

Epidemiology, diagnostic delay and outcome of tuberculosis in North Jutland, Denmark

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ABSTRACT

INTRODUCTION: The objective of this study was to evaluate the clinical outcome of tuberculosis (TB) with regards to epidemiology, symptoms, delay, diagnostics, use of HIV-test, treatment, treatment outcome and mortality in the North Jutland Region from 2000 through 2008.

MATERIAL AND METHODS: The present study is a retrospective study of all new TB cases in the 2000-2008 period.

RESULTS: The period saw a total of 251 TB patients (an average of 28 per year). Almost 60% of the patients were not Danish-born, being mostly from Somalia and Greenland. The mean age was 43 years. 31% were alcohol abusers. 2% had AIDS. Cough was the most frequent symptom followed by weight loss, fever and fatigue. In 78.5% of the cases, it was possible to retrieve a positive culture, 53% had a positive sputum smear. However, in 8% of all patients, it was not possible to isolate *Mycobacterium tuberculosis* and these cases were diagnosed in accordance with the clinical signs. Almost all patients received the standard treatment comprising four antibiotics. 83% were treated successfully, while 5% ended their treatment prematurely. At the end of the study, 14% were dead. In all, 55% of all patients were HIV-tested. Two tested positive before their TB diagnosis and three after.

CONCLUSION: The incidence of TB did not seem to decrease over the course of the study period as seen in the rest of Europe. The relatively high rate of alcohol abusers as compared with earlier Danish literature seems to be due to previous underreporting. A treatment success of 83% is high. This first study of HIV testing in Danish TB patients revealed that it was an acceptable result compared with other studies in this field, but the result was not satisfactory because we may miss patients with HIV/TB co-infection when only half of the patients are tested.

A century ago tuberculosis (TB) was well-known by the Danish population and all Danish physicians. The number TB cases since decreased dramatically in all industrialised countries, and during the past 20 years the incidence in Denmark has stabilized around 300-400 annual cases. Consequently, the disease continues to be present [1]. Given its low prevalence in Denmark, knowledge of the disease in the health care system may wane and this may, in turn, affect TB detection and treatment.

A new Danish clinical guideline on TB has recently been published [2] and a review of TB in Denmark in 1992 was prepared on the basis of notifications to Statens Serum Institut [3]. However, no recent population-based review of the disease has been published. In addition, the emergence of HIV/AIDS has influenced the spread of TB which has had important consequences in cases with concurrent HIV infection. We have therefore found it appropriate to review all recent cases of TB in the North Jutland Region with respect to diagnosis, treatment and results.

MATERIAL AND METHODS

Patient population

We identified patients with TB from the North Jutland County (counting an average population of 495,141 residents in the 2000-2006 period) and the North Jutland Region (with an average population of 577,906 residents in the 2007-2008 period). Identification was achieved by linking the unique personal identification number assigned to each Danish subject via the patient identification system (PAS) with the International Classification of Diseases code A15-A19 during the period 1 January 2000 to 31 December 2008. Only patients with a first-time registration of TB were included. All patients were treated at Aalborg Hospital. All medical records were reviewed and after exclusion of cases with misclassification, a total of 251 patients constituted the study population.

Data retrieval

We reviewed medical records to obtain data on 1) clinical symptoms and signs, 2) demographics, 3) duration of symptoms prior to contact with the health care system (patient delay) and subsequent duration prior to diagnosis (doctor delay) (due to incomplete registration in some medical records, we estimated the approximate delay in these cases), 4) results from microbiological, biochemical and radiological examinations, 5) treatment and adverse events, and 6) outcome after therapy as assessed by clinical examination at completion of therapy and during follow-up. Due to incomplete registration, contacts could not be traced in all cases.

ORIGINAL ARTICLE

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 TABLE 1

Demographic and clinical characteristics of 251 patients with tuberculosis in North Jutland, 2000-2008.

	n	%	Age, years, median (range)
<i>Gender</i>			
Male	127	50.6	–
Female	124	49.4	–
<i>Place of birth</i>			
Denmark	102	40.6	–
Somalia	60	23.9	–
Greenland	39	15.5	–
Asia	36	14.3	–
Other	14	5.6	–
Alcoholism	78	31.1	–
Drug abuse	7	2.8	–
Immunosuppressive therapy	5	2.0	–
<i>Co-morbidity</i>			
COPD	22	8.8	–
Diabetes	11	4.4	–
Liver disease	11	4.4	–
Malignancy	11	4.4	–
Peptic ulcer	9	3.6	–
AIDS	5	2.0	–
Heart failure	4	1.6	–
Danish	–	–	53 (0-86)
Non-Danish	–	–	36 (1-101)

AIDS = acquired immune deficiency syndrome; COPD = chronic obstructive pulmonary disease.

Statistical analysis

Study data were entered into EPIDATA and the software programme Stata for Windows was used for all analyses. χ^2 test and Student's t-test were used for categorical and continuous variables. A significance level of 5% ($p < 0.05$) was used in all cases.

RESULTS

In North Jutland, a minimum of 251 patients had a first-time TB diagnosis in the 2000-2008 period, corresponding to an incidence of 5.4/100,000 residents. We observed between 19 and 46 annual cases. There was no gender difference, but less than half of the patients were born in Denmark (Table 1). On average, immigrant TB cases had stayed in Denmark for 6.8 years (median five years) before the diagnosis, and they were significantly younger than Danish patients ($p < 0.00001$). The majority of the patients who were not born in Denmark were from Somalia and Greenland. A number of patients had co-morbidity including chronic disorders commonly seen in the population; alcoholism was frequently seen (31%) and alcohol-related diseases had also frequently been diagnosed (Table 1). Only few cases had drug-induced immunosuppression or HIV infection.

 TABLE 2

Symptoms and organ involvement in 251 patients with tuberculosis in North Jutland, 2000-2008.

Symptoms	n	%
<i>Pulmonary symptoms</i>		
Coughing	175	69.7
Thoracic pain	166	66.1
Dyspnoea	26	10.4
Haemoptysis	21	8.4
Weight loss	141	56.6
Fever	112	44.6
Fatigue	108	43.0
Gastrointestinal symptoms	88	35.1
Lymphadenopathy	63	25.1
Central nervous system symptoms	26	10.4
Other	29	11.6
Pulmonary tuberculosis	178	70.9
<i>In addition</i>		
Extra-pulmonary	27	10.8
Extra-pulmonary tuberculosis	73	29.1
Lymph nodes	61	24.3
Bone and joint	15	6.0
Pleura	10	4.0
Gastrointestinal	7	2.8
Central nervous system	4	1.6
Urogenital	4	1.6
Other	4	1.6

The clinical symptoms observed were often non-specific (weight loss, fever, fatigue, night sweats, loss of appetite), but many had pulmonary symptoms (Table 2). Haemoptysis was only reported infrequently. Following diagnostic work-up, 71% had pulmonary TB, whereas 29% had extra-pulmonary TB (Table 2). The majority of the extra-pulmonary cases had lymph node TB, whereas other organs were only rarely involved. The most important diagnostic laboratory test was culture for *Mycobacterium tuberculosis complex* from relevant specimens, but polymerase chain reaction (PCR) and direct sputum microscopy were also instrumental in establishing the diagnosis in some cases. Among 197 cases with positive culture of *Mycobacterium tuberculosis complex*, 53% had a high risk of transmission as evidenced by concomitant positive sputum microscopy. During the study period, only one case of multidrug-resistant TB was observed. In a minority of cases (8.4%), microbiological tests were negative, and the diagnosis was made by clinical criteria supported by *interferon-gamma release assay* (IGRA) or evidence from radiological imaging studies or histopathology of biopsies.

The period from first symptom to contact with the health care system (*patient delay*) was longer than three months in 23% of patients (Figure 1), and the majority of these patients waited more than six months. After their

first contact with a physician, one third of the patients were diagnosed correctly within a week, one third of the patients waited between one and three weeks, and one third had a delay of more than one month before receiving the correct diagnosis (Figure 1). We found no difference in *doctor delay* between pulmonary and extra-pulmonary cases ($p = 0.64$). In 50% of the cases, the *total delay* from first symptoms to diagnosis was exceeded 61 days. From time of diagnosis, 83% of patients initiated therapy within one week (data not shown).

It is recommended that all cases of TB be tested for HIV infection. For the 2000 to 2008 study period, a test result was available in 139 patients (55%) of whom 64 had been HIV-tested before TB was detected. Another 75 patients had had an HIV-test performed as a direct consequence of the TB findings. The mean age of patients who were HIV-tested was 39 years, while the mean age of the remaining patients was 47 years ($p = 0.002$). The subgroups with the highest rates of testing were drug abusers and immigrants from Somalia. Among patients born in Denmark, only 36% were tested for HIV infection (Table 3). Among a total of 139 patients who had been examined, five had concomitant HIV infection.

Patients were hospitalized for an average period of 16.8 days (median 12.5 days). The vast majority, more than 95%, received standard four-drug antibiotic therapy for the time period recommended in the guidelines. In 11% of the cases, modifications of drugs occurred, e.g. with a fluoroquinolone. Approximately half of the patients (117 of 251) reported one or more adverse events during therapy, mostly nausea/vomiting (21%) or cutaneous reactions (20%). Hepatotoxicity was rare (2%).

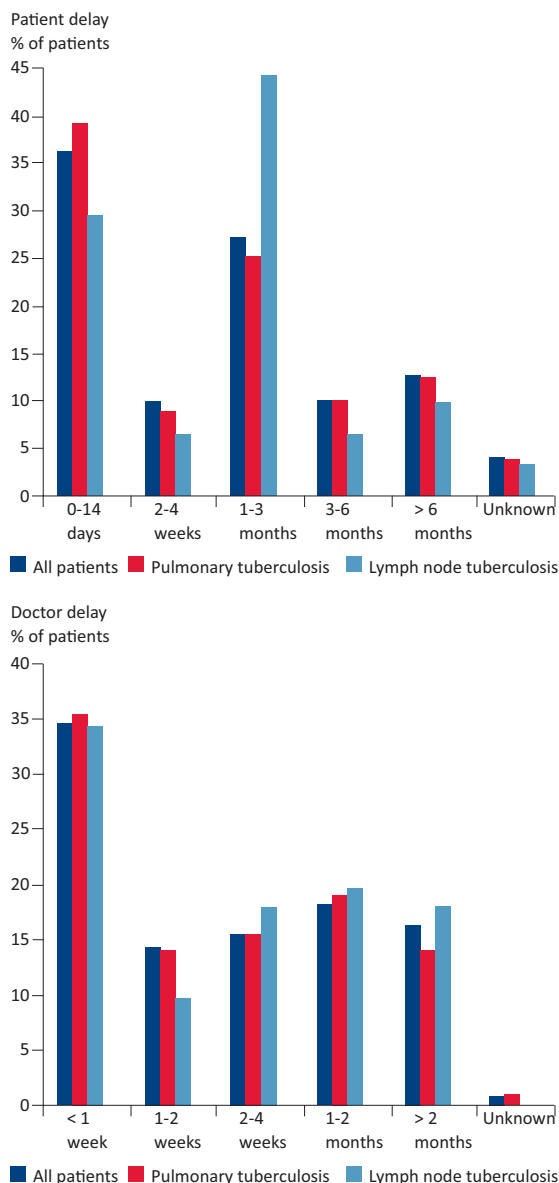
Outcome evaluation showed that 209 (83%) patients had been cured as they had finished the scheduled treatment, had no signs of active infection on follow-up and were not subsequently referred to hospital within the study period. Five percent of the patients interrupted treatment permanently before schedule, whereas 13% had suboptimal compliance with drug therapy and hospital control visits. Crude mortality with a mean observation time of four years was 14% (34 patients). It should be noted that several patients had co-morbidity, and it is very difficult to determine if TB is the direct cause of death.

DISCUSSION

In this study we reported that the occurrence of TB in the North Jutland Region remained stable in the period 2000 to 2008 with an incidence similar to that of the Danish average incidence. The strength of our study lies in its population-based design with only one hospital caring for TB patients in our region. Thanks hereto it was

FIGURE 1

Patient delay among patients with pulmonary and lymph node tuberculosis in North Jutland, 2000-2008.



possible – for the first time since 1992 – to report a non-selected cohort of patients in Denmark with respect to demography, clinical characteristics, co-morbidity, diagnostic delay and therapy outcome.

In the North Jutland Region we observed no gender difference, whereas in Denmark as a total most patients are males [1]. A number of commonly occurring chronic illnesses were present in our TB patients, and a surprisingly high fraction (31%) had concomitant alcoholism. This fraction is higher than previously reported through disease notifications [1, 3]. By carefully reviewing the medical records, we arrived at the conclusion that in-

 TABLE 3

HIV infection tests performed in 251 patients with tuberculosis in North Jutland, 2000-2008 (%).

	n/N (%)
<i>HIV-testing</i>	
Total number of tests performed	139/251 (55.4)
Prior to diagnosis	64/251 (25.5)
After diagnosis	75/251 (29.9)
<i>Place of birth</i>	
Denmark	50/102 (50)
Not Denmark	89/149 (60)
Somalia	43/60 (72)
Asia	18/36 (50)
Alcoholism	49/78 (63)
Drug abusers	6/7 (86)
<i>Positive HIV test</i>	
Of patients examined	5/139 (3,6)
Of all patients	5/251 (2,0)

complete information on alcoholism and other risk factors in the notifications may have led to underreporting. Alcoholism was a striking risk factor in our patient population, as the prevalence of alcoholism in the general population is much lower. We therefore believe that previous reports may have underestimated this association.

In agreement with the worldwide distribution of TB, we found the infection mainly (59%) in patients born outside of Denmark, mostly in highly endemic countries. A recent study from the Western Region of Sweden also documented that only 26% of TB patients were born in Sweden [4]. The two most prevalent places of origin in our study were Somalia and Greenland. The duration of residence in Denmark prior to the diagnosis was long (mean 6.8 years), which is slightly longer than the duration reported for France [5] and Norway [6], but in agreement with the long latent phase of mycobacterial infection that prevails before clinically overt symptoms occur.

Signs and symptoms were mostly non-specific and shared with many other disorders. Consequently, some patients may have waited for prolonged periods before contacting the health care system, and such delay is possibly exacerbated by pre-existing marginalisation among the cohortees. Cases with extra-pulmonary lymph node disease had slightly longer delays throughout the course from first symptom to initiation of treatment than was the case for patients with pulmonary TB. Studies from Norway [6] and Canada [7] have reported similar findings. Patients with lymph node TB may present with mild non-specific disease which may explain both *patient* and *doctor delay*. It has been reported that immigrants have longer patient delays than domestic patients [4], which

may be associated with differences in culture, with language barriers or with social stigma. In our cohort, we observed prolonged delays in some TB patients. The challenge for both the primary and the secondary health care sector is to keep in mind that TB may be a differential diagnosis in non-specific cases. Due to symptoms overlapping with symptoms of other disorders commonly seen in Denmark, diagnosis and proper treatment may easily be delayed. Still, the general perception of TB as a disease limited to developing countries may facilitate a shorter doctor delay for immigrants than for domestic patients, as has been reported from other industrialized countries [8, 9]. In the present study, we observed a doctor delay exceeding one month in 35% of the cases. Furthermore, 53% of the patients had a positive sputum smear reflecting advanced disease presentation and high potential for active transmission. These facts indicate a need for improvement in the health care system for early identification of TB cases.

HIV infection is highly endemic in the same regions of the world as those where TB is prevalent, e.g. sub-Saharan Africa and Asia. It is therefore particularly important to test for HIV co-infection in patients from high-risk regions. In our cohort, 55% of all patients had an HIV test performed, of whom two thirds were non-Danish. From Somalia 72% were tested and from Asia only 50%, indicating that the remaining patients from these highly endemic regions may have missed an HIV diagnosis due to lack of testing. The median age of the patients who were not HIV-tested was 48 years. It seems unlikely that such relatively low age should be able to explain why some patients were not tested. The frequency of HIV testing in a non-selected group of Danish TB patients has not previously been reported, and underreporting may occur in the order of 50% as only half of the patients had been tested. An anonymous testing study in Southern London in 1998-1999 observed an alarmingly high prevalence of 11.4% HIV-positives among TB patients, even after excluding cases already known to be co-infected [10]. Other countries have also reported insufficient HIV testing in TB patients [11-16], and the reasons for this underreporting are probably multifactorial. However, the consequences of failure to establish an HIV diagnosis can be serious for the patient. Although the prevalence of HIV-TB co-infection is low in Denmark, we believe that all TB patients in the Danish health care system should be asked for informed consent to perform HIV testing [2].

Due to the psychosocial status of the TB patient and other co-morbidities, full compliance to antibiotic treatment for prolonged periods is difficult to achieve. Likewise, assessment of transmission in society is difficult and contact-tracing is hampered by the marginalisation of some patients. Due to incomplete registration, we

were unable to assess the impact of contact tracing on disease transmission in the North Jutland Region. The majority of all patients (83%) completed treatment as scheduled and were cured as documented by follow-up in the specialized hospital department. This is in agreement with national and international findings. A previous Danish study found that 80.8% had been cured [3], whereas reports from France and Norway quoted 70.1% [17] and 83 % [6] cure rates. From a public health perspective, however, early detection and treatment of TB is important to reduce transmission. Eradication of the disease is only possible through a more active search-and-destroy policy involving all patients' potential contacts. A reduction in patient delay as well as doctor delay would also support a better control of TB in Denmark. Finally, a higher coverage of HIV testing among patients with TB is needed.

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