

Extrapulmonary tuberculosis, epidemiology and patterns in Saudi Arabia

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ABSTRACT

Annual incidence rates of extrapulmonary tuberculosis have been increasing over the last few years in the Kingdom of Saudi Arabia. True rates may even be higher due to incomplete reporting. Diagnosis of this condition requires high clinical suspicion, special diagnostic procedures, special staining, and culture media for acid fast bacilli. Delayed diagnosis results in increasing morbidity, mortality, and cost to the health care system. Particularly in areas of high endemicity of *Mycobacterium tuberculosis*, clinicians should be aware of the various forms of extrapulmonary tuberculosis. The available epidemiology and patterns of various forms of extrapulmonary tuberculosis in the Kingdom of Saudi Arabia are presented in this review.

Keywords: *Mycobacterium tuberculosis*, extrapulmonary tuberculosis, epidemiology.

Neurosciences 2002; Vol. 7 (3): 153-158

Extrapulmonary tuberculosis (TB) comprises a significant proportion of patients with TB. It requires tissue sampling to confirm diagnosis by histopathology or microbiology. High level of clinical suspicion is important, surgical specimens are sent for special stains and inoculated in special culture media for acid fast organisms. These requirements may not be performed or available in many health care facilities. Subsequently, diagnosis of extrapulmonary TB was delayed compared to the rate of diagnosing pulmonary TB. The difficulties associated with diagnosing extrapulmonary TB were attributed to the fact that several forms of extrapulmonary TB lack any of the localizing symptoms or signs. Cutaneous anergy to purified protein derivative (PPD) was noted in 35 to 50% of patients with some forms of extrapulmonary TB, and no clinical or radiological evidence of pulmonary TB could be found in up to one 3rd of these patients.¹ The result was more severe disease, morbidity, mortality and cost to the health care system.

Considering the reporting difficulties of TB in general, particularly extrapulmonary TB, the size of the problem at the community level may be underestimated using the current reporting system. In this review, we attempt to present epidemiology data of extrapulmonary TB in the Kingdom of Saudi Arabia (KSA) and review the reported distribution and patterns of the disease.

Epidemiology of extrapulmonary tuberculosis. Although, reported pulmonary TB in KSA was compiled, and annual rates were calculated as early as 1970,² extrapulmonary TB annual rates started coming regularly in 1989. During the first few years of reporting, the rate was dropping. The annual incidence rate of reported extrapulmonary TB dropped to 1.7 cases per 100,000 population in 1993 nation-wide.³ This rate had been steadily increasing to 4.7 cases per 100,000 population in 1997, **Figure 1.**⁴ During the same time frame, reported pulmonary TB rates were decreasing.⁴ The increasing rates of

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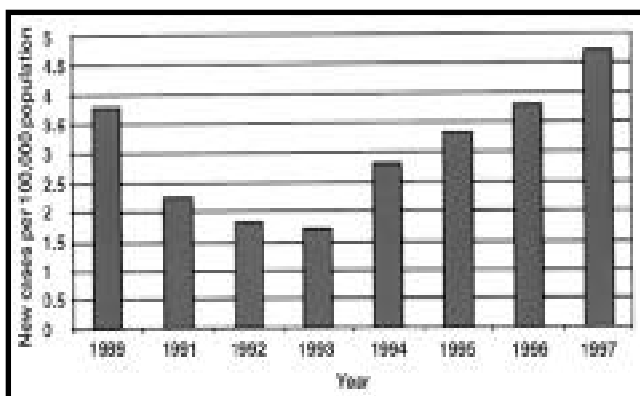


Figure 1 - Reported annual incidence rates of extrapulmonary tuberculosis in the Kingdom of Saudi Arabia between 1989-1997.

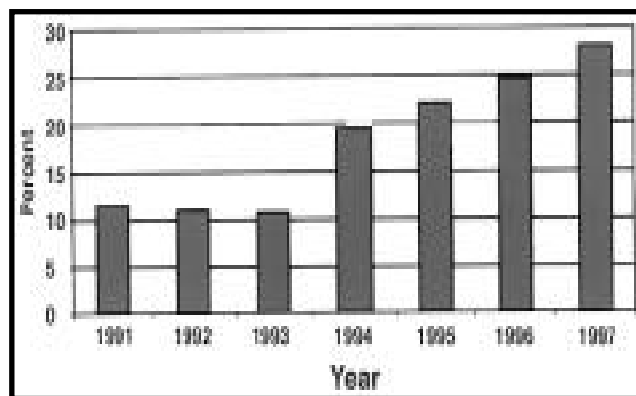


Figure 2 - Extrapulmonary tuberculosis depicted as percentage of all reported tuberculosis cases in the Kingdom of Saudi Arabia, 1991-1997 (Adapted from annual Health Report of the Ministry of Health, Kingdom of Saudi Arabia).²

reported extrapulmonary TB may have resulted from better diagnostic facilities identifying more cases and better reporting by health providers. Extrapulmonary TB represented 28.2% of all reported TB cases in 1997.⁴ In 1991, this proportion was 11.7%.³ In fact, the annual incidence rates of extrapulmonary TB was not the only increasing parameter in the 1990s, the proportion of all reported TB cases that was related to an extrapulmonary involvement was also increasing to around 3 folds, **Figure 2**. The increase in the proportion of all TB cases that have extrapulmonary TB was also noted in other countries. In the United States of America (USA), 8% of all cases of TB represented extrapulmonary infection in 1964. It increased to 15% in 1981, and 18% in 1990 without a clear explanation.^{5,6} The proportion of TB cases representing extrapulmonary involvement varied widely between hospitals and at different time periods in KSA reflecting variations in referral patterns. In 1982, Froude and Kingston⁷ reviewed 162 cases diagnosed with extrapulmonary TB between 1979 and 1981 from King Faisal Specialist Hospital and Research Centre (KFSHRC), KSA.⁷ The ratio of pulmonary and extrapulmonary TB was 1:1 during the 27-month period of the study. In another early report, Shanks et al⁸ reviewed TB cases in a general hospital in Riyadh, KSA for 9 months between 1981 and 1982. Out of 47 cases, pulmonary TB was documented in 57% of cases, followed by lymphadenopathy in 19% of cases. The remaining 24% was other extrapulmonary cases including spine, bone, and abdomen. In a recent report from Riyadh in 2001, extrapulmonary TB was culture-confirmed in 2 out of every 3 cases at KFSHRC.⁹ Looking at other areas of the country, Mokhtar and Salman¹⁰ published details of 125 patients with extrapulmonary TB from Jeddah, KSA. Extrapulmonary TB was found in 15% of all cases identified. More recently, Zaman¹¹ reviewed isolates

of *Mycobacterium tuberculosis* (*M. tuberculosis*) from Jeddah. Between 1987-1989, extrapulmonary TB accounted for 59% of all cases.¹¹ Very few reports detailed the distribution of various forms of extrapulmonary TB. Froude and Mokhtar^{7,10} had detailed the distribution in 2 reports from Riyadh and Jeddah. Although they cover around the same time periods, they have variations in the distribution of extrapulmonary forms and definitions. **Table 1** summarizes the percent distribution of the 2 reports. Froude,⁷ noted the delayed diagnosis of extrapulmonary TB chest radiological findings were consistent with TB in 37% of them, and PPD was positive in 50% of patients tested. The morbidity associated with extrapulmonary TB was high, 17 patients (11%) had spinal cord damage related to vertebral involvement.

Patterns of extrapulmonary tuberculosis. Lymphadenitis. Although, TB adenitis was the most common extrapulmonary TB,¹⁰ literature on this disease is limited and late from KSA.¹²⁻¹⁴ Cervical lymphadenopathy is commonly related to TB.¹⁴ Out of 212 cases with cervical lymphadenopathy in the southwest region of the country between 1987-1990, 45% had caseating granuloma, 30% had reactive hyperplasia, and 15% had malignant lymphoma as reported.¹⁴ Purified protein derivative was positive in 94% of TB patients compared to 21% of patients with malignant disease. The mean age was the same, 31-32 years, but more females had tuberculous lymphadenopathy whereas more males had malignant lymphadenopathy. Constitutional symptoms of fever, anorexia and weight loss were more common in TB patients compared to malignancy. The wrong diagnosis of tuberculous lymphadenopathy was made in 28% of patients with malignant lymphadenopathy. Of the patients with tuberculous lymphadenitis, 21% were initially given a different diagnosis. In another series,

Table 1 - Percent distribution of various extrapulmonary forms of tuberculosis in 2 series.^{7,10}

Site of tuberculosis involvement	Froude and Kingston ⁷ (%)	Mokhtar and Salman ¹⁰ (%)
N of cases	162	125
Lymph nodes	(22)	(54)
CNS	(36)*	(1)
Gastrointestinal	(16)	(16)
Urogenital	(5)	(16)
Bone and joints	(4)	(10)
Others	(17)	(3)

* - included spinal/vertebral tuberculosis, N - number, CNS - central nervous system

the disease was noted at an early age, affects more females (2:1), was associated with abnormal chest x-ray in 14% of patients, and 92% of had a positive PPD test.¹³ Lymphadenopathy that is not considered reactive lasting for few weeks has to be investigated. It is very important to attempt to establish a histopathological and microbiological diagnosis of lymphadenopathy by fine needle aspiration. This procedure is safe, rapid and reliable for diagnosis.^{15,16} It will assist in making early diagnosis, initiation of appropriate therapy and avoid unnecessary treatment.

Central nervous system. Tuberculosis of the central nervous system was the most common type of extrapulmonary TB in a large series from Riyadh.⁷ In a review of central nervous system (CNS) infections in a university hospital in Riyadh, covering in-patient admissions between 1983 and 1986, TB was the most common cause.¹⁷ Out of 121 cases with CNS infection, 39 cases (32%) were related to TB, mostly adults, followed by pyogenic meningitis in 38 patients. Intracranial and intraspinal tuberculoma were seen in 14 patients. The cranial lesions presented with intracranial hypertension or focal neurological manifestations. Six patients had multiple lesions. Intracranial lesions were thought to be related to TB as it is a very common problem in KSA. There were 13 patients with spinal lesions who had cord compression. Eleven patients had tuberculous meningitis, 5 of them had miliary TB. In a different report by Bahemuka and Murungi¹⁸ addressing tuberculous CNS infections, morbidity was significant and mortality was 5%. Two patients with tuberculous central nervous infection out of 39 in the series died, one had meningitis and the other had a cerebral tuberculoma. Lesions demonstrating a vascular enhancement and surrounded by marked edema associated with relatively less severe clinical manifestations than would have been expected from the size and location of the lesion, may benefit from empirical anti-tuberculous therapy and conservative

management as advocated by some investigators in Riyadh.¹⁹ However, in the same institute; KFSHRC, and due to referral pattern, only 10-15% of all cerebral mass lesions were parenchymal tuberculomata.²⁰ Tuberculous meningitis seems to be rare in children. Among 140 children with meningitis in Riyadh, only 4 had TB.²¹ Other forms of CNS TB are also infrequent in children. Out of 39 cases with CNS TB, only 2 were children.¹⁷ None of the 2 children were among the 11 patients who had meningitis. Spinal TB remains a significant type of neurological and bone TB. Over a 5-year period ending in 1982, 123 confirmed cases were seen in one hospital in Riyadh.²² Again, this is a disease of adults as only 4 (3%) were children. There were 137 areas of spinal involvement, thoracic spine was involved in 56% of patients, followed by lumbar spine in 26%, and cervical spine in 14%. Six patients had no bone involvement but rather spinal cord disease alone. Around 50% of the time 2 adjacent bodies were affected. Paravertebral abscess was seen on plain radiography in 58% of patients. Encroachment on the vertebral canal was seen in 38% of patients and neurological impairment was seen in 42% of patients. The positive yield by smear and culture was noted in 60% of patients undergoing fine needle aspiration on out-patient basis. Tissue diagnosis should be attempted in all patients with spinal lytic lesions, as 100 patients over the same time period thought to have TB of the spine, were confirmed to have other causes. Of note, bone scanning was unreliable for spinal lesions in this series.²²

Abdominal and gastrointestinal tuberculosis. Abdominal TB accounted for 16% of all extrapulmonary TB in 2 large series from Riyadh and Jeddah.^{7,10} Several other reports focused on abdominal or gastrointestinal TB. The largest series was published from the Armed Forces Hospital, Riyadh, KSA. Gastrointestinal TB was the 2nd most common type of TB after pulmonary disease among 820 patients with TB between 1982 and 1990.²³ It accounted for 16% of all TB cases. The 130 patients with TB affecting the alimentary tract had small bowel involvement in 34% of them, tuberculous peritonitis in 31%, large bowel in 22%, hepatic in 15% and upper gastrointestinal tract in 9%. Sixteen patients (12%) presented with acute surgical abdomen requiring emergency intervention. Twelve patients died (9%), 3 after surgery and the rest due to causes not related to TB. Radiological evidence of pulmonary involvement was noted in 31 patients (24%). Al Karawi et al²³ noted large bowel TB in 22% of patients with extrapulmonary TB. They make a note of how rare Crohn's is in KSA and that one of their patients had both. In a large review of 1600 lower alimentary tract biopsies at the same hospital between 1979-1985, TB accounted for 0.6% of patients compared to 0.2% who had Crohn's.²⁴

Diagnosis has to be documented in patients with large bowel disease as treatment for Crohn's may impact negatively on TB. Isbister and Hubler²⁵ found 6 patients who were thought to have TB of the bowel to have Crohn's out of 101 patients in Riyadh, with inflammatory bowel disease. In the same hospital 10 cases of colonic TB were reported between 1980 and 1988.²⁶ Crohn's is relatively rare in KSA,²⁷ an empirical trial of anti-TB therapy without steroids may be an option. Favorable response to chemotherapy should be expected after the first 2 months if TB is the cause of the bowel disease.²⁶ In another series, Al-Quorain et al²⁸ reported on 65 cases of abdominal TB from the Eastern Province between 1984-1990 mostly Saudis 69% (45 patients). Mean age was 30 years, duration of symptoms was 6 months, PPD was positive in 70% of tested patients, and abnormal chest radiology was found in 27% of patients only. Most patients (46%) had peritoneal disease, followed by ileocecal involvement in 26% of patients, then hepatic involvement in 17%. During the same time period, there were 297 exploratory laparotomies, 31 patients had caseation necrosis and evidence of TB. Laparoscopy was performed on 48 patients, 21 of them had diagnostic features of TB. Five patients died after initiation of therapy. Imaging is a common diagnostic tool for abdominal illnesses, the radiological findings in TB of the abdomen have been studied in KSA.²⁹ Over a 5-year period from 1986, Denton²⁹ reviewed all abdominal TB cases from a hospital in Jeddah. Twenty-three patients were diagnosed with abdominal TB. Purified protein derivative was positive in 85% of patients tested. Pulmonary involvement as evidenced on chest radiology was seen in 43% of patients. Tuberculous peritonitis was the most common form seen in 52% of patients. Ultrasound and computerized tomography (CT) scan of the abdomen were useful in identifying lymphadenopathy, ascites, and omental thickening. The most useful diagnostic tool for tuberculous peritonitis was laparoscopy and peritoneal biopsy. Ultrasound of the abdomen and CT scan were also helpful in identifying focal lesions in liver and other organs, and directing percutaneous biopsies. The alimentary tract was affected in 30% of the cases and barium studies were useful for this type of involvement. Peritoneal TB was reported among 41 cases from one center in KSA.³⁰ Alrajhi et al³⁰ found that patients who received corticosteroids along with antituberculous therapy had less complications in terms of intestinal obstruction and need for surgery. However, certain safeguards have to be considered in these patients before corticosteroids are added to empirical antituberculous therapy.^{30,31} Hepatic granuloma deserves a special mention as it is encountered often in clinical practice. These lesions were seen in 59 out of 404 liver biopsies (15%) between 1982-1988 in the Eastern Province.³² Satti et al³² tried to

determine an etiology for each of these biopsies. Bilharziasis accounted for 54% of the cases, followed by TB in 32% of the cases, 7% were due to brucellosis. Only 3 patients had caseating granuloma. If no *Schistosoma* ova are seen in a liver biopsy showing granuloma and *Brucella* serology is negative, TB is the most likely cause in KSA.

Bone and joint tuberculosis. Tuberculosis of the bones and joint is a common type of extrapulmonary TB. Worldwide, out of 20,000 cases of extrapulmonary TB, 19% were bone and joints related.³³ It constituted between 4 and 10% of extrapulmonary TB cases in 2 large series from KSA.^{7,10} In a detailed report of bone and joint TB in KSA, El Titi et al³³ reviewed 68 cases diagnosed between 1982 and 1985 in Riyadh. They included spine cases as bone. These were up to 57% of all bone and joint cases. Knee joint was involved in 14% of patients followed by hip in 10%. Diagnosis was mostly confirmed by sampling. Histopathology was diagnostic in 91% and culture was positive in 60% of sampled patients.

Pleural tuberculosis. Pleural effusion is a well-known manifestation of TB. In developed countries, it is considered the 2nd most common form of extrapulmonary TB accounting for 24% of cases in 1990.⁵ In contrast, in both of the 2 large series of extrapulmonary TB, pleural effusion was not mentioned. It was probably considered part of pulmonary disease.^{7,10} In a prospective review of all pleural effusion cases over 5 years ending in 1991 in the Eastern Province, TB was the most common cause accounting for 37% of the 201 patients matching the definition.³⁴ It was followed by neoplastic etiology in 18%, then parapneumonic and congestive cardiac failure in 14% of patients for each. All cases of tuberculous pleural effusion were unilateral. The mean age of patients with tuberculous effusion was lower than the mean for all patients with pleural effusion, 33 years versus 43 years. Of note, only one of every 3 patients with tuberculous effusion was a national. The same investigators reported the clinical details of patients with tuberculous effusion.³⁵ Out of 253 patients with pleural effusion, 89 (35%) were related to TB. Purified protein derivative was positive in 92% of patients, and only 3.4% had abnormal chest radiography. Diagnosis was confirmed using pleural biopsy. Histopathology was consistent with TB in 64% and increased to 74% after 2nd biopsy. Culture for TB was positive from the biopsy in 69% of patients compared to 10% positive culture rate from pleural fluid. In another report of tuberculous pleurisy from Riyadh, 10 out of 61 (16%) patients with tuberculous pleurisy had paradoxical response with increased effusion after antituberculous chemotherapy without corticosteroids.³⁶

Miliary tuberculosis. Miliary TB refers to the radiological pattern of the lungs in patients with

unchecked hematogenous dissemination of *M. tuberculosis*. Disseminated TB may not be associated with miliary disease in pulmonary radiography. The 2 terms are used interchangeably in the literature.³⁷ From one institute, KFSHRC, disseminated TB accounted for 14% and 10% during the late 1970s and late 1990s.^{7,9} The disease has been quantified in one series from KSA.³⁸ Dahmash et al³⁸ noted that in elderly patients, miliary TB was found in 20% of all TB cases. The largest series of miliary TB was from Riyadh.³⁷ Out of 780 patients with TB between 1990-1997, 47 (6%) had miliary disease. The mean age for these patients was 61 years. The most common associated condition was diabetes mellitus, noted in 26% of the patients. Miliary pattern on chest radiology was noted in 89% of the patients. Mortality was 21% and occurred within the first month of diagnosis. The investigators believe that reactivation is an important feature in their patients as 25% of them had history of TB.

Other forms of extrapulmonary tuberculosis. Among all cases of extrapulmonary TB, pericardial involvement was noted in 3% of patients from one hospital in Riyadh,⁷ and 1% from a hospital in Jeddah.¹⁰ Tuberculosis is the most common cause of constrictive pericardial disease requiring intervention in KSA. It was found to be the cause of 83% of patients undergoing pericardectomy for constrictive pericarditis between 1981-1989 in Jeddah.³⁹ Another less frequent form of extrapulmonary TB that has been noted and reported from KSA is urogenital.^{10,40,41} Chattopadhyay et al⁴⁰ reported on 40 female patients with genital TB over 5 years between 1979 and 1983. They constituted 0.45% of all gynecological admissions, and 4.2% of 945 infertile women. The disease was cured in 77% of patients with anti-TB chemotherapy and complicated with tubal pregnancy, and absence of uterine conception. Prostatic and epididymal TB was reported to constitute 16% of extrapulmonary TB.¹⁰ Other rare forms had been reported and are mentioned to remind clinicians that TB can present with countless ways and involvement especially in an area of high endemicity. Examples include TB of the breast,⁴² parotid glands,⁴³ the pancreas,⁴⁴ the sternum,⁴⁵ and even neonatal TB.⁴⁶ The availability of better access to care and diagnostic facilities should be coupled with better clinician awareness about extrapulmonary TB and its forms. Surrogate markers of TB like PPD and chest radiology may not be helpful for extrapulmonary TB. Tissue diagnosis by histopathology and culture for acid fast bacilli should be attempted. Drug-resistant *M. tuberculosis* is of concern and not limited to pulmonary disease.^{9,47} The recent increase in rates and proportions of extrapulmonary TB in KSA make the importance of early diagnosis and treatment to impact even on health care cost and planning.

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