

A study of Sarcoidosis in South East Queensland, Australia: (Part 1)

Dr F Heyworth and Dr RKA Allen

Abstract

This paper was presented 40 years ago, and contains valuable information about the epidemiology of sarcoidosis in the State of Queensland, Australia. Unfortunately, it was not submitted for publication. From 1948 until 1975 this predominantly white population underwent compulsory mass survey chest X-rays for the control of pulmonary tuberculosis. Estimates of the sample years 1965, 1966 and 1967 showed that approximately 90% of the eligible adult population could be expected to participate in such surveys. Information was collected on all known patients diagnosed as having sarcoidosis who attended the Brisbane Chest Clinic, Chest Hospital or were admitted to other major Brisbane hospitals from December 1st 1962 to November 30th 1967. This 5-year period included those found during a complete mass X-Ray survey of S.E. Queensland, where lay the main concentration of population in Queensland, carried out between December 1962 and May 1966. A total of 209 patients resulted from this search. As a result, a total of 209 patients were diagnosed with sarcoidosis. In the three years (1965-7), a total of 1,044,988 people were surveyed with a massive number of 948,839 chest radiographs and an incidence of sarcoidosis of 10.1 per 100,000 was found. However this is probably a significant underestimate of the whole “sarcoid” population possibly by a factor of 50% as many patients with sarcoidosis have normal chest radiographs and many are asymptomatic. The condition was more common in younger males and older females and the incidence is similar to that of data from the state of Victoria. The paper outlines the clinical and epidemiological features of patients as well as treatment and follow-up over a three-year period with resolution of disease in the majority of patients. Over twenty years of follow-up of a larger cohort from a similar population, a stable incidence of 8.35/100,000 was found in Victoria.

Key Words

Sarcoidosis, epidemiology, mass survey chest radiograph, incidence, clinical features, treatment, follow-up

Background

The late Dr Anil Patel, the Director of the Queensland Chest Clinic, gave a copy to the second author in the early 1990's to assist him in a prospective study on sarcoidosis in Queensland at the Prince Charles Hospital. The author's name was not on the paper but there was a clue to the author's name as a hand-written name on the manila folder in which it was found. It was rediscovered in the second author's filing cabinet in 2006 at the time of writing a paper based on the 1990's data published previously as abstracts¹⁻⁸ and a paper on neurosarcoidosis⁹. The second author traced Dr Frederick Heyworth who is now in his late seventies and lives in retirement in Perth, Western Australia having moved there to work as a physician in the W.A. Chest Clinic. The paper has been revised by the second author in consultation with Dr Heyworth and complements the second paper on the same subject done in the 1990's (Part 2). It is unlikely two such studies on sarcoidosis in Queensland will be done again. Hence these papers are of historical interest as well as casting light on the nature of this condition in the Australian population.

This paper contains invaluable data which is unlikely to be replicated as it was conducted in a bygone era when essentially the whole adult population (approximately 90%) underwent over a period of years, compulsory chest radiographs for the mass screening of tuberculosis. This radiographic “trawling” revealed to the Health Department Medical Officers a wide range of

pathologies, mostly asymptomatic and including sarcoidosis which was manifest most typically by hilar adenopathy with or without pulmonary infiltrates. Thus it was possible to obtain a fairly accurate incidence of this condition which was apparent radiographically. However it would have failed to reveal those patients with no radiographic abnormality and which accounts for approximately another 50%¹⁰. The incidence of erythema nodosum was similar in the two studies. The second author has also added the invaluable data of Dr. Gordon Price who studied sarcoidosis patients at the Victorian Mass X-ray Division of the Victorian Health Commission.

The study on sarcoidosis was a by-product of this public health initiative and was in effect a “low power” view of sarcoidosis done with a relatively crude instrument, the chest X-ray. The latter study done 30 years later in the 1990’s is a “close up” of the same condition using more modern diagnostic tools and with more data on each individual. It does not give data on prevalence or incidence. The information on age and gender interestingly showed the same distributions as in the later study by Allen in the 1990’s i.e. that sarcoidosis occurs more often in Queensland in two cohorts of younger males and older females. It is uncommon to find two such complementary studies spaced thirty years apart on sarcoidosis. Today it would be unthinkable to conduct a mass survey epidemiological study using chest radiographs where the compliance was as high as 90%.

Introduction:

Sarcoidosis is a condition which Scadding¹¹ described as a disease affecting multiple organs characterized by the presence in all affected organs or tissues of epithelioid cell tubercles without caseation. One of the ways in which sarcoidosis comes to light is by mass radiography surveys. Kerley¹² estimated that for every patient presenting with symptoms, at least five are detected by mass radiography without symptoms. Because sarcoidosis thus exists hidden in an individual who feels well, its incidence should be greater where mass x-ray surveys of the population are carried out¹³.

Figures taken from the then reports of the Director-General of Health for Queensland (1965, 1966) that at least nine out of ten individuals of the adult population of Queensland could reasonably be expected to be x-rayed during the compulsory mass x-ray surveys. By checking the number of microfilms taken against the estimated number of persons over 14 years, it was possible to estimate the percentage of adults x-rayed (Table 1).

Therefore in Queensland one might expect that during a microfilm survey at least 90% of individuals with pulmonary sarcoidosis at that time would be discovered.

Table 1. Percentage of adults who had a chest radiograph between 1965-1967

	Year	Estimated No. of persons over 14 yrs in area surveyed	Number of microfilms taken	Percentage adults “x-rayed”
(a)	1965	376752	351456	93.3%
(a)	1966	350675	304128	86.7%
(b)	1967	317561	293255	92.3%
Mean		348329	316280	90.8%
Totals		1,044,988	948,839	90.8%

(a) Annual report of the Director General of Health and Medical Services, Queensland, 1966 and 1967

(b) Figures supplied by Director of Tuberculosis, Queensland.

Methods

Information was collected on all known patients diagnosed as having sarcoidosis who had attended the Brisbane Chest Clinic or Chest Hospital within the previous five years. These include those discovered during a complete survey of the population of South- East Queensland, carried out between December 1962 and May 1966. In addition information was also obtained on patients admitted to the major hospitals in the area during the five years from 1 December 1962 to 30 November 1967.

Results:

Age and gender

The study revealed a total of 209 patients; 93 males and 116 females. Using the age as that obtained at first interview or admission, the most prevalent age cohort was in the 19-29 year in both sexes. There was a greater proportion of females over 40 years of age (42.24%) than was the case in the male patients (25.8%) (Table 2). No other significant component could be isolated, although it appears likely that there was an excess of females in the "60 and over group".

Table 2. Age distribution of patients surveyed with sarcoidosis

	Male	Female
Under 20	10	13
20 – 39	59	54
40-59	20	39
60 & over	4	10
	93	116

$\chi^2 = 13.07$, 3 d.f., $P < .01$ (Significant)

The component of chi square for "Under 40" versus "Over 40" is $\chi^2 = 6.13$, 1 d.f., $P < .02$ (significant)

Incidence and race

Of the total of 209, 105 were discovered during the period of the aforementioned complete mass x-ray survey of the population. Using the population total for S.E. Queensland for 1966 this gave an incidence of 10.1 per 100,000.

The crude data on racial breakdown of the patients was known in 169 patients as follows: Australian born 152 (89.9%), non-Australian born 15 (8.9%), and Australian native 2 (1.2%). The corresponding racial distribution of the Queensland population at the time of the study (1966) based on the Commonwealth Bureau of Census and Statistics were 86.9%, 12% and 1.1% respectively.

Source of patients

The majority of the patients were discovered by mass radiography (128/209). There were another 19 patients where the condition was found accidentally by routine x-ray examination, making a total of 147 in this category, or 70.3% of the total. In 3 patients sarcoidosis was found in organs at post-mortem and in none of these was sarcoidosis the cause of death. In 8 patients their source of diagnosis was uncertain and the remaining 51 (24.4%) of patients were direct referrals or diagnosed because of the presence of symptoms.

Tuberculin Skin Testing

The results of tuberculin skin testing by the Heaf or Mantoux (usual dose 10 tuberculin units) methods were known in 183 patients. Of these 154 (84.15%) were negative and 29 (15.85%) were positive. Sixteen patients were known to have had B.C.G vaccination previously of whom 5 (31.25%) were positive and 11 (68.75%) became negative to tuberculin skin testing.

Erythema Nodosum

Nine patients were known to have had erythema nodosum and 8/9 were female and the age range of the 9 patients was very narrow; between 23 and 29 years. The number of cases involved is too small for statistical analysis but the female preponderance consistent with clinical experience¹⁴. In addition 4 of these female patients complained of arthralgia at the same time.

Histological Evidence

Histological confirmation of sarcoidosis was found in 82/209 subjects with 125 diagnosed on clinical grounds without histological support. Among the 82 with histological evidence were two patients with positive Kveim Test as this was still available in Queensland at the time. The most favoured histological examination was lymph node or lung biopsy. In two patients it was uncertain whether histological confirmation had been obtained or not.

The prevalence of anergy to the tuberculin skin test was as follows; there were 56 (86.15%) with histological proof and negative skin test and nine (13.85%) with histological proof and a positive skin test. In those without histological proof, 90 had negative skin tests (83.05%) and 20 (16.95%) had positive skin tests.

Chest x-ray Findings

The radiographic stage found depends upon the particular point in the disease process at which the chest radiograph is taken. Many patients when first seen had had microfilms taken in previous surveys. By re-examination of these chest radiographs it was often possible to prove that the patient had previously had a normal chest radiograph. Following this, the changes were the usual ones of pulmonary sarcoidosis. Stage I being hilar enlargement often with upper mediastinal expansion especially on the right side. Stage II included various pulmonary shadows which were most commonly miliary or mottled changes of a generalised kind most obvious in the mid zones. These changes sometimes became confluent or nodular. Stage III was resolution of the hilar enlargement but with the remaining pulmonary shadows which then resolved in due course. A number finally showed minor residual fibrotic strands and a smaller proportion showed persistent major changes attributed to chronic disease (Stage IV).

The simplest category found was that of hilar enlargement followed by reversion to normal without development of shadows in the lung fields. James¹⁵ referred to this type as subacute sarcoidosis. In this category there were 41 patients whose chest radiographs had reverted to normal. In these, the shortest period taken to reach normality was seen to be 3 months; the longest period was 36 months.

There were 14 patients in whom hilar enlargement was later followed by pulmonary shadows and of these, three subsequently developed a normal chest radiograph leaving 59 which were first seen at Stage II. Of these, 29 were subsequently found to have a normal chest radiograph.

There were 62 patients who were first seen with a Stage III chest radiograph. The remainder had previous Stage I & II changes. Of these, 24 were subsequently reverted to normal.

There were a number of patients in which the radiographic changes became chronic. An arbitrary time of 3 years continuing abnormality has been used to separate this group.

There were 35 patients with abnormalities continuing after 3 years, 18 female & 17 male. Of these, 13 (72.2%) of the 18 females were aged 40 or over and 7 (41.1%) of the 17 males were aged 40 or over. A total of 15 patients presented with Stage III x-rays, 14 patients with Stage II, and 6 patients with Stage I.

Respiratory Function Tests

Respiratory function tests were done in 86 patients. Of the 86 patients, abnormal ventilatory results were found in 30. These included 26 (30.2%) of the restrictive type. Diffusion tests were carried out in 73 patients of which 38 (52.05%) of these showed a reduced diffusion capacity.

Calcium Metabolism

Results of calcium estimations were known in 139 patients. Taking upper normal values as up to 11 mg% for serum calcium and a 24-hour urinary calcium excretion per 24 hours of 400mg, there were 37 (26.6%) patients with one or more abnormal results. Two patients had nephrocalcinosis and another patient had a history of ureteric calculus.

Extra-thoracic sarcoidosis

There were 6 patients without radiological or histological evidence of pulmonary disease. One patient had cutaneous sarcoidosis and another patient was found to have splenic sarcoidosis accidentally at cholecystectomy. Another patient who died from carcinomatosis was found to have incidental sarcoid granulomata in the spleen at post-mortem. One patient who died from a perforated duodenal ulcer was found to have sarcoid changes in the para-aortic glands. Another patient who died from myocardial infarction was found to have sarcoidosis affecting the lungs, liver and intestinal glands. In a similar case the patient died from a pulmonary embolus but was found to have sarcoidosis in the lungs and lymph nodes at post-mortem. One patient had hepato-splenomegaly with hypercalcemia and hypercalciuria leading to nephrocalcinosis with a normal chest x-ray.

Deaths where sarcoidosis may have contributed

- (1) Male 76 years Died from a superimposed pneumonia.
Diffuse pulmonary changes known to be present
46 months before death. Widespread disease proven at post-mortem.
- (2) Female 36 10 years history with diffuse lung changes but not proved sarcoidosis.
Death reported as cor pulmonale due to sarcoidosis. Post-mortem
histology of lung was reported as showing "honeycomb lung".
- (3) Male 54 Positive lung biopsy. After 5 years committed suicide. He was known to
be dyspnoeic but respiratory function tests were not done.
- (4) Female 65 Persisting diffuse lung changes from 1957. Not proven sarcoidosis.
Followed up for 10 years before death reported from pneumonia and
cardiac failure due to sarcoidosis.
- (5) Female 65 Post-mortem diagnosis. Disease found in spleen and lung. Cause of death
reported as acute tracheo-bronchitis.

- (6) Female 67 Died of renal failure. At post-mortem sarcoidosis was found affecting lungs, lymph glands and spleen. Whether sarcoidosis caused the renal failure is not known.

Treatment with corticosteroids

Thirty-four patients were known to have been treated by steroids. Improvement of the chest x-ray appearances was almost invariable. In only one patient was failure to improve noted. Aside from this in three patients x-ray clearing was noted during pregnancy when the plasma cortisol is elevated. Calcium abnormalities improved in all five patients there were two pregnancies during the course of the disease with x-ray improvement in each occasion. Ventilatory tests showed improvement in eight patients and no improvement in six. Diffusion capacities were improved in two patients but not so in four patients. Skin lesions improved in one patient treated for these.

Discussion

This survey of local experience reveals the more obvious manifestations of sarcoidosis. It forms the basis for future work to develop individual aspects of the problem of sarcoidosis which is shown in the sequel to this paper by the second author (Part 2). There appeared to be little difference between incidence in the Australian Native and the remainder of the population but a significant increase was found in females over 40.

The incidence of sarcoidosis in SE Queensland in the mid 1960's of 10.1 per 100,000 is remarkably similar to the 9.2 found by Marshman in the state of Victoria, Australia over the period from 1959-1962, also as result of mass chest radiographs for the screening of pulmonary tuberculosis¹⁶. A total of 1,571,011 chest radiographs were examined by the Mass X-ray Division in Victoria and although the title of the Marshman's paper uses the word "prevalence", the body of the short paper uses incidence. As these were new cases diagnosed but clearly present for some time, there may be some debate whether this constitutes "prevalence" or "incidence". In any event the methods used in the two states (viz. Queensland and Victoria) were essentially the same and new cases were identified over the years of the respective studies.

In a paper by Price¹⁷ presented at the Twelfth Australian Tuberculosis Clinical Conference (29 September – 3 October 1980) in Melbourne, Victoria, "Sarcoidosis: A Twenty Year Review" reported the prevalence of sarcoidosis in Victoria from 1956-1975 detected by chest radiograph. Dr Price acknowledged the assistance of Dr Ray Marshman and Dr Peter Bull for their permission to undertake this study. Dr Gordon Price who worked at the Victorian Chest Clinic gave this data to the second author. During that period, 10,396,523 chest radiographs were done with approximately 600,000 per annum from 1965 onwards and with 95% of adults complying as checked by electoral rolls. The "prevalence rates" (*sic.* incidence) remained unchanged at 8.35/100,000 over the twenty years of the study while the incidence of active pulmonary tuberculosis fell from 106/100,000 in 1956 to 11/100,000 in 1975. The incidence of carcinoma of the lung rose from 20-25/100,000 in the late 1950's to 40/100,000 in 1975.

This study by mass radiograph revealed a number of asymptomatic subjects who had sarcoidosis. It would have been desirable to have histological confirmation in a greater percentage of patients. The histological results confirmed that the disease can be present even with positive tuberculin skin tests although the majority were negative.

The use of steroids was found to produce radiographic clearing but did not necessarily improve respiratory function tests. As the disease is often self-limiting with spontaneous remissions, steroids should be reserved for the chronic cases with deteriorating respiratory function tests or other serious organ involvement. It was noteworthy that two patients had histories of a sibling

also having had the disease. Unfortunately, histological confirmation of the disease was not obtained in either of these patients.

From this survey one might expect an “average” patient with sarcoidosis in S.E. Queensland will show hilar or mediastinal lymphadenopathy with or without pulmonary mottling. Sometimes, strikingly abnormal chest radiographs may be found in totally asymptomatic patients. A restrictive type of ventilatory defect is common along with a reduced diffusing capacity. Complete radiographic resolution of the disease may be expected within three years in the majority of patients. However, particular attention should be paid to those showing evidence of more indolent and chronic form of the disease and objective measurements such as lung function should be used in follow-up to help direct appropriate management.

Acknowledgements

References

1. Allen RKA, Dean VR, Burstow DJ, Masterson ML. A prospective study of cardiac sarcoidosis in an Australian population. Proceedings 12th World Congress on Sarcoidosis. 1995; 63:P/153.
2. Allen RKA, Fong KM, McNeil KD. Male predominance in 205 Australian patients with sarcoidosis. Aus NZ J Med 1991; 21: 652 (suppl 2).
3. Allen RKA, McIndoe NC, Fong KM, McNeil KD. The presenting features of sarcoidosis in 313 Australian patients. Aus NZ J Med 1992 (April, Annual Scientific Meeting).
4. Allen RKA, Mills GD, Timms P. Search for chlamydia pneumoniae in tissue from patients with sarcoidosis by PCR. Proceedings World Association of Sarcoidosis and Other Granulomatous Disorders, Kensington, London. 1995; 63:P/045.
5. Allen RKA, Sellers RE and Sandstrom PA. Neurological involvement in sarcoidosis. A prospective Australian study. Proceedings World Association of Sarcoidosis and other Granulomatous Disorders, Kensington, London. 1995; 63:P/154.
6. Allen RKA, Smith I, Fong KM, McNeil KD. A Proposal to establish a worldwide database for sarcoidosis. Sarcoidosis 1992; 9: 267-268 (suppl 1).
7. MacGinley RJ, Allen RKA. Sarcoidosis in an Australian aborigine and a Torres Strait islander. Sarcoidosis 1997; 14: 83-85.
8. Mills GD, Allen RKA, Timms T. Chlamydia pneumoniae DNA is not detectable within sarcoidosis tissue. Pathology 1998; 30: 295-298.
9. Allen RKA, Sellers RE and Sandstrom PA. A Prospective Study of 32 Patients with Neurosarcoidosis. Sarcoidosis Vasc Lung Dis 2003; 20: 118-125.
10. Romer FK, Paulsen S, Antonius V, Nielsen JL and Hommelgaard P. Sarcoidosis in a Danish “Amt” – a retrospective epidemiological study of sarcoidosis in Ringkøbing Amt in the period 1960 to 1969. Dan Med Bull 1973; 20: 112-120.
11. Scadding JG. Discussions on Sarcoidosis. Proceedings of the Royal Society of Medicine. 1956; 49: 799.
12. Kerley P. Discussion on Sarcoidosis. Proceedings of the Royal Society of Medicine. 1956; 49: 803.
13. Wegelius C. Case Findings & Roentgen Diagnostics of Pulmonary Sarcoidosis” Third International Conference on Sarcoidosis. Acta Med Scand 1964 (Suppl 425); 176: 92-95.
14. Douglas AC. The Prognosis of Early Sarcoidosis. Third International Conference on Sarcoidosis. Acta Med. Scand. 1964 (Suppl 425); 176: 92-95.
15. James DG. Proceedings of the International Conference on Sarcoidosis. Amer Rev Resp Dis 1961; 84: 14.
16. Marshman RSA. Prevalence of pulmonary sarcoidosis in the state of Victoria, Australia. Acta Med Scand 1964; Suppl. 425: 167-168.
17. Price G. Sarcoidosis: A twenty year review. Proceedings of the Twelfth Australian Tuberculosis Conference, Melbourne, 29 September – 3 October 1980: 131-135.
18. Price G. Sarcoidosis in Victoria, Australia. Proceedings of the World Association of Sarcoidosis and Other Granulomatous Diseases, 15-20 October 1995. London. 45, P/081.