

# Sarcoidosis

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The term sarcoidosis, also known as Morbus Besnier-Boeck, was coined by the Norwegian dermatologist Caesar Boeck in 1899 to describe the clinical features of this granulomatous disorder. The word “sarcoidosis” is derived from the Greek words for “sark” and “oid”, meaning “fleshy condition”. These lesions are noncaseating granulomas, a hallmark of sarcoidosis [1]. A more informative and still useful definition of the disease, as reported at the World Congress in Kyoto in 1991 and updated since the proclaimed definition dating from 1976, reads as follows: “Sarcoidosis is a multisystem disorder of unknown cause. It commonly affects young and middle-aged adults and frequently presents with bilateral hilar lymphadenopathy, pulmonary infiltration, ocular and skin lesions. Other organs may also be involved. The diagnosis is established when clinicoradiological findings are supported by histological evidence of noncaseating epithelioid cell granulomas. Granulomas of known causes and local sarcoid reactions must be excluded. Frequently observed immunological features are depression of cutaneous delayed-type hypersensitivity and increased CD4/CD8 ratio at the site of involvement. Circulating immune complexes along with signs of B-cell hyperactivity may also be detectable. The course and prognosis may correlate with the mode of the onset and the extent of the disease. An acute onset with erythema nodosum or asymptomatic bilateral hilar lymphadenopathy usually heralds a self-limiting course, whereas an insidious onset, especially with multiple extrapulmonary lesions, may be followed by relentless, progressive fibrosis of the lungs or other organs. Corticosteroids relieve symptoms and suppress inflammation and granuloma formation” [2].

As >90% of patients have involvement of the lungs and thoracic lymph nodes sarcoidosis management is most often done by pulmonary physicians. However, most physicians may encounter sarcoidosis in their practice. Therefore, a multidisciplinary approach is mandatory. This chapter of the *European Respiratory Monograph* aims to provide a “state of the art” for all those involved in the care and basic research of this particular disease.

## Scientific background

### *Epidemiology*

Sarcoidosis is thought to be a disease of all races and ethnic groups, although the incidence of this disease varies widely throughout the world [1]. This is attributed to differences in predisposing human leukocyte antigen (HLA) genes and other genetic

factors, environmental exposures, and surveillance methods. The highest incidence of sarcoidosis in Europe has been reported from Sweden: 24 cases per 100,000 [3]. Incidence studies from the USA showed a remarkable higher incidence rate among black compared with white Americans (35.5 cases per 100,000 compared with 10.9 per 100,000) [4]. In many epidemiological studies, females have a slightly higher incidence compared with males, and in Scandinavian countries and Japan, besides a peak between 20–40 year of age, a second incidence peak in females over 50 yrs of age has been reported [1, 3].

There are not only differences in incidence across ethnicities, but also marked phenotype differences have been observed. For example, the Löfgren's syndrome, which is common in northern European countries, is very rare in patients of African or Japanese origin [5–7]. Conversely, uveitis and cardiac involvement are especially common in Japanese sarcoidosis patients.

### Genetics

The familial associations in sarcoidosis have been reported for many years. Early twin studies have shown a preponderance of monozygous (13 reported cases) over dizygous twins (one reported case) concordant for sarcoidosis [8]. More recently, familial aggregation of sarcoidosis was closely studied by RYBICKI *et al.* [9] in A Case–Control Etiological Study of Sarcoidosis (ACCESS) in the USA. They found that patients with sarcoidosis reported five times more often siblings or parents with this disease as controls. Furthermore, a Danish and Finnish population-based twin study has reported an 80-fold increased risk of developing sarcoidosis in monozygotic twins, whereas the increased risk in dizygotic twins was only sevenfold [10].

These and other observations have led to the hypothesis that gene variants are involved in the development of sarcoidosis or might affect disease presentation. Thus, SCHÜRMAN *et al.* [11] investigated 138 individuals from 63 German families and used microsatellite markers to identify areas of the genome linked to the disease. The most prominent finding was that of linkage to a section within major histocompatibility complex (MHC) on the short arm of chromosome 6 (including marker D6S1666). A series of other studies were consistent and have shown associations between class II MHC alleles and disease susceptibility or phenotype [12]. For example, HLA-DQB1\*0201 and HLA-DRB1\*0301 are strongly associated with acute type sarcoidosis, *i.e.* Löfgren's syndrome, and a good prognosis [13]. Haplotype analysis including these alleles and the tumour necrosis factor (TNF) promoter polymorphism -308A shows that 76% of Löfgren patients carry this haplotype compared with 24% of controls (odds ratio 9.9) [14]. Chronic and severe type sarcoidosis has been consistently associated with HLA-DQB1\*1501 and HLA-DQB1\*0602 [13, 15]. Given the fact that antigen-presenting cells are thought to initiate the formation of granulomas, these genetic HLA-associations are as intriguing as difficult to prove causation. Decoding the antigen-binding properties of the HLA class II peptide-binding grooves might, however, help the identification of candidate (auto-)antigens in sarcoidosis [15, 16].

Of the reported genetic associations between sarcoidosis and non-HLA gene that are based in the MHC region, only the TNF-308A allele has been shown to be consistently associated with Löfgren's syndrome across different populations in northern Europe [17–19]. The question remains, however, if this TNF allele is causative, or if the association is merely due to linkage across the MHC region. One of the most recent associations of MHC based non-HLA genes has been reported by VALENTONYTE *et al.* [20] in German sarcoidosis patients. A variant of the butyrophilin-like 2 gene (BTNL2) was found to associate with sarcoidosis independently of variations in HLA-DRB1. The

BTNL2 single nucleotide polymorphism (rs2076530 G→A) leads to the production of a truncated variant of what is believed to be a co-stimulatory molecule, related to the CD80 and CD86 co-stimulatory receptors, that could influence the T-lymphocyte activation and regulation. The BTNL2 association was replicated in a US study on white but not on black Americans [21]. A recent study by SPAGNOLO *et al.* [22], however, questioned the independence of the BTNL2 association with sarcoidosis. They found that the association of the rs2076530 A allele in British and Dutch sarcoidosis patients disappeared after excluding patients with Löfgren's syndrome and adjusting for HLA-DRB1. Thus, the tight linkage disequilibrium (LD) across the HLA complex makes it again very difficult to identify exactly the susceptibility locus for sarcoidosis in this region. Larger sample sets from different ethnic groups, finer mapping, and more robust LD analyses across the HLA region are required to resolve this problem.

Finally, many genetic variants of non-MHC based genes have been studied during the last decade, but the results are largely inconsistent or not convincingly replicated so far [23, 24]. Table 1 shows a summary of these studies.

### **Environment**

Environmental factors may also have an important role in the aetiology of sarcoidosis. There are various reports on spatial clustering of disease, *e.g.* living in rural areas, occupations such as those involving fire, and latitude (north *versus* south of Japan) [81, 82]. There is also an association between presentation of sarcoidosis and season: cases with erythema nodosum present most commonly in the winter and early spring months, in both the northern and the southern hemispheres [83, 84]. Recently, exposure to photocopier toner dust was found to increase the risk of sarcoidosis in African-American siblings [85]. This and other findings suggest a transmissible and most likely airborne factor that triggers the disease [84, 86]. The concept of a transmissible agent was also strongly supported by the Kveim-Siltzbach test [87]. The characteristic alpha-beta TCR+ T-cell infiltrate in Kveim-induced granuloma consists predominantly of CD4+ T-cells, and V beta gene sequencing has revealed marked clonality and oligoclonality strongly suggesting a T-cell response to a single or limited number of antigens in Kveim [88].

Through the years many potential micro-organisms or organic/inorganic substances have been suggested to trigger sarcoidosis (table 2) [1, 89–94]. Two of the best studied aetiological agents are propionibacterium species and *Mycobacterium tuberculosis* and also other mycobacterial species, or its acid-fast cell-wall-deficient forms [95, 96]. Using PCR techniques, EISHI *et al.* [97] have retrieved propionibacterial DNA from almost all lymph node biopsies of sarcoidosis patients from different cohorts in Europe and Japan. Other groups have reported that serum samples from patients with sarcoidosis contain antibodies to *M. tuberculosis* catalase-peroxidase (mKatG) in ~50% of cases, compared with 0% in controls [98]. In addition, CARLISLE *et al.* [99] found evidence for a strong Th1 immune response to various mycobacterial antigens in almost half of their sarcoidosis patients. Remarkably, the interferon (IFN)- $\gamma$  production capacity of peripheral blood mononuclear cells of these subjects after stimulation by mKat-G, early secreted antigenic target protein-6 and superoxide dismutase A antigens showed a similar pattern to subjects with latent tuberculosis, as opposed to purified protein derivative (PPD)-negative, healthy controls.

A role for mycobacteria in the aetiology of sarcoidosis was further supported by a recent meta-analysis of 31 studies, including 875 sarcoidosis patients [100]. In approximately one-quarter of cases, molecular evidence for the role of mycobacteria was found [100]. Furthermore, a computer simulation study has recently suggested an

**Table 1. – Alphabetic list of non human leukocyte antigen gene studies in sarcoidosis giving an overview of positive (#) and negative (†) associations**

Gene	Variant	Sample origin <sup>+</sup>	Sample size <sup>§</sup>	Type of association <sup>f</sup>	First author [Ref.]
ACE1 <sup>#</sup>	I/D	German C	62 families: 140a–104ua; 100c	S (increased)	SCHÜRMANN [25]
ACE1 <sup>#</sup>	-5466 A>C			S (increased)	SCHÜRMANN [25]
ACE1 <sup>#</sup>	4656(CT)2/3			S (increased)	SCHÜRMANN [25]
ACE1 <sup>#</sup>	I/D	US Afr-Am + C	Afr-Am 183s–111c C 60s–48c	S (increased)	MALIARIK [26]
ACE1 <sup>#</sup>	I/D	Finnish C	59s–70c	C (worse prognosis)	PIETINALHO [27]
ACE1 <sup>#</sup>	I/D	Japanese	21s–18c	P (bronchial hyperresponsiveness)	NIIMI [28]
ACE1 <sup>#</sup>	I/D	Japanese	103s–341c	S (increased)	FURUYA [29]
ACE1 <sup>#</sup>	I/D	Swedish C	62s–107c (30 autoimmune, 32 nonautoimmune)	P (autoimmune manifestations)	PAPADOPOULOS [30]
ACE1 <sup>#</sup>	I/D	Slovenian C	105s–80c	S (increased)	SALOBIR [31]
ACE1 <sup>†</sup>	I/D	Spanish C	177s–104c (84L–87acute–65chronic)		ALIA [32]
ACE1 <sup>†</sup>	I/D	Italian C	Italian: 61s–80c		ARBUSTINI [33]
ACE1 <sup>†</sup>	I/D	British C; Czech C	British 118s–386c; Czech 56s–179c		MCGRATH [34]
ACE1 <sup>†</sup>	I/D	US Afr-Am	225 families		RYBICKI [35]
ACE1 <sup>†</sup>	I/D	Swedish C	73s–65c		PLANCK [36]
ACE1 <sup>†</sup>	I/D	Japanese	207s–314c		TOMITA [37]
ACE1 <sup>†</sup>	I/D	Japanese	100s–247c		TAKEMOTO [38]
ACE1 <sup>†</sup>	I/D	British C	47s–146c		SHARMA [39]
ACE1 <sup>†</sup>	I/D	Meta-analysis	Data from 12 studies		MEDICA [40]
CCL5/RANTES <sup>#</sup>	-403G/A	Japanese	114s–136c	P (extent of disease, <i>i.e.</i> ≥3 organ involvement)	TAKADA [41]
CCR2 <sup>#</sup>	8 SNPs-haplotypes	Dutch C	90s–47L–167c	P (Löfgren's syndrome)	SPAGNOLO [42]
CCR2 <sup>#</sup>	64I	Japanese	100s–122c	S (increased)	HIZAWA [43]
CCR2 <sup>†</sup>	64I	Czech C	66s–80c		PETREK [44]
CCR5 <sup>#</sup>	delta32	Czech C	Czech	S (increased)	PETREK [44]
CCR5 <sup>#</sup>	8 SNPs delta32	British C; Dutch C	British 106s–142c; Dutch 112s–169c	P (parenchymal disease)	SPAGNOLO [45]
CFTR <sup>#</sup>	mutation screening	Italian C	5s–33c	S (increased)	BOMBIERI [46]
CFTR <sup>#</sup>	mutation screening	Italian C	26s–89c	S (increased)	BOMBIERI [47]
CFTR <sup>†</sup>	R75Q	German C	63 families		SCHÜRMANN [48]
CFTR <sup>†</sup>	mutation screening	Italian C	53s		BOMBIERI [49]
CR1 <sup>#</sup>	C5507G	Italian C	91s–94c	S (increased)	ZORZETTO [50]
CR1 <sup>†</sup>	C5507G	Czech C; Dutch C	Czech 210s–203c; Dutch 116s–112c		MRAZEK [51]
CTLA4 <sup>#</sup>	-318CT ex1+49AG	Japanese	106s–100c	P (ocular involvement)	HATTORI [52]
IFNA <sup>#</sup>	551TG	Japanese	102s–110c	S (increased)	AKAHOSHI [53]
IFNG <sup>#</sup>	12-15CA repeats	Polish C	43s (14L)	P (Löfgren's syndrome)	WYSOCZANSKA [54]
IL18 <sup>#</sup>	-607A>C	Japanese	119s–130c	S (increased)	TAKADA [55]
IL18 <sup>†</sup>	-607A>C	Dutch C	133s–103c		JANSSEN [56]
IL1A <sup>#</sup>	-889	Czech C	95s–199c	S (increased)	HUTYROVÁ [57]
IL1A <sup>†</sup>	-889	British C; Dutch C	British 147s–101c; Dutch 102s–166c		GRUTTERS [58]
IL1A <sup>#</sup>	*137	US Afr-Am	105s–95c	S (increased)	RYBICKI [59]
IL6 <sup>#</sup>	-174C	British C; Dutch C	British 147s–101c; Dutch 102s–166c	P (fibrosis)	GRUTTERS [58]
IRF4 <sup>#</sup>	F13A*188	US Afr-Am	105s–95c	S (increased)	RYBICKI [59]

Table 1. – Continued.

Gene	Variant	Sample origin <sup>+</sup>	Sample size <sup>§</sup>	Type of association <sup>f</sup>	First author [Ref.]
MIF <sup>#</sup>	-173C	Spanish C	28s–122c	P (erythema nodosum)	AMOLI [60]
MIF <sup>†</sup>	5-CATT repeat promoter	Irish C	173s–166c		PLANT [61]
MMP1 <sup>#</sup>	1G/2G (G insertion)	Japanese	103s–106c	P (ocular involvement)	NINOMIYA [62]
NFKBIA <sup>#</sup>	-297T	British C; Dutch C	British 115s–99c; Dutch 90s–102c	S (increased)	ABDALLAH [63]
ORM1 <sup>#</sup>		Swedish C		S (increased)	FAN [64]
PTGS2 <sup>#</sup>	-765G>C	British C; Austrian C	British 198s–166c; Austrian 76s–130c	S (increased) P (fibrosis)	HILL [65]
SCGB1A1 <sup>#</sup>	G38A	Japanese	265s–258c	S (increased) C (progressive disease)	OHCHI [66]
SCGB1A1 <sup>†</sup>	G38A	Dutch C; Japanese	Dutch 138s (41L) – 114c; Japanese 100s–117c		JANSSEN [67]
SELE <sup>#</sup>	+561AC=ser128arg (GT)n	Spanish C	31s (L)–66c	S (increased)	AMOLI [68]
SLC11A1 <sup>#</sup>	promoter repeat (CA)n 5' repeat	Polish C	86s–93c	S (increased)	DUBANIEWICZ [69]
SLC11A1 <sup>#</sup>	+several others	US Afr-Am	157s–111c	S (increased)	MALIARIK [70]
STAT4 <sup>#</sup>	SNPs+micros	Japanese	83s–96c	S (increased)	TANAKA [71]
TGFB1 <sup>#</sup>	-509CT	ACCESS	ACCESS	C (chronic disease)	JONTH [72]
TGFB1 <sup>†</sup>	5 SNPs	Dutch C	50acute, 46L, 34chr-nonfibr, 24chr-fib–315c		KRUIT [73]
TGFB1 <sup>†</sup>	Codon 10 T869C	Japanese	104s–110c		NIIMI [74]
TGFB1 <sup>†</sup>	codon 25	German C	51s–72c		MURAKÓZY [75]
TGFB2 <sup>#</sup>	59941 G	Dutch C	50acute, 46L, 34chr-nonfibr, 24chr-fib–315c	P (fibrosis)	KRUIT [73]
TGFB3 <sup>#</sup>	4875 A	Dutch C	50acute, 46L, 34chr-nonfibr, 24chr-fib–315c	P (fibrosis)	KRUIT [73]
TLR4 <sup>†</sup>	Asp299Gly	Dutch C	156s–200c		VELTKAMP [76]
VDR <sup>#</sup>	B-allele	Japanese	101s–105c	S (increased)	NIIMI [77]
VDR <sup>†</sup>	TaqI	German C	85s–80c		GULEVA [78]
VDR <sup>†</sup>	TaqI 352 T>C	US Afr-Am	225 families		RYBICKI [35]
VEGF <sup>#</sup>	+813 C>T	Japanese	103s–146c	S (decreased)	MOROHASHI [79]
VEGF <sup>#</sup>	+813 C>T	Turkish C	70s–80c	S (decreased)	SEYHAN [80]

<sup>+</sup>: Afr-Am: African American; C: Caucasian; ACCESS: A Case–Control Etiological Study of Sarcoidosis.

<sup>§</sup>: a: affected subject; ua: unaffected subject; c: control subject; s: sarcoidosis patient; L: Löfgren's syndrome; chr-nonfibr: chronic parenchymal disease without fibrosis; chr-fibr: chronic parenchymal disease with fibrosis.

<sup>f</sup>: S: susceptibility; C: course of disease; P: disease phenotype.

increased recognition of *Mycobacterium avium* epitopes in patients with Löfgren's syndrome compared with chronic sarcoidosis, and suggested that this syndrome represents the hyper-reactive end of a spectrum of granulomatous responses to specific mycobacteria while pulmonary tuberculosis and atypical mycobacterial infections might represent the opposite end [101].

Given the multiple environmental risk factors and potential causes reported to date, it seems plausible that sarcoidosis is the end result of an altered or incomplete immune response to various ubiquitous environmental triggers in genetically susceptible hosts, and that specific HLA gene–environmental interactions play a fundamental role [102].

**Table 2. – Potential infectious organisms or organic/inorganic substances triggering sarcoidosis**

Category of trigger	Trigger
Infectious agents	<i>Mycobacterium tuberculosis</i> Atypical mycobacterial species Cell wall-deficient mycobacterial forms <i>Propionibacterium acnes/granulosum</i> <i>Rickettsia helvetica</i> <i>Borrelia burgdorferi</i> <i>Mycoplasma</i> spp.
Inorganic substances	Viruses (e.g. human herpes viruses, Epstein–Barr) Aluminium Zirconium Man-made mineral fibres Silica Silicone Clay Talc
Organic substances	Pine tree pollen Starch

Data from [1, 89–93].

### ***Pathogenesis***

In the last two decades, our understanding of the immunopathogenesis of sarcoidosis has progressed significantly, at least in part by studies of bronchoalveolar lavage (BAL) cells and recent biotechnological research. The current models of its pathogenesis are based on data from patient studies, interpreted in the context of experimental models of immune responses [103]. In these models the granulomatous response is thought to start with the presentation of (still unknown) antigenic peptides in the context of MHC to the T-cell receptor (TCR) (MHC-peptide-TCR trimolecular complex; phase 1) [104]. This event initiates a second phase which is characterised by granuloma formation. Subsequently, a third phase can be typed by either disease remission or persistence of granuloma formation leading to chronic sarcoidosis, with or without lung fibrosis.

***Phase 1.*** The initial phase of sarcoidosis is thought to involve the exposure to still unknown exogenous or endogenous antigenic proteins which are taken up by antigen-presenting cells. After processing into peptide fragments the antigen is loaded onto the peptide-binding groove of MHC class II molecules and presented to naive CD4+ T-lymphocytes (Th0). This formation of the MHC-peptide-TCR trimolecular complex and binding of co-stimulatory molecules (B7 to CD28, CD40 to CD40L) gives rise to at least two intracellular signals, both essential to activate the CD4+ T-cell. Activated CD4+ T-cells are subsequently polarised to T-helper type 1 (Th1) cells under the influence of interleukin (IL)-12 and -18 (fig. 1). Dendritic cells may play a critical role in this polarisation process from Th0 into Th1 effector cells [105].

***Phase 2.*** Initiation of granuloma formation is central to phase 2 and thought to involve ongoing antigen presentation by lung macrophages to Th1 effector cells. Due to orchestrated production of host chemokines and cytokines by these cells, there is coordinated recruitment, migration, retention and local proliferation of cells, especially T-lymphocytes and monocytes/macrophages. Figure 2 shows a model of the major events in this phase.

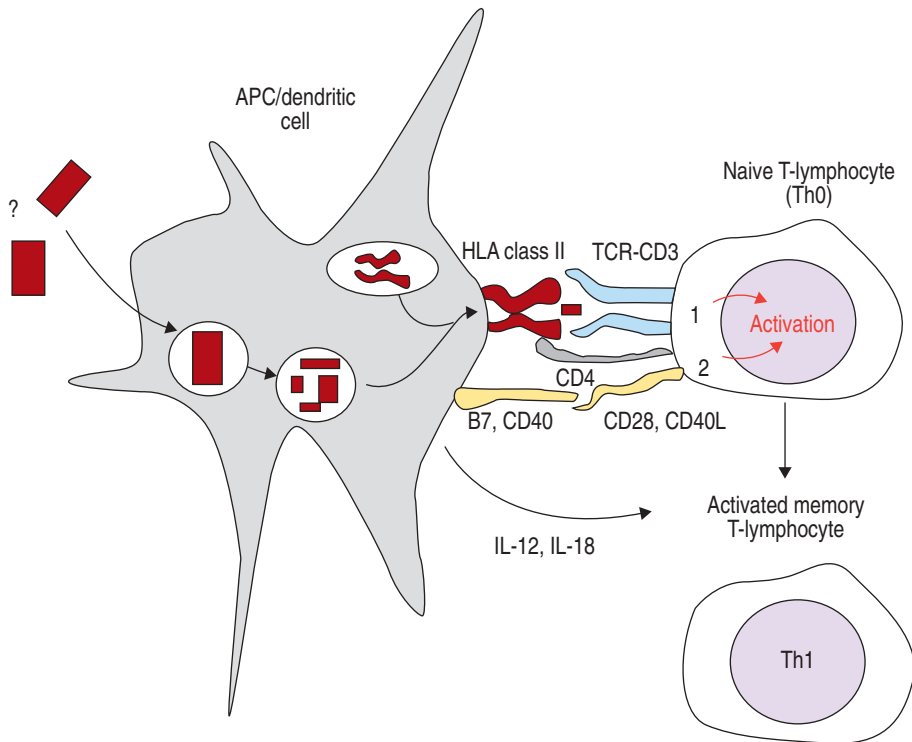


Fig. 1. – Induction of the primary immune response in sarcoidosis. A yet unknown exogenous antigenic agent is internalised and processed into peptides by antigen-presenting cells (APC). Peptides are loaded onto major histocompatibility complex class II molecules and presented to T-cell receptors (TCR) of CD4<sup>+</sup> T-lymphocytes (Th0) in the context of co-stimulatory molecules (B7 to CD28, CD40 to CD40L). Two intracellular activation signals subsequently lead to activation of the Th0 cells, which are polarised to T-helper type 1 (Th1) cells under the influence of interleukin (IL)-12 and -18. HLA: human leukocyte antigen.

Interestingly, there is evidence of oligoclonal expansion of T-cells at sites of disease. For example, in Scandinavian subjects, remarkable expansion of AV2S3(V $\alpha$ 2.3)<sup>+</sup> T-cells has been demonstrated in BAL fluid from HLA-DR17<sup>+</sup> (now designated DRB1\*0301) patients. This finding supports the hypothesis that granulomatous inflammation in sarcoidosis involves conventional antigen-driven responses [106–108]. Oligoclonal expansion of other specific V $\beta$ <sup>+</sup> or V $\alpha$ <sup>+</sup> T-cell subsets has also been documented in the lung, skin and blood of other patients with sarcoidosis [88, 109, 110].

Related to this ongoing immunological response the cells organise spatially into immune granulomas. Granulomas, which are the pathological hallmark of sarcoidosis, are usually non-necrotising, but occasionally necrosis is found [111]. However, granulomas are a feature not only of sarcoidosis, but of many chronic interstitial diseases, *e.g.* hypersensitivity pneumonitis, berylliosis and pulmonary Langerhans' cell histiocytosis [103].

**Phase 3.** Phase 3 involves the evolution of the granulomatous inflammation, which can be classified as either spontaneous resolution or persistence of disease, *i.e.* a chronic course of disease. Spontaneous resolution may be associated with a general down-regulation of the immune response, but before this occurs it is likely that a critical component of this outcome depends on clearance of the initial pathogenic antigen(s).

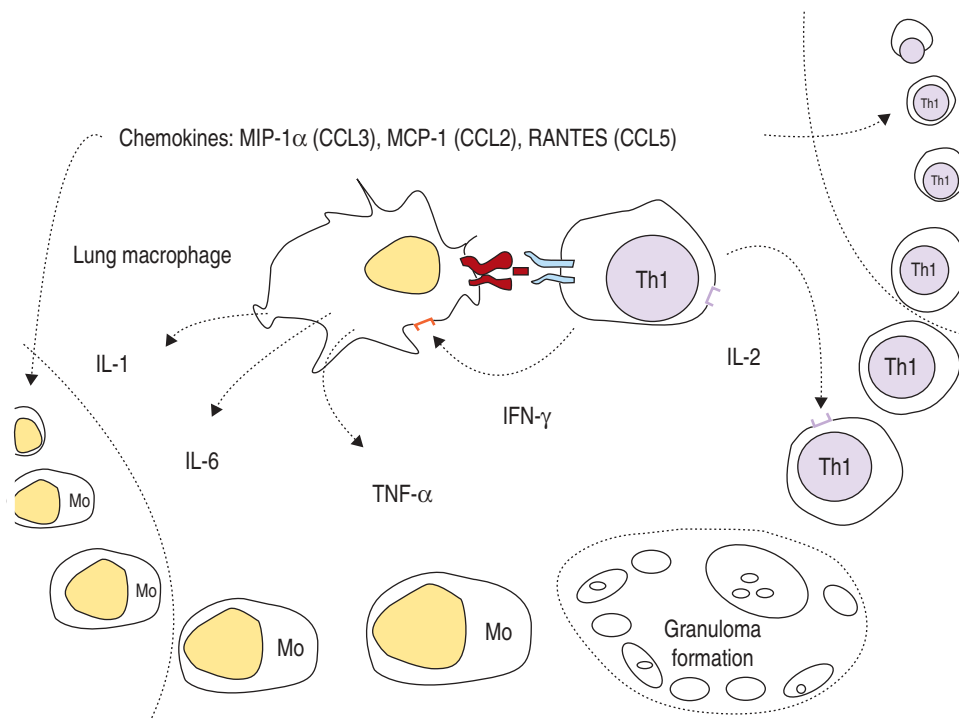


Fig. 2. – Phase 2 of the pathogenesis of sarcoidosis is characterised by granuloma formation due to ongoing antigen presentation by lung macrophages to T-helper type 1 (Th1) effector cells. Due to orchestrated production of host chemokines and cytokines by these cells, there is coordinated recruitment, migration, retention and local proliferation of cells, especially T-lymphocytes and monocytes/macrophages (Mo). Tumour necrosis factor (TNF)- $\alpha$  is thought to be a key cytokine in the spatial organisation of cells into granuloma. CCL: CC chemokine ligand; IFN: interferon; IL: interleukin; MCP: monocyte chemoattractant protein; MIP: macrophage inflammatory protein.

Recently, a hypothetical model for this phase was proposed by MOLLER and CHEN (fig. 3) [104]. In this model, a shift in Th1/Th2 balance is central to an effective humoral response, which could help the clearance of pathogenic antigens by either Fc-receptor-mediated mechanisms or by removal of relevant immune complexes through complement receptor (CR)-1-mediated pathways [104]. In this respect it is of note that early studies in patients with Löfgren's syndrome have reported the presence of circulating immune complexes in almost all cases [112]. In addition, the recent finding of CR-1, a glycoprotein involved in immune complex clearance by circulating erythrocytes, to be a candidate susceptibility gene in sarcoidosis might be relevant [50, 113]. Unfortunately, this could not be confirmed by others [51]. Other pathogenic pathways that could influence the final outcome in phase 3, such as apoptosis of immune cells, have also been suggested [114].

An additional and clinically very important event in phase 3 is the onset of a fibrotic response, which is seen in only a small percentage of patients. In these patients sarcoid granulomas result in significant fibrotic changes. If progressive, this process may lead to end-stage sarcoidosis, characterised by parenchymal fibrosis and honeycombing of the lung. A role for granulocytes has been proposed, and there is recent support for the importance of genotype differences in transforming growth factor- $\beta$  [73, 115]. Unfortunately, exact mechanisms are still largely unknown.

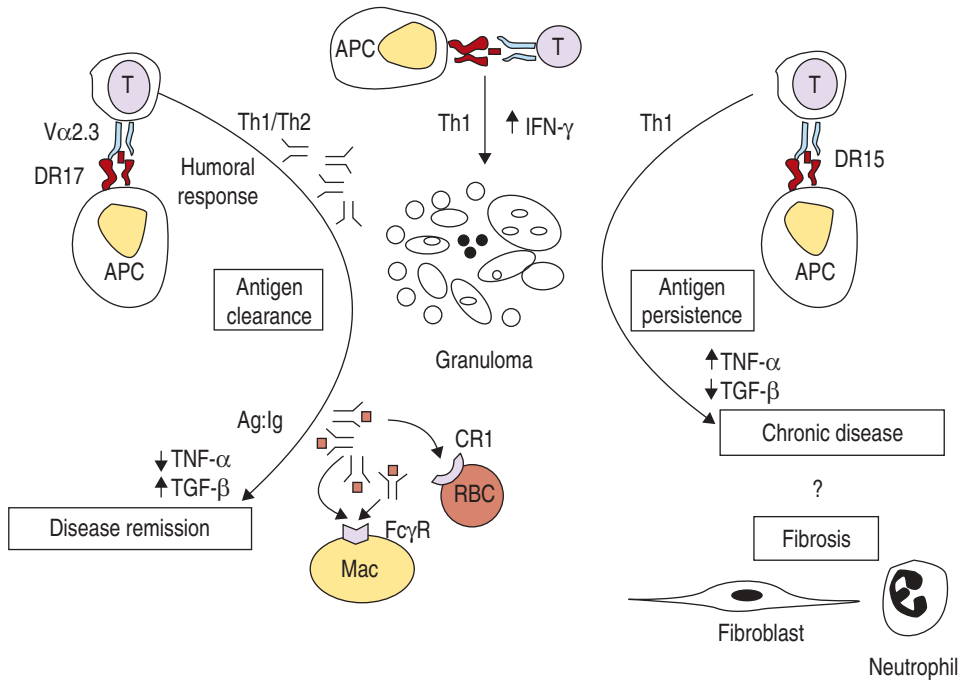


Fig. 3. – Hypothetical model of the evolution of the granulomatous inflammation as proposed by MOLLER and CHEN [104]. In this model, remitting sarcoidosis is characterised by antigen-presenting cells (APCs) bearing favourable human leukocyte antigen (HLA)-DR17 molecules, which present putative sarcoidosis peptides to V $\alpha$ 2.3+ T-cells, initiating a cellular (T-helper type 1 (Th1) cell) and humoral (Th2) response that fosters clearance of pathogenic antigen-antibody complexes through Fc-receptor (Fc $\gamma$ R)- and complement receptor (CR)1-mediated mechanisms and disease remission. APCs bearing unfavourable HLA-DR15 molecules present different sarcoidosis-related peptides to T-cells, promoting a more pathogenic Th1 response that is ineffective in removing the causal antigens, resulting in continual granuloma formation and chronic disease. The relation between chronic disease and lung fibrosis in sarcoidosis is presently largely unknown, although fibroblast and neutrophils are thought to be key cells in this process. Ag: antigen; IFN: interferon; Ig: immunoglobulin; Mac: macrophage; RBC: red blood cell; TGF: transforming growth factor; TNF: tumour necrosis factor.

## Clinical aspects

### Presentation

The clinical presentation of sarcoidosis varies significantly. There are several reasons for this. First, there is a strong influence from the ethnic background of a patient. For example, cardiac involvement is rare in Caucasians, whereas it is a frequent manifestation of sarcoidosis in the Japanese population. Secondly, strong heterogeneity of clinical presentation depends on the fact that the extent and/or activity of the granulomatous process may differ per organ, and that virtually every organ can be involved. Thirdly, there are clear differences in the mode of onset of the disease. The acute onset type sarcoidosis with bilateral hilar lymphadenopathy, erythema nodosum and arthralgia was first recognised in Sweden by Sven Löfgren and has been known since then as Löfgren's syndrome [116]. Moreover, the disease may have an insidious onset or may even be discovered by accident.

**Pulmonary involvement.** The lung parenchyma and the mediastinal lymph nodes are affected in >90% of patients with sarcoidosis [1]. Dyspnoea, dry cough and chest pain

occur in approximately one-half of all patients. Massive hilar and/or mediastinal lymphadenopathy is often asymptomatic, but may cause fatigue, retrosternal pain and/or dysphagia in some patients [117, 118]. Although parenchymal involvement is more common, the airways (larynx, trachea and bronchi) may also be involved leading to airway obstruction and bronchiectasis [1]. Airway hyperreactivity has been reported in up to 20% of patients, and has been attributed to the extensive epithelial damage demonstrated by electron microscopy in these subjects, possibly increasing epithelial permeability and uncovering superficial afferent nerve endings [119, 120]. Pleural manifestations are rare and include pleural thickening due to granulomatous inflammation, fibrosis, and/or calcification, pleural effusion and chylothorax [1].

In ~10–20% of patients with pulmonary sarcoidosis, the granulomatous inflammation becomes chronic with concomitant wound healing of the inflamed tissue that ultimately leads to the formation of scar tissue, *i.e.* fibrosis (fig. 4) [121].

**Extrapulmonary disease.** In addition to involvement of the respiratory and lymphatic systems, sarcoidosis can affect almost any other organ. Table 3 summarises the range of extrapulmonary manifestations of sarcoidosis, related diagnosis, and gives an index of severity (IOS). We hereby propose four categories that might be useful for clinical decision-making. IOS is defined as organ manifestations that are harmless and without symptoms, so that the patients' quality of life will hardly be impaired (*e.g.* mild liver involvement). IOS 2 means organ involvement that is in itself harmless but is associated with substantial reduction of quality of life (*e.g.* lupus pernio). Extrapulmonary manifestations of sarcoidosis that cause severe loss of organ function and/or irreversible damage are classified as IOS 3 (*e.g.* posterior-segment involvement of the eye). And finally, a small percentage of extrapulmonary disease is associated with increased risk of death (IOS 4; *e.g.* cardiac sarcoidosis). The proposed IOS classification for organ involvement in sarcoidosis is further outlined in table 4.

As with cardiac involvement, central nervous system involvement can be a severe and potentially life-threatening manifestation of sarcoidosis. The central nervous system is involved in up to 25% of patients who undergo autopsy [81]. The most common

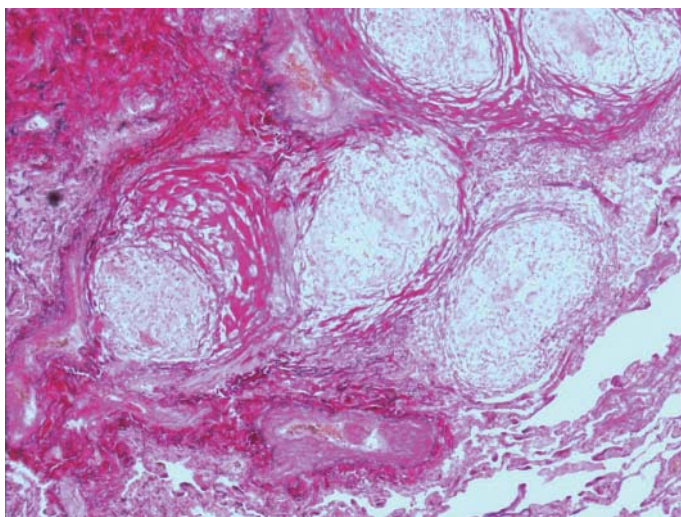


Fig. 4. – Lung tissue biopsy from a sarcoidosis patient who succumbed to respiratory failure due to advanced pulmonary fibrosis. Elastic-Van Gieson staining; magnification 20 $\times$ .

**Table 3. – Alphabetic list of various extrapulmonary manifestations of sarcoidosis with diagnosis and index of severity (IOS)**

Organ	Diagnosis	IOS <sup>#</sup>
Central nervous system	Cranial nerve palsy	3
	Meningitis	3
	Space-occupying lesions	3–4
Endocrine system	Hypopituitarism	3
	Hypercalcaemia	2–3
	Hypercalciuria	1–2
Eyes	Anterior uveitis	1
	Posterior uveitis	3
	Optic neuritis	3
Heart	Complete heart block	4
	Ventricular tachycardia, fibrillation	4
	Congestive heart failure	4
Kidney	Intrarenal calcium deposition	2–3
	Granulomatous nephritis	3
	Renal failure	3–4
Liver	Elevated liver enzymes (<3 × upper limit)	1
	Cholestatic hepatitis	2–3
	Portal hypertension and/or hepatic failure	3–4
Lymph nodes	Peripheral lymphadenopathy	1
Peripheral nervous system	Peripheral neuropathy	2–3
	Small fibre neuropathy	2–3
	Arthralgia/arthritis	1–2
Skeleton	Scattered solitary lesions	1–2
	Plaques, nodules	1–2
Skin	Erythema nodosum	1–2
	Lupus pernio	2
	Splenomegaly	1–2

<sup>#</sup>: see table 4 for criteria for IOS.

manifestation of neurosarcoidosis is facial nerve palsy. The mechanism of facial nerve involvement remains unclear, but cranial nerve polyneuritis or demyelination, and sarcoid lesions at the brainstem level have been suggested [122]. Other cranial nerves that can be commonly affected are the optic nerve, the glossopharyngeal, the vagus, the oculomotor and the auditory nerves [122]. A variety of peripheral neuropathic manifestations have also been described in sarcoidosis [122]. Furthermore, evidence of small fibre neuropathy was recently reported in some patients with unexplained pain and dysaesthesia [123]. Seizures occur in 5–22% of patients with neurosarcoidosis and are associated with chronicity and increased risk of death [122].

Cardiac sarcoidosis is a rare but severe manifestation of sarcoidosis. Approximately 5% of patients have clinically apparent myocardial localisation, but much higher

**Table 4. – Proposed criteria for severity of organ involvement in sarcoidosis**

IOS	Severe symptomatology/ decrease of QoL	Severe loss of organ function	Risk of death
IOS 1	No	No	No
IOS 2	Yes	No	No
IOS 3	#	Yes	No
IOS 4	#	#	Yes

Criteria derived from the clinical practice of the authors. IOS: index of severity; QoL: quality of life. <sup>#</sup>: may be either “yes” or “no”.

frequencies of myocardial granulomas have been reported in autopsy studies, suggesting the occurrence of subclinical myocardial disease in a significant number of patients [124]. The most common localisation for granulomas and scars is the left ventricular wall, followed by the intraventricular septum, explaining the low diagnostic yield of endomyocardial biopsies *via* right heart catheterisation (<20%) [81].

Due to the high risk of mortality, a careful cardiac clinical history and ECG is recommended for every patient with the diagnosis of sarcoidosis [1]. If there is a high index of suspicion, such as a history of palpitations or conduction abnormalities on ECG, further evaluation should be undertaken and may include 24-h Holter monitoring, cardiac magnetic resonance imaging (MRI) with gadolinium and <sup>18</sup>F-fluorodeoxyglucose-positron emission tomography (<sup>18</sup>FDG-PET) scanning [81, 125]. Diagnostic criteria are scarce and only available from the Japanese Ministry of Health and Welfare [126]. An adapted form of these criteria is used in the authors' institutes and is shown in table 5. Electrophysiological studies should be considered for risk stratification in all patient with (strongly suspected) cardiac sarcoidosis. In those showing potentially dangerous conduction defects or arrhythmias, and in patients with markedly reduced left ventricular function an implantable cardioverter-defibrillator is strongly recommended as it is likely to be life-saving [129]. In addition, immunosuppressive therapy is recommended in patients with active sarcoidosis and/or reduced left ventricular function [81, 130, 131].

**Chronic fatigue.** Fatigue is one of the symptoms most often reported by patients [132]. In many patients, it can be qualified as skeletal muscle weakness and reduced exercise tolerance [133]. The consequence of this symptom is a substantial reduction of health status and quality of life [133, 134]. Remarkably, in some patients the fatigue seems to persist even when the disease has come into remission. This prolonged fatigue is referred to in the literature as “post-sarcoidosis chronic fatigue syndrome”, a complex of clinical features including incapacitating fatigue, low spirit, wide-spread myalgia and sleep disturbances [135, 136].

**Autoimmune phenomena.** The association of autoimmune disorders has frequently been observed in sarcoidosis in up to 20% of the cases [137]. In a case-control study, ANTONELLI *et al.* [138] demonstrated a higher prevalence of clinical and subclinical hypothyroidism in female sarcoidosis patients (5% and 17%, respectively). Also, a

**Table 5. – Criteria for the diagnosis of cardiac sarcoidosis according to the Japanese Ministry of Health and Welfare [126, 127], including magnetic resonance imaging and <sup>18</sup>F-fluorodeoxyglucose-positron emission tomography (FDG-PET)**

Histological diagnosis

Evidence of non-necrotising granulomas in myocardial biopsy in a patient suspected of sarcoidosis

Clinical diagnosis

In patients with histological proof of noncardiac sarcoidosis, diagnosis of myocardial involvement is justified when item (a) and one or more of items (b)–(f) are present

- a) Complete right bundle branch block, left axis deviation, atrioventricular block, ventricular tachycardia, PVCs (>2 in the classification according to Lown, *i.e.* multiform PVCs, >2 consecutive PVCs or R-on-T phenomenon), or abnormal Q or ST-T changes in the ECG or the ambulant 24-h Holter recording
- b) Mid-wall and/or epicardial hyperenhancement pattern on cardiac magnetic resonance imaging
- c) Abnormal wall motion, local thinning or thickening of the wall or left ventricle dilatation on the echocardiogram
- d) Abnormal, localised uptake on *fasting* cardiac FDG-PET
- e) Abnormal intra-cardiac pressure, low cardiac output, abnormal wall motion or depressed ejection fraction of the left ventricle on left heart catheterisation
- f) Nonspecific interstitial fibrosis or mononuclear cell infiltration in endomyocardial biopsy

PVC: premature ventricular contraction. Reproduced from [128], with permission from the publisher.

significantly higher prevalence of Graves' disease was observed. Other autoimmune diseases associated with sarcoidosis include celiac disease, Addison's disease, polyglandular autoimmune syndromes, diabetes mellitus, pernicious anaemia and vitiligo [137, 139, 140]. The exact mechanism of the relation between sarcoidosis and autoimmune disease is not yet known. Recently, WAHLSTRÖM *et al.* [141] identified 78 amino acid sequences from proteins presented in the lungs of sarcoidosis patients, some of which were well-known autoantigens such as vimentin and ATP synthase. This may be interpreted as suggesting that autoantigens should still not be overlooked as a possible triggering agent in some cases of sarcoidosis. Alternatively this finding might offer a clue regarding the coexistence of sarcoidosis with a range of autoimmune disorders.

Sarcoidosis may also be associated with common variable immunodeficiency (CVID). Approximately 10% of patients with CVID will develop granulomatous changes in one or more organs [142]. Conversely, the diagnosis CVID should be considered in patients with sarcoidosis who do not show the characteristic hypergammaglobulinaemia (and who may actually have hypogammaglobulinaemia) and who have a history of recurrent infections.

### ***Diagnostic approach***

The diagnosis of sarcoidosis is based on a compatible clinical picture, histological demonstration of noncaseating granulomas, and the exclusion of other diseases that show a similar histological or clinical picture [1]. The presence of noncaseating granulomas in a single organ such as the skin does not establish the diagnosis of sarcoidosis. In the diagnostic process the following approaches may be useful.

**Blood tests.** Patients with sarcoidosis may show an increased serum and/or urine calcium concentration, and increased levels of serum angiotensin-converting-enzyme (sACE), soluble IL-2 receptor (sIL-2R) and/or C-reactive protein [143]. However, normal values of these tests do not exclude activity of sarcoidosis, especially in chronic disease or when immunosuppressive therapy is used. In this context sACE is especially regarded as an insensitive and nonspecific diagnostic test for sarcoidosis [81]. However, recent studies of the gene encoding sACE have revealed new insights into its performance. ACE activity in blood was found to be strongly influenced by the insertion (I)/deletion (D) polymorphism (ACE I/D). As a consequence, significant differences exist in the normal range of sACE across the three genotype groups, *i.e.* D/D, D/I and I/I [144, 145]. As I/I carriers (25% of the population) have the lowest normal range, a mild-to-moderate increase of sACE in these subjects will not be recognised with the use of one reference interval only. However, with the use of three genotype-specific reference intervals the interpretation of the test substantially improves [39, 145].

The other frequently used blood test is serum sIL-2R. It is especially useful in evaluation of disease activity in pulmonary sarcoidosis [143, 146]. Furthermore, when high levels are found in patients with little lung involvement this should put the physician on the alert for extrapulmonary organ involvement [146].

Recently, two other potential biomarkers for sarcoidosis have gained attention. A study on CC chemokine ligand 18 (CCL18) suggested this marker could be a novel test for the pulmonary fibrotic response in sarcoidosis [147]. Some other studies have suggested that measurement of chitotriosidase (a chitinase produced by activated macrophages) might be a new marker. Nevertheless, both markers will need further validation before they should be used in routine clinical practice [148, 149].

**Radiology.** Chest radiographs in patients with sarcoidosis have been classified into four stages: stage I, bilateral hilar lymphadenopathy, which may be accompanied by paratracheal lymphadenopathy; stage II, bilateral hilar lymphadenopathy accompanied by parenchymal infiltration; stage III, parenchymal infiltration without hilar adenopathy; and stage IV, advanced fibrosis with evidence of honeycombing, hilar retraction, bullae, cysts and/or emphysema (fig. 5) [150, 151]. Despite the nomenclature, patients do not all progress through stages I–IV and these stages have no sequential order. A patient may present with stage III, which normalises during follow-up, or a patient may present with stage I, which normalises but recurs with parenchymal disease only (stage III). The staging system, however, has important limitations. There is great inter-observer variability, especially between stages II and III, and III and IV.

High-resolution computed tomography (HRCT) of the chest has brought important advances in this respect due to its higher sensitivity over chest radiography, and high accuracy in characterising airway, airspace or interstitial processes in sarcoidosis. Also, complications such as aspergilloma can best be detected with HRCT. However, although some attempts have clearly been made, a reproducible and easy to use sarcoidosis computed tomography scoring system that correlates well with functional impairment and has prognostic significance is still not available for use in clinical practice [152].

Finally, it should be noted that MRI with gadolinium is useful for detecting cardiac and central nervous system involvement, and for guiding therapy in some cases.

**Molecular imaging.** Recently, several reports have shown that  $^{18}\text{F}$ FDG-PET can be used for imaging sarcoidosis. In particular, it appears useful in assessing the extent of organ

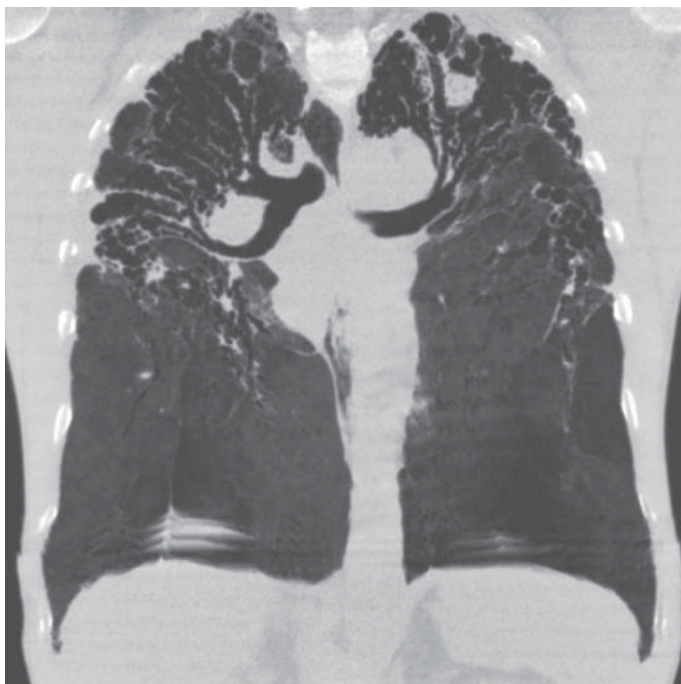


Fig. 5. – Coronal high-resolution computed tomography scan of the thorax of a sarcoidosis patients with severe advanced fibrosis, especially in the upper lobes (minimal intensity projection image).

involvement, and in finding the best target area for a diagnostic biopsy.  $^{18}\text{F}$ FDG-PET appears to be a very sensitive technique to access disease activity, especially in patients with normal serum values for sIL-2R and/or (genotype-corrected) ACE [153]. Also it may be of use for monitoring disease activity during treatment in cardiac sarcoidosis, especially in patients with an implantable cardioverter-defibrillator [125].

**BAL.** BAL is safe, minimally invasive, and provides useful information for the diagnosis of sarcoidosis. There is no single cell type present in BAL fluid that appears to be predictive for sarcoidosis. However, BAL fluid analysis can be very helpful in the differential diagnosis. A grouping of features, an elevated total cell count, predominantly lymphocytes, together with a nearly normal percentage of eosinophils and polymorphonuclear neutrophils and the absence of plasma cells, distinguish the most likely diagnosis of sarcoidosis from the most common interstitial lung diseases, extrinsic allergic alveolitis, nonspecific interstitial pneumonia and idiopathic pulmonary fibrosis. In sarcoidosis, the majority of cases have an increased number of lymphocytes and a normal amount of eosinophils and neutrophils [154]. Disease presentation or activity at the time the BAL is performed as well as the smoking status is crucial for interpretation of individual BAL fluid analysis results. In severe cases with lung fibrosis, the number of neutrophils can also be increased. For an individual case, the CD4:CD8 ratio is of less importance because it can be increased, normal, and even decreased [155]. In cases that are already confirmed by a positive biopsy, there appears to be limited diagnostic value of performing a BAL; however, it should be stressed that sarcoidosis is a diagnosis *per exclusionem* and that thorough microbial and nonmicrobial analysis of BAL fluid may contribute to this.

HERON *et al.* [156] have recently evaluated the contribution of the finding of the integrin CD103, expressed on CD4+ T-lymphocytes in the BAL fluid to the diagnosis in 56 patients with sarcoidosis and 63 patients with other interstitial lung diseases. The authors demonstrated that the combined use of CD103+CD4+/CD4+ ratio ( $<0.2$ ) with either the BAL CD4+/CD8+ ratio ( $>3$ ) or the relative BAL/peripheral blood CD4+/CD8+ ratio ( $>2$ ) could diagnose sarcoidosis with a sensitivity of 66% and a specificity of 89% [156].

In the follow-up predicting prognosis and response to treatment, BAL fluid analysis has less clinical relevance.

**Histology.** A diagnosis of sarcoidosis is reasonably certain without biopsy in patients who present with Löfgren's syndrome [1, 81]. Also, in asymptomatic patients presenting with symmetrical bilateral lymph adenopathy on chest radiography, histopathological confirmation may not be necessary for making the diagnosis [157, 158]. Only if lymphadenopathy shows asymmetry, significant progression, or large paratracheal involvement, is histopathological confirmation strongly recommended [159]. Also, in all other situations, a biopsy specimen should be obtained from the involved organ that is most easily accessed, such as the skin, peripheral lymph nodes or lungs [1]. Bronchial biopsy during bronchoscopy should always be considered in this respect as it may provide histological evidence of granulomas in 30% of cases with normal-appearing endobronchial mucosa [160]. Transbronchial biopsy has a higher diagnostic yield of 60–85%, but involves an increased risk of complications such as pneumothorax and bleeding [81, 160]. Endoscopic ultrasound-guided fine-needle aspiration of intrathoracic lymph nodes has been reported to provide a diagnostic yield of  $\sim 82\%$  and may obviate the need for mediastinoscopy, which procedure is currently hardly used any more for the diagnosis of sarcoidosis in our centres [161].

Due to important differential diagnoses, including infectious diseases, special stains for acid-fast bacteria and fungi and microbial cultures are essential, especially when the patient has fever or when granulomas exhibit focal necrosis. Granulomas can also be found in the regional lymph nodes of carcinomas or in primary tumours such as breast carcinoma and seminoma. Immunohistologically, these latter granulomas are B-cell positive, whereas granulomas in sarcoidosis are B-cell negative [162].

***Pulmonary function tests.*** All varieties of abnormalities of lung function can be seen in sarcoidosis: obstructive, restrictive lung function, diffusion impairment, or combinations of these. Outcome of lung function tests can also be (near) normal despite apparently extensive parenchymal involvement, or may decrease only during the course of disease. However, despite (near) normal diffusion capacity, some patients may show significant desaturation during exercise, supporting the role of exercise tests in the initial assessment of functional impairment.

Bronchial hyperresponsiveness is a frequent finding in pulmonary sarcoidosis (up to 20% of cases) and is associated with the presence of microscopic non-necrotising granulomas in the endobronchial mucosa [119, 160, 163].

Sometimes impairment of lung function may be due to weakness of respiratory muscles. And in patients with active granulomatous inflammation, basal oxygen consumption may be increased due to higher basal metabolism rate.

***Additional work-up recommended by the European Respiratory Society, American Thoracic Society and World Association of Sarcoidosis and Other Granulomatous Disorders.*** After the diagnosis is established and other causes of granulomatous disease have been excluded, an additional work-up is recommended for all patients, including peripheral blood counts (white blood cells, red blood cells, platelets), serum chemistry (calcium, liver enzymes, creatinine), urine analysis (calcium), ECG and routine ophthalmological examination [1].

***Multidisciplinary approach.*** Although the lungs are affected in roughly 90% of cases, the pulmonologist is not the only clinician involved in the patient management. Due to its multisystemic nature it may also present to other specialists, or they may need to be consulted because of the suspicion of extrapulmonary organ involvement. A multidisciplinary approach in diagnosis and management is therefore strongly recommended and is of undoubted benefit for the patient [164].

### ***Monitoring***

After establishing the diagnosis, and after any additional work-up, all patients with sarcoidosis will have to be monitored for evolution of their disease. Although no evidence-based guidelines are available, some expert opinion based recommendations have been made. Evaluations every 3–6 months are advised during the first 2 yrs after presentation, in order to assess prognosis and determine the need (if any) for therapy. After complete remission, with or without therapy, all patients (irrespective of radiological stage) should be monitored for a minimum of 3 yrs. Persistent, stable asymptomatic stage I disease should be monitored longitudinally (annually). Regardless of whether treatment is offered, patients with persistent stage II, III or IV sarcoidosis should be monitored indefinitely (at least annually). Patients with serious extrapulmonary involvement require long-term follow-up, irrespective of the chest radiographic stage [1].

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It might be expected that, in the near future, genetic and other biomarkers markers will help clinicians in better predicting the prognosis of sarcoidosis, therefore allowing for individualised patient surveillance.

### ***Treatment of sarcoidosis***

Although corticosteroids and other immunosuppressive or immunomodulatory drugs can clearly be effective in sarcoidosis, they are not a curative treatment, as relapses frequently occur after tapering of the dosage. Two principles are generally used to guide decisions on whether or not patients should be given immunosuppressive therapy. The first principle is “danger”, *i.e.* the disease is life threatening or may cause severe and/or irreversible organ dysfunction (*e.g.* IOS 3–4 in table 3). Here, the clinician will generally advise the patient to take therapy. The other principle is “quality of life”. In this situation the disease is not dangerous to the patient, but may cause serious and unacceptable complaints with significant loss of quality of life (*e.g.* IOS 1–2 in table 3). Before offering therapy, the patient should be explicitly warned about the limitations of immunosuppressive therapy, and the risks of side-effects that may also seriously impact the quality of life; in other words, the cost/benefit ratio of the proposed treatment.

***Corticosteroids.*** Corticosteroids are very potent and effective drugs in preventing and suppressing inflammation caused by mechanical, chemical, infectious and immunological stimuli. They act mainly by repression of inflammatory genes, *e.g.* IL-1 and TNF- $\alpha$ , adhesion molecules and receptors, and partly by inducing anti-inflammatory genes such as IL-1 receptor antagonist. Together, 10–100 genes are thought to be directly or indirectly regulated by corticosteroids [165]. In sarcoidosis, corticosteroids have been shown to restore the balance between locally produced Th1 and Th2 cytokines [166]. However, corticosteroid resistance has also been described in some cases, and is characterised by exaggerated TNF- $\alpha$  release by alveolar macrophages compared with cases with a favourable responses to steroids [167]. This finding suggests that steroid-refractory disease might benefit from anti-TNF- $\alpha$  antibody treatment, *e.g.* infliximab.

Systemic corticosteroids remain the first-choice therapy in organ- and/or life-threatening sarcoidosis. Although most criteria for treatment are empirical, there is reasonable evidence from randomised controlled trails that these drugs have a short-term effect in patients with (progressive) parenchymal disease and impaired lung function. In addition, it is generally accepted that severe nonpulmonary sarcoidosis, including sight-threatening ocular, cardiac and neurological involvement, and severe hypercalcaemia (usually  $>3.0 \text{ mmol}\cdot\text{L}^{-1}$ ), should be treated systemically [81, 168]. However, no long-term benefit with regard to outcome, *e.g.* prevention of lung fibrosis and/or loss of functional capacity, has yet been proven. Moreover, taking into account the potentially severe side-effects, one should consider starting a corticosteroid sparing agent at an early phase of therapy.

***Methotrexate.*** Methotrexate and its active metabolites compete for the folate binding site of the enzyme dihydrofolate reductase. Folic acid must be reduced to tetrahydrofolic acid by this enzyme for DNA synthesis and cellular replication to occur. Although methotrexate was first introduced as an antiproliferative agent that inhibits the synthesis of purines and pyrimidines for the therapy of malignancies, it is now clear that many of the anti-inflammatory effects of methotrexate are mediated by adenosine [169]. Use of methotrexate leads to elevation of the concentration of this nucleoside in the

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extracellular space. Adenosine, acting on P1 receptors, exerts a number of actions on a variety of cell types relevant to the anti-inflammatory effect of methotrexate [169].

Published data on the use of methotrexate in patients with sarcoidosis are largely anecdotal and based on small series [170]. In the present authors' experience, methotrexate is, however, fairly effective and well tolerated in the majority of cases at a dosage of up to 15 mg·week<sup>-1</sup>, although close monitoring of liver function is required. Furthermore, there is evidence that methotrexate can be given as a steroid-sparing agent. A randomised controlled trial by BAUGHMAN *et al.* [171] showed that patients receiving methotrexate required significantly smaller amounts of corticosteroids after 12 months, than the control group.

***Azathioprine, cyclophosphamide, cyclosporin and mycophenolate.*** A number of other cytotoxic drugs have been used in the treatment of severe and/or refractory cases of sarcoidosis. These include azathioprine, cyclophosphamide, cyclosporin and mycophenolate. However, the current body of evidence supporting the use of these agents is very limited, and severe side-effects are the risk, especially with cyclosporin [170, 172].

A few case report on the use of mycophenolate have appeared in the literature since 2003. Mycophenolate mofetil (MMF) is a selective inhibitor of inosine 5'-monophosphate dehydrogenase type II, the enzyme responsible for the *de novo* synthesis of the purine nucleotide guanine within activated T- and B-lymphocytes and macrophages. It is well known as a potent immunosuppressant in organ transplantation, but its use is now also expanding into autoimmune and inflammatory diseases. On the basis of the current literature MMF may provide an interesting rescue treatment option, especially for cases of severe neurosarcoidosis, but further evaluation is needed.

***Hydroxychloroquine.*** The antimalarial agents chloroquine and hydroxychloroquine have been used with some success in the treatment of sarcoidosis, particularly for hypercalcaemia, skin disease and neurological involvement [1, 173]. Hydroxychloroquine is preferred to chloroquine because of the lower risk of ocular toxicity [1]. The recommended dose is 400 mg daily, but patients may also benefit from a 200-mg once-a-day regimen [172]. Eye examination is recommended while the patient is on treatment, usually every 6–12 months, to identify early signs of retinal damage [172].

***Anti-TNF- $\alpha$  antibodies.*** The use of biological agents that block TNF- $\alpha$ , including infliximab and adalimumab, can provide effective treatment for the diverse manifestations of sarcoidosis [174, 175]. Their use has recently become a valuable therapeutic option in severe patients where corticosteroids and/or steroid sparing agents, such as methotrexate, fail or cause unacceptable side-effects [174, 175].

Three biological agents with anti-TNF activity are commercially available. Although all three drugs are classified as anti-TNF inhibitors, the mechanism of action and route of administration vary. Both infliximab and adalimumab are monoclonal antibodies targeted against TNF- $\alpha$ , and capable of neutralising all forms (extracellular, transmembrane and receptor-bound) of this cytokine. Etanercept is a different subclass of TNF antagonists (TNF receptor-construct fusion protein), and, because of its modified form, cannot neutralise receptor-bound TNF- $\alpha$ .

Of the biological agents that inhibit TNF- $\alpha$ , infliximab has been studied most extensively in sarcoidosis with fewer reports available for adalimumab and etanercept. Two randomised, double-blind placebo trials have been performed in pulmonary sarcoidosis [176, 177]. Both showed a modest but statistically significant improvement of vital capacity in the infliximab arms. In open-label as well as randomised trials, many

patients with various manifestations of extrapulmonary sarcoidosis responded also to infliximab. Case reports suggest that this agent can be especially beneficial in neurosarcoidosis, patients suffering from severe fatigue associated with small fibre neuropathy, as well as ocular disease [174, 175, 178].

However, the appearance of these drugs for treatment of sarcoidosis should also hold some precaution. First, there are currently many unresolved questions, *e.g.* which patients will benefit most, and what treatment schedule is most effective? Secondly, all three agents are associated with increased risks for opportunistic infections, especially tuberculosis. An increase in other granulomatous infections, such as deep seated fungal infections, and bacterial infections can also be encountered [175]. Screening for prior tuberculous infection with a detailed history and PPD is required prior to administering anti-TNF therapy. Although a PPD test is recommended, many patients with sarcoidosis will be anergic. Use of IFN- $\gamma$  release assays is therefore preferable over tuberculin skin testing in these patients [175]. Latent tuberculosis is a relative contraindication to anti-TNF therapy since chemoprophylaxis in patients with latent tuberculosis may not prevent emergence of active tuberculosis during anti-TNF therapy [174, 175]. Third is the problem of immunogenicity of these drugs. Antibody formation is associated with allergic reactions and loss of response. Strategies to avoid antibody formation to infliximab are combination therapy with low-dose methotrexate, steroid administration prior to an infusion, and probably the installation of maintenance of therapy [175]. Finally, anti-TNF biological agents are relatively expensive (*e.g.* an infusion infliximab may cost around € 3,000), and reimbursement can be a problem as anti-TNF treatment may not yet be accepted as standard care for sarcoidosis by the national health insurance authorities, *e.g.* in the Netherlands.

**Local therapy.** Local immunosuppressive therapy in sarcoidosis mainly includes topical or inhaled corticosteroids. Topical corticosteroids can be tried in cases of mild involvement of the skin if there are no organ involvements that demand more systemic treatment. Corticosteroids might also been given by local injection in case of a nodule. Steroid containing eye drops are most often used for anterior uveitis. Inhaled corticosteroids can be helpful in some patients with marked symptoms of dry cough that may or may not be attributable to bronchial hyperresponsiveness due to endobronchial sarcoidosis [168]. They have no effect on lung function or chest radiographic appearance [179].

It is of note that topical tacrolimus has been reported to have been used successfully in some cases of refractory cutaneous sarcoidosis [180].

### ***Complications or associated conditions***

***Pulmonary hypertension.*** Pulmonary hypertension is a well known complication of sarcoidosis, and is associated with increased mortality. The incidence has recently been estimated at ~5% in a large Japanese series [181]. It is mostly associated with fibrosis, but may also be caused by external compression of enlarged mediastinal or hilar lymph nodes or granulomatous infiltration of the pulmonary arterioles. Sildenafil treatment has been reported to be associated with significant improvement in haemodynamic parameters [182]. Other pulmonary vasodilator therapy might also be effective, but evidence from randomised controlled trials is currently not available [183–185].

***Fungal infections and aspergilloma.*** Infections, especially tuberculosis and fungal infections, can complicate immunosuppressive therapy, especially anti-TNF therapy. Although relatively rare, opportunistic infections can occur in sarcoidosis. Aspergilloma

can occupy lung cavities of sarcoidosis patients, and invasive aspergillosis has been reported with anti-TNF therapy for various conditions [186].

***Chronic fatigue.*** Management of fatigue in sarcoidosis patients remains a major clinical challenge. Currently there are no guidelines that can help make the right management decision for any individual patient. In patients suffering from severe fatigue in the context of active disease, low-to-medium doses of immunosuppressive treatment can sometimes be of major benefit, but risk of side-effects should be carefully assessed. Recently, promising results are reported with anti-TNF- $\alpha$  drugs.

Persistent and incapacitating fatigue in some patients with a history of sarcoidosis remains an even bigger clinical challenge. Adequate management strategies for subjects with so-called “post-sarcoidosis chronic fatigue syndrome” are lacking. The central reason is the absence of scientific knowledge of the underlying mechanisms. Some pilot studies have reported successful treatment with methylphenidate, suggesting a role for the dopamine system in the brain [187, 188]. Other studies have suggested that skeletal muscle weakness and exercise intolerance is increased in patients who complain of fatigue, suggesting that exercise training might also be considered as a treatment strategy [132]. Furthermore, autonomic dysfunction related to small fibre neuropathy has been linked to fatigue. Especially in these cases, anti-TNF- $\alpha$  drugs might be of benefit.

### ***Mortality***

The overall mortality rate of sarcoidosis in large series is ~5% [172]. The most common causes are severe parenchymal disease with secondary fibrosis (vital capacity <1.5 L), and cardiac and neurological involvement [172].

### ***Lung transplantation***

Sarcoidosis is a rare but well-recognised indication for lung transplantation. The International Society for Heart and Lung Transplantation data show that up to June 2007, ~500 patients with sarcoidosis worldwide have received a single or bilateral lung transplantation (2.6% of indications for adult lung transplantation) [189]. Recurrence of disease in the donor organs of transplanted sarcoidosis patients has been reported [190]. Remarkably, the occurrence of sarcoidosis in an allogeneic bone marrow recipient, of which the donor had a history of pulmonary sarcoidosis has also been reported [191, 192].

It is noteworthy that the presence of pulmonary arterial hypertension in severe pulmonary sarcoidosis is an ominous sign and warrants referral for lung transplantation [193]. In some of these cases, heart–lung transplantation might even be indicated in case of irreversible right ventricular failure.

## Summary

Despite decades of research, sarcoidosis remains an enigmatic disorder in terms of aetiology, and also its pathogenesis is only partly understood. The prevailing hypothesis is that the disease is due to an altered or incomplete immune response to an auto- or alloantigen, such as (in-)organic particles of dust, a virus or a bacterium, that is inhaled into the lung of genetically susceptible hosts.

Sarcoidosis is probably not a single disease, but a constellation of granulomatous diseases, each with its own triggering agent, a specific human leukocyte antigen (HLA) background, and a shared multitude of genes involved in granuloma formation and resolution. In particular, the acute form of sarcoidosis, *i.e.* Löfgren's syndrome, has a very strong association with HLA-DRB1\*0301/DQB1\*0201. In addition, the onset of this syndrome is associated with spring, giving rise to speculations concerning the triggering agent.

To date, there is no single and specific test for the diagnosis sarcoidosis. It depends on the presence of compatible clinical, radiological and histological findings, and the exclusion of well-known causes of granuloma formation. Recent advances in the imaging of sarcoidosis include <sup>18</sup>F-fluorodeoxyglucose positron emission tomography and magnetic resonance imaging, especially for the detection of cardiac involvement. Although there is still no curative treatment for sarcoidosis, there are several case reports, some case series, and a randomised, controlled trial showing promising results for the use of the tumour necrosis factor- $\alpha$  blocker infliximab, especially in cases of severe and/or refractory disease. However, further studies are needed to increase our knowledge on the optimal use of anti-tumour necrosis factor treatment in sarcoidosis.

**Keywords:** Anti-tumour necrosis factor therapy, diagnosis, genetics, sarcoidosis, treatment.

## Statement of interest

None declared.

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