# Sarcoidosis: a delayed or missed diagnosis in children

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Sarcoidosis is an idiopathic granulomatous disease, most commonly affecting young adults and presenting with bilateral hilar lymphadenopathy and pulmonary infiltrates.[1] In children it is relatively rare and its clinical spectrum varies according to the age of onset.[1-2] It is more common during adolescence and usually presents with clinical features similar to the adult type. In children under the age of 4 years it is rare and has a different presentation. Clinical features are characterized by a triad of rash, uveitis, and arthritis.[3] Sarcoidosis has a worldwide distribution, but is more frequently reported from developed countries.[4,5] To our knowledge, there are no reports of childhood sarcoidosis from Saudi Arabia. We describe the clinical and laboratory features, treatment and outcome of 8 children with sarcoidosis seen at our hospital.

## Methods

We retrospectively reviewed data of children with sarcoidosis seen at King Faisal Specialist Hospital and Research Center (KFSHRC), Riyadh. KFSHRC is the major tertiary care center in Saudi Arabia for most sub-specialties including pediatric rheumatology. Data included demographics, clinical presentation, laboratory parameters, radiological and histopathological features, treatment, disease course, and outcome of these patients.

## Results

Eight children (6 girls, 2 boys) were diagnosed to have sarcoidosis during the study period (1999-2004). The age of onset ranged from 4 months to 9 years (mean, 4.8 years) while the age at time of diagnosis ranged from 2 to 11 years (mean, 7.1 years). None of the patients were diagnosed correctly before the referral to our center. The most frequent referral diagnosis of these patients was pyrexia of unknown origin (Table 1).

The clinical features, treatment and outcome of the patients are summarized in Table 2. The most frequent symptoms were fever (7 patients) and eye involvement (6 patients, including 4 patients with anterior uveitis, and 1 each with panuveitis, and bilateral optic neuritis). Two patients had the typical triad of rash, uveitis and arthritis. Unfortunately, these patients had progressive eye disease complicated by glaucoma, cataract and severe vision impairment. Four patients developed polyarthritis affecting small and large joints, leading to contractures and deformities in 2 patients. Five patients had generalized lymphadenopathy. No patient had the typical hilar lymphadenopathy. However, 3 patients had pulmonary infiltrates. Non-specific skin rash was seen in 4 patients. In 1 patient, the rash was incorrectly diagnosed as pustular psoriasis. One patient developed interstitial nephritis.

Laboratory investigations were not specific. The complete blood count showed leukopenia and low hemoglobin (4 patients), and thrombocytopenia (3 patients). The erythrocyte sedimentation rate (ESR)

Table 1. Demographic data and referral diagnoses in eight Saudi children with sarcoidosis.

| Patient | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|
| Age (yrs) | 6 | 14 | 14 | 7 years | 7 | 11 | 9 | 2 ½ |
| Gender | Female | Female | Female | Male | Female | Female | Male | Female |
| Age at onset (yrs) | 4 ½ | 6 ½ | 3 | 6 ½ | 4 months | 9 | 8 | 6 months |
| Age at diagnosis (yrs) | 4 9/12 | 7 | 11 | 6 9/12 | 7 years | 9 3/12 | 8 9/12 | 2 |
| Referral diagnosis | Pyrexia of unknown origin | Pustular psoriasis | Juvenile idiopathic arthritis | Pyrexia of unknown Origin | Juvenile idiopathic arthritis | Pyrexia of unknown origin | Lymphoma | Leukemia |

was elevated in all patients. Two patients had mildly elevated liver enzymes. Electrolytes, calcium, renal function and urinalysis were normal. One patient with interstitial nephritis had proteinuria. Four patients had weakly positive antinuclear antibodies, and 7 patients had elevated angiotensin-converting enzyme (ACE). Different radiological studies were obtained. Skeletal x-ray performed in 4 patients with arthritis showed osteopenia and joint effusion but without erosions or joint space loss. Chest computed tomography showed multiple nodular-like lesions in 3 patients. A gallium scan was negative in the 2 patients who had the scan.

Tissue biopsy from lung, skin, lymph node, liver, synovial membrane, or bone marrow was done in 7 patients. Four patients had biopsies from more than one organ. All tissue biopsies showed confirmed non-caseating granulomas. Cultures and special stains of biopsy specimens for bacteria, fungi and mycobacteria were negative. Seven patients were treated with non-steroidal anti-inflammatory drugs and corticosteroids. Five of these patients failed to achieve remission, requiring immunosuppressive therapy with methotrexate (5 patients) and cyclosporine (3 patients). One patient with eye involvement was treated with local steroid alone. The disease course was favorable in most patients. All are alive. Unfortunately, joint deformities and impaired vision were noticed in 2 patients.

## Discussion

Childhood sarcoidosis is a granulomatous disease with a wide spectrum of clinical features. It manifests as a multi-system disease. Although the clinical presentation can vary greatly depending up on the onset of disease, patients usually present with non-specific symptoms such as fever, lymphadenopathy or musculoskeletal complaints. Accordingly, few common disease entities including juvenile idiopathic arthritis and malignancy or rare disease such as Blau syndrome mimic the clinical features of sarcoidosis.[2,6-8] All our patients had inaccurate referral diagnosis. All were symptomatic with clinical findings involving most organs. Fever was the most frequent clinical presentation (87%). Most of the patients had eye involvement (75%) and lymphadenopathy (62%). Half of the patients had skin and musculoskeletal features.

Sarcoidosis is described throughout the world, but there is marked variation among countries. Although the developed countries have the highest incidence, it is seen in different developing countries with an almost similar frequency as in the developed countries.[8-12] However, there are only scarce data for childhood sarcoidosis from the developed countries.[13] Recognition of this disease is often delayed because of the lack of awareness and unfamiliarity with its clinical features that eventually led to an unfavorable outcome. Two patients had the disease for more than 6 years before referral to us, and unfortunately they had severe morbidity while other patients who were referred earlier had favorable outcome. Early referral to a specialized center is important to make the diagnosis and initiate treatment.

Two distinct forms of sarcoidosis recognized in children, the early onset form that characterized by the clinical triad (uveitis, arthritis and arthritis) for children under the age of 4 and late onset that mimic adult onset.[2] However, young children may present with multi-system disease. In our series, three patients had the disease before 4 years of age, and two followed the typical triad while the third one had multi-system disease affecting the lung, reticuloendothelial system and bone marrow.

Sarcoidosis is a disease of exclusion; there is no diagnostic laboratory test. However, demonstration

Table 2. Clinical features, laboratory findings, treatment and outcome in eight Saudi children with sarcoidosis.

| Patient | Clinical features | Non-caseating granuloma | ACE level | Treatment | Outcome |
|---|---|---|---|---|---|
| 1 | Fever, lymphadenopathy, hepatosplenomegaly, lung infiltrates | Lung, liver | High | NSAIDs, prednisone, MTX | Improved |
| 2 | Skin rash, uveitis, lymphadenopathy, | Skin | High | NSAIDs, prednisone, MTX, CSA | Improved |
| 3 | Fever, skin rash, arthritis, uveitis, glaucoma | Negative: (skin, synovial membrane) | High | NSAIDs, prednisone, MTX, CSA | Deformed arthritis, impaired vision |
| 4 | Fever, weight loss, lymphadenopathy, hepatosplenomegaly | Liver | High | NSAIDS, prednisone | Improved |
| 5 | Fever, weight loss, skin rash, arthritis, panuveitis | Synovial membrane | Normal | NSAIDs, prednisone, MTX, CSA | Deformed arthritis, impaired vision |
| 6 | Fever, weight loss, arthritis, bilateral optic neuropathy, interstitial nephritis | Bone marrow | High | NSAIDs, prednisone, MTX, topical eye drops | Improved |
| 7 | Fever, lymphadenopathy, uveitis, lung infiltrates | Lymph node, bone marrow | High | Topical steroid (eye drop) | Improved |
| 8 | Fever, skin rash, uveitis, arthritis, lymphadenopathy, hepatosplenomegaly, lung infiltrates | Lymph node, liver, bone marrow | High | NSAIDs, Prednisone, MTX, CSA | Improved |

of typical non-caseating granuloma in the absence of other possible causes of such granuloma in combination of elevated ACE remains the most important diagnostic tool. Certain diseases like mycobaterial infection, brucellosis and fungal infection need to be excluded. Biopsy from the involved organs confirmed the diagnosis of sarcoidosis in 87% of our patients. ACE levels were elevated in seven patients (87%), which is similar to what has been reported (14). Other laboratory and radiographic evaluations were non-specific. All patients had elevated ESR, which prove the inflammatory process. Serum ACE and acute phase reactants may be helpful in monitoring the disease activity.

Various medications have been used to control inflammation and minimize end-organ damage. Corticosteroids are commonly used. However, in refractory disease, there are reports of successful use of immunosuppressive drugs. Methotrexate was found to be effective and safe in childhood sarcoidosis.[15] In our series, corticosteroids appeared to be partially efficacious in seven patients. The addition of methotrexate or cyclosporine was followed by a control of the disease activity. Although all patients are surviving and are in stable condition, two patients had blindness. We believe that was due to late referral and diagnosis.

In summary, we describe a series of children with sarcoidosis in Saudi Arabia. This report indicates that sarcoidosis may be overlooked. Early diagnosis and treatment are required to avoid serious complications.

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