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A high prevalence of culture-positive extrapulmonary tuberculosis in a large Dutch teaching hospital

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ABSTRACT

Background: In the Netherlands the incidence of tuberculosis (TB) has increased during the last decade. Growing immigration and international travel were important determining factors. To determine if this has resulted in altered clinical manifestations of the disease, we assessed the clinical spectrum of all TB cases diagnosed at our hospital in the period 1994 to 2000.

Methods: All culture-proven TB cases during the study period were retrospectively reviewed for clinical and demographic data.

Results: Sixty-five patients were identified. Solitary pulmonary TB was diagnosed in 33.9%, extrapulmonary TB in 51.8% and combined pulmonary and extrapulmonary TB in 14.3% of all cases. Patients were of foreign descent in 78.6% of all cases. Incidence peaked between 15 to 45 years. Decreased immunity was an important determining factor in the older patients. Presenting symptoms were mostly aspecific causing an important doctor's delay in establishing the diagnosis in 25%. Mortality was 3.6% and isoniazid resistance 3.6%

Conclusions: Our data suggest an increase in the percentage of extrapulmonary TB concomitantly with an increasing percentage of patients of foreign descent. Because of aspecific presenting symptoms, TB was often diagnosed late. Treatment is mainly hindered by non-compliance and a high index of suspicion is necessary in making the diagnosis.

INTRODUCTION

Tuberculosis (TB) remains one of the largest global health problems of our time. It accounts for approximately three million deaths each year and 1.7 billion people, one third of the world's population, are infected with *Mycobacterium tuberculosis*. This reservoir of infected persons results in eight million new cases of TB each year.[1-3] The spread of HIV/AIDS, the breakdown in health services and the emergence of multidrug-resistant *M. tuberculosis* are contributing to the impact of the disease.[2-6] The growing epidemic led the World Health Organisation to declare TB a global emergency in 1993.

In the Netherlands the incidence of TB decreased during the course of the 20th century. However, in the last decade an important increase occurred, with numbers rising from 1227 TB cases in 1987 to 1535 cases in 1999.[7,8] Immigration and international travel seem to be the most important determining factors.[3,7,9,10] Besides alterations in incidence and demographic characteristics, the presentation of TB has changed. In the US the proportion of extrapulmonary TB remained fairly constant in the period 1977 to 1981. However, during subsequent years, as the incidence of pulmonary TB declined at a faster rate than that of extrapulmonary TB, the proportion of extrapulmonary TB gradually rose, with its incidence rising from 14.4% of all TB cases in 1977 to 17.5% in 1986.[11-13] In the Netherlands extrapulmonary TB accounted for 576 (31%) of all TB cases in 1999, compared with 383 cases (24%) in 1993. When nationality is taken into account, the incidence of extrapulmonary TB is much higher among patients of foreign descent than among natives of the Netherlands.[7]

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In Rotterdam, and in other large cities, the incidence of TB is much higher than in rural areas. The higher incidence of TB and the growing number of newly diagnosed patients can be explained by the increasing number of people belonging to risk groups, such as immigrants and the socially marginalised.[7,14] To test the hypothesis whether the clinical presentation of TB has changed in recent years due to its altered epidemiology, we retrospectively reviewed all cases of bacteriologically confirmed TB and compared our data with published series from the literature.

PATIENTS AND METHODS

Rijnmond-Zuid Medical Centre, location Clara, is a 553-bed hospital and serves a community of 147,197 persons, accounting for 205,316 outpatient contacts each year. Patients come from Rotterdam (592,673 inhabitants), as well as from the surrounding areas. It is the largest haemodialysis centre in the area and approximately 40 residents are being trained. The hospital is not a centre for HIV/AIDS. These patients are referred to the nearby university hospital.
By screening the database of the microbiology laboratory of our hospital, we identified all patients who had one or more positive culture results for *Mycobacterium* species and were treated between 1 January 1994 and 31 August 2000. TB cases which were not bacteriologically confirmed were not included. We reviewed the records of all thus identified patients for demographic and clinical data, such as age, gender, country of birth, presenting symptoms, localisation of TB and comorbidity. Treatment and follow-up were studied, as well as *Mycobacterium* species and resistance to antituberculosis drugs. Pulmonary TB was defined as a positive culture from sputum or bronchoalveolar lavage (BAL) fluid. Pleural and mediastinal TB were considered as extrapulmonary localisations of TB.
During the study period two solid culture media were used, the agar-based Middlebrook 7H11 and the egg-based Löwenstein-Jensen media. Histological material was evaluated with both a fluorochrome stain with phenolic auramine and a Ziehl-Neelsen stain. Other specimens were evaluated with Ziehl-Neelsen staining only.

RESULTS

Bacteriological studies

Between January 1994 and August 2000 a total of 63 patients with a positive culture for *Mycobacterium* species were identified. Seven cultures were atypical *Mycobacteria*. These patients were not included in the study. Of the seven cases of atypical mycobacterial infections, one patient was a two-year-old girl, who developed an abscess on her shoulder after local BCG vaccination. Culture demonstrated an *M. bovis* BCG. After surgical incision and drainage the patient recovered and no further treatment was necessary. Three patients had a positive culture for *M. avium*. All three patients had either chronic obstructive pulmonary disease (COPD) with chronic corticosteroid use or an underlying malignancy. *M. avium* caused no serious pulmonary illness and the patients received no antimycobacterial treatment. Two of the other patients had an infection with *M. malmoense* and one had *M. kansasii*. Mycobacterial infection caused pulmonary illness in these three patients and all were treated with tuberculostatic drugs. Again, a malignancy or COPD with chronic corticosteroid use were present in these patients. In 56 patients a *Mycobacterium* from the *M. tuberculosis* complex was identified. Two patients had an infection with *M. bovis*. A patient from Morocco presented with a painless swelling of a cervical lymph node. The lymph node was excised and histological examination showed a caseating granuloma. Biopsy culture and Mantoux testing were positive. The other patient was a native from the Netherlands and presented with slowly progressive shortness of breath, weight loss and non-productive cough. She had been treated for TB some fifty years before. Chest X-ray demonstrated unilateral pleural effusion. Pleural biopsy showed granulomatous, caseating inflammation. *M. bovis* was isolated from pleural fluid. Culture was positive for *M. tuberculosis* in 54 patients. Seven patients carried a strain of *M. tuberculosis* which was resistant to one antituberculosis drug: two to isoniazid (INH), one to rifampicin, three to streptomycin and one to pyrazinamide. No multidrug resistance was observed. Of the seven subjects with drug resistance, six were of foreign descent. None of these patients had a history of previous TB treatment.

A total of 66 positive cultures were obtained. Nine patients had a positive culture from two or more localisations. *M. tuberculosis* was most frequently cultured from lymph nodes (25.8%), sputum (22.7%) and BAL fluid (18.2%). The remaining positive cultures were obtained from an abscess (12.1%), pleural fluid (7.6%) or another source in 13.6%. Of the 15 sputum culture-positive patients, seven were smear-positive (Ziehl-Neelsen method) and five were smear-negative. Of the 12 positive BAL cultures, microscopic examination was positive in four patients and negative in six. Information on microscopic examination could not be retrieved in five patients.

Demographics

Twenty-seven patients were male with a mean age of 40.2 years (range 18 to 75 years) and the 29 females had a mean age of 40.7 years (range 13 to 83 years). Of all 56 patients, 21.4% were natives of the Netherlands and 78.6% of foreign descent. Patients from Turkey, Morocco and Surinam, the three largest ethnic groups in the Netherlands, accounted for 5.4, 10.7 and 12.5% of all

cases, respectively. Of the remaining patients 21.4% were of African (other than Morocco) and 25% of Asian descent. Two patients were of European origin.

Clinical manifestations

As illustrated in *table 1*, presenting symptoms were often aspecific (cough, fever and wasting). Of all patients, solitary pulmonary TB accounted for 19 cases (33.9%). A total of 29 patients were diagnosed with extrapulmonary TB, representing 51.8% of all cases. In eight patients (14.3%) a diagnosis of both pulmonary and extrapulmonary TB was made. Localisation and frequency of extrapulmonary TB are summarised in *table 2*.

Table 1

Presenting symptoms in 56 patients with tuberculosis

SYMPTOM	NUMBER	PERCENT
Cough	28	50.0%
Fever	23	41.1%
Wasting	23	41.1%
Lymph node swelling	15	26.8%
Malaise	11	19.6%
Dyspnoea	9	16.1%
Haemoptysis	6	10.7%
Abscess	5	8.9%
Abdominal complaints	5	8.9%
Bone pain	5	8.9%
Night sweating	5	8.9%
Chest pain	3	5.4%
Other	6	10.7%

Table 2

Localisation and frequency of tuberculosis in 56 patients[*]

ORGAN SYSTEM	NUMBER	PERCENT
Pulmonary	19	33.9%
Pleural	7	12.5%
Lymphatic	18[§]	32.1%
Cervical	14	25.0%
Mediastinal	5	8.9%
Intra-abdominal	4[‡]	7.1%
Colon	1	1.8%
Small bowel	1	1.8%
Peritoneum	3	5.4%
Skeletal	6	10.7%
Vertebral column	4	7.1%
Clavicle	1	1.8%
Knee	1	1.8%
Skin/abscess	5	8.9%
Cerebrum	1	1.8%
Total	**62**	

[*] *Six patients had two EP localisations of TB,* [§] *one patient had both cervical and mediastinal lymphatic TB,* [‡] *one patient had both small intestinal and colonic TB.*

Tuberculin status

Of the 56 patients, 12 underwent tuberculin testing (Mantoux method). Nine patients were considered to have a positive result (>10 mm induration) and three were negative. Of these three patients one had pulmonary TB, one had tuberculous peritonitis and one tuberculous pleuritis. Immune suppression was present in one of the three patients, who was suffering from multiple myeloma and was treated with prednisone and melphalan. He had a history of pulmonary TB some 50 years before.

History of previous TB

Six patients had in the past been treated for TB. In two patients (aged 36 and 72 years) TB had been diagnosed in another hospital several years before. Due to non-compliance both had been treated inadequately. Four patients (two aged 67, one 75 and one 80 years) were treated for TB in a sanatorium some 30 to 50 years earlier. One of them received prednisone and melphalan shortly before reactivation of TB occurred. All four patients were natives of the Netherlands.

Associated medical problems/underlying diseases

Of all patients, 39 had no underlying disease or any other medical problems. Six patients had diabetes mellitus, three patients had a malignancy and four patients were receiving cytostatic or immunosupressive treatment. Five patients were on chronic intermittent haemodialysis. Five patients had other associated medical problems such as drug or alcohol abuse. No patients were found to be positive for HIV or suspected of having HIV/AIDS. It should be noted that routine HIV screening was started after 1996.

Delay in diagnosis

In 60.7% of all cases a diagnosis of TB was made within four weeks following admission. In 14.3% the diagnosis was established between four and eight weeks. In 17.9% (ten cases) it took between eight weeks and six months before a definitive diagnosis of TB was made. Of these ten patients, two had pulmonary TB, six had extrapulmonary TB and two had both types of TB. In 3.6% (two cases) it took between six months and a year before a diagnosis of TB was made. Both had extrapulmonary TB. It took more than a year to establish the diagnosis in two patients. One patient had extrapulmonary TB and one pulmonary TB.

Treatment

Fifty-five patients (98.2%) received INH and 54 (96.4%) rifampicin. Thirty-eight patients (67.9%) were treated with ethambutol and 48 (85.7%) with pyrazinamide. None of the patients were treated with streptomycin. Sixteen patients (28.6%) received antituberculous treatment for a duration of six to nine months and 26 patients (46.4%) were treated for nine to 12 months. One patient was treated for more than

one year. Five patients had not completed the full course of treatment by the time of writing. Of six patients exact information on the duration of treatment could not be retrieved. Four patients suffered from polyneuropathy, five had liver enzyme abnormalities and five patients had other complications. Two patients died. One patient had multiple myeloma with renal insufficiency complicated by pneumonia. Culture from BAL fluid revealed *M. tuberculosis* post mortem. The second patient was on chronic intermittent haemodialysis and developed a tuberculous chest abscess. On top of uraemic and diabetic polyneuropathy he developed a severe polyneuropathy due to tuberculostatic drugs leading to respiratory insufficiency. After five months of mechanical ventilation the patient died of sepsis.

Follow-up

Of all patients, 31 (55.5%) completed their full course of antituberculosis treatment without any complications. Non-compliance occurred in 11 (19.6%) patients, leading to complete loss to follow-up in six patients and prolongation of treatment in five.

DISCUSSION

The increased TB incidence in the Netherlands during the last decade was mainly caused by immigration from countries of high TB prevalence.[7,8] The aim of our study was to assess the clinical spectrum of TB and to determine whether these epidemiological and demographic changes have led to a different clinical presentation of the disease. We found 78.6% of all patients with culture-proven TB to be of foreign descent, which is a high percentage compared with the national data. In 1998, patients of foreign descent accounted for 60% of all TB cases in the Netherlands.[7]

In a recent study conducted at Amsterdam's university hospital, patients of foreign descent were found to account for 70% of all TB cases.[10] In comparison, Smelt *et al.* found 25% of TB patients to be of foreign descent in their study conducted in the early eighties.[15] The national data of 1985 showed 30% of all TB cases to be of foreign descent.[7] Our results reflect the demographics of the Rotterdam area, where people of foreign descent made up approximately 40% of the total population in 2000 (source: www.cbs.nl) and are consistent with the view that TB is becoming increasingly concentrated in urban areas.[16-18]

The age distribution showed a peak in (young) adults and in the elder population. Patients in the younger age group were most often of foreign descent and had primary infections without associated medical problems. Elderly patients were mostly born in the Netherlands. Reactivation of TB accounted for 80% of all TB cases in Dutch patients of over 60 years of age. Decreased immunity, due to underlying diseases or immunosupressive treatment, was an important determining factor in this age group and is consistent with the view that the elderly are a population at risk for TB.[19,20]

Presenting symptoms were mostly aspecific as described by other authors.[12,16,18] This can be attributed in part to the remarkably high number of solitary extrapulmonary TB (51.8%) in our population. Another 14.3% of all patients had extrapulmonary combined with pulmonary TB. In the Netherlands, the incidence of extrapulmonary TB was 36% in 1998 with combined pulmonary and extrapulmonary TB accounting for 8% of all cases.[7] Extrapulmonary TB is more frequent among patients of foreign descent (40%) than among natives of the Netherlands (30%).[7] *Table 3* summarises the results of 20 studies from various parts of the world.[10-13,15,17-19,21-32] On average the percentage of extrapulmonary TB varies between 20 and 40%. The higher percentage we observed could be explained by the large number of patients of foreign descent and the fact that in the Netherlands immigrants routinely undergo screening for pulmonary TB by means of chest radiography. Extrapulmonary TB will not often be diagnosed in this way.

An important doctor's delay in diagnosis occurred in 25% of the patients. We found three main reasons for this delay. Sometimes inconclusive histology or negative culture results together with aspecific presenting symptoms led the clinician to consider diseases other than TB, such as sarcoidosis, Brucellosis or cat-scratch disease. After failure to respond to the instituted therapy, and repeated biopsies and cultures, TB was diagnosed. A second group of patients experienced delay because of concomitant diseases masking TB. Respiratory tract infections caused by pathogens other than *Mycobacteria* were most often implicated. Treatment failure or recurrence of symptoms led to reconsideration of the differential diagnosis and a more thorough search for TB. Finally, a low index of suspicion by general practitioners or other medical specialists caused late referral to the departments of pulmonology or internal medicine. Weir *et al.* observed a similar range in delay in diagnosis, which varied from days to years, with a median of two months.[13] A lack of experience with TB on the part of physicians due to its decreasing incidence in the postsanatorium era has been implicated.[24] The elderly and patients not belonging to traditionally high-risk populations appear to be at greatest risk of having unsuspected disease.[19]

Sputum culture was positive in 55.6% of cases of pulmonary TB and culture from BAL fluid in the remaining 44.4%. Approximately 40% of patients with pulmonary TB were found to be smear positive on direct microscopic examination. Reviews on sputum analysis in the diagnosis of TB have found the incidence of smear positivity ranging from 32 to 55.3% and culture positivity from 70 to 96% of patients.[18,33]

Table 3
Trends since 1962 in the prevalence of extrapulmonary (EP) TB in various parts of the world

NO.	AUTHOR	REFERENCE	COUNTRY	STUDY PERIOD	N	% EP TB
1	Alvarez *et al.*	11	USA	1968-1977	1593	4.5
2	Weir *et al.*	13	USA	1970-1980	104	37.0
3	Goldstein *et al.*	21	Canada	1977-1980	487	12.9
4	Rose *et al.*	17	USA	1980	70	3.5
5	Page *et al.*	22	USA	1976-1981	108	31.0
6	Mehta *et al.*	12	USA	1977-1981	7172	11.3
7	Byram *et al.*	23	United Kingdom	1973-1982	1673	20.0
8	Porat *et al.*	24	Israel	1979-1982	26	69.0
9	Brett *et al.*	25	New Zealand	1980-1982	235	11.0
10	Smelt *et al.*	15	The Netherlands	1980-1984	76	35.5
11	Counsell *et al.*	19	USA	1983-1987	38	18.0
12	Hurley *et al.*	26	Australia	1962-1989	482	42.9
13	Pang *et al.*	27	Australia	1980-1989	485	21.5
14	Svane *et al.*	28	Norway	1974-1993	32	65.6
15	Kuyvenhoven *et al.*	29	The Netherlands	1993	1582	24.5
16	O'Reilly *et al.*	18	Ireland	1991-1995	107	22.0
17	Juffermans *et al.*	10	The Netherlands	1993-1995	100	43.0
18	Gilad *et al.*	30	Israel	1992-1997	249	20.0
19	Melzer *et al.*	31	United Kingdom	1996-1997	47	57.0
20	Bonadio *et al.*	32	Italy	1996-1998	88	15.9
21	Hesselink *et al.*		The Netherlands	1994-2000	56	51.8

The percentage of INH-resistant *Mycobacteria* was low (3.6%) and comparable with the national number of 6 to 7%.[7] All strains of single-drug resistant *Mycobacteria*, except for one, were isolated from immigrants from areas of high TB prevalence. None of these patients had been treated for TB in the past. Non-compliance was an important problem and all cases occurred in patients of foreign descent. Side effects of antituberculosis drugs caused non-compliance in two patients. In addition, one patient experienced worsening of a psychiatric disorder, causing loss to follow-up. Close cooperation with the public health service often led to early detection of defaulting and to measures ensuring completion of treatment, such as directly observed therapy (DOTS). Recently, Borgdorff *et al.* found an overall risk of defaulting from TB treatment of approximately 10% per year.[34] Recent and illegal immigrants showed higher rates of defaulting. The high percentage of patients of foreign descent may explain the relatively high percentage of non-compliance in our study. Shortening the duration of standard treatment from nine to six months, as was recommended in 1996,[8,35,36] more frequent application of DOTS and improved coordination with the public health service in the follow-up of high-risk patients, may further improve treatment outcome in the future.

CONCLUSIONS

Extrapulmonary tuberculosis was present in 51.8% of all cases, which was high compared with earlier surveys showing percentages ranging between 10 and 40%. This change in the incidence of extrapulmonary TB occurred concomitantly with an increase in the percentage of TB patients of foreign descent (78.6% versus around 30% in the mid-80s). Mortality of TB was 3.6%. Extrapulmonary TB was often diagnosed late because of mostly aspecific presenting symptoms. This resulted in a greater than expected doctor's delay. Treatment was mainly hindered by non-compliance. Drug resistance was not a major problem during treatment. Although TB remains a relatively rare disease, a high index of suspicion is necessary in making the diagnosis.

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