Sarcoidosis in the pediatric age

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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 progression 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-
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.** Peripheric 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 hypopigmented or hyperpigmented areas. Lupus pernio is frequent in adults but rare in children. **Eyes.** Ocular involvement is extremely common in sarcoidosis, and is one of 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 synchiae. Granulomata are also frequent in the conjunctivae. Complications include optic neuritis, band keratopathy, cata-

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

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

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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 1α-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-renal, 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 children than in adults, so abnormal results should be compared with reference values adjusted for age (51, 52).

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

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

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