicular masses. Pediatrics 1997;100(3 Pt 1):392-394.
45 Schulte W, Kirsten D, Drent M, Costabel U. Cardiac involvement in sarcoidosis. European Respiratory Monograph 2005;10(Monograph 32):130-149.
46 Fernandes SR, Singsen BH, Hoffman GS. Sarcoidosis and systemic vasculitis. Semin Arthritis Rheum 2000;30:33-46.
47 Kwong T, Valderrama E, Paley C, Ilowite N. Systemic necrotizing vasculitis associated with childhood sarcoidosis. Semin Arthritis Rheum 1994;23:388-395.
48 Hoitsma E, Sharma OP. Neirosarcoidosis. Eur Respir Monogr 2005;10 (Monogr 32):164-187.
49 Koné-Paut I, Portas M, Wechsler B, Girard N, Raybaud C. The pitfall of silent neurosarcoidosis. Pediatr Neurol 1999;20:215-218.
50 Basdemir D, Clarke W, Rogol AD. Growth hormone deficiency in a child with sarcoidosis. Clin Pediatr (Phila) 1999;38:315-316.
51 Baumann RJ, Robertson WC Jr. Neurosarcoid presents differently in children than in adults. Pediatrics 2003;112: e480-e486.
52 Mañá J. Nuclear imaging. 67Gallium, 201thallium, 18F-labeled fluoro-2-deoxy-D-glucose positron emission tomography. Clin Chest Med 1997;18:799-811.
53 Bean MJ, Horton KM, Fishman EK. Concurrent focal hepatic and splenic lesions: a pictorial guide to differential diagnosis. J Comput Assist Tomogr 2004;28:605-612.
54 Zsolway K, Sinai LN, Magnusson M, Tunnessen WW Jr. Two unusual pediatric presentations of sarcoidosis. Arch Pediatr Adolesc Med 1998;152:410-411.
55 Sharma GD. Pediatric Sarcoidosis. http://emedicine.medscape.com/article/1003964-overview (accessed July 20, 2010).
56 Bénéteau-Burnat B, Baudin B, Morgant G, Baumann FC, Giboudeau J. Serum angiotensin-converting enzyme in healthy and sarcoidotic children: comparison with the reference interval for adults. Clin Chem 1990;36:344-346.
57 Brunner J, Scholl-Bürgi S, Prelog M, Zimmerhackl LB. Chitotriosidase as a marker of disease activity in sarcoidosis. Rheumatol Int 2007;27:1185-1186.
58 Bargagli E, Maggiorelli C, Rottoli P. Human chitotriosidase: a potential new marker of sarcoidosis severity. Respiration 2008;76:234-238.
59 Rust M, Bergmann L, Kühn T, Tuengerthal S, Bartmann K, Mitrou PS, et al. Prognostic value of chest radiograph, serum-angiotensin-converting enzyme and T helper cell count in blood and in bronchoalveolar lavage of patients with pulmonary sarcoidosis. Respiration 1985;48:231-236.
60 Boot RG, Hollak CE, Verhoek M, Alberts C, Jonkers RE, Aerts JM. Plasma chitotriosidase and CCL18 as surrogate markers for granulomatous macrophages in sarcoidosis. Clin Chim Acta 2010;411:31-36.
61 Bargagli E, Mazzi A, Mezzasalma F, Perrone A, Olivieri C, Prasse A, et al. The analysis of tryptase in serum of sarcoidosis patients. Inflammation 2009;32:310-314.
62 Park HJ, Jung JI, Chung MH, Song SW, Kim HL, Baik JH, et al. Typical and atypical manifestations of intrathoracic sarcoidosis. Korean J Radiol 2009;10:623-631.
63 Mana J, Van Kroonrnburg M. Clinical usefulness of nuclear imaging techniques in sarcoidosis. Euro Respir Monogr 2005;10 (Monogr 32):284-300.
64 Bolat S, Berding G, Dengler R, Stangel M, Trebst C. Fluorodeoxyglucose positron emission tomography (FDG-PET) is useful in the diagnosis of neurosarcoidosis. J Neurol Sci 2009;287:257-259.
65 Costabel U, Bonella F, Ohshimo S, Guzman J. Diagnostic modalities in sarcoidosis: BAL, EBUS, and PET. Semin Respir Crit Care Med 2010;31:404-408.
66 Clement A, Epaud R, Fauroux B. Sarcoidosis in children. Euro Respir Monogr 2005;10(Monogr 32): 251-258.
67 Mallory SB, Paller AS, Ginsburg BC, McCrossin ID, Abernathy R. Sarcoidosis in children: differentiation from juvenile rheumatoid arthritis. Pediatr Dermatol 1987;4:313-319.
68 White ES, Lynch JP 3rd. Current and emerging strategies for the management of sarcoidosis. Expert Opin Pharmacother 2007;8:1293-1311.
69 Shetty AK, Gedalia A. Sarcoidosis in children. Curr Probl Pediatr 2000;30:149-176.
70 Kiper N, Anadol D, Ozçelik U, Göçmen A. Inhaled corticosteroids for maintenance treatment in childhood pulmonary sarcoidosis. Acta Paediatr 2001;90:953-956.
71 Chadelat K, Baculard A, Grimfeld A, Tournier G, Boule M, Boccon-Gibod L, et al. Pulmonary sarcoidosis in children: serial evaluation of bronchoalveolar lavage cells during corticosteroid treatment. Pediatr Pulmonol 1993;16:41-47.
72 Cron RQ, Sharma S, Sherry DD. Current treatment by United States and Canadian pediatric rheumatologists. J Rheumatol 1999;26:2036-2038.
73 Shetty AK, Zganjar BE, Ellis GS Jr, Ludwig IH, Gedalia A. Low-dose methotrexate in the treatment of severe juvenile rheumatoid arthritis and sarcoid iritis. J Pediatr Ophthalmol Strabismus 1999;36:125-128.
74 Gedalia A, Molina JF, Ellis GS Jr, Galen W, Moore C, Espinoza LR. Low-dose methotrexate therapy for childhood sarcoidosis. J Pediatr 1997;130:25-29.
75 Lower EE, Baughman RP. Prolonged use of methotrexate for sarcoidosis. Arch Intern Med 1995;155:846-851.
76 Yasui K, Yashiro M, Tsuge M, Manki A, Takemoto K, Yamamoto M, et al. Thalidomide dramatically improves the symptoms of early-onset sarcoidosis/Blau syndrome: its possible action and mechanism. Arthritis Rheum 2010;62:250-257.
77 Yee AM, Pochapin MB. Treatment of complicated sarcoidosis with infliximab anti-tumor necrosis factor-alpha therapy. Ann Intern Med 2001;135:27-31.
78 Milman N, Andersen CB, Hansen A, van Overeem Hansen T, Nielsen FC, Fledelius H, et al. Favourable effect of TNF-alpha inhibitor (infliximab) on Blau syndrome in monozygotic twins with a de novo CARD15 mutation. APMIS 2006;114:912-919.
79 Milman N, Hoffmann AL. Childhood sarcoidosis: long-term follow-up. Eur Respir J 2008;31:592-598.
80 Marcille R, McCarthy M, Barton JW, Merten DF, Spock A. Long-term outcome of pediatric sarcoidosis with emphasis on pulmonary status. Chest 1992;102:1444-1449.

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