EXTENDED REPORT

Sarcoid arthritis: clinical characteristics, diagnostic aspects, and risk factors

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Objectives: (*a*) To describe the clinical characteristics of acute sarcoid arthritis and the diagnostic value of its presenting clinical features; (*b*) to evaluate whether disease onset is seasonal; and (*c*) to evaluate whether smoking behaviour or the presence of HLA class II alleles is a risk factor for the disease.

Methods: 579 consecutive patients with recent onset arthritis who had been newly referred to a rheumatology outpatient clinic were included in a prospective cohort study. The presenting clinical features, the smoking behaviour, and the results of HLA-DQ and HLA-DR DNA typing of 55 patients with sarcoid arthritis, 524 patients with other arthritides of recent onset, and samples of the normal population were compared.

Results: In all cases the disease showed a self limiting arthritis and overall good prognosis. The diagnostic ability of a combination of four clinical features—symmetrical ankle arthritis, symptoms of less than two months, age below 40 years, and erythema nodosum—was exceptionally high. When test positivity is defined as the presence of at least three of four criteria the set rendered a sensitivity of 93%, a specificity of 99%, a positive predictive value of 75%, and a negative predictive value of 99.7%. The disease clustered in the months March–July. The disease was negatively associated with smoking (odds ratio (OR) 0.09; 95% confidence interval (95% CI) 0.02 to 0.37) and positively associated with the presence of the DQ2 (DQB1*0201)-DR3 (DRB1*0301) haplotype (OR 12.33; 95% CI 5.97 to 25.48).

Conclusion: The disease entity acute sarcoid arthritis has highly diagnostic clinical features. The seasonal clustering, the protective effect of smoking, and the association with specific HLA class II antigens support the hypothesis that it results from exposure of susceptible hosts to environmental agents through the lungs.

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Sarcoidosis is a heterogeneous multigranulomatous disease that primarily affects the lungs and lymphatic system, which is characterised by its pathological hallmark, the non-caseating granuloma.[1] Arthritis is found in 15–25% of patients with sarcoidosis. The clinical characteristics of sarcoid arthritis have been described in several studies.[2–16] Based on the clinical course of the disease, two major types of arthritis have been classically distinguished: the acute transient type and the persistent or chronic type. The acute form is the most common rheumatic manifestation of sarcoidosis, often being the presenting manifestation of the disease and generally having a favourable outcome. Löfgren first described its presentation as a triad with bilateral hilar adenopathy and erythema nodosum.[13 14] The chronic type of arthritis appears either early or late during the course of sarcoidosis, which is generally active in other organ systems.

It is unknown whether, and to what extent, acute sarcoid arthritis can be distinguished from other forms of arthritis by its presenting clinical features. The cause of sarcoidosis is also unknown. It has been suggested that the disease results from exposure of genetically susceptible hosts to specific environmental agents.[1] The many epidemiological studies of sarcoidosis carried out during the past 30 years have demonstrated relatively few risk factors for this disease. A higher incidence of sarcoidosis was found in the young adult, black population in the United States and in women; familial and seasonal clustering of the disease were also found.[17] Several studies have suggested that smoking reduces the incidence of clinically overt pulmonary sarcoidosis.[18–24] Many studies have searched for associations between sarcoidosis and HLA genes.[1 25] It is likely that genetic factors not only play a part in

the susceptibility of the disease but are also important in defining the pattern of disease presentation and progression as well as its overall prognosis.[1 25] Studies on risk factors of sarcoid arthritis, a homogeneous subset of sarcoidosis, are scarce.

A prospective study was performed on acute sarcoid arthritis in order to (*a*) describe its clinical features and their diagnostic value in a group of consecutive, newly referred patients with early arthritis; (*b*) evaluate whether seasonal clustering of the disease exists; (*c*) evaluate whether a negative association exists between smoking and the disease; and (*d*) identify HLA class II alleles associated with the disease in a Dutch population, using DNA typing.

PATIENTS AND METHODS
Patients
All patients who visited the early arthritis clinic (EAC) of the Department of Rheumatology, Leiden University Medical Centre, between 1993 and 1999 and were diagnosed as sarcoid arthritis, were analysed. Patients were admitted to the EAC if they had arthritis in at least one joint and symptom duration of less than two years.[26] The diagnosis sarcoid arthritis was based on the presence of arthritis in combination with bilateral hilar lymph node enlargement on a chest *x* ray examination routinely made upon presentation of any patient to the

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Abbreviations: CI, confidence interval; EAC, early arthritis clinic; NSAIDs, non-steroidal anti-inflammatory drugs; OR, odds ratio

EAC. All inflammatory joint swellings were recorded as "arthritis" as it was not important for the purpose of this study to determine whether swelling of the ankles was due to arthritis, pure involvement of the periarticular tissues ("peri-arthritis"), or a combination of these two, Other diseases with hilar lymph node enlargement, such as malignancies, were excluded by observing the disease course or, if clinically indicated, by transbronchial lung biopsy. The 55 patients with sarcoid arthritis were compared with 524 consecutive patients with other forms of arthritis who visited the EAC between 1993 and December 1996. Thus the controls were gathered over a shorter time period than the patients with sarcoidosis. This was done to limit the number of control patients because the prevalence of sarcoidosis was only 4.4%. Diagnoses were made according to international classification criteria or the information in rheumatology textbooks, as previously described.[26]

Assessments
A standard diagnostic investigation was performed at the first visit, comprising patient history, physical examination, and laboratory and radiological examination.[26] Chest radiographs were taken at baseline in all patients. The sarcoid lung stages were classified according to the staging proposed by James and Thomson.[27] Pulmonary function tests and transbronchial lung biopsy were performed if clinically indicated. All patients were followed up for at least one year, except for the patients with transient arthritis due to crystal induced conditions, who were not followed up routinely. A smoking history was taken at the first visit for all patients when both patient and doctor had no knowledge of the chest x ray results or the final diagnosis. Patients who smoked at least one cigarette a day at the time of the first visit were categorised as "smokers". The smoking habits of the patients with sarcoid arthritis were compared with those of the patients with other diagnoses and with the general population in the region of the hospital, using the data collected by the National Office for Statistics in the period 1996–98. Patients with sarcoid arthritis who had stopped smoking less than three months before the first visit because of new onset respiratory symptoms were categorised as "smokers". All patients were HLA-DQ and HLA-DR typed. DNA isolation, DRB1 and DQB1 medium resolution typing were performed as described previously.[28] The patients with other forms of arthritis and a panel of 299 Dutch cadaveric organ donors were used as control groups.

Statistics
Based on the incidence of clinical features at the first visit in the patient groups with and without sarcoid arthritis, the sensitivities, specificities, and predictive values of these features were calculated for discrimination between sarcoid arthritis and other forms of arthritis. The most optimal combination of features to diagnose acute sarcoid arthritis was obtained by entering the features with the highest diagnostic ability into a logistic regression model. A backward variable selection procedure was performed, with p removal = 0.05, to remove the non-significant variables. The χ^2 test was applied to test differences between percentages using Yates's correction for continuity, if necessary. Odds ratios (OR) with 95% confidence intervals (95% CI) were calculated using the method of Woolf. p Values were calculated using a two sided Fisher's exact test.

RESULTS
Demography and seasonal onset
The diagnosis sarcoid arthritis was made in 4.4% of the patients with early arthritis; in total, 55 patients with sarcoid arthritis were included in the study. The control group consisted of 524 consecutive patients with other forms of arthritis who were diagnosed as follows: rheumatoid arthritis

Table 1 Demographic characteristics of 55 patients with sarcoid arthritis and 524 patients with other arthritides

	Sarcoid arthritis (n=55)	Other arthritides (n=524)
Median age (range)	32 (21–50)	51 (8–90)
No (%) women	27 (49)	283 (54)
Median symptom duration at first visit in days (range)	21 (1–61)	89 (0–730)
No (%) of patients with disease onset in the months March–July	37 (67)*	237 (45.2)*

*p=0.0037.

(31%), undifferentiated arthritis (29%), crystal induced arthritis (11%), psoriatic arthritis (6%), osteoarthritis (6%), reactive arthritis (3%), spondyloarthropathy (3%), and other forms of arthritis (11%). Table 1 shows the demographic characteristics of both groups. The onset of sarcoid arthritis clustered in the months March to July, whereas onset of the other forms of arthritis was spread equally over the year (table 1 and fig 1).

Clinical features
In the majority of the 55 patients with sarcoid arthritis the joint symptoms started symmetrically (76%) in the large joints (95%) of the leg (96%). The arthritis was monoarticular in one patient (2%), oligoarticular (two to four joints) in 48 patients (87%), and polyarticular in six patients (11%). The ankle was affected in 54/55 (98%) patients at the first visit, the majority (52 (95%)) having swelling in both ankles. One patient presented with arthritis of the right wrist without ankle involvement. Arthritis of the small hand joints was found in five patients, all of whom had a symmetrical polyarthritis including bilateral ankle involvement. Half of the patients had fever. Skin abnormalities often found were erythema nodosum in 22 (40%) patients and a red-bluish discolouration around the ankles in 16 (29%). Enthesopathies mainly located at the Achilles tendons and heels were present in 18 (33%) of the patients. Ten of 55 patients (18%) had symptoms of slight cough or dyspnoea at entry.

A raised erythrocyte sedimentation rate was found at the first visit in 46/55 (84%) patients. None of the patients were markedly hypercalcaemic. All patients with sarcoid arthritis had, by definition, hilar adenopathy on the chest x ray examination routinely carried out at admission. None of the 524 patients with other diagnoses had hilar adenopathy. Parenchymal lung infiltrations (stage II) were present in seven patients; four of them had pulmonary symptoms at presentation. Pulmonary function tests, performed in all patients with stage II chest x ray findings, were normal in five patients and showed slight restrictive changes in combination with a normal carbon monoxide transfer factor in two patients.

A histological examination was carried out in seven patients. Transbronchial biopsies were performed in six patients, yielding non-caseating epithelioid cell granulomas in five cases and insufficient material in one case. In one patient a liver biopsy was performed, yielding non-caseating epithelioid cell granulomas.

Disease course
Most patients with sarcoid arthritis (51/55) were treated only with non-steroidal anti-inflammatory drugs (NSAIDs). One pregnant patient with parenchymal lung disease temporarily received inhalation corticosteroids. Three patients were treated with oral corticosteroids. In one of these patients NSAIDs were contraindicated because of an NSAID allergy.
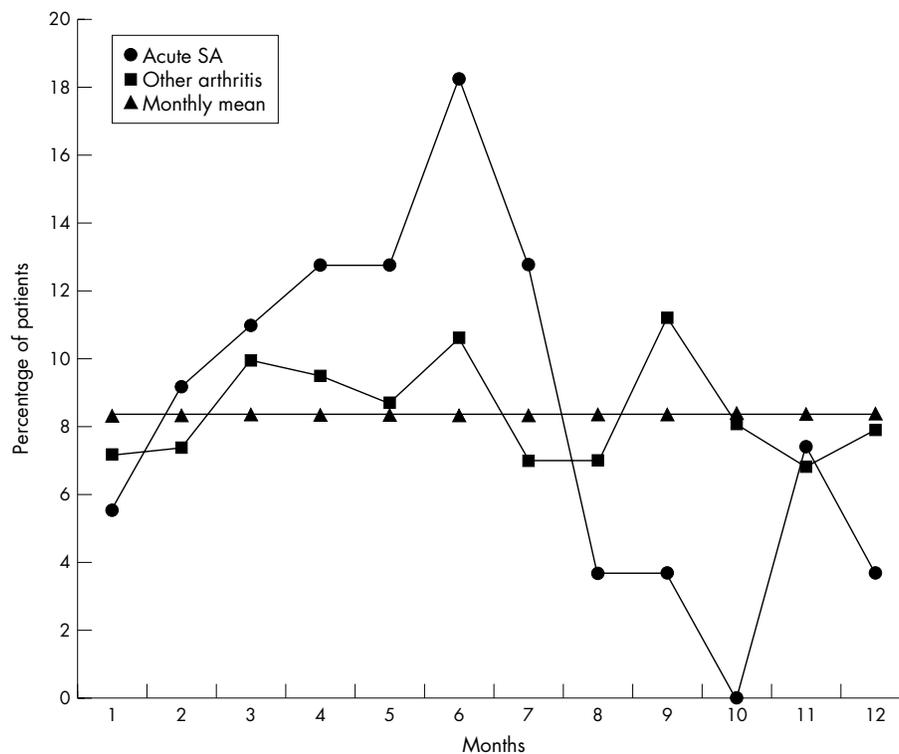
Figure 1 Distribution of disease onset over the months of the year for patients with sarcoid arthritis (n=55) and with other forms of arthritis (n=524). The monthly proportion of disease onset without influence of seasonality would be 8.3% (dividing 100% by 12).

Table 2 Diagnostic characteristics of the clinical features used to discriminate between acute sarcoid arthritis and other forms of arthritis, at disease presentation. The prevalence of these features in patients with and without sarcoid arthritis is shown, together with the sensitivities, the specificities, and the positive and negative predictive values. Pretest probability of sarcoid arthritis = 4.4%

	Sarcoid arthritis (n=55)	Other arthritides (n=524)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Bilateral ankle arthritis	52	43	95	92	35	99.7
Bilateral ankle arthritis + symptoms <2 months	52	15	95	97	61	99.7
Bilateral ankle arthritis + symptoms <2 months + age <40	47	6	85	99	78	99.3
≥3 of 4 criteria*	51	7	93	99	75	99.7

PPV, positive predictive value; NPV, negative predictive value; symptoms, duration of symptoms at first visit.
*The four criteria are bilateral ankle arthritis, symptom duration <2 months, age <40 years, and erythema nodosum.

Another patient developed a severe thrombocytopenia (platelet count 2×10⁹/l), with platelet associated antibodies responding well to prednisone treatment. The third patient presented with a left sided facial nerve palsy in combination with bilateral parotid gland enlargement. Treatment with prednisone led to a complete resolution of the palsy in two months. In all patients the arthritis entered remission within three months after the first visit. A chest x ray examination was repeated during follow up in 44/55 patients with sarcoid arthritis, showing normalisation or marked improvement of the abnormalities in 39 (89%) patients. In one patient an increase in hilar adenopathy was found at the six month follow up with otherwise complete resolution of symptoms. In four patients the chest x ray abnormalities were unchanged at a median follow up time of three months.

Diagnosis
Table 2 shows the diagnostic ability of clinical features that had the highest ability to discriminate between sarcoid arthritis and other forms of arthritis at disease presentation. Symmetrical ankle arthritis was the clinical feature with the

highest diagnostic value. It had a sensitivity of 95% and a specificity of 92%, resulting in a positive predictive value of 35% and a negative predictive value of 99.7%. For calculation of the predictive values, the observed pretest probability of acute sarcoid arthritis in the EAC of 4.4% was used. The diagnostic ability increased when the criterion symmetrical ankle arthritis was combined with other clinical features of the disease such as symptom duration of less than two months, age below 40 years, and the presence of erythema nodosum. The best diagnostic criteria set consisted of four variables: symmetrical ankle arthritis, symptom duration of less than two months, age below 40 years, and erythema nodosum. When test positivity was defined as the presence of at least three of four criteria, this diagnostic set gave a sensitivity of 93%, a specificity of 99%, a positive predictive value of 75%, and a negative predictive value of 99.7%.

Smoking
A smoking history obtained at the first visit was available for all patients with sarcoid arthritis and 488 of the 524 control patients. Table 3 shows the proportion of smokers in the

Table 3 Proportion of smokers in patients with sarcoid arthritis, patients with other arthritides, and the general population. Shown are the data for all subjects and separately for men and women, and for subjects aged 25–44

	Prevalence of smokers							
	Sarcoid arthritis		Other arthritides		General population			
	No	%	No	%	No	%	Odds ratio* (95% CI)	Odds ratio† (95% CI)
All	4/55	7	161/ 488	33	4528/12827	35.3	0.16 (0.06 to 0.44)	0.14 (0.05 to 0.39)
Men	2/28	7	77/229	34	2464/6302	39.1	0.15 (0.04 to 0.65)	0.12 (0.03 to 0.50)
Women	2/27	7	84/259	32	2062/6525	31.6	0.17 (0.04 to 0.72)	0.17 (0.04 to 0.73)
25–44 years	2/44	5	54/154	35	2139/5294	40.4	0.09 (0.02 to 0.37)	0.07 (0.02 to 0.29)

*Sarcoid arthritis versus other arthritides; †sarcoid arthritis versus normal controls.

Table 4 The frequencies of the DQ2-DR3 haplotype in the group with sarcoid arthritis, in the group with other arthritides, and in Dutch controls

	Sarcoid arthritis (n=49)		Other arthritides (n=524)		Controls (n=299)			
	No	%	No	%	No	%	OR* (95% CI)	OR† (95% CI)
DQ2-DR3/DQ2-DR3	1	2	8	1.5	8	3	4.95 (0.56 to 43.4)	2.94 (0.33 to 25.81)
DQ2-DR3/x	38	78	122	23.3	56	19	12.33 (5.97 to 25.48)	15.95 (7.49 to 33.93)
x/x	10	20	396	75.6	235	79	1.00	1.00

OR, odds ratio (x/x subjects are used as references); CI, confidence interval; x, any haplotype other than DQ2-DR3.
*Sarcoid arthritis versus other arthritides; †sarcoid arthritis versus normal controls.

patients with sarcoid arthritis, in the patients with other forms of arthritis, and in the normal Dutch population categorised by sex and age. Only the data for the age category 25–44 years is shown because the numbers of patients with sarcoid arthritis in the other age categories were small. A highly significant negative association was found between sarcoid arthritis and smoking. This association was present for both men and women and was even more marked for the age category 25–44 years, which contained the majority of the patients with sarcoid arthritis.

HLA

The results of HLA-DQ and HLA-DR typing were available for 49 of the 55 patients with sarcoid arthritis. The demographic and clinical characteristics of the six patients who were not typed did not differ from those of the typed patients. The distributions of DQB1 and DRB1 alleles and corresponding haplotypes in 49 patients with sarcoid arthritis were compared with the distributions in 524 patients with other forms of arthritis and 299 Dutch controls. Strongly significant associations with sarcoid arthritis were found for DQ2 (DQB1*0201) and DR3 (DRB1*0301). The associations of both alleles with sarcoid arthritis were identical because of their strong linkage disequilibrium. Table 4 shows that 38/49 (78%) patients with sarcoid arthritis carry a single copy of the DQ2-DR3 haplotype as compared with 122/524 (23.3%) patients with other arthritides and 56/299 (19%) of the Dutch population. Noticeably only one (2%) patient with sarcoid arthritis was DQ2-DR3 homozygous. This means that the predisposition to sarcoid arthritis carried by the DQ2-DR3 haplotype appears to be transmitted as a dominant genetic trait. For the other HLA-DQ and HLA-DR alleles the frequencies in the patients with sarcoid arthritis and the control group did not differ significantly.

DISCUSSION
Clinical features

Acute sarcoid arthritis was diagnosed in 4.4% of the patients presenting an EAC. The overall prognosis of the disease was good. The self limiting course of the joint involvement found in this study is in accordance with previous observations in white populations.[2 3 6–8 10 12 29]

Although parenchymal lung infiltrations (stage II) were found at presentation in 15% of the patients, none of them needed treatment with corticosteroids for the development of chronic pulmonary disease. The proportions of patients with acute sarcoid arthritis with stage II pulmonary disease in other studies varied from 0 to 23.5%.[2 3 6 8 12] In most previous studies, like this study, the outcome of lung involvement was favourable in the acute form of sarcoid arthritis.[3 6 8 12 30] In one retrospective study the proportion of patients with acute sarcoid arthritis developing chronic pulmonary disease was higher than in the other studies (4/49 (8%)).[2] However, because of the small patient numbers the difference from the other studies was not significant.

Diagnosis

The presenting clinical features of acute sarcoid arthritis have a high diagnostic ability. Symmetrical ankle arthritis is the most powerful diagnostic feature, with a sensitivity of 95% and a specificity of 92%. Combining it with other clinical features further increases this ability. The diagnostic ability of a combination of four clinical features: symmetrical ankle arthritis, symptoms of less than two months, age below 40 years, and erythema nodosum is exceptionally high. When test positivity is defined as the presence of at least three of four criteria, it produces a sensitivity of 93%, a specificity of 99%, a positive predictive value of 75%, and a negative predictive value of 99.7%. This means that when all three criteria are present in any new patient with arthritis, the probability of having acute sarcoid arthritis rises from 4.4% to 75%, and a chest x ray examination can be performed to confirm the diagnosis. When, on the other hand, fewer than three criteria are present, the probability of not having sarcoid arthritis is 99.7%, which makes the performance of a chest x ray examination to detect hilar adenopathy unnecessary.

The clinical features of acute sarcoid arthritis have been described in several studies.[2–5 8–16 31] In all studies ankle arthritis and bilateral ankle arthritis were found to be the most sensitive diagnostic variables, occurring in 75–100% of the patients. The specificities of these and other presenting clinical features for the disease were unknown, however, because no

previous diagnostic studies had been performed using unselected patients with other arthritides as controls.

Some cases of sarcoid arthritis might have been missed because of normal chest *x* ray findings. These patients then would have been wrongly allocated to the group of patients with other arthritides (control group). We do not think that this markedly influenced the results of the study. The small proportion of acute patients with sarcoid arthritis that is estimated to have normal chest *x* ray findings (<10%), in combination with the low prevalence of the disease, means that the absolute number of wrongly classified patients with sarcoidosis probably is very small. It is unlikely that this affected the characteristics of the large control group.

Risk factors
Seasonality
An evident clustering of the onset of the disease in the months March to July was found in this study. This confirms the findings of previous studies, in which seasonal variation of the onset of sarcoidosis was reported in different regions of Europe and Japan.[2 3 12 31–37] The peak months in all studies were the months of increasing temperatures.[17] In one study in the United States the seasonal variation in the incidence of sarcoidosis was found to be minimal, with a small non-significant peak in spring.[38] Only in our study and one earlier study[3] has the seasonal variation in onset of sarcoid arthritis been compared with that of other arthritides, thus allowing for observation and correction of a possible seasonal variation in the referral behaviour of general practitioners. The observed seasonality suggests that an environmental factor, infective or not, may play a part in the pathogenesis of the disease. The finding that the peak months of disease onset in most studies are the months of increasing temperatures does not point to a particular infective agent. It is interesting, however, that the seasonal variation of sarcoid arthritis onset found in this study resembles the seasonal variation of tuberculosis onset reported in the United Kingdom.[39] The peak for tuberculosis was found to occur in June, whereas for acute respiratory disorders it was in January/February.

Smoking
A highly significant negative association between sarcoid arthritis and smoking was found in this study, suggesting that smoking reduces the incidence of clinically overt sarcoid arthritis. The proportions of smokers in the patient control group and the normal Dutch population were comparable. The association was not influenced by sex and was even stronger in the age category 25–44 years, which contained the majority of the patients with sarcoid arthritis. It is suggested that the lower incidence of pulmonary sarcoidosis in smokers may be attributed to the various alterations in the number, type, and functional activity of lung immune and inflammatory cells which cigarette smoking is known to produce.[19 22 40–44] Possibly, these alterations afford partial protection against the initiation of immune responses in the lung directed against an aetiological, exogenous agent and prevent the development of granulomatous lung disease. In this respect it is interesting that a similar association has been found between non-smoking and the development of another granulomatous disease of the lung—namely, extrinsic allergic alveolitis in farmers.[45 46] Surprisingly, for a disease that in most cases affects the respiratory tract, relatively little attention has been given to the possible role of tobacco smoking in its pathogenesis. The results of this study confirm the findings of previous studies, in which a negative association was found between smoking and sarcoidosis.[18–24] In two studies this negative association was not found.[45 47] The patients with sarcoid arthritis in these two studies differed in two important aspects from those of the other studies: in one study the majority of the patients were black[47] and in the other study a considerable proportion of the patients had advanced disease.[45] In other studies both aspects were found to reduce the negative association between smoking and sarcoid arthritis.[19 23] In our study of a homogeneous subgroup of patients with sarcoidosis, the strongest association reported so far was found. At the same time it is the first report on smoking behaviour in patients with the acute form of sarcoid arthritis, as all previous studies were performed in patients attending chest clinics with pulmonary sarcoidosis. These results suggest that in acute sarcoid arthritis the lung is the starting point of the disease.

HLA
The present study shows a highly significant association between the acute form of this disease and the presence of the DQ2-DR3 haplotype. The existence of an immunogenetic predisposition to sarcoidosis is likely on the basis of both different prevalences in different ethnic populations[48] and the occasional familial clustering of cases.[49] Because the pathophysiology of sarcoidosis probably involves antigen recognition, processing, and presentation, many studies have searched for associations with HLA related genes.[1 25] An allele commonly found to be associated with sarcoidosis is HLA-B8,[50–57] which is in linkage disequilibrium with DQ2-DR3 in our population. However, other studies have found different associations, mainly owing to the ethnical and clinical differences of the patients studied.[25] It is likely that genetic factors not only play a part in the susceptibility to the disease but may also be important in defining the pattern of disease presentation and progression as well as its overall outcome.[1 53] An association of HLA-DR3 with the acute form of sarcoidosis and with a good prognosis, spontaneous resolution, and short duration of the disease was found in several studies.[50 52–56 58] The association between HLA and the susceptibility to the acute form of sarcoid arthritis was evaluated in four studies, all using serological typing.[50–52 58] In all these studies significant associations were found with HLA-B8/DR3. The present study, using molecular typing for DR and DQ, confirms the findings of the serological studies. Moreover, the study shows that predisposition to acute sarcoid arthritis as carried by the DQ2 (DQB1*0201)-DR3 (DRB1*0301) haplotype, appears to be transmitted as a dominant genetic trait.

In conclusion, this study on acute sarcoid arthritis in Dutch patients with early arthritis confirms previous observations of an overall good prognosis, seasonal clustering of disease onset, and an association of the disease with the DQ2-DR3 haplotype. The diagnostic value of its presenting clinical features appears to be remarkably high. A new finding is also the highly negative association that exists between acute sarcoid arthritis and smoking. It is suggested that the disease results from exposure of genetically susceptible hosts to environmental agents through the lungs.

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Sarcoid arthritis: clinical characteristics, diagnostic aspects, and risk factors

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