Risk factors for uveitis in sarcoidosis

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Abstract **Uveitis is a potentially sight-threatening complication of sarcoidosis. The object of this study was to determine which patients with sarcoidosis are at greater risk of developing uveitis. We retrospectively assessed 136 patients with clinical, radiological and histological features of sarcoidosis. Of the 48 patients (35,3%) with signs of intra-ocular inflammation, 28 had anterior uveitis, 2 had posterior uveitis and 18 had signs of panuveitis. When patients with uveitis were compared with patients without ophthalmic involvement, no significant demographic, clinical or laboratory differences were found. On linear discriminant analysis, however, the presence of ocular inflammation could be predicted in 32 out of 48 patients (66,6%); age at diagnosis and an elevated serum calcium level were relative risk factors. Awareness of the high incidence of uveitis and education of those at greater risk may result in earlier diagnosis and treatment of ocular inflammation.**

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Sarcoidosis is a chronic granulomatous disease of unknown aetiology. The clinical manifestations of the disorder depend on the organ system involved in the granulomatous process. The disease particularly causes changes in the chest, which range from mediastinal lymph node enlargement to parenchymal infiltration and severe restrictive and obstructive lung disease. Extra-thoracic sarcoidosis most commonly involves the lymphoreticular system, the skin and the eyes.[1]

Ocular disease is found in 22 - 63% of patients, and there is a wide spectrum of inflammatory conditions.[2-8] The commonest of these are acute or chronic anterior uveitis and panuveitis.[6] Conjunctival granulomas, follicular conjunctivitis, episcleritis, retinal periphlebitis, choroidal granulomas, exudative retinal detachment, papillitis and lacrimal gland infiltration with keratoconjunctivitis sicca have also been described.[2-8]

This report presents the clinical and laboratory findings in 48 patients with uveitis associated with sarcoidosis. To determine the factors that may increase the risk of ocular inflammation, these 48 patients were compared with a group of 72 patients with sarcoidosis in whom ocular disease was not present.

Subjects and methods

A retrospective review of 136 patients with sarcoidosis was undertaken. They had been examined in the Ophthalmology Department at Groote Schuur Hospital during the 17-year period August 1974 - August 1991. These patients had been referred for ophthalmic evaluation by the Respiratory Clinic. During this period, not all patients with sarcoidosis seen in the Respiratory Clinic underwent ophthalmic examination and patients were more likely to have been referred because of eye symptoms.

The diagnosis of sarcoidosis was made on the basis of typical clinical, radiographic and laboratory features, and compatible histological findings. Diseases such as tuberculosis and fungal infection were excluded by spe-

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cific histological and bacteriological examination.

Chest involvement was assessed radiologically and the patients divided into four groups: those with a clear chest (type 0), those with hilar lymphadenopathy alone (type I), those with hilar adenopathy and pulmonary infiltration (type II) and those with pulmonary infiltration alone (type III). The serum angiotensin-converting enzyme (SACE) level was considered elevated if above 45 nmol/ml/min.

Two groups of patients were identified: those with intra-ocular inflammation and those with no ophthalmic involvement. The two groups were compared in respect of demographic features, the associated systemic complications, the radiological changes and the laboratory findings.

Statistical analysis was performed by means of Fisher's exact test. A finding was considered significant at $P < 0,05$. Data from the two groups of patients were subjected to linear discriminant analysis. The variables used for generating the discriminant function were sex, age at onset of sarcoidosis, race, other organ involvement, radiographic changes, SACE level and serum calcium concentration.

Results

Of the 136 patients with sarcoidosis, 48 (35,3%) had signs of ocular inflammation including 15 with non-granulomatous anterior uveitis, 13 with granulomatous anterior uveitis, 2 with posterior uveitis alone and 18 with panuveitis. A further 16 patients (11,8%) had other ophthalmic complications of sarcoidosis, 12 a dry-eye syndrome, 3 follicular conjunctivitis and 1 lacrimal gland involvement. No clinical evidence of ocular inflammation was found in 72 patients (52,9%).

Patient characteristics are shown in Table I. There were no statistically significant differences in demographic features between those patients with uveitis and those without ophthalmic complications. No differences were found between the two groups when other organ involvement was assessed (lymphoreticular system, alimentary tract, skin, locomotor system, kidney and central nervous system) (Table II). Sixteen patients with uveitis (33,3%) had two or more extra-ocular systems involved, compared with 18 patients without ocular inflammation (25%). Five patients in each group had sarcoidosis in three extra-ocular systems. The differences were not statistically significant.

The SACE concentration, serum calcium level and radiological features are shown in Table II. There were no statistical differences between the two groups.

By means of multivariate analysis, a discriminant function was obtained with a sensitivity of 61,3% and specificity of 66,6%. A younger age at onset and an elevated serum calcium concentration contributed most to the discriminant function.

Discussion

The association of ocular disorders with sarcoidosis has been well documented.[2-8] The reported incidence of ocular involvement varies from 22% to 63%, which reflects differences in population demographics, duration of follow-up and extent of ophthalmic examination.[2,9] In particular, the incidence of conjunctival granulomatosis may have been underestimated in the past.[10] While the incidence of ocular involvement in this study was found to be 47,1% (64/136), selection bias played a role because patients with eye symptoms were more likely to have been referred than asymptomatic patients.

Previous studies have reported an incidence of uveitis ranging from 8% to 40%, although most studies have found uveitis in about 25% of patients.[2,3,6,10] Uveitis was found in 35,3% of our patients (48/136); it involved the anterior segment alone in 58% (28/48), the posterior segment alone in 4% (2/48) and both the anterior and the posterior segments in 37,5% of these patients (18/48). It has previously been reported that white patients are more likely to have posterior inflammation than black patients.[11] This was not found in our study, because most of the patients were of mixed racial ancestry and only small numbers of white and black patients were involved.

The prevalence of extra-ocular manifestations and involvement of other organ systems in patients with ocular inflammation did not differ from the findings in patients without eye disease. Similarly, patients with uveitis were not significantly more likely to have multisystem sarcoidosis than patients without uveitis. While this finding is in accordance with most previous studies, one study found a significant association between ocular sarcoidosis, dermatological changes and peripheral lymphadenopathy.[10] Because most of the ocular disease in that study consisted of conjunctival inflammation, this finding may not relate to patients with uveitis.

TABLE I.
Demographic findings in ocular sarcoidosis

	With uveitis ($N = 48$)				Other ocular disease ($N = 16$)		Without ocular disease ($N = 72$)	
			Total					
	Ant.	Post./pan.	No.	%	No.	%	No.	%
Sex								
Male	6	9	15	31	3	19	21	29
Female	22	11	33	69	13	81	51	71
Race								
White	—	1	1	2	—		6	8
Coloured	22	15	37	77	12	75	58	81
Black	6	4	10	21	4	25	8	11
Age at onset (yrs)								
< 20	1	2	3	6	—		1	1
20 - 30	12	8	20	42	3	19	18	25
31 - 40	8	4	12	25	9	56	22	31
41 - 50	5	2	7	15	1	6	19	26
> 50	2	4	6	12	3	19	12	17

Ant. = anterior; post./pan. = posterior/panuveitis.

TABLE II.
Clinical, laboratory and radiological findings

	With uveitis ($N = 48$)		Without ocular disease ($N = 72$)	
	No.	%	No.	%
Extra-ocular organ involvement				
Central nervous system	6	12,5	5	6,9
Gastro-intestinal tract	11	22,9	11	15,3
Dermatological	12	25	22	30,6
ENT	2	4,2	5	6,9
Musculoskeletal	6	12,5	6	8,3
Urogenital	1	2,1	4	5,5
Lymphoreticular	9	18,8	13	18,1
Cardiovascular	1	2,1	0	0
SACE level				
< 46 nmol/ml/min	12	25	23	31
> 45 nmol/ml/min	31	65	45	63
Not recorded	5	10	4	6
Serum calcium level				
< 2,1 mmol/1	1	2	1	1
2,1 - 2,6 mmol/1	29	60	53	74
> 2,6 mmol/1	10	21	7	10
Not recorded	8	17	11	15
Radiographic findings				
0 (clear)	4	8	2	3
I (hilar lymphadenopathy alone)	17	35	22	31
II (adenopathy and infiltration)	14	29	22	31
III (pulmonary infiltration alone)	13	27	26	36

To determine risk factors for the development of uveitis in sarcoidosis, 48 patients with uveitis were compared with a group of 72 patients with sarcoidosis and no ocular inflammation. With multivariate analysis, ocular inflammation could only be predicted in 32 out of 48 patients (66%). A younger age at diagnosis and an elevated serum calcium level were found to be relative risk factors. This differs from the findings obtained in a study from Amsterdam where race was considered a risk factor for uveitis in sarcoidosis, but not age.[11] Elevated serum calcium levels have previously been reported to be a risk factor for ocular disease, but not for uveitis.[10]

Because patients with uveitis may lose vision if treatment is delayed, early diagnosis is important. Patients with sarcoidosis and physicians treating the disease should be aware of the high incidence of uveitis, which may be asymptomatic, in association with sarcoidosis. While those patients at risk of developing uveitis cannot be accurately predicted, patients who are younger at diagnosis and those with elevated serum calcium levels should be warned of their relatively greater risk and followed up at regular intervals by an ophthalmologist.

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