Sarcoidosis in the pediatric age

R. Cimaz[1], B.M. Ansell[2]

[1]Rolando Cimaz, MD, Clinica Pediatrica, Via Commenda 9, 20122 Milan, Italy. E-mail: Rolando.Cimaz@unimi.it

[2]Barbara M. Ansell, MD, Dumgoyne, Stoke Poges, United Kingdom. Dr. Ansell passed away on September 14, 2001.

Received on February 1, 2002; accepted on February 11, 2002.

Clin Exp Rheumatol 2002; 20: 231-237.

Introduction

Sarcoidosis is a systemic granulomatous disorder of unknown cause characterized by the presence of non-caseating granulomata. Its clinical features are protean, with a disease expression ranging from asymptomatic individuals with abnormal chest radiographs to multiorgan failure. Although many organ systems can be involved, the lung is most commonly affected and accounts for the majority of morbidity and mortality from the disease. Sarcoidosis is well recognized in adults and is most commonly diagnosed between the ages of 20 and 40 years, but it can also occur in children (1-8).

Although sarcoidosis in children may be underdiagnosed, it is in fact quite rare in the pediatric age. The incidence of the disease increases from birth to adolescence, with most cases typically diagnosed in the pre-adolescent or adolescent period. There seems to be two forms of juvenile sarcoidosis, according to the age of onset. The early-onset form (i.e. patients presenting in the first 4-5 years of life) is usually characterized by the triad of arthritis/rash/uveitis (9-11), while older children and adolescents have a form of sarcoid that is similar to the adult one, with hilar adenopathy, pulmonary infiltrates, and systemic features such as weight loss and fever (12). The most important differences between these two forms are listed in Table I.

Epidemiology

The prevalence and incidence of sarcoidosis are not well known, due to the high frequency of asymptomatic individuals. The disease seems to be quite rare in childhood: a recent Danish study has estimated an annual incidence of 2-3 cases per million children (5). However, routine chest X-ray screenings of children performed in Hungary and Japan have disclosed many subclinical cases (4, 6, 13).

In the majority of reported pediatric series the frequency of sarcoidosis is similar in the two genders (14). The racial distribution seems to be different according to the age of onset, with African-Americans comprising the majority in older children and Caucasians in the younger group. Certain areas, such as Sweden in Europe and the South Atlantic and Gulf states in the USA, have been reported to have a higher incidence of this disease (14, 15).

Etiology and pathogenesis

The etiology of sarcoidosis is unknown. It is thought that the disease characteristics are secondary to an altered immune response to unknown agent(s). The macrophage most likely initiates the inflammatory response, and the accumulation of activated T cells and mononuclear phagocytes at the lesion precedes granuloma formation (16). CD4+ lymphocytes perpetuate inflammation by releasing cytokines such as IL-2, IL-6, and -interferon, while TNF- seems to be critical in order to maintain the granulomatous lesion. In addition, B-lymphocytes are stimulated to produce increased amounts of immunoglobulins and fibroblasts are stimulated to proliferate.

Clinical features

The clinical features of sarcoid are diverse. We will list the most common according to the organ systems involved. In the majority of cases constitutional symptoms such as fever, weight loss, or fatigue are present.

Respiratory tract. The lung is the most frequently involved organ in sarcoidosis. Dry cough and dyspnea are the most common symptoms, and radiological evidence of bilateral hilar lymphadenopathy, with or without parenchymal involvement, is present almost universally in adolescent and pre-adolescent patients (17). Radiological features are staged using the same system as that used in adults, i.e. stage I (normal chest radiograph) to stage IV (fibrosis and emphysema with forma-

Table I. Features of classical and early-onset sarcoidosis.

	Classical juvenile sarcoidosis	Early-onset form
Age group (onset)	Mostly adolescence	First 4 years of life
Prevalent racial background	African-American	Caucasian
Familial	No	Possible (Blau syndrome)
Pulmonary involvement	Present, usually from the onset	Absent (or present only later in the disease course)
Lymphadenopathy	Yes	Not prominent
Systemic symptoms (e.g. weight loss, fever)	Yes	No
Arthritis	Rare	Yes (mostly tenosynovitis)
Uveitis	Yes	Yes
Rash	Yes	Yes
Prognosis	Variable, but can be good in a significant proportion of cases	Usually unrelenting and progressive course, frequent severe complications

tion of bullae) (15). Chest pain may occasionally be present. Abnormalities in pulmonary function are also similar to those seen in adults; although any aspect of lung functioning may be compromised, restrictive lung disease is the most common manifestation (18). Chest X-ray and pulmonary function tests are frequently abnormal at the very onset of disease. Affected children often improve gradually, and can develop normal lung functioning over a period of years. On rare occasions, not only the lower but also the upper respiratory tract may be affected (19-21).

Lymphatic system. Peripheral lymphadenopathy is a common physical finding in children, and lymph nodes are a useful tissue site for a diagnostic biopsy. Nodes are typically firm, freely movable, shotty, and non-tender.

Skin. Cutaneous manifestations are also frequent and include papules, plaques, nodules, erythema nodosum, and hypo- or hyperpigmented areas. Lupus pernio is frequent in adults but rare in children.

Eyes. Ocular involvement is extremely common in sarcoidosis, and is one the most serious complications. The granulomatous inflammation can affect almost all of the ocular structures (22, 23). The most common form is granulomatous uveitis, which can be a panuveitis in about 25% of cases. The uveitis of sarcoidosis is characterized by firmly edged keratic precipitates in the limbus, iris nodules, and focal synechiae. Granulomata are also frequent in the conjunctivae. Complications include optic neuritis, band keratopathy, cataract, glaucoma, and retinal vasculitis (24). Ocular symptoms are usually not prominent, so that an opthalmologic evaluation is mandatory in any case diagnosed as sarcoidosis. A blind conjunctival biopsy can be diagnostic for the presence of granulomata in 10-30% of the cases, with sensitivity raised to 75% if the biopsy is performed in the presence of conjunctival nodules. Magnetic resonance of the orbit is an excellent diagnostic procedure when a direct eye examination is unrevealing.

Nervous system. Clinically evident neurological dysfunctions secondary to sarcoidosis are rare in childen (25-27). Although any part of the nervous system can be involved, granulomata are most common in the basal area of the meninges and brain, producing obstructive hydrocephalus and seventh nerve palsy (15). In the case of central nervous system (CNS) involvement, concurrent systemic disease is usually present. Growth deficiency has been described in association with brain MRI abnormalities, and hypothalamic infiltration can manifest as diabetes insipidus (28, 29). Clinically silent intra-cranial sarcoidosis has also been recently described (30).

Kidney. Renal involvement can be related to the presence of granulomata in the renal parenchyma, or to hypercalciuria with nephrocalcinosis (31-35). Biopsy-proven renal granulomatous sarcoidosis has been recently described in 11 children, 9 of whom developed renal failure (36). Although reported cases of renal sarcoid are few, these authors reviewed published series (for a total of 328 children with sarcoidosis) and could calculate the prevalence of hypercreatininemia (26%), proteinuria or abnormalities in the urinary sediment (31%), hypercalciuria (47%), and hypercalcemia (21%). Kidney stones were reported in 8 cases. Therefore, renal involvement might be more common than currently thought. The frequencies of renal abnormalities were similar in granulomatous and calcaemic nephropathy. Membranous nephropathy has also been described in childhood sarcoidosis, and the altered immune response has been postulated to be responsible for the formation of immune complexes within the glomeruli (37).

Not only the kidney but also the urogenital tract can be involved, since testicular and epididymal sarcoidosis have been described in children (38, 39).

Liver. Hepatic involvement by sarcoid granulomata may be present in up to 90% of patients, according to the different series, and liver enzymes (bilirubin and alkaline phosphatase) are often mildly elevated. However, symptoms are usually present in a much lower percentage of cases. In the presence of hepatic involvement, sarcoid granulomata are usually numerous enough on liver specimens to make sampling errors unlikely; therefore a diagnostic biopsy can be reliable since false negative results in this setting are rare (40).

Heart and blood vessels. Cardiac involvement has been thoroughly described in adult sarcoidosis (41-44), but rarely in the pediatric age. On the other hand, vasculitis seems to be a promi-

nent feature in some of the described juvenile cases. This can take the form of large vessel vasculitis, such as abdominal aortic aneurysm (45), or medium or small vessel vasculitis. A recent review of sarcoidosis and systemic vasculitis has identified 28 patients and, despite the relative rarity of the disease in the pediatric age, almost half of these patients were children (46).

Musculoskeletal system. Arthritis is more common in the early-onset group than in older children (see below). Bone involvement is rare, and has been described in the distal ends of the phalanges, and the metacarpal and metatarsal bones. Punched-out lesions, a lacy reticular trabecular pattern, or acro-osteolysis have all been reported (6). Myositis with granulomata in the muscles has also been described (47-50).

Diagnosis

The currently accepted diagnostic standard for sarcoidosis is the demonstration of non-caseating granulomata in one or more organs in the setting of consistent radiographic or clinical findings. Granulomata can be found in any of the organs involved; however, they may also be found in a variety of other diseases, such as infections, malignancy, or hypersensitivity reactions (15). The typical sarcoid granuloma consists of sharply circumscribed epithelioid histiocytes with foreign body giant (or Langhans) cells surrounded by a rim of lymphocytes. The giant cells may contain blue laminate concretions of calcium and proteins (Schaumann bodies), or stellate-shaped inclusions (asteroid bodies).

Laboratory testing often does not contribute to the diagnosis. Serum calcium levels are sometimes elevated, and hypercalcemia is likely to be more prevalent in children than in adults. The mechanism that leads to elevated calcium levels is related to a specific metabolic dysregulation. The epithelioid cells in the sarcoid granuloma are in fact transformed, fixed macrophages which have retained the ability to produce 1- hydroxylase, and cultured alveolar macrophages from sarcoid patients are able to transform 25-OH-vitamin D to 1,25-OH-vitamin D. The excess circulating 1,25 dihydroxyvitamin D produced extra-renally, together with the loss of the normal feed-back mechanisms, cause the increased intestinal absorption and urinary excretion of calcium.

Serum levels of angiotensin-converting enzyme (ACE), which is also produced from the epithelioid cells of the sarcoid granuloma, are often elevated as well. However, an elevated ACE is not specific for sarcoidosis, since it can be present in a variety of other disorders (15); it is also less sensitive in the childhood than in the adult form of the disease. Moreover, ACE levels tend to be higher in childen than in adults, so abnormal results should be compared with reference values adjusted for age (51, 52).

The Kviem-Siltzbach skin test, in which non-caseating granulomata are shown in a biopsy after the intra-dermal injection of human sarcoid homogenate, has been abandoned because it is not widely available and not well standardized (12).

Bronchoalveolar lavage demonstrates an increased number of lymphocytes (53), most of which are activated T-cells, and preferential cytokine expression patterns (54). However, the usefulness of this procedure in children has not gained wide acceptance. Fine needle aspiration biopsy cytology has been suggested as an adjunct in the diagnosis of children with suspected sarcoidosis, through the demonstration of epithelioid histiocytes and multinucleated foreign-body type giant cells without accompanying necrosis or acute inflammation (55). Gallium scans are also useful, but only as a research tool at the present time, since the increased uptake in the lungs is not specific for sarcoidosis but can be present in other disorders as well.

In children who present with fever of unknown origin, magnetic resonance imaging has been useful in establishing the diagnosis of sarcoidosis, showing multifocal nodular lesions in the bone marrow of the lower extremities (56).

Prognosis

Even if long-term studies in children are lacking, it seems that the prognosis of childhood sarcoidosis is not significantly different from that in adults, with most children showing improvement in their pulmonary status (15, 57) and the vast majority of patients recovering with minimal or no therapy (6). Severe involvement at presentation and multiorgan involvement are associated with a worse prognosis. As described later, patients with onset in the first years of life usually have an unfavourable outcome.

Treatment

Generally, it is believed that corticosteroids may accelerate symptomatic improvement, although the long-term prognosis is probably not affected. Asymptomatic patients can only be followed clinically, while steroid treatment should be instituted in the presence of respiratory symptoms such as dyspnea, cough or chest pain, or in the presence of severe impairment of pulmonary function tests. In the case of a scarce response to corticosteroids,methotrexate has been used with success. An open-label trial (58) has evaluated the efficacy of weekly oral low-dose methotrexate in 7 children with biopsy-proven sarcoidosis. Each of them had previously undergone at least one unsuccessful attempt to taper the prednisone dosage. At the end of the follow-up period (mean, 13.4 months, range, 6-28 months) there was a significant improvement in the clinical signs and symptoms and laboratory parameters; moreover, the mean prednisone dosage could be reduced from 1.3 mg/kg/day to 0.1 mg/kg/day.

Other immunosuppressive medications that have been used in adult patients include cyclosporine, azathioprine, and cyclophosphamide.

Early-onset sarcoidosis

We and others (3, 4, 6, 9, 10, 11, 14, 15, 59-62) believe that patients in this early-onset group are suffering from a disease distinct from classic sarcoidosis, and some authors have even suggested a different name for it – "juvenile systemic granulomatosis" (63). Onset always occurs within the first years of life, frequently in the first 12 months. The classic appearance of sar-

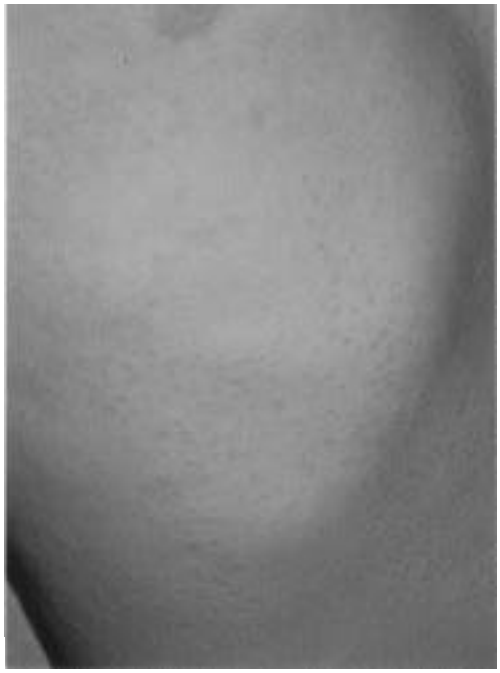
coid in the very young child is characterized at the onset by rash or arthritis without pulmonary involvement, followed by uveitis and various other clinical manifestations which can be multisystem. The typical triad of early-onset sarcoidosis is shown in Figure 1. This disease is particularly challenging, since it can be easily confused with juvenile idiopathic arthritis (JIA) (40, 64-69) and often has a progressive and debilitating course. The most useful differentiating features between early-onset sarcoidosis and JIA are shown in Table II.

The arthritis of early-onset sarcoidosis is typically a tenosynovitis, frequently with massive swelling of the wrists and ankles and sometimes the knees. Its clinical appearance is usually distinctive from the arthritis of JIA, in that synovial hypertrophy in the joints, and especially in the tendon sheaths, is typically accompanied by a relative lack of pain, tenderness or restricted motion (70). With disease progression the arthritis can become erosive, with deformities and functional limitations. Rosenberg *et al*. (71) compared children with sarcoidosis who had arthritis to those without articular involvement. Patients with arthritis had a significantly lower age at disease onset (mean, 2.3 vs. 10.8 years) and a significantly higher prevalence of skin and eye disease ($P < 0.001$).

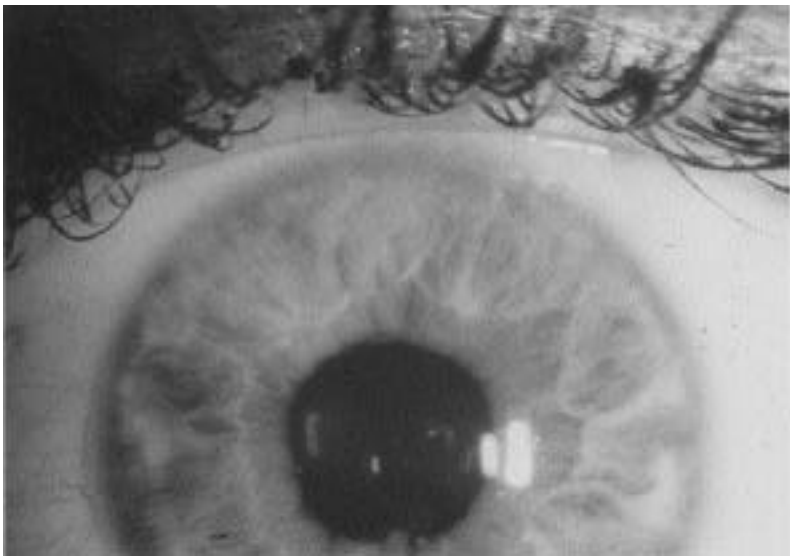
The rash of sarcoidosis may assume different forms, and is usually macular or nodular. It can be distinguished from the rash of systemic JIA, which is typically evanescent and not fixed, usually salmon-pink and not nodular or follicular as is sarcoid. Erythema nodosum (72) and other unusual dermatologic manifestations (73, 74) have been described at the onset of disease.

Ocular involvement is particularly grave in this age group, and can lead to blindness. It is rarely present at the disease onset. The differential diagnosis is again mainly from JIA. However, uveitis is rare in systemic onset disease, and there are features that help to distinguish between the two conditions. In particular, in JIA-associated uveitis, which is anterior in most cases, nodule formation is usually not present, and

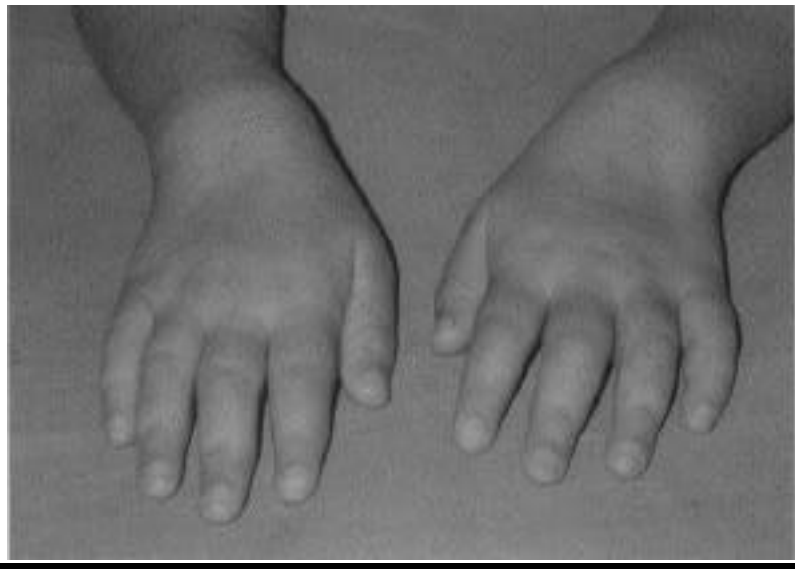
Fig. 1. The triad (skin, eye, and joint involvement) of early-onset sarcoidosis. (**a**) Papular rash on the trunk; (**b**) granulomas at the inferior pole and irregularities of the pupillar rim; (**c**) swelling of the wrists.



(a)



(b)



(c)

Table II. Diagnostic differentiation between early-onset sarcoidosis and juvenile idiopathic arthritis.

	Early-onset sarcoidosis	Juvenile idiopathic arthritis
Arthritis	Mostly tenosynovitis (effusion along tendon sheaths), with massive and boggy swelling (usually wrists and/or ankles)	Arthritis (effusion within synovial spaces) can occur in large and small joints
	No comparable pain and restricted range of motion	Swelling is accompanied by restricted range of motion, sometimes with pain
	Erosive changes occur only with long-standing disease	Erosions can be present also in early disease Juxta-articular osteoporosis.
Uveitis	Granulomatous, can be anterior and posterior	Usually anterior
	Focal synechiae	Diffuse synechiae
	Nodules	No nodules
	Possible vascular and retinal involvement	No vascular/retinal involvement
	Peripheral corneal aggregates	Central corneal aggregates
Rash	Persistent, can assume different forms (even nodular)	Evanescent, maculopapular

synechiae with the lens are mostly diffuse, while in sarcoidosis they tend to be focal; corneal deposits tend to be in the periphery in sarcoid and in the centre or diffuse in JIA. When present, retinal and optic nerve involvement will exclude the diagnosis of JIA.

Pulmonary involvement is not usual in early-onset sarcoid, but can ensue later during the disease course. Almost every organ system can be affected in childhood sarcoidosis: among the other clinical manifestations, renal involvement with hematuria, hypercalciuria and nephrocalcinosis can occasionally lead to renal failure (75). Cardiac involvement by sarcoid granulomata, hepatosplenomegaly, and short stature have all been described. Osseous sarcoidosis is reported in approximately 5% of adult patients (76), but has only occasionally been described in young children (77, 78). Also, vasculitis has been described in this group (46), including large vessel vasculitis with aortic arch involvement indistinguishable from Takayasu arteritis (79), renal artery stenosis (80), and systemic necrotizing vasculitis with skin infarction and digital gangrene (81).

The diagnosis of early-onset sarcoidosis is, as in the classic form, established on clinical grounds with the support of histology. Sometimes skin manifestations precede the other features (82, 83), making the diagnosis very difficult at the onset of disease. The presence of non-caseating granulomata in the appropriate clinical setting is pathognomonic. Chest-X ray is not useful for diagnosis in the very young child, but can become abnormal with the disease course. Circulating levels of calcium and ACE are not useful for the diagnosis, but when increased they can be used with sequential measurements to monitor disease activity in individual patients.

The prognosis seems to be worse in the early-onset form than in the classic sarcoid. We have described 6 patients followed for as long as 23 years; their complications included blindness, dwarfism, renal failure, and heart involvement (61). Despite continuous systemic corticosteroid treatment, one of these patients died 10 years after the disease onset from multiple organ failure and chronic congestive heart failure secondary to widespread granulomata invasion. We can only comment on (not analyse) the efficacy of treatment, since the rarity of this disease has not allowed controlled trials to be conducted. Corticosteroids are the mainstay of treatment, but methotrexate has also been used with success in a few patients (58).

Blau syndrome

Genetic factors also seem to play a role: a familial form of autosomal dominant granulomatous disease of childhood (Blau syndrome) has in fact been described, with clinical features almost identical to early-onset sarcoidosis (84). Genetic linkage analysis has shown a disease susceptibility locus on the pericentromeric region of chromosome 16 (85). Several other families with this disorder have been reported in the literature (86-90).

There has been debate on whether the two forms represent separate entities (91-93), based in part on the presumed absence of visceral involvement in Blau syndrome. However, renal (94) and hepatic (95) granulomata have recently been described in this disease as well. Moreover, granulomata of a skin and synovial biopsy from a patient with Blau syndrome could not be distinguished from those seen in sarcoidosis, either by light microscopy or by immunocytochemical studies (96). It is now believed by some authors that these two diseases constitute part of the same spectrum, and Blau himself agreed with this concept when discussing the nomenclature of the disease that carries his name (97).

Conclusions

Sarcoidosis is rare in childhood. When it presents during adolescence, its clinical features mirror those in adults, and pulmonary involvement is the most frequent finding. In contrast, the early onset form, which occurs in children during their first years of life, seems to be a quite different disease. Respiratory symptoms are often absent, while the predominant manifestations are skin rash, arthritis/tenosynovitis, and uveitis. This disease can be progressive and severe, with multisystemic involvement and frequent complications. The diagnosis can be difficult, because the full-blown picture may not be apparent at the onset, and the disease can mimic

other disorders such as juvenile idiopathic arthritis.

References

1. JASPER PL, DENNY FW: Sarcoidosis in children. *J Pediatr* 1968; 73: 499-512.
2. PATTISHALL EN, STROPE GL, SPINOLA SM, DENNY FW: Childhood sarcoidosis. *J Pedi - atr* 1986; 108: 169-77.
3. CLARK SK: Sarcoidosis in children. *Pediatr Dermatol* 1987; 4: 291-9.
4. JAMES DG, KENDIG EL: Childhood sarcoidosis. *Sarcoidosis* 1988; 5: 57-9.
5. MILMAN N, HOFFMANN AL, BYG KE: Sarcoidosis in children. Epidemiology in Danes, clinical features, diagnosis, treatment, and prognosis. *Acta Paediatr* 1998; 87: 871-8.
6. KEESLING CA, FRUSH DP, O'HARA SM, FORDHAM LA: Clinical and imaging manifestions of pediatric sarcoidosis. *Acad Radiol* 1998; 5: 122-32.
7. SHETTY AK,GEDALIA A: Sarcoidosis in children. *Acta Paediatr* 1999; 88: 235.
8. SHETTY AK,GEDALIA A: Sarcoidosis in children. *Curr Problems Pediatr* 2000; 30: 149-76.
9. RASMUSSEN JE: Sarcoidosis in young children. *J Am Acad Dermatol* 1981; 5: 566-70.
10. HETHERINGTON S: Sarcoidosis in young children. *Am J Dis Child* 1982; 136: 13-5.
11. HAFNER R, VOGEL P: Sarcoidosis of early onset. A challenge for the pediatric rheumatologist. *Clin Exp Rheumatol* 1993; 11: 685-91.
12. NEWMAN LS, ROSE CS, MAIER LA: Sarcoidosis. *N Engl J Med* 1997; 336: 1224-34.
13. KENDIG EL, NIITU Y: Sarcoidosis in Japanese and American children. *Chest* 1980; 775: 514-6.
14. SHETTY AK, GEDALIA A: Sarcoidosis: A pediatric perspective. *Clin Pediatr* 1998; 37: 707-17.
15. PATTISHALL EN, KENDIG EL: Sarcoidosis in children. *Pediatr Pulmonol* 1996; 22: 195-203.
16. BARNARD J, NEWMAN LS: Sarcoidosis: Immunology, rheumatic involvement,and therapeutics. *Curr Opin Rheumatol* 2001;13:84-91.
17. KENDIG EL: Sarcoidosis. *Am J Dis Child* 1982; 136: 11-2.
18. PATTISHALL EN, STROPE GL, DENNY FW: Pulmonary function in children with sarcoidosis. *Am Rev Respir Dis* 1986; 133:94-6.
19. MCHUGH K, DESILVA M, KILHAM HA: Epiglottic enlargement secondary to laryngeal sarcoidosis. *Pediatr Radiol* 1993; 23:71.
20. ROGER G, GALLAS D, TASHJIAN G, BACULARD A, TOURNIER G, GARABEDIAN EN: Sarcoidosis of the upper respiratory tract in children. *Int J Pediatr Otorhinolaryngol* 1994; 30: 233-40.
21. KENNY TJ, WERKHAVEN J, NETTERVILLE JL: Sarcoidosis of the pediatric larynx. *Arch Otolaryngol - Head Neck Surg* 2000; 126: 536-9.
22. LENNARSON P, BARNEY NP: Interstitial keratitis as presenting ophthalmic sign of sarcoidosis in a child. *J Pediatr Ophthalmol Strabismus* 1995; 32: 194-6.
23. HEGAB SM, AL-MUTAWA SA, SHERIFF SM: Sarcoidosis presenting as multilobular limbal corneal nodules. *J Pediatr Ophthalmol Stra - bismus* 1998; 35: 323-6.
24. OHARA K, OKUBO A, SASAKI H, KAMATA K: Branch retinal vein occlusion in a child with ocular sarcoidosis. *Am J Ophthalmol* 1995; 119: 806-7.
25. LIPNICK RN, HUNG W, PANDIAN MR: Neurosarcoidosis presenting as secondary amenorrhea in a teenager. *J Adolescent Health* 1993; 14: 464-7.
26. NG KL, MCDERMOTT N, ROMANOWSKI CA, JACKSON A: Neurosarcoidosis masquerading as glioma of the optic chiasm in a child. *Post - grad Med J* 1995; 71: 265-8.
27. LEIBA H, SIATKOWSKI RM, CULBERTSON WW, GLASER JS: Neurosarcoidosis presenting as an intracranial mass in childhood. *J Neuro-Ophthalmol* 1996; 16: 269-73.
28. BASDEMIR D, CLARKE W, ROGOL AD: Growth hormone deficiency in a child with sarcoidosis. *Clin Pediatr* 1999; 38: 315-6.
29. KONRAD D, GARTENMANN M, MARTIN E, SCHOENLE EJ: Central diabetes insipidus as the first manifestation of neurosarcoidosis in a 10-year-old girl. *Horm Res* 2000; 54: 98-100.
30. KONE-PAUT I, PORTAS M, WECHSLER B, GIRARD N, RAYBAUD C: The pitfall of silent neurosarcoidosis. *Pediatr Neurol* 1999; 20: 215-8.
31. MARTINI A, SERENELLA SCOTTA M, MAGRINI U: Sarcoidose granulomateuse des reins avec insuffisance renale chez une fille de douze ans. *Nephrologie* 1980; 1: 117-9.
32. STANWORTH SJ, KENNEDY CT, CHETCUTI PA, CARSWELL F: Hypercalcaemia and sarcoidosis in infancy. *J Roy Soc Med* 1992; 85: 177-8.
33. HOFFMANN AL, MILMAN N, NIELSEN HE, THODE J: Childhood sarcoidosis presenting with hypercalcaemic crisis. *Sarcoidosis* 1994; 141-3.
34. MORRIS KP, COULTHARD MG, SMITH PJ, CRAFT AW: Renovascular and growth effects of childhood sarcoid. *Arch Dis Child* 1996; 75: 74-5.
35. HERMAN TE, SHACKELFORD GD, MCALISTER WH: Pseudotumoral sarcoid granulomatous nephritis in a child: case presentation with sonographic and CT findings. *Pediatr Radiol* 1997; 27: 752-4.
36. COUTANT R, LEROY B, NIAUDET P, *et al.*: Renal granulomatous sarcoidosis in childhood: a report of 11 cases and a review of the literature. *Eur J Pediatr* 1999; 158: 154-9.
37. DIMITRIADES C, SHETTY AK, VEHASKARI M, CRAVER RD, GEDALIA A: Membranous nephropathy associated with childhood sarcoidosis. *Pediatr Nephrol* 1999; 13: 444-7.
38. WEINBERG A, GINSBURG CM: Epididymal sarcoidosis in a prepubertal child. *Am J Dis Child* 1982; 136: 71-2.
39. EVANS SS, FISHER RG, SCOTT MA, KENNEDY BG, BROCK JW, WILSON GJ: Sarcoidosis presenting as bilateral testicular masses. *Pediatrics* 1997; 100: 392-4.
40. SARIGOL SS, HAY MH, WYLLIE R: Sarcoidosis in preschool children with hepatic involvement mimicking juvenile rheumatoid arthritis. *J Pediatr Gastroenterol Nutr* 1999; 28: 510-2.
41. SILVERMAN KJ, HUTCHINS GM, BULKLEY BH: Cardiac sarcoid: A clinicopathologic study of 84 unselected patients with systemic sarcoidosis. *Circulation* 1978; 58: 1204-11.
42. FLEMING HA: Sarcoid heart disease. *Br Med J* 1986; 292: 1095-6.
43. SWANTON RH: Sarcoidosis of the heart. *Eur Heart J* 1988; 9: 169-74.
44. UEDA M, FUJIMOTO T, SHOJI S, NAGAO M, SBRACHI K, ITO T: Cardiac sarcoidosis. *Jpn Heart J* 1990; 31: 251-8.
45. GEDALIA A, SHETTY AK, WARD K, CORREA H, VENTERS CL, LOE WA: Abdominal aortic aneurysm associated with childhood sarcoidosis. *J Rheumatol* 1996; 23: 757-9.
46. FERNANDES SR, SINGSEN BH, HOFFMAN GS: Sarcoidosis and systemic vasculitis. *Semin Arthritis Rheum* 2000; 30: 33-46.
47. LANJEWAR DN, MAHESHWARI MB, LAKHANI SN, PATEL RB, HOLLA VV: Childhood sarcoid myopathy manifesting as joint contractures. *Indian Pediatr* 1996; 33: 128-30.
48. CELLE ME,VENESELLI E, ROSSI GA, DORIA LAMBA L, PESSAGNO A, FERRIERE G: Childhood sarcoidosis presenting with prevalent muscular symptoms: Report of a case. *Eur J Pediatr* 1997; 156: 340-1.
49. ZSOLWAY K, SINAI LN, MAGNUSSON M, TUNNESSEN WW JR: Two unusual pediatric presentations of sarcoidosis. *Arch Pediatr Adolescent Med* 1998; 152: 410-1.
50. ROSSI GA, BATTISTINI E, CELLE ME *et al.*: Long lasting myopathy as a major clinical feature of sarcoidosis in a child: Case report with a 7-year follow-up. *Sarcoidosis* 2001; 18: 196-200.
51. RODRIGUEZ GE, SHIN BC, ABERNATHY RS, KENDIG EL: Serum angiotensin-converting enzyme activity in normal children and in those with sarcoidosis. *J Pediatr* 1981; 99: 68-72.
52. BENETEAU-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: 344-6.
53. CHADELAT K, BACULARD A, GRIMFELD A, *et al.*: Pulmonary sarcoidosis in children: Serial evaluation of bronchoalveolar lavage cells during corticosteroid treatment. *Pediatr Pulmonol* 1993; 16: 41-7.
54. TESSIER V, CHADELAT K, BACULARD A, HOUSSET B, CLEMENT A: BAL in children: a controlled study of differential cytology and cytokine expression profiles by alveolar cells in pediatric sarcoidosis. *Chest* 1996; 109: 1430-8.
55. WAKELY PE, SILVERMAN JF, HOLBROOK CT, FAIRMAN RP, DAESCHNER CW, JOSHI VV: Fine needle aspiration biopsy cytology as an adjunct in the diagnosis of childhood sarcoidosis. *Pediatr Pulmonol* 1992; 13:117-20.
56. GEDALIA A, SHETTY AK, WARD KJ, CORREA H,HEINRICH S: Role of MRI in diagnosis of childhood sarcoidosis with fever of unknown origin. *J Pediatr Orthop* 1997; 17: 460-2.
57. MARCILLE R, MCCARTHY M, BARTON JW, MERTEN DF, SPOCK A: Long-term outcome of pediatric sarcoidosis with emphasis on pulmonary status. *Chest* 1992; 102: 1444-9.
58. GEDALIA A, MOLINA JF, ELLIS GS JR, GALEN W, MOORE C, ESPINOZA LR: Low-

dose methotrexate therapy for childhood sarcoidosis. *J Pediatr* 1997; 130: 25-9.
59. BRUYNEEL-RAPP F, MALLORY SB: Diffuse papular eruption with swelling of joints in a preschooler. Sarcoidosis in a preschooler. *Arch Dermatol* 1991; 127: 1051-4.
60. HOOVER DL, KHAN JA, GIANGIACOMO J: Pediatric ocular sarcoidosis. *Surv Ophtalmol* 1986; 30: 215-28.
61. FINK CW, CIMAZ R: Early onset sarcoidosis: not a benign disease. *J Rheumatol* 1997; 24: 174-7.
62. FINK CW, CIMAZ R: Childhood sarcoidosis - Does age of onset predict clinical manifestations ? *J Rheumatol* 1997; 24: 1655-6.
63. MILLER JJ: Early-onset "sarcoidosis" and "familial granulomatous arthritis (arteritis)": the same disease. *J Pediatr* 1986; 109:387-8.
64. LINDSLEY CB, GODFREY WA: Childhood sarcoidosis manifesting as juvenile rheumatoid arthritis. *Pediatrics* 1985; 76: 765-8.
65. MALLORY SB, PALLER AS, GINSBURG BC, MCCROSSIN ID, ABERNATHY R: Sarcoidosis in children: differentiation from juvenile rheumatoid arthritis. *Pediatr Dermatol* 1987; 4: 313-9.
66. SAHN EE, HAMPTON MT, GAREN PD, WARRICK J, SMITH D, SILVERRM: Preschool sarcoidosis masquerading as juvenile rheumatoid artrhitis: Two case reports and a review of the literature. *Pediatr Dermatol* 1990; 7: 208-13.
67. UKAE S, TSUTSUMI H, ADACHI N, TAKAHASHI H, KATO F, CHIBA S: Preschool sarcoidosis manifesting as juvenile rheumatoid arthritis:A case report and a review of the literature of Japanese cases. *Acta Pediatr Jpn* 1994; 36: 515-8.
68. SAKURAI Y, NAKAJIMA M, KAMISUE S, *et al.*: Preschool sarcoidosis mimicking juvenile rheumatoid arthritis:the significance of gallium scintigraphy and skin biopsy in the differential diagnosis. *Acta Paediatr Jpn* 1997; 39: 74-8.
69. YOTSUMOTO S, TAKAHASHI Y, TAKEI S, SHIMADA S, MIYATA K, KANZAKI T: Early onset sarcoidosis masquerading as juvenile rheumatoid arthritis. *J Am Acad Dermatol* 2000; 43: 969-71.
70. NORTH AF, FINK CW, GIBSON WM *et al.*: Sarcoid arthritis in children. *Am J Med* 1970; 48: 449-55.
71. ROSENBERG AM, YEE EH, MACKENZIE: Arthritis in childhood sarcoidosis. *J Rheumatol* 1983; 10:987-90.
72. CANCRINI C, ANGELINI F, COLAVITA M, *et al.*: Erythema nodosum: a presenting sign of early onset sarcoidosis. *Clin Exp Rheumatol* 1998; 16: 337-9.
73. MORRISON JG: Sarcoidosis in a child presenting as an erythroderma with keratotic spines and palmar pits. *Br J Dermatol* 1976; 95: 93-7.
74. WALDMAN DJ, RICHARD E: Cutaneous sarcoidosis of childhood. *J Pediatr* 1977; 91: 271-3.
75. NOCTON JJ, STORK JE, JACOBS G, NEWMAN AJ: Sarcoidosis associated with nephrocalcinosis in young children. *J Pediatr* 1992; 121: 937-40.
76. SHORR AF, MURPHY FT, KELLY WF, KAPLAN KJ, GILLILAND WR, SHAPEERO L: Osseous sarcoidosis. Clinical, radiographic, and therapeutic observations. *J Clin Rheumatol* 1998; 4: 186-92.
77. ADLER DD, BLANE CE, HOLT JF: Case report 220. *Skeletal Radiol* 1983; 9: 205-7.
78. TOOMEY F, BAUTISTA A: Rare manifestations of sarcoidosis in children. *Radiology* 1970; 94: 569-73.
79. ROSE CD, EICHENFIELD AH, GOLDSMITH DP, ATHREYA BH: Early onset sarcoidosis with aortitis – "juvenile systemic granulomatosis ?". *J Rheumatol* 1990; 17: 102-6.
80. GROSS KR, MALLESON PN, CULHAM G, LIRENMAN DS, MCCORMICK AQ, PETTYRE: Vasculopathy with renal artery stenosis in a child with sarcoidosis. *J Pediatr* 1986; 108: 724-6.
81. KWONG T, VALDERRAMA E, PALEY C, ILOWITE N: Systemic necrotizing vasculitis associated with childhood sarcoidosis. *Semin Arthritis Rheum* 1994; 23: 388-95.
82. O'DRISCOLL JB, BECK MH, LENDON M, WRAITH J, SARDHARWALLA IB: Cutaneous presentation of sarcoidosis in an infant. *Clin Exp Dermatol* 1990; 15: 60-2.
83. FALCINI F, BATTINI ML, CERUSO M, CIMAZ R: A 4-year-old with a rash. *Lancet* 1999; 354: 40.
84. BLAU EB: Familial granulomatous arthritis, iritis, and rash. *J Pediatr* 1985; 107: 689-93.
85. TROMP G, KUIVANIEMI H, RAPHAEL S, *et al.*: Genetic linkage of familial granulomatous inflammatory arthritis, skin rash, and uveitis to chromosome 16. *Am J Hum Genet* 1996; 59: 1097-107.
86. PRIEUR AM, MENKES CJ, BESSIS JL, HAQUET D, GRISCELLI C: Sarcoidose articulaire familiale. *Arch Fr Pediatr* 1982; 39: 311-3.
87. ROTENSTEIN D, GIBBAS DL, MAJMUDAR B, CHASTAIN EA: Familial granulomatous arteritis with polyarthritis of juvenile onset. *N Engl J Med* 1982; 306: 86-90.
88. JABS DA, HOUK JL, BIAS WB, ARNETT FC: Familial granulomatous synovitis, uveitis, and cranial neuropathies. *Am J Med* 1985; 78: 801-4.
89. PASTORES GM, MICHELS VV, STICKLER GB, SU WPD, NELSON AM, BOVENMYER DA: Autosomal dominant granulomatous arthritis, uveitis, skin rash, and synovial cysts. *J Pediatr* 1990; 117: 403-8.
90. MANOUVRIER-HANU S, PUECH B, PIETTE F, *et al.*: Blau syndrome of granulomatous arthritis, iritis, and skin rash: A new family and review of the literature. *Am J Med Genetics* 1998; 76: 217-21.
91. MALLORY SB, PALLER A: Blau syndrome versus sarcoidosis. *J Pediatr* 1991; 119: 503.
92. JAMES DG: A comparison of Blau's syndrome and sarcoidosis. *Sarcoidosis* 1994; 11: 100-1.
93. CIMAZ R, FALCINI F: Blau's syndrome and sarcoidosis. *Lancet* 1999; 354: 1035.
94. TING SS, ZIEGLER J, FISHER E: Familial granulomatous arthritis (Blau syndrome) with granulomatous renal lesions. *J Pediatr* 1998; 133: 450-2.
95. SAINI SK, ROSE CD: Liver involvement in familial granulomatous arthritis (Blau syndrome). *J Rheumatol* 1996; 23: 396-9.
96. DE CHADAREVIAN JP, RAPHAEL SA, MURPHY GF: Histologic, ultrastructural, and immunocytochemical features of the granulomas seen in a child with the syndrome of familial granulomatous arthritis, uveitis, and rash. *Arch Pathol Lab Med* 1993; 117: 1050-2.
97. BLAU EB: Autosomal dominant granulomatous disease of childhood: The naming of things. *J Pediatr* 1998; 133: 322-3.