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Original Article

Assessment of Extrapulmonary Tuberculosis in Two Provinces of Turkey

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Abstract

Background: Tuberculosis (TB) is one of the main health issues in Turkey. Extrapulmonary TB cases have significant proportion comparing pulmonary TB cases. The aim of the study was to evaluate the extrapulmonary tuberculosis (EPTB) cases in two regions of Turkey, which have different demographic and socioeconomic characteristics.

Methods: In this retrospective cohort study, EPTB cases between 2000 and 2005 in Van and Izmir Provinces of Turkey were analyzed and compared for symptoms, age groups, vaccination status, diagnostic procedures and social-economical conditions within two provinces. Descriptive analytic methods were used.

Results: Total of 397 EPTB cases were reviewed retrospectively in Izmir and Van provinces. Pleural TB was most often seen EPTB form (47.6% vs. 32.6%) and female/male ratio was similar in both groups. Patients were in older ages in Izmir Province. Chest pain (20% vs. 32%), cough (33% vs. 26%) and night sweatiness (29% vs. 36%) were leading complaints. Low BCG vaccination rate and higher childhood EPTB were found in Van group, in contrary elderly EPTB was more often in of Izmir group.

Conclusion: Frequency of severe forms of EPTB is more often in younger ages in lower social economical condition areas.

Keywords: Extrapulmonary tuberculosis, Socioeconomic factors, Turkey

Introduction

Tuberculosis (TB) primarily affects lungs, as well as almost any organ in the body. The term of extrapulmonary TB (EPTB) describes the occurrence of TB at organs other than the lung. EPTB was manifested the most commonly at lymph nodes, genitourinary tract, pleura, bones and joints, meninges and the central nervous system and peritoneum organs (1).

TB bacilli spread by lymphatic and bloodstream and reach extrapulmonary organs. Regional lymph nodes are generally involved in TB infections. Lympho-hemotogenous spreading is restricted by immune system and more than 90% of infected people recovered as tuberculin skin test (TST) conversion. EPTB occurs via either reactivation of dormant TB bacilli in extrapulmonary organs or very rarely direct neighborhood to infection site (2). TB is a major public health problem in developing countries. Low socioeconomic status is association with TB disease. The majority of highest burden countries (17 of the 22 country) counted for 80% of the world's TB cases are graded as low income (3). The World Health Organization (WHO) estimates that 98% annual TB deaths and 95% of the new TB cases occur in developing countries (4). In developed countries, it is a re-emerging health care problem due to immigration and increasing human immunodeficiency virus (HIV) prevalence. How-

ever, socioeconomic factors are independent variables from the HIV status (5).

In 2012, an estimated 8.6 million people developed TB and 1.3 million died from the disease (including 320 000 deaths among HIV-positive people). Approximately 0.8 million EPTB cases were notified (6). National data have been started to report regularly since 2007 by ministry of health of Turkey. Turkey is a country that has a moderate level of TB. Prevalence 23 per 100.000, incidence 22 per 100.000 with 5121 EPTB (14139 all new TB cases; 36%) were notified (6). However, in official national TB report, totally 5811 EPTB cases were reported. Lymph nodes and pleural involvement were most cited, 32% and 31%, respectively. At the regional level, total TB incidence is reported 19.4 and 14.0, in Izmir and Van provinces, as well as EPTB was notified as 33.2% and 53.1% in the same order (7). Izmir and Van provinces were selected as they are the opposite in terms of socioeconomical features and farthest for distance. Aim of the study was evaluating if there is any difference among characteristics of EPTB between these different regions.

Materials and Methods

Setting

In this study, records of clinical features, socioeconomic and demographic characteristics of patients with EPTB followed up by two regional dispensary between 2000 and 2005 (Dispensaries are the official places in health care system were TB patients are followed up for therapy, reporting treatment outcomes and also distributing TB drugs to the patients free of charge) were investigated, retrospectively. The first dispensary is one of the eight central dispensaries in Izmir, which is the third biggest city of the country in Western side of Turkey. Another one is in Van, which is the city at the Eastern side of Turkey. The populations of these two provinces have different demographic and socioeconomic characteristics (Table 1 and Fig. 1)

Definition of EPTB

EPTB refers to a case of TB involving organs other than the lungs, e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges. Diagnosis should be based on at least one specimen with confirmed *M. tuberculosis* or histological or strong clinical evidence consistent with active EPTB, followed by a decision by a clinician to treat with a full course of tuberculosis chemotherapy. The case definition of an EPTB case with several sites affected depends on the site representing the most severe form of disease (6).

Study subjects

Records of the patients followed up by local TB dispensaries with a diagnosis of EPTB between 2000 and 2005 were analyzed retrospectively. A total of 397 EPTB cases from Van and Izmir provinces were included in the study.

Ethical consent was taken from hospital scientific Ethical Committee for this study according to Helsinki declaration 2008.

Table 1: Demographic features of Van and Izmir provinces

Age group (yr)	Gender	Izmir Province	Van Province	Country total
<15	T	797 900	415 900	20 220 000
	M	410 100	217 800	10 453 000
	F	387 800	198 100	9 767 000
15-64	T	2 243 600	441 300	43 724 625
	M	1 089 400	220 300	22 143 735
	F	1 154 200	221 000	21 580 890
>65	T	229 500	20 240	3 859 300
	M	99 500	9 940	1 750 000
	F	130 000	10 300	2 109 300

T: Total, M: Male, F: Female

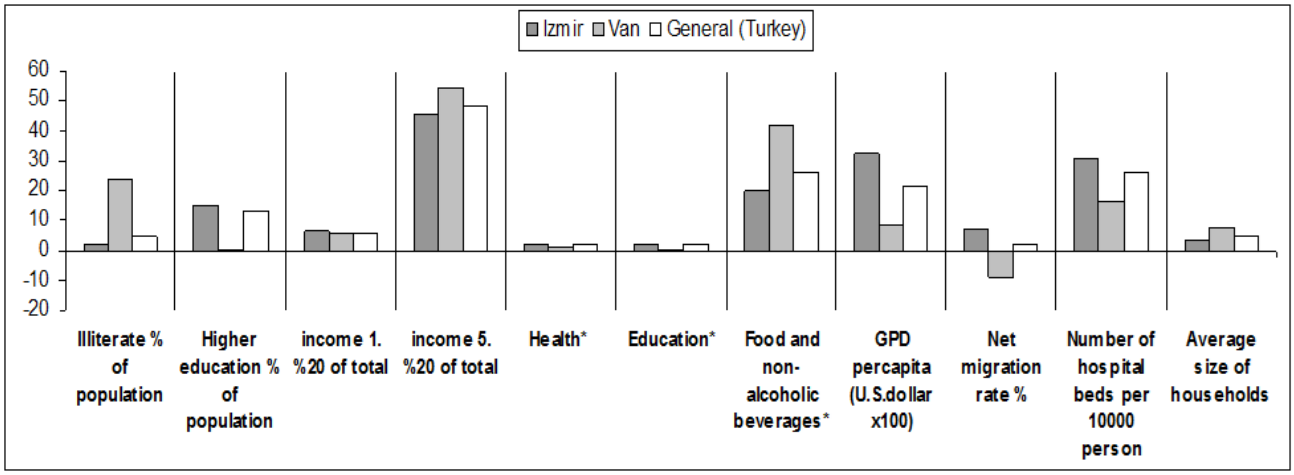

Fig. 1: Various variables of socioeconomic status

Collection of data

Records of medical history and physical examination details were investigated for all compatible patients who met EPTB definition during analyzing period. Definitive diagnosis was established by histopathologically, bacteriological and radiological methods. Cases with missing or insufficient data in their records were excluded.

TST (BB-MCIPD, Sofia, Bulgaria, 5 TU/0.1 ml) was applied as 0.1 ml (5 TU) via intradermal route. Skin responses were evaluated 72 hours after the application, a transverse diameter of an induration of more than 10 mm was judged as a positive reaction.

In order to detect a pulmonary manifestation, all subjects underwent chest radiographs and were asked for sputum analysis from expectorating patients. Patients showing cavernous or disseminated patterns on the radiographs and patients with smear test (*i.e.*, Ziehl-Neelsen staining) results that were positive for the presence of acid-fast bacilli in sputum were excluded from study.

Histological and/or microbiological analyses have been done for the presence of mycobacteria in the tissue except 84 (20.3%) cases. These cases were diagnosed with just clinical and radiological findings. Fine-needle aspiration (FNA), lymph node excision and tissue biopsy were used to diagnosis.

In FNA method one aliquot of FNA samples was fixed in 95% ethyl alcohol and was stained by Giemsa for cytological analysis. A second aliquot was used for microscopic detection using Ziehl-Neelsen staining as well as Lowenstein Jensen and automated culture (BACTEC; Becton Dickinson; USA) in where the bacteriological examinations were available, and the same procedure was followed in samples from tissue biopsies. Histological analysis was performed on samples fixed in formalin.

In Turkey, national reference laboratory and epidemiology unit was established in Refik Saydam National Public Health Agency in 1999. Soon after, more reliable epidemiological TB data had obtained.

Definition of socioeconomic status (SES)

To determine socio-economic development level of regions and provinces, data were taken from the State Planning Organization (DPT) report including 41 variables (Fig. 1). The most important variables were percentage of illiterate, higher education rate and gross domestic product (GDP) per capita (8).

Statistics

SPSS 15 program (Chicago, IL, USA) was used for statistical analysis. Distribution of data was evalu-

ated by Kolmogorov Smirnov test. Analysis of parametric variables was performed *t* test; Kruskal Wallis and Mann-Whitney tests were applied for nonparametric distributed variables. Chi-square test was used for analyzing categorical data.

Results

Van and Izmir provinces have shared 1.3% and 5.3% of the country population, respectively. In Van, 52.5% of population lives in urban areas, whereas 85% of population residences in cities and towns in Izmir Province. Country population lives in urban settings in ratio of 70.3%. Socio-economic development index was reported as 9.2 (in 3rd order) and -5.9 (in 76th order) in Izmir and Van, respectively in 81 provinces of country (8). Most significant differences in SES variables were found as illiterate and higher education rates. Furthermore difference in GDP per capita and migration rates were meaningful.

Between 2000 and 2005, 397 cases were diagnosed as EPTB in both provinces [225 (59.7%) in Izmir Province and 172 (40.3%) in Van Province]. Demographical aspects, BCG vaccine, TST test status and predisposing factors of cases were seen in Table 2. Diagnostic methods, clinical features and type of EPTB were given Table 3 and 4.

In Van group, EPTB/total TB ratio was higher [225/882 (25.5%) vs. 172/606 (28.4%)] (P= 0.35) but not statistically significant. EPTB cases were more frequent in elderly in Izmir group, in contrary in children of Van group.

Percentage of illiterate, higher education rate and gross domestic product (GDP) per capita were notified 3% and 24%; 15% and 2%; 30% and 10% in Izmir and Van, respectively. Other components of socioeconomical factors were given in Fig. 1.

While as pleural TB and lymph node TB were detected as most frequent EPTB form in both group, in third position, gastrointestinal TB and genitourinary TB was found in Van and Izmir groups, respectively. The most severe form of TB, central nervous system TB was notified significantly higher in Van group [4 (1.8%) vs. 15 (8.7%)] (P<0.001).

None of the patients had declared alcohol addiction, although 132 (35%) patients have declared smoking habit mean duration of ten years.

Table 2: Demographic data of the patients

Characteristics	Izmir Province (n=225) n (%)	Van Province (n=172) n (%)	*P*
Gender			
Female	112 (50)	91 (53)	>0.05
Male	113 (50)	81 (47)	>0.05
Age, yr			
Mean ± SD	38.41±16.79	30.33±14.88	0.008
TB contact history	57 (25.3)	41 (23.8)	>0.05
BCG status	209 (93)	66 (38.4)	0.0001
No. of TST tested	102 (45.3)	36 (21)	0.0001
TST* (+)	86* (85)	15*(40)	0.0001
Predisposing factors			0.0001
HIV	0	0	
Others**	66 (29.3)	18 (10.5)	

*Numbers of TST tested cases were used as denominator. NA: Low number of data. ** Diabetes mellitus, chronic renal failure, malignancy, psychotic disorder, cardiac disorder and gastritis, rheumatoid arthritis, SLE

Table 3: Clinical symptoms and diagnostic procedures of the EPTB patients

	Izmir Province (n=225) n (%)	Van Province (n=172) n (%)	*P*
Symptoms			
Fever	46 (20.4)	56 (32.6)	0.006
Cough	75 (33.3)	46 (26.7)	>0.05
Night sweatiness	67 (29.8)	62 (36.0)	>0.05
Chest Pain	79 (35.1)	38 (22.1)	0.005
Weakness	56 (24.9)	32 (18.6)	>0.05
Weight loss	37 (16.4)	39 (22.7)	>0.05
Palpable lymph node	32 (14.2)	52 (30.2)	0.000
Lack of appetite	23 (10.2)	22 (12.8)	>0.05
Dispnea	27 (12.1)	20 (11.6)	>0.05
GİS disorders	23 (10.2)	6 (9.09)	>0.05
Urinary disorders	15 (6.7)	4 (2.3)	0.045
Neurological disorders	6 (2.7)	14 (8.1)	0.013
Dermatolojical disorders	2 (0.9)	3 (1.7)	>0.05
Histopathological diagnosis	170 (75.6)	100 (58.1)	0.000
Bacteriological tests			
Smear (n)/positivity (n)	101/31	89/11	0.016
ulture (n)/positivity (n)	90/24	81/15	0.37
DST (n)	3	0	
Clinico-radiological diagnosis	24 (10.7)	60 (34.9)	0.000

* Total numbers of cases are unknown. NA: Low number of data

Table 4: Localizations of EPTB cases

Localization	Group 1 (%) n (%)	Group 2 (%) n (%)	*P*	Total n (%)
Pleura	107(47.6)	56 (32.6)	0.003	163 (41.4)
Lymph node	53 (23.6)	49 (28.5)	>0.05	102 (25.7)
Genitourinary	19 (8.4)	12 (7.0)	>0.05	31 (7.8)
Gastrointestinal	11 (4.9)	23 (13.4)	0.003	34 (8.6)
Bone-joint	11 (4.9)	13 (7.6)	>0.05	24 (6.0)
Pericard	9 (4.0)	1 (0.6)	0.031	10 (2.5)
Milier form	6 (2.7)	0	0.031	6 (1.5)
Larinx	5 (2.2)	0	0.049	5 (1.3)
CNS	4 (1.8)	15 (8.7)	0.001	19 (4.8)
Dermal	2 (0.9)	3 (1.7)	>0.05	5 (1.3)
Mammalian	1 (0.4)	0	>0.05	1 (0.3)

Anti –HIV was found negative in all patients. Additional disorders were found in 66 (29.3%) and 18 (10.5%) in Izmir and Van groups, respectively (diabetes mellitus, chronic renal failure, malignancy, psychotic disorder, cardiac disorder and gastritis, rheumatoid arthritis, SLE).

Most frequent complaints of the patients were night sweatiness and fatigue in both groups. Fever and palpable lymph nodes were encountered in Van group as statistically different compared to Izmir group ($P < 0.001$).

TST and BCG application rates were higher in Izmir group ($P<0.001$). Compliance problem to treatment (2.2% vs. 6.4%, $P= 0.036$) was another unfavorable condition in Van Province.

Discussion

Effective treatment regimens and improvement in life standards helped to decrease of TB incidence in most geographic areas in the world. Spreading of HIV infection and TB drug resistance disrupted the TB control and re-emerged the TB in some regions of the world. This fluctuating situation of pulmonary TB infection, incidence of EPTB conserved its increasing trend in both developing and developed countries (6). For example, in India, while 15-20 percent of the immunocompetent adult TB cases were EPTB (9), in Netherlands, the frequency of EPTB was found to be 15%, similar to the eastern and central Europeans, 58.9% among the Somali, 36.6% among people of other African origins, and 44% among the Asians (10). According to WHO, EPTB was notifies as low as <1 in China and as high as 40% in Cambodia (6).

Turkey is a developing country and the proportion of EPTB among all TB cases in Turkey had increased from 19.6% in 1996 to 32.5% in 2007 according to national report (7). However, the reason for such that increasing remains largely unknown. The leading reasons could be improvement of diagnostic testing and notification systems probably. In our study, EPTB rates were close to each other among the provinces as 25.5% and 28.4%. It is considered that socio-economic and geographic conditions did not affect the EPTB ratio.

In high prevalence regions, people are exposed more intensively to TB bacilli and show signs of TB in earlier age. Pleural TB and lymph node TB are the early post primary manifestations of TB. Lymph node TB is a common cause of lymphadenopathy in areas where TB is endemic. In low TB prevalence countries, lymph node TB is the most frequent extrapulmonary TB form. In high prevalence areas, incidence of lymph node TB is second after the incidence of TB pleuritis (9).

Distribution of forms of EPTB has varied among studies conducted in different populations. Lymph node TB (40%) has been most frequent form of EPTB, second as pleural TB (20%) in USA (11). Contrary, in Europe, pleural TB (40%) is leading form in front of lymph node TB (20%) (12). Among 1267 cases registered for treatment of all forms of TB, 528 (41.67%) had EPTB. Pleural TB was the commonest type of EPTB (n = 148, 28.03%), followed by lymph node TB (n = 131, 24.81%). Involvement of lymph nodes was the commonest manifestation among the less than 14 years' age group (27, 58.7%), while involvement of pleura was more common among > 65 yr age group (23, 45.1%) (13).

In Brazil as an example of moderate endemisity countries, with very wide numbers of cases (53 853 EPTB cases; 13.3% of all TB cases) pleural TB (42%) is leading, next to lymph node TB (21%) the meningeal (6%), bone (5%) and genitourinary (3%) (14).

EPTB rates were different among provinces of Turkey, for example, 19.4% in Zonguldak (north coast of Turkey) and 62.5% Hakkari (southeast border). Forms of EPTB have shown varieties in several studies in country. The most frequently seen forms of EPTB were reported as pleural TB (15, 16), lymphatic TB (17), and central nerves system TB (18) and genitourinary TB (19).

Relationship between SES and TB is a considerable topic but literature has not indicated certain judgment although general trends show that TB is generally has higher incidence in poor conditions. None of the SES and demographical variables showed a significant association with the rate of recurrence in Iran. However, percentage of illiterate was very high in their patient population. Special feature of this article is setting of the study was very close to our Van district geographically. The settings were adjacent neighbors around country border (20).

Significant difference between pulmonary TB and EPTB in terms of ratio of education levels, dwelling as well as age, gender and race in Brazil (14).

Van Province represents characteristics of developing countries. However, Izmir has developed country socioeconomic conditions. Therefore,

lower socio-economic conditions could explain the accumulation of ages of cases in earlier decades in Van province. It is estimated that old ages and associated diseases of elderly encouraged reactivation in Izmir. It also was thought that the reason of lower incidence of TB cases in Van province than Izmir Province is the result of notification errors dealing with compliance issues to national TB programme (7).

Although BCG vaccination is mandatory in the country, it could not be performed regularly in every district of country. In our study, there are very different vaccination rates between two districts. Accessibility to health service and compliance to official regular health ministration of people lives in that areas were dissimilar due to diversified socio-cultural issues.

TST values were not useful in the diagnosis of TB due to a moderate prevalence of TB and of BCG vaccination in the country TST positivity is between 24-77% in a worldwide population; there is 56-69% rate in TB patients in Turkey (21). Therefore, TST is a valuable but nonspecific test for the assessment of TB in patients in Turkey. BCG vaccination rate was higher in Izmir Province than Van Province and TST positivity was found similar rates. In one way, this is a normal result of vaccination ratio. In another way, that finding could indicate immune response to TB infection and/or BCG due to better life conditions. It is difficult to distinguish. In literature, TST and history of contact with a TB patient could help diagnosis for lymph node TB especially in pediatric group. In adult group, they have less diagnostic value. In high endemic areas, wide BCG vaccine application has indicated a high rate of false positive TB skin test in the healthy population. False positive reactions to the TST also have been clearly identified in relationship to prior infections with nontuberculous mycobacteria. This renders interpretation of a positive TST difficult; especially in a case with symptoms of an active TB infection are not present. However, false negative reactions occur. Some portion of individuals harboring latent tuberculosis does not react to the TST. This is particularly the case with infants or HIV-infected persons who have been recently exposed to a case of communicable TB. Another variety of false negative TST merits attention: tests which truly yield a significant amount of induration, but are erroneously read by health professionals as negative (21, 22). Although TST positivity was high, it was not concluded a strong indicator for EPTB in this study.

Patients with EPTB may manifest constitutional symptoms such as fever, anorexia, weight loss, malaise and fatigue. Swelling and pain in the affecting site such as slowly enlarging lymph nodes , chest pain, non-productive cough and dyspnea, CNS symptoms, chronic lower abdominal or pelvic pain, or alterations in the menstrual pattern , skin lesions were main signs and symptoms (9,13,19). TB of CNS remains a major cause of neurological impairment in the developing world fuelled by poor socio-economic conditions (23). Especially, in high TB endemicity regions, subacute onset meningitis could be indicated meningeal TB in children. In our study groups, fever and neurological disorders were more often in Van Province.

Genitourinary TB is frequent form of TB and it is responsible female infertility widely, especially in high endemic countries. In our study, it is forth ranked among all EPTB cases and prevalence did not differ between two districts.

Interpretation of study results is difficult due the two-stage nature of TB, characterized by an infection and a disease stage. Studies do not generally differentiate clearly between TB infection and TB disease, and it is not clear how social - economical conditions are associated with the risk of infection and the risk of developing the disease, or both. In most studies, data suggest a strong effect of both household crowding and SES on the risk of TB infection. Crowding and SES perhaps explain different cases of TB infection: 1) Infections at household level through overcrowding in poor households, and 2) those infected people at community level. Wealthier households but also likely to reflect a more urban-type setting, characterized by greater population density and a higher chance of human interaction are likely to be fostering TB transmission has been demonstrated in previous studies, showing that in high TB prevalence set-

tings, especially high densely populated settings like this one, extensive TB transmission can occur via complex social networks that are likely to be as important as households contact in maintaining transmission (23-28).
Limitations of the study were considered probable notification errors in Van Province and relative low patient number. Bacteriological methods were studied approximately half of the cases.

Conclusion

Any gender and age are under risk for EPTB in Turkey. However, EPTB rates were higher in low SES region younger ages. TST cannot help the diagnosis. Lymph node TB should be considered as first step of differential diagnosis of lymphadenopathies, foremost for the cervical ones. Subacute or chronic meningeal infections in children in Van province and female infertility cases in the country, EPTB should be considered. In low social-economical index areas, national TB system should be strength for both correct data collection and finding cases.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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