Overview and Report on International Registry of Sarcoid Arthritis in Childhood

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Interest in childhood sarcoidosis prompted the formation of an international registry in 1991. Over the next 5 years, 53 patients were registered by 23 physicians from 14 countries. All the patients had definite histologic evidence of sarcoidosis: noncaseating granulomas of the skin (31), synovium (15), liver (10), lymph node (eight), lung (five), muscle (four), conjunctiva (three), or kidney (one). All but nine patients developed polyarthritis; 38 of 44 had persistent arthritis. Of those with persistent polyarthritis, arthritis occurred at presentation in 16 of 38 patients and inflammation of the uveal tract of the eye occurred in 44 with involvement of both anterior and posterior segments in 21. One patient was blind at the time of the report. Other ocular complications included chorioretinitis, glaucoma, and phthisis bulbi. Laboratory abnormalities included mild anemia and elevated erythrocyte sedimentation rate (39 out of 45). Angiotensin converting enzyme levels were elevated in 14 out of 37 patients. Information on these patients with sarcoidosis helps develop a better understanding of this rare childhood disease. These patients are discussed in conjunction with an overview of sarcoid arthropathy.

Introduction

Sarcoidosis is an uncommon, multisystem granulomatous disease of unknown etiology. Approximately 5% of reported cases have arthritis [1]. Initial reports of pediatric cases described children with mild arthritis and systemic manifestations including lung disease and hypercalcemia [2]. However, in 1966 a group of preschool children with the triad of skin, joint, and eye disease were described [3]. Later studies reinforced these two patterns. More recent studies, however, have blurred this distinction. Hafner and Vogel [4] reported 12 children with disease onset before 4 years of age who had characteristic arthritis, uveitis, and rash but who also had significant systemic symptoms including lung and renal disease. Cron *et al*. [5•] reported six children with arthritis, young age, and pulmonary involvement. Familial occurrence was reported in 1923 [6] with later reports describing many different combinations of parent-offspring and sib pairs [7–13]

The disease is characterized by noncaseating granulomas, which are epithelial cell nodules associated with giant cells. Delayed type cutaneous hypersensitivity is depressed and a peripheral lymphopenia occurs [14]. T lymphocytes from patients with sarcoidosis release interleukin-l, monocyte chemotactic factor, and migratory inhibitory factor [15,16]. The offending antigen or other factors that stimulate the T lymphocyte response is not known.

Sarcoidosis in childhood may manifest primarily as arthropathy and uveitis, mimicking juvenile rheumatoid arthritis. It is a rarely diagnosed childhood disorder, partly due to the fact that the early manifestations are frequently unrecognized and the evolving course poorly understood. The registry was undertaken to further our understanding of this disease.

The registry was initiated in 1991 by an interested group of pediatric rheumatologists at the Park City III meeting, an international meeting in Park City, UT focusing on childhood rheumatic disease. The goal was to better define the characteristics of sarcoid arthopathy and its associated features in children and its associated features. A standard questionnaire was designed by Drs. Lindsley and Petty and sent to all interested attendees and subsequently to any requesting physician. The questionaires were collected over a 5-year period, from 1991 to 1996. Preliminary data were presented in abstract form at Park City IV meeting in Park City, Utah, March, 1998 [17•]. Of the 60 questionnaires that were submitted, 53 had biopsy confirmation of the sarcoidosis diagnosis and were used for subsequent data analysis. Data was received from 23 physicians in 14 countries in North America, Europe, and Asia.

Table 1. Characteristics of patients (38) with persistent arthritis

Race	Age/Onset, *mo*	Biopsy	Arthritis	Presenting symptom	X-Ray
Caucasian	3	skin	poly	rash	periosteal
Caucasian	5	liver	poly	e. nodosum	jt swelling
Caucasian	24	synovium	poly	arthritis	neg
Caucasian	10	skin/synovium	poly	arthritis	neg
Caucasian	11	skin/synovium	poly	dev. delay	osteopenia
Caucasian	25	synovium	poly	fever/arthritis	NR
Caucasian	25	synovium	poly	fever/arthritis	erosions
Asian	17	skin	poly	e. nodosum	NR
Caucasian	18	skin/synovium	pauci/poly	rash/arthritis	erosions
Caucasian	20	skin/synovium	poly	joint pain	erosions
Caucasian	29	skin/synovium	poly	cuteaneous sarcoid	NR
Caucasian	18	skin	poly	rash	NR
Caucasian	19	skin	pauci/poly	arthritis	
Black	24	conjuctiva	pauci/poly	arthritis	soft tissue swelling
Caucasian	1	skin/synovium	poly	arthritis	
Black	104	testicular mass	poly	uveitis	soft tissue swelling
Caucasian	6	skin	poly	dev. delay	
Caucasian	48	skin/synovium	poly	arthritis	erosions
Other	24	skin/synovium	pauci/poly	arthritis	
Caucasian	3	skin	pauci/poly	rash	
Caucasian	12	synovium	poly	rash/arthritis	erosions
Caucasian	36	skin/synovium	poly	arthritis	erosions
Caucasian	36	skin	poly	arthritis	erosions
Other	24	synovium	poly	rash/arthritis	
Caucasian	24	skin	poly	rash	erosions
Caucasian	3	skin	poly	rash	erosions
Caucasian	24	skin	poly	rash	erosions
Caucasian	2	skin	poly	rash	erosions
Caucasian	2	skin	poly	rash	erosions
Caucasian	5	skin	poly	rash	
Caucasian	6	liver/muscle	poly	arthritis	erosions
Caucasian	24	lung	poly	rash	erosions
Caucasian	108	synovium	poly	arthritis/uveitis	
Caucasian	2	bone/muscle	poly	fever/rash	lytic lesions
Caucasian	24	skin	poly	rash	sclerosis
Caucasian	180	skin	poly	uveitis	osteoporosis
Caucasian	22	skin	pauci	rash	
Black	14	skin	pauci/poly	rash	

Results

Demographics

The age at disease onset ranged from 0.1 years to 16 years, with a mean of 10.6 years. Of note, 38 of the 53 patients had onset at 5 years of age or less (72%). Thirty of the 53 patients were girls and 23 were boys. Thirty nine patients were white, three were Asian, seven were black, one was Hispanic, and three were of other ethnic backgrounds.

Pattern of arthritis

Disease duration at the time of report ranged from 1 month to 192 months, with a mean of 43.2 months. Thirty eight children had persistent arthritis, one with a pauciarticular course and 37 with polyarticular. In addition, five children had transient arthritis, nine had no arthritis, and the pattern was unknown in one patient. Of those with persistent arthritis, arthritis occurred at the time of presentation in 16 of 38 patients (50%) (Table 1). The most commonly involved joints were knees and ankles but almost any joint could be involved.

Clinical manifestations

The most frequent presenting symptoms were rash (18 patients), arthritis (16 patients), fever (eight patients), and soft tissue swelling (five patients). Other manifestations at presentation included developmental delay and uveitis.

Ocular disease

Ocular disease occurred in 44 patients and all had some form of uveitis. Twenty-one patients had anterior and posterior disease, 21 had anterior only, and two had posterior only. In 43 patients the disease was bilateral (Table 2).

Table 2. Ophthalmologic involvement (44 patients)

Patient	Uveitis	Uveitis	Biopsy	Arthritis	Vision	Other
1	bilateral	A/P	skin	positive	diminished	cataract/synechiae
2	bilateral	A	lymph node	negative		
3	bilateral	A/P	lung/liver	positive	diminished	cataract/synechiae
4	bilateral	A/P	skin/synovium	positive		cataract/synechiae/keratitis
5	bilateral	P	skin	positive		
6	bilateral	P	skin/synovium	positive		
7	bilateral	A/P	synovium	positive		cataract/synechiae
8	bilateral	A/P	synovium	positive		cataract/synechiae
9	bilateral	A/P	liver	negative	diminished	synechiae/band
10	bilateral	A/P	skin	positive		
11	bilateral	A/P	skin	positive	blind	
12	bilateral	A/P	skin/synovium	positive	blind	cataract/synechiae
13	bilateral	A/P	lymph node	positive		
14	left	A	kidney	positive		
15	bilateral	A	mediastinal node	negative		
16	bilateral	A/P	skin/synovium	positive		
17	bilateral	A/P	skin	positive		cataract/synechiae/conjunctival cysts
18	bilateral	A/P	lymph node	positive	blind	cataract/band
19	bilateral	A	conjunctiva	positive		cataract/conjunctival granuloma
20	bilateral	A/P	skin/synovium	positive		
21	bilateral	A/P	testicular mass	positive		synechiae
22	bilateral	A/P	skin	positive		synechiae
23	bilateral	A	skin/synovium	positive	diminished	cataract/synechiae
24	bilateral	A/P	skin/synovium	positive		synechiae
25	bilateral	A	skin	positive	diminished	cataract/synechiae
26	bilateral	A	synovium	positive		sicca
27	bilateral	A	skin/synovium	positive		cataract/synechiae
28	bilateral	A	skin	positive		
29	bilateral	A	synovium	positive		cataract/synechiae/band/chorioretinitis
30	bilateral	A	skin	positive		synechiae
31	bilateral	A	skin	positive		
32	bilateral	A	skin	positive		synechiae/band
33	bilateral	A	skin	positive		corneal lesions
34	bilateral	A	skin	positive	diminished	cataract/synechiae/glaucoma
35	bilateral	A	liver/muscle	positive		synechiae
36	bilateral	A	lung/liver	positive		cataract/synechiae/band
37	bilateral	A	mediastial node	negative		
38	bilateral	A	synovium	positive		
39	bilateral	A	bone	negative		
40	bilateral	A/P	bone/muscle	positive		
41	bilateral	A/P	skin/conjunctiva	positive		
42	bilateral	A/P	skin	positive	diminished	cataract
43	bilateral	A	skin	positive		
44	bilateral	A/P	skin	positive	diminished	conjunctival nodules

Ocular complications were frequent, with 12 children having vision loss, 13 having glaucoma, and 16 with cataracts at the time of report. Other complications included chorioretinitis and phthisis bulbi.

Biopsy site

Characteristic histologic abnormalities of noncaseating granulomas were required for a definitive diagnosis. The most frequent site was the skin (31), followed by the synovium (15), liver (10), lymph nodes (eight), lungs (five), muscles (four), and conjunctivae (three). Some children had more than one positive biopsy. One patient underwent a biopsy of a testicular mass.

Laboratory abnormalities

Common laboratory abnormalities included mild anemia and elevated erythrocyte sedimentation rate (39 of 45 patients). The angiotensin converting enzyme (ACE) levels were elevated in 14 of 37 patients. Two out of 44 had a positive ANA, one out of 40 had a positive rheumatoid factor, nine out of 38 had hypercalcemia, and six out of 22 had hypercalcuria.

Radiographs

Of the 53 patients, 24 had radiographic studies reported. Erosive disease was common, occurring in 13 patients. Other abnormalities included periosteal reaction, soft tissue swelling, and osteopenia. Lytic lesions were seen in one patient.

Familial pattern

Twelve of the 53 patients had close relatives with sarcoidosis diagnosis, including six mother-daughter pairs, two father-daughter, two brother-sister, one mother-son, and one grandmother-grandson pair.

Discussion

The most common presentation of children with sarcoidosis is bilateral hilar adenopathy, which is often asymptomatic [18]. Retroperitoneal adenopathy is also common [19]. Hepatosplenomegaly often accompanies the lymph node involvement. Seven of the registry patients had evidence of liver or spleen involvement. In the registry of children with joint disease, the most common presenting symptoms were rash and joint inflammation. Skin lesions varied from maculopapular to vesicular or nodular to classic erythema nodosum [20,21].

Pulmonary involvement is common in children with generalized sarcoidosis who frequently present with chronic cough or other respiratory symptoms [20]. Usually, adenopathy is accompanied by parenchymal involvement, but the latter can occur alone. The parenchymal involvement includes interstitial infiltrates, pleural effusions, and atelectasis, and occurs approximately 25% of time [20,22]. Nine percent of registry patients had lung disease.

Neurologic manifestations are quite varied and include mass lesions, cranial nerve involvement, seizure disorders, encephalopathy, aseptic meningitis, myelopathy, and spinal cord involvement [4,23,24]. Six of 22 registry patients had evidence of neurologic involvement.

Other systemic manifestations include gastrointestinal, cardiac, parotid, and renal involvement. Gastrointestinal involvement is infrequent but usually involves the stomach and can lead to obstruction [25]. No registry patients reported gastrointestinal involvement. Cardiac disease can include pericardial or myocardial disease [26]. Cardiac involvement occurred in eight of the registry patients. Renal involvement may be asymptomatic or patients may present with abnormal urinary sediment or nephrolithiasas [27,28]. Two of the registry patients had evidence of renal disease. Parotid swelling and Sjögren's syndrome occur [4]. Six registry patients had evidence of involvement.

Musculoskeletal manifestations occurred in 38 registry patients (71%) having persistent arthritis. Although seven patients had a pauciarticular onset, a polyarticular course developed in all patients. This is in contrast to earlier reports emphasizing the pauciarticular nature [29]. The arthritis is characteristically a boggy thickening of the synovium with large effusions, often with tendon sheath as well as joint involvement. As the duration of disease increases the arthritis mimics that of juvenile rheumatoid arthritis with morning stiffness, symmetrical small joint involvement, and often progressive deformity [4,30]. Twenty two of 34 registry patients with radiographic studies had abnormalities, either soft tissue swelling, osteopenia, or erosions (Table 1). Knees and ankles were the most frequently involved joints but most any joint could be involved. Both osseous and muscle involvement can also occur but less commonly. Four registry patients had muscle involvement.

Ocular involvement is often an initial manifestation of sarcoidosis and a frequent cause of morbidity. Disease includes uveitis, conjunctival granulomas, lacrimal gland involvement, choreoretinitis, optic nerve involvement, and proptosis [31–34]. Forty four of 53 registry patients had ocular involvement, all but one with bilateral involvement. The uveitis was both anterior and posterior in 21 patients, posterior only in two, and anterior only in 21. Eight children had diminished vision and an additional three were blind (Table 2).

Definitive diagnosis requires pathologic findings of noncaseating granulomatous disease. Multiple tissues lend themselves to biopsy, depending on the individual case clinical data. The most frequent biopsy sites in registry patients were the skin (31 patients) and synovium (15 patients). Other areas included conjunctivae (three), liver (10), lymph nodes (eight), lung (five), and muscle (four). Some patients had more than one positive biopsy.

Laboratory tests are nondiagnostic, but common abnormalities include leukopenia, eosinophilia, increased levels of immunoglobulins and acute phase reactants, and hypercalciumia/hypercalciuria. The ACE level is elevated in up to 80% of both adults and children with generalized disease [35,36]. Only 14 out of 37 registry patients had elevated ACE levels. There appears to be less reliability of this test in patients with musculoskeletal disease.

The possible familial nature of sarcoidosis is of interest. Several familial syndromes with autosomal dominant patterns of inheritance in families with multisystem granulomatous disease have been described, including Blau syndrome [37–39]. The latter syndrome includes camptodactily and evidence of a susceptibility locus on chromosome 16 [40,41]. Twelve of 53 registry patients had a familial pattern. This is higher than many reports and lends support to familial pattern in sarcoidosis itself.

Treatment

The registry did not look at the different therapies used in the treatment of children with sarcoid arthropathy. The general approach has been to use corticosteroid therapy in patients that have significant involvement [42]. Patients with arthritis alone often respond to conventional doses of nonsteroidal anti-inflammatory drugs. Low-dose methotr-

exate used in a similar manner to that in juvenile rheumatoid arthritis has been shown to be effective as well as allowing a reduction of the corticosteroid dose [43]. Other agents reported of benefit in limited numbers of adult patients include chloroquine, cyclosporin, and cyclophosphamide [44–46].

Conclusions

Sarcoid arthropathy is rare in childhood but should be considered in any child with arthritis, uveitis, and skin lesions. Although the pattern of joint involvement at onset may be pauicarticular, the course is almost always polyarticular. Although delayed, joint erosions do occur in about one third of the patients. Age at arthritis onset is generally less than 5 years and the main presenting symptoms are joint-related swelling, pain, or a rash. Most patients with arthritis also have uveitis, and vision loss or serious ophthalmologic complications are frequent. A familial pattern is common.

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