Sarcoidosis in Turkey: 1954-2000

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Background: Sarcoidosis is a multisystemic disease of unknown etiology. The presentation and frequency of different organ involvement can vary according to race, geographical location and gender. Because of the multiorgan involvement and its mimicking nature, the diagnosis is usually a challenge, even to specialists. Therefore, knowledge of the epidemiologic features of the disease is important.

Methods: The first case report of sarcoidosis in Turkey was published in 1954. We obtained data from case series by hand searching of journals and congress abstract books on pulmonary medicine between 1954 and 2000. Series of 5 or more cases were included in our compilation of data.

Results: Data for 1327 patients with the diagnosis of sarcoidosis were obtained from 29 reports. There were nearly twice as many females as males with the disease in these case series. Most of the patients were at stage 1 or 2 at the time of diagnosis. Peripheral lymph node enlargement was reported in 119 patients, skin involvement in 22 and nervous system involvement in 12 patients. Erythema nodosum was reported in 137 patients. Serum angiotensin-converting enzyme was elevated in 52% and the tuberculin skin test was positive in 24% of patients. Organ biopsies seemed to be the preferred diagnostic method in the initial papers while recent papers revealed the value of obtaining a bronchoscopic biopsy.

Conclusion: Despite several limitations of our study, this is the first compilation of 46 years of data on sarcoidosis in Turkey. Further studies on the geographical distribution and incidence and prevalence are needed for our country.

Key words: Sarcoidosis, Turkey, neurosarcoidosis, erythema nodosum, epidemiology, diagnosis

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More than a century ago an English dermatologist, Hutchinson, described the first case of sarcoidosis. The systemic nature of the disease was not recognized at that time. Sarcoidosis was described as a form of skin disease. During the last century, investigators have become aware of the multisystemic nature of the disease. In the past two decades, they have also discovered that sarcoidosis is not confined to certain populations. Whether the disease is under-recognized in some other countries due to the high prevalence of other granulomatous disorders is still a matter of discussion. Epidemiological data from India and other eastern countries reveal that sarcoidosis is not as rare as previously thought in developing countries.[1-4]

In Turkey, a country that bridges Europe and Asia, the first case of sarcoidosis was described in 1954.[5] As more physicians came to recognize the disease, the number of reports increased correspondingly, but so far there are no data on the incidence and prevalence of sarcoidosis in the Turkish population. We gathered all published case series since the first report in 1954 with the aim of profiling the disease in Turkey.

Methods

Since there is no established Turkish medical literature index, all available Turkish pulmonary journals published from 1954 to January 2000 were identified and searched manually. Abstracts presented in international and national meetings were hand searched from the abstract books. We selected all articles and abstracts containing five or more sarcoidosis cases. To ensure that most published articles were found, we asked investigators with experience in this field about other publications on this subject. To avoid duplication of data collected and published at different times, the authors were contacted to clarify which publication should be included in the current study. Some articles focused on particular aspects of sarcoidosis and did not report other outcomes. Those articles were analyzed collectively based on the specific measures reported. Therefore, for any given outcome (like organ involvement frequencies), articles without data on that outcome were excluded to avoid underestimation of that outcome. To assess the status of sarcoidosis, publications before 1990 were analyzed separately and compared to the data for the entire time period (1954 to 2000).

Results

We found 32 reports that met our inclusion criteria.[6-37] After exclusion of articles identified as earlier reports of the same data, a total of 29 reports were selected, 11 of which were abstracts. The goal was to get specific numbers and a general idea of several features of sarcoidosis for the Turkish population. The 29 reports included data on 1327 patients. The female/male ratio was 1.83/1. Average ages ranged between 29.8 to 48.38 years. Unfortunately, peak incidence could not be calculated since age was reported as mean data in most of the articles.

Fever was reported in 46 patients. Fatigue and weight loss could not be determined precisely since some of the symptoms were reported as constitutional symptoms. Pulmonary symptoms were the most common symptoms. Hemoptysis was reported in 4 patients. None of the patients were reported to have mycetoma.

Among 931 patients in 15 publications that mentioned tuberculin skin test results, 110 patients (24%) had a reactive tuberculin skin test. Serum angiotensin-converting enzyme (ACE) was evaluated in 10 papers with 185 cases; it was elevated in 52% of the patients. Hypercalcemia was reported in 25 (6.6%) of 378 patients. Other laboratory values such as hematological and other biochemical values were not evaluated due to lack of data on the laboratory threshold levels.

Nervous system involvement was reported in 12 patients, including 5 with central nervous system involvement and 2 with facial nerve palsy (Table 1). Diabetes insipidus was reported in 3 cases. Peripheral lymph node enlargement was reported in 119 patients. Skin involvement was reported in 22 patients. Erythema nodosum (EN) was reported in 137 patients. No gastrointestinal tract involvement, (esophagus, appendix, rectum) was reported. Bone involvement was recognized in 22 patients. In 127 patients, arthralgia was present. However, no deforming arthritis was reported. Radiological stages were mentioned in 20 papers (Table 2). Most patients were at stage 1 or 2 at the time of diagnosis. Bronchoscopic methods seemed to be the most popular diagnostic approach, especially in the last decade (Figure 1).

Among 32 publications, only 7 were published before 1990.[6-12] As shown in Figure 2, the number of patients increased tremendously in the last decade. Before 1990, clinical-radiological diagnosis and scalene and peripheral lymph node biopsies seemed to the choice in diagnosis (Figure 1). In the last decade, bronchoscopic biopsy seemed to be the most popular tool for diagnosis. Video assisted thoracoscopic (VATS) biopsy has been used in a small group of patients, but only within the last decade.

Discussion

Sarcoidosis is a multisystemic disease of unknown etiology. Diagnosis is usually based on a compatible clinical presentation and supportive histological evidence of noncaseating granulomas. The diagnosis is usually a challenge, even for specialists, because of the presentation, the frequency of different organ involvement, and the mimicking nature of the diagnosis. Therefore, knowledge of the epidemiological features of the disease is important so that physicians can know what to expect. There are no estimates of incidence and prevalence in the Turkish population because the Ministry of Health does not require reporting. That the disease is not as rare among the Turkish population as once thought is evident from the increasing number of reports. The lack of data on incidence and prevalence as well as differences in presentation and frequency of different organ involvement, led us to summarize the data from these various reports.

The rate of positive tuberculin skin tests (23.6%) was higher than reported rates for sarcoidosis. This might be explained by routine BCG (Bacille-Calmette-Guerin) vaccination in Turkey, or the high incidence of tuberculosis

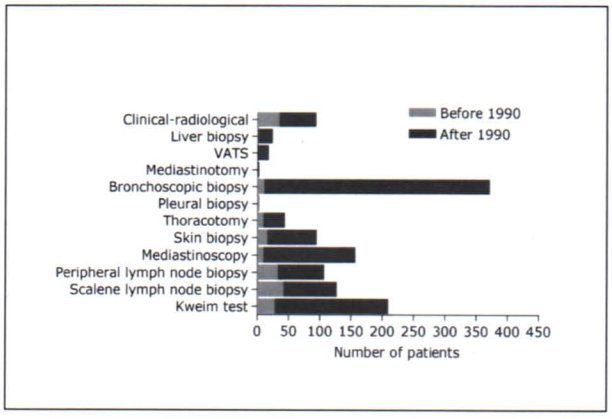

Figure 1. Diagnostic procedures used in the assessment of sarcoidosis from 1954 to 1989 and from 1990 to 2000.

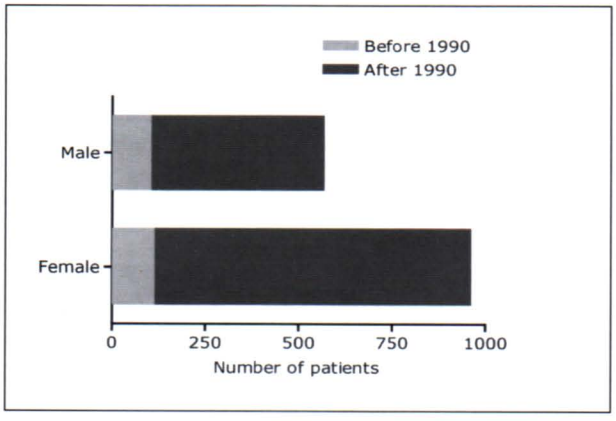

Figure 2. The female/male ratio among sarcoidosis patients from 1954 to 1989 compared with 1990 to 2000.

Table1. Organ involvements other than pulmonary parenchyma and intrathoracic lymph nodes in sarcoidosis patients described in the Turkish medical literature.

Organ involved	Number of cases
Eye	66
Joint	31
Bone	22
Muscle	1
Heart	2
Tonsils	1
Pleura	6
Liver	62
Spleen	47
Renal	2
Nervous system	12
Lacrimal gland	14
Erythema nodosum	137
Skin	22
Salivary gland	51

Table 2. Radiological stages in sarcoidosis patients described in the Turkish medical literature.

Stage	No. of Cases
0	74
I	466
II	448
III	144
Unidentified	195

(TB). However, in India, a country with a high TB rate, 90% of patients had a negative tuberculin skin test.[3] Some of our patients with a positive tuberculin skin test may not have had sarcoidosis, but most of the patients were diagnosed histologically, as shown in Figure 1.

Clinical evidence of myocardial involvement was reported in 5% of sarcoidosis patients, which seems less than in other countries. Though electrocardiography is a common procedure, routine Holter monitoring was not performed and therefore underreporting of cardiac involvement may be possible. For clear evidence of cardiac involvement, autopsy studies are required.

The rate of erythema nodosum formation was 18.95%, which is higher than the 11% reported for six other European cities.[2] Reported rates of erythema nodosum formation among sarcoidosis patients in other parts of the world include 53% in Scandinavia, 31% in Britain, 33% in Barcelona, and 2 to 4% in Japan.[2] Neurosarcoidosis was diagnosed in 12 patients (0.9%). This number is much less than that reported in other series.[38-40] Stern and colleagues reported a neurosarcoidosis incidence of 5.1% with 85% of cases being African-American.[41]

Ocular involvement is reported in 11 to 83 percent of patients.[1] In the reports we examined, ocular involvement was not that common. In the study by Sen et al routine ocular examination was performed in 34 sarcoidosis patients and eye involvement in only 3 (8.8%).[28] In a study by Aytemur et al, only 3 (5%) had eye involvement among 60 patients having a routine eye examination.[22] Eye involvement in the Turkish population is not as high as reported for other countries. Eye involvement was reported as 27% for London, 32% for Tokyo, 20% for New York and 4% for Eastern Europe.[2] The low rate of eye involvement in Turkey, which is similar to rates in East Europe, might reflect geographical relationships in the etiology of the disease.

Lymph node biopsies seemed to be the most popular diagnostic method before 1990. Bronchoscopic methods have become more prominent in the last decade since their introduction. The decreased rate of clinical-radiological diagnosis after 1990 can be explained by the eagerness of physicians to get histological confirmation. Also the inherent difficulties in diagnosing sarcoidosis in a region with high TB rates might explain why the physicians obtain a biopsy. Although evaluation of therapy results would be very enlightening, we did not gather detailed descriptions of drug therapy due to the lack of data on follow-up. However, steroids were the therapy of choice.

There was a tremendous increase in reported cases after 1990. This increase can be due either to under-recognition of sarcoidosis before this period or an increased incidence of the disease in recent years in Turkey. Increased awareness of the problem and greater recognition of the disease due to advances in the investigational methods in the last two decades seems to be most likely. As the recognition of the disease is increased, large centers are being formed for referral of sarcoidosis patients. Also registries are being formed in these units to get the exact data on the epidemiology of the disease.

Our study has many limitations. The non-standardized format of the publications and inclusion of all the articles can cause underestimation of some of the organ involvement rates or the most popular diagnostic methods. To avoid underestimation of organ involvement frequencies we only evaluated papers that included these measures while we were calculating the frequency rates. The absence of therapy and follow-up is another limitation of our study. The absence of a well-established Turkish medical literature index might also restrict us from accessing and identifying some of the publications. However, we tried to minimize this risk by communicating personally with investigators in addition to very careful and thorough hand searching. Excluding the

case reports may lead to a distorted clinical picture of the disease since the patients presented in these reports would have unusual clinical presentations. We excluded case reports since the purpose of the study was to develop an idea of the general profile of the disease and also to reduce the risk of duplicating the number of patients.

In summary, this study shows that recognition of sarcoidosis in Turkey has increased greatly, especially in the last century. Despite limitations, our study is a useful compilation of 46 years of sarcoidosis data. Further studies on the geographical distribution and incidence and prevalence are needed for our country.

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