A tale of two cities: a comparison of sarcoidosis in London and Paris

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Summary

Two large series of patients with sarcoidosis in London and Paris have been analysed and compared for differences in ethnic background, clinical features, mode of onset and duration, chest radiographic resolution, laboratory investigation and treatment.

It is found that in both capitals, sarcoidosis is a multisystem disorder. Most organ-systems of the body are invaded, emphasizing the fact that sarcoidosis transcends boundaries of various specialties, making it a disorder of general medical interest.

The diagnosis was confirmed by various histological techniques and the Kveim-Siltzbach test was found to be positive in three-quarters of patients in both series.

Depression of delayed type hypersensitivity, abnormal serum globulins and hypercalcaemia were observed in a significant proportion of both series.

Corticosteroids were administered to one-third of the London and to two-thirds of the Paris patients. The patient has the same chance of survival whether he lives in London or Paris, for the overall mortality is about 5% in both countries.

As a gesture of goodwill towards Britain's entry into the European Common Market, we have analysed and compared a series of personally studied patients with both clinical and histological evidence of sarcoidosis in London with a group delineated by the same rigid diagnostic criteria in Paris. It is clear from these data that most organ-systems of the body are invaded, emphasizing the fact that sarcoidosis transcends boundaries demarcating various specialties, making it a disorder of wide general medical interest.

Sex, age and ethnic background

There is no particular sex predilection for in both series (Table 1) the female: male ratio is about equal. The majority are white, but an increasing number of patients from the West Indies are now attending the Sarcoidosis Clinics at the Royal Northern Hospital, London, and the Hôpital Bichat, Paris.

The majority of patients were under the age of 40 years at the time of first presentation in both London and Paris.

Mode of onset and duration

The mode of onset of sarcoidosis is pinpointed most accurately by an attack of erythema nodosum or acute uveitis or by the development of hilar adenopathy. When it is first recognized as a result of routine mass radiography, it is more difficult to identify the onset unless serial radiography indicates a change of a normal to an abnormal chest radiograph. In both series, there were five ways in which sarcoidosis was first recognized—namely routine chest radiography, respiratory symptoms, erythema nodosum or other skin lesions, and uveitis (Table 1). Asymptomatic or silent sarcoidosis, detected by routine chest radiography, was nearly as frequent as its symptomatic counterpart, particularly in Paris. This underlines the hypothesis that sarcoidosis is an iceberg syndrome in which the undiagnosed silent subclinical variant may be far more common than is realized.

Intrathoracic sarcoidosis

By international convention, the chest radiographic appearances are staged as follows:

Stage 0

A clear chest radiograph, which was noted in 6% in Paris and 16% in London.

Stage 1

Bilateral hilar lymphadenopathy is the earliest change, noted in one-third of the Paris and just under one-half of the London radiographs. It is a feature of acute, early reversible sarcoidosis, being associated with reversible lesions such as erythema nodosum and acute iritis. This is not always so, for some of these patients exhibit persistence of hilar adenopathy, and these may be associated with lupus pernio and bone cysts. Nevertheless a high incidence

TABLE 1. Features of sarcoidosis patients attending the Royal Northern Hospital, London and the Hôpital Bichat, Paris

Features		London		Paris	
		No.	%	No.	%
Total		537	100	329	100
Sex	Women	302	56	146	45
Race	White	474	86	277	84
	Negro	2	1	3	1
	Caribbean	33	6	39	12
	Other	28	5	10	3
Age at presentation (years)	Under 40	358	67	238	72
	Over 40	179	33	91	28
Onset	Routine chest X-ray	119	22	156	47.5
	Respiratory symptoms	49	9	53	16
	Erythema nodosum	150	28	22	7
	Other skin lesions	37	7	14	4
	Ocular symptoms	53	10	29	8.5
Presenting chest X-ray stage	0	85	16	20	6
	1	243	45	123	37.5
	2	129	24	162	49
	3	80	15	24	7.5
Skin tests	Positive Kveim-Siltzbach	384	82	187/243	77
	Negative tuberculin	246	55	266/329	81
Blood tests	Hyperglobulinaemia	85	34	48/212	22.5
	Hypercalcaemia	57	24	17/249	7
Treatment	Corticosteroids	185	34	224	68.5
	No steroids	352	66	89	27
Mortality	Due to sarcoidosis	25	5	6	1.8
	Due to other causes	8	1.5	7	2

of spontaneous resolution is expected at this stage in both Paris and London (Table 2).

Lung function studies show few abnormalities in Stage 1, but depression of pulmonary gas transfer factor may be demonstrated.

Stage 2

Bilateral hilar lymphadenopathy is associated with pulmonary infiltration which may be fine or coarse miliary nodulation or a fluffy cotton-wool appearance. The disparity between the extensive pulmonary involvement visible on the chest X-ray film and the paucity of symptoms is noteworthy, and quite different from diffuse interstitial pul-

monary fibrosis in which symptoms overshadow the radiographic signs. This is a transition stage between Stages 1 and 3, for, as the hilar lymph nodes shrink, the pulmonary shadowing becomes more obvious. The incidence of clearing lies somewhat between the good prognosis of Stage 1 and the poor outlook of Stage 3 sarcoidosis (Table 2).

Lung function studies show reduction of vital capacity, reduction of gas transfer, diminished lung compliance and an increase in both dead space ventilation and venous admixture. On the other hand, maximum breathing capacity is still well-maintained.

Stage 3

A small number of patients in both series had already reached a late stage of diffuse pulmonary mottling with or without fibrosis when first seen. The prognosis is poorer at this stage for there may be dense fibrosis, bulla formation, right ventricular hypertrophy and pulmonary hypertension, with corresponding physiological evidence of pulmonary insufficiency.

Extrathoracic sarcoidosis

There was close similarity in the extent and

TABLE 2. Resolution of chest radiographic changes in sarcoidosis

Stage	London		Paris	
	No. of patients	% clearing	No. of patients	% clearing
0	85	—	20	—
1	243	75	123	87
2	129	54	162	74
3	80	26	24	0
Total	537	62	329	69

TABLE 3. Frequency of involvement of various tissues in sarcoidosis in Paris and London

	Paris (329)		London (537)	
	No. of patients	%	No. of patients	%
Intrathoracic	300	90	452	84
Hilar nodes	227	70	372	70
Lung parenchyma	186	56.5	209	40
Peripheral lymph nodes	75	23	153	29
Eyes	37	11	147	27
Skin	39	12	135	25
Erythema nodosum	22	6.5	167	31
Spleen	20	6	62	12
Bone cysts	6/165	3.5	19/475	4
Salivary glands	21	6	33	6
Nervous system	14	4	38	7

frequency of involvement of other organs in both series (Table 3).

Lymphadenopathy

Hilar and peripheral lymphadenopathy and splenomegaly occur sufficiently often to demarcate sarcoidosis as a lymphoproliferative disorder, a fact which should be taken into account in any understanding of its pathogenesis.

Ocular lesions

These include acute and chronic iridocyclitis, choroidoretinitis, papilloedema, keratoconjunctivitis, conjunctival follicles, and the late complications of cataract and secondary glaucoma. There are certain well-defined clinical syndromes of sarcoidosis with eye involvement. Acute iritis, erythema nodosum and bilateral hilar lymphadenopathy have a benign self-limiting course, whereas chronic iridocyclitis, associated with lupus pernio or skin plaques, bone cysts and pulmonary fibrosis, is persistent and troublesome. Keratoconjunctivitis sicca with, or without, parotid and lacrimal gland enlargement, mimics Sjögren's syndrome. Parotid gland enlargement, anterior uveitis and facial nerve palsy constitute Heerfordt's syndrome.

Skin lesions

Lesions other than erythema nodosum include lupus pernio, plaques, scars, keloids and transient maculopapular eruptions.

Erythema nodosum due to sarcoidosis is associated with bilateral hilar lymphadenopathy, polyarthralgia and occasionally acute iritis. It predominates in women of the child-bearing years of life, often associated with pregnancy or lactation, suggesting a hormonal factor in its genesis. It has a predilection for Irish women in London.

Neurosarcoidosis

Central nervous system involvement occurred in

less than 10% of either series (Table 3). Facial palsy is a frequent neurological presentation either alone or with other cranial palsies or with papilloedema. Other presentations include peripheral neuritis, myopathy, meningitis and space-occupying brain lesions.

Histology

Whenever possible the clinical diagnosis of sarcoidosis should be confirmed by histology. The diversity of tissues involved is matched only by the diversity of techniques used for obtaining tissue samples. This is well-illustrated by the different techniques employed in Paris and London (Table 4). Irrespective of the technique used, the earlier it is sought the more likely is a positive biopsy obtained. At the late stage of hyaline fibrosis it may be difficult to find the characteristic epithelioid granulomas which characterize the earlier stage of sarcoidosis.

The Kveim-Siltzbach skin test was also positive in about three-quarters of patients in both series (Table 4). We have found it to be a reliable, specific, safe and simple outpatient technique invaluable in delineating multisystem sarcoidosis from the numerous other causes of nonspecific local sarcoid-tissue reactions.

TABLE 4. Initial histological confirmation of sarcoidosis

Tissue	No. positive	
	Paris	London
Bronchial biopsy	142	
Lymph node	46	100
Skin	14	82
Liver biopsy	11	76
Others	31	42
Total	244	300
Positive Kveim-Siltzbach test	187/243 = 77%	384/466 = 82%

Other investigations

Tuberculin reaction

The tuberculin skin test reaction was negative to all conventional strengths in 81% of the Paris series and in 55% of the London series (Table 1). Those patients exhibiting some degree of tuberculin hypersensitivity had only weakly positive tests. Insensitivity to tuberculin, and to other antigens like dinitrochlorobenzene, is only a relative and not an absolute characteristic, nor does the insensitivity appear to be as profound as it is in malignant lymphoproliferative disorders.

Biochemical abnormalities

Serum globulin levels above 3.5 g/100 ml and serum calcium levels above 11 mg/100 ml were

noted in a significant proportion of both series (Table 1).

Treatment

Corticosteroids were indicated in one-third of the London and in two-thirds of the Paris series (Table 1). Corticosteroids suppress new granuloma formation, so the treated patient should, on theoretical grounds, have less scarring than he might if granulomas are allowed to multiply unhindered.

The absolute indications for corticosteroid therapy are ocular involvement; persistent hypercalciuria; hypersplenism; alveolar-capillary block; involve-

ment of the central nervous system, myocardium, and lungs; disfiguring cutaneous, salivary and lacrimal gland lesions; facial palsy and troublesome polyarthralgia.

Mortality

The patient seems to have the same chance of survival whether he lives in London or Paris (Table 1). The overall mortality was about 5% in both countries, some of whom died directly as a result of sarcoidosis and the remainder due to unrelated diseases.