RESEARCH PAPER

Clinical Profile and Outcome of Pediatric Sarcoidosis

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Objectives: To document clinical features and outcome of children with sarcoidosis. **Methods:** Case records of 18 children (mean (SD) age 9 (2.2) years) diagnosed with sarcoidosis between 2006 and 2016 were reviewed. All children were followed up every 2-3 months and monitored for clinical and laboratory parameters. Their treatment and outcome were recorded. **Results:** Clinical features at the time of diagnosis were fever (83%), uveitis (50%), difficulty in breathing (44%), hepatosplenomegaly, weight loss, arthritis and peripheral adenopathy. Imaging findings included: hilar adenopathy (94%), abdominal nodes (50%) and pulmonary infiltrates (44%). All children were treated with steroids (range 6-12 months) and weekly low dose oral methotrexate. All patients showed significant improvement over a mean (SD) duration of follow-up of 3.1 (0.9) years, as assessed by resolution of clinical symptoms, and improvement in spirometry parameters, erythrocyte sedimentation rate, and serum angiotensin converting enzyme levels. ***Conclusions*:** Children with sarcoidosis seem to respond well to systemic steroids and low dose methotrexate. Delayed diagnosis and ocular involvement are probably associated with poor outcome.

Keywords: *Corticosteroids, Hilar lymphadenopathy, Non-caseating granuloma*.

Pediatric sarcoidosis is a chronic disease characterized by non-caseating granulomatous inflammation [1]. It most commonly affects young adults, and is very rare in children [2]. Sarcoidosis is a multisystem disorder; however, mediastinal lymphadenopathy, pulmonary parenchymal infiltration, and cutaneous and ophthalmic disease are common. Moreover, it may involve liver, central nervous system and kidneys [3]. In young children (<5 year old), a triad of skin rash, uveitis and arthritis is more common than pulmonary and mediastinal involvement [4]. Information on course of illness, effective treatment and outcome on childhood sarcoidosis is limited to few reports. Diagnostic criteria are well defined but monitoring and treatment regimen are not well defined. We describe our experience of sarcoidosis in children with emphasis on role of treatment regimen that included methotrexate.

METHODS

We reviewed the case records of children with diagnosis of sarcoidosis between 2006 and 2016, who were followed-up at Pediatric Pulmonology services at AIIMS, New Delhi, India. Details including clinical symptoms and signs, investigations, treatment given, follow-up and outcomes were recorded in a predesigned proforma. The study was approved by Institute Ethics Committee.

Diagnosis of sarcoidosis was based on clinical features, documentation of non-caseating granuloma from various body tissues, raised serum Angiotensin converting enzyme (ACE) levels and raised urinary calcium to creatinine ratio. Patients who had doubtful diagnosis or who were confirmed with an alternative diagnosis, were excluded from the study.

Treatment protocol consisted of systemic steroids, low-dose weekly methotrexate or other medications as indicated. All children were followed-up every 2-3 months. On each visit, children were evaluated clinically, spirometry was done in older children, and hematological investigations and liver and kidney function tests were performed. Other laboratory investigations and imaging were carried out as indicated.

Data were processed with Microsoft Excel, and analyzed with SPSS V 16.0. Statistical significance was analyzed with paired *t* test and Wilcoxon signed rank test.

RESULTS

A total of 18 children (10 boys) diagnosed with sarcoidosis during study period were included. The mean (SD) age at diagnosis and onset of disease was 9 (2.5) and 7.5 (2.0) years, respectively. All patients were symptomatic at presentation. Clinical symptoms, signs and laboratory findings are described in ***Table* I**.

Eight children had previously received anti-tubercular therapy. Six children had Mantoux test positivity; four of them had already received anti-tubercular therapy and remaining two were administered prophylactic isoniazid therapy after ruling out active tuberculosis while they were prescribed systemic steroid therapy.

Sixteen (88%) children had intrathoracic involvement with hilar lymphadenopathy; eight of them had parenchymal involvement classifying them as stage 2 illness. None had stage 3 or 4 illness. Nine (50%) children had abdominal lymphadenopathy.

A tissue diagnosis was available in 16 (88%) children, and all showed non-caseating granulomatous inflammation with negative stain for acid fast bacilli. The sites of biopsy included lymph node in 10 (63%), skin in 4 (25%), lacrimal gland in 1 (6%) and liver in 1 (6%).

Table* II** shows laboratory parameters from diagnosis to remission. Laboratory markers [mean (SD)] documented at diagnosis were: serum calcium 10.6 (0.96) mg/dL, serum phosphate 4.16 (0.68) mg/dL, serum alkaline phosphatase 259 (120) mg/dL, serum 25-hydroxy vitamin D 150.2 (20.9) ng/mL, and urinary calcium: creatinine ratio 0.54 (0.21). None of the patients had rheumatoid factor, anti-nuclear antibody or anti-nuclear cytoplasmic antibody test positive. Eight children had pulmonary function assessments at diagnosis and at follow-up. The FVC (Forced Vital Capacity), FEV1 (Forced Expiratory Volume in 1 sec), and PEF (Peak Expiratory Flow) significantly improved at remission (Table* II**). Therapy with systemic steroids (oral prednisolone) was commenced (dose 1-2 mg/kg/day) for 17 patients while one patient experienced a spontaneous recovery. Steroids were tapered successfully over mean (SD) duration of 7.6 (1.9) months (range 6-12); the mean (SD) duration to achieve remission was 2.5 (0.6) months. However, two patients experienced relapses while tapering off steroids; they subsequently had successful outcome.

TABLE I CLINICAL FEATURES AT PRESENTATION IN CHILDREN WITH SARCOIDOSIS (*N*=18)

Clinical features	*Number (%)*
Fever	15 (83)
Difficulty in respiration	8 (44)
Uveitis	9 (50)
Hepatomegaly	8 (44)
Splenomegaly	7 (38)
Enlarged peripheral nodes	6 (33)
Weight loss	6 (33)
Arthritis of large joints	5 (28)
Skin rash	5 (28)
Impaired vision	3 (17)
Cough	2 (11)
Erythema nodosum	1(6)
Seizure	1 (6)

Weekly oral methotrexate 10 mg/m^2/week was administered in 11 (61%) patients and continued for 9-12 months with significant improvement. Oral hydroxychloroquine 5 mg/kg/day for 12 months were prescribed to 4 patients, and azathioprine to 2 patients along with steroids.

Seventeen patients followed-up regularly. Mean (SD) duration of follow-up was 3.12 (0.88) years with overall outcome of complete recovery in all. Three children who had uveitis and cataract needed surgical intervention; however, two continued to be visually impaired even after surgical therapy.

TABLE II COMPARISON OF LABORATORY PARAMETERS AT DIAGNOSIS AND AT REMISSION

Parameters	*At Diagnosis*	*At Remission*	*P value*
Blood parameters (*n*=18)			
Total leucocyte count (per mm^3)	10861 (3202)	6346 (847)	<0.001
Hemoglobin (g/dL)	9.5 (0.8)	11.6 (0.7)	<0.001
Erythrocyte sedimentation rate	51 (19.7)	17 (4.7)	0.001
Serum angiotensin converting enzyme (U/mL)	147 (48.0)	62 (11.4)	0.001
Pulmonary function test parameters (n=8)			
Forced vital capacity (% of predicted)	62.5 (17.3)	90.5 (3.0)	0.01
FEV1 (% of predicted)	63.5 (17.0)	88.5 (2.5)	0.02
FEV1/FVC (% of predicted)	88.1 (3.8)	90.6 (2.8)	0.41
Peak expiratory flow (% of predicted)	70.1 (10.5)	90.1 (2.0)	0.02

All values are in mean (SD); FEV1: Forced Expiratory Volume in 1 s.

WHAT THIS STUDY ADDS?

- High index of suspicion is required to diagnose sarcoidosis in children as many cases are treated as tuberculosis.
- Sarcoidosis in children responds well to steroids and methotrexate, if treatment is started early.

All children who received systemic steroids developed transient adverse effects (weight gain, cushingoid appearance); however, none of them had steroid-induced impaired glucose tolerance, hypertension or cataract. No significant adverse effects were documented for methotrexate, hydroxychloroquine and azathioprine.

Sixteen children had school absenteeism of minimum of 6 months during the course of illness; four children could never be readmitted to school after diagnosis.

DISCUSSION

In this series, we described clinical manifestations, course of illness and treatment outcomes in 18 children with sarcoidosis. All had multisystem involvement with intrathoracic findings in majority. Systemic steroids and methotrexate improved their outcome.

Prevalence of sarcoidosis in literature has bimodal distribution with a small peak around 14 years [5,6]. Actual prevalence and incidence of sarcoidosis among pediatric population is unknown largely due to its rarity. One of the largest series on pediatric sarcoidosis was a Danish study where 48 cases (35 confirmed by histology) were reported [2]. The estimated incidence is approximately 0.25 per 100,000 per year under 15 years according to Danish study [2].

Sarcoidosis has multisystem involvement in majority of patients [2,6-8]. Ophthalmological manifestations, principally uveitis and conjunctival granuloma are the commonest manifestations in younger age group [9,10]. In our study, half the group (9/18 children) had ocular involvement as uveitis and conjunctival involvement and three children had blindness and underwent surgical management. Pulmonary involvement in children is reported in around 40% [2,7,11]. Skin manifestation in childhood sarcoidosis occurs in up to one fourth of cases in the form of papules and plaques [12].

Demonstration of non-necrotizing epithelioid granuloma without any evidence of tuberculosis is the hallmark for diagnosis of sarcoidosis [13]. The index series had non-necrotizing epithelioid granuloma in biopsy in almost all cases. Erythrocyte sedimentation rate (ESR) and angiotensin converting enzyme (ACE) may be markers of disease activity [6,14]. We also found significantly decrease in ESR and ACE levels with treatment.

Systemic steroids (oral prednisolone) and methotrexate are cornerstone of the therapy of sarcoidosis [6]. In this series also, children responded well to prednisolone and methotrexate.

There are some limitations of our study. As it was a retrospective case record review, some data were missing and comparison of different therapeutic measures was difficult. The small sample size due to rarity of this condition in children was a major limitation.

To conclude, pediatric sarcoidosis is a rare multisystem disease with significant proportion having intrathoracic involvement. Tissue examination is essential part of diagnosis. Serum ACE level and ESR are helpful in monitoring disease activity. It has good prognosis in pulmonary involvement if diagnosed in early stage. Late diagnosis may have poor prognosis with regard to ocular and lung disease.

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