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Tuberculosis among Dislocated North Koreans Entering Republic of Korea since 1999

The collapse of North Korea's public health system has increased the development of tuberculosis (TB) in its populace. This study investigated the prevalence of active and latent TB infection (LTBI) in such people who have settled in the Republic of Korea since 1999. From 1999 to August 2006, 7,722 dislocated North Koreans entered the Republic of Korea and all were screened immediately for active TB. Demographic and clinical characteristics were reviewed from the official records of the Settlement Support Office for Dislocated North Koreans, based in the Ministry of Unification. Of 7,722 participants, 87 (1.13%) were diagnosed with active TB from 1999 to August 2006. Of these, 78 (90%) had pulmonary TB. Checking for the presence of a *Bacille Calmette-Guérin* (BCG) scar and tuberculin skin test has been performed in all dislocated North Koreans since November 2005. Of 1,112 participants, BCG vaccination scars were found in 67.4%. The tuberculin-positive rate using two tuberculin unit doses of the purified protein derivative RT23 (≥10 mm in diameter) was 81.5%. The prevalence of active TB and LTBI in dislocated North Koreans was high. Because this group bears a disproportionate burden of TB, we need to initiate a specific control programme and to plan for the impact of this disease in the Republic of Korea.

Key Words : *Tuberculosis; Dislocated North Korean; Refugees; Latent TB infection*

Chang-Min Choi, Jung-Hee June*, Cheol-In Kang, Jung-Tak Park, Soo-Yon Oh†, Jin-Beom Lee†, Chang-Hoon Lee‡,§, Jae-Joon Yim§, Hee-Jin Kim†

Department of Internal Medicine, Armed Forces Capital Hospital; Management and Welfare Team*, Settlement Support Office for Dislocated North Koreans, Ministry of Unification; The Korean Institute of Tuberculosis†; Division of HIV and TB Control‡, Korean Center for Disease Control & Prevention; Division of Pulmonary and Critical Care Medicine§, Department of Internal Medicine and Lung Institute, Seoul National University College of Medicine, Seoul, Korea

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Address for correspondence
Hee-Jin Kim, M.D.
The Korean Institute of Tuberculosis, 14 Woomyeon-dong Seocho-gu, Seoul 137-140, Korea
Tel : +82.2-575-1547, Fax : +82.2-573-1914
E-mail : hatchingbird@yahoo.co.kr

INTRODUCTION

Tuberculosis (TB) is a major cause of human mortality and a worldwide public health problem (1). There are large discrepancies in the rates of TB infection between countries in each major region and among different locations and demographic groups within each country. Local and regional increases in the incidence of TB have occurred because of limited health care resources and societal disruptions (2).

North Korea's economic and public health problems began in the early 1990s as a result of the gradual loss of economic support from its communist allies, combined with an inordinate number of natural disasters (3, 4). This public health tragedy has increased the development of active TB in North Korea; 11,050 cases were reported in 1997 and this increased to 41,810 in 2003 (184 per 100,000 of the population) (1).

Dislocated North Koreans have been identified entering the Republic of Korea since 1954; the number increased from 60 in 1999 to 1,364 in 2005. Such individuals may carry a significant infectious disease burden as a result of the prevalence of disease in their country of origin, exposure during migration, adverse conditions during migration such as poor nutrition, and exposure to multiple psychological and physical stress (5).

Therefore, the goal of this study was to investigate the prevalence of active TB and latent TB infection (LTBI), morbidity, drug resistance, and *Bacille Calmette-Guérin* (BCG) coverage among dislocated North Koreans settled in the Republic of Korea. Our aim is to initiate a specific control programme and to plan for the impact of this disease.

MATERIALS AND METHODS

Dislocated North Koreans

Dislocated North Koreans were defined as refugees from North Korea, and the study did not include those born to

refugees outside that country. Since such displaced persons from North Korea were first identified, the government of the Republic of Korea has welcomed them officially. To facilitate the early settlement of these refugees, the government of the Republic of Korea established "Hanawon", the Settlement Support Office for Dislocated North Koreans based in the Ministry of Unification, in 1999. This body provides board, lodging, education for settlement, and medical care for three months.

Routine health screening and examination

Health screening is performed for dislocated North Koreans at Incheon Red Cross Hospital, immediately after their arrival in the Republic of Korea. Screening includes taking a detailed history of previous diseases and current symptoms, a physical examination, leukocyte, platelet and differential leukocyte counts, measurements of hemoglobin and glucose levels, evaluations of renal and liver functions, serologic testing for human immunodefficiency virus (HIV), hepatitis, and syphilis, and a chest radiograph. In addition, each individual completes a questionnaire about any possible risk of exposure to *Mycobacterium tuberculosis.* For refugees with abnormal chest radiographs, bacteriological examinations are performed at the Armed Forces Capital Hospital; these include direct smears, cultures, drug susceptibility testing, and species identification. Checking for the presence of a BCG scar has been done since November 2005. This study was approved by the ethics review committee and the Institutional Review Board of the Korean Institute of Tuberculosis (Seoul, Republic of Korea).

Identification of latent TB infection

The tuberculin skin test (TST) has been performed in all dislocated North Koreans since November 2005. TST was done by the Mantoux method, with two tuberculin unit doses of the purified protein derivative RT23 (Statens Serum Institute, Copenhagen, Denmark), injected intradermally to the volar surface of the right forearm. The largest transverse diameter of palpable induration was measured by a trained nurse after 48-72 hr.

Identification and examination of active TB

When dislocated North Koreans have sought medical advice, the Armed Forces Capital Hospital has given a medical examination and treatment. Using the computerized database of the Settlement Support Office for Dislocated North Koreans of the Ministry of Unification and the Armed Forces Capital Hospital, we identified reported instances of active TB from January 1999 to August 2006. We reviewed baseline demographic and clinical information, including age, sex, previous treatment for active TB or contact history, laboratory reports of bacteriological studies, and radiological reports. If patients' sputa showed acid-fast bacilli, mycobacterial culture with species identification was performed by the Korean Institute of Tuberculosis. We examined the drug susceptibility testing (DST) results of initial cultures against the first-line anti-tuberculosis medications: isoniazid (INH), rifampicin, ethambutol, pyrazinamide, and streptomycin.

Statistical analysis

To compare the prevalence of active and LTBI of the dislocated North Korean subjects with those of civilians of the Republic of Korea, we calculated the prevalence ratio (PR) adjusted by age and sex as follows: PR=(observed number of TB cases in dislocated North Koreans)/(expected number of TB cases in South Koreans). The expected number of TB cases in the Republic of Korea was taken from the data of the nationwide TB prevalence surveys in the country in 1995 (6) after being adjusted for age and sex. Student's *t*-test was performed for continuous variables and Pearson's chi-square test or Fisher's exact test (if the expected number was less than five in at least one cell) were used for categorical variables. $p<0.05$ was regarded as statistically significant. Analyses were performed using SPSS software, version 11.0 (SPSS Inc, Chicago, IL, U.S.A.).

RESULTS

Characteristics of dislocated North Koreans

Since 1954, 8,313 North Koreans have entered the Republic of Korea; 7,722 entered between 1999 and August 2006 and were eligible in this study. Of these, 2,828 (36.6%) were men and 4,894 (63.4%) were women, with a median age of 32 yr (range, 0-85). The median duration of migration outside of both Koreas was 27 months (range 0-205). The mean body mass index was 21.2 ± 2.76 kg/m^2 in men and 21.7 ± 2.81 kg/m^2 ($p<0.001$) in women. No subject was HIV seropositive. The countries the dislocated North Koreans arrived from were China (30.4%), Mongolia (22.4%), Cambodia (18.7%), Thailand (11.9%), and others (16.6%). The areas where persons originally lived in North Korea were North Hamgyong (70.2%), South Hamgyong (11.3%), South Pyongan (3.4%), Ryanggang (3.2%), North Pyongan (3.0%), and others (8.9%).

Cases of active TB

Eighty-seven individuals with active TB were identified from 1999 to August 2006. Of these, 78 (90%) had pulmonary TB, three (3%) had TB pleurisy, four (5%) had TB lymphadenitis, one (1%) had TB meningitis, and one (1%) had TB spondylitis. In 27 individuals (31%), the diagnosis of active TB was confirmed bacteriologically. Thus, the preva-

Table 1. The prevalence of active TB infection and demographic features among the dislocated North Koreans

	1999	2000	2001	2002	2003	2004	2005	2006*	Total
Total	60	297	572	1,111	1,175	1,935	1,364	1,208	7,722
No. TB cases	–	–	8	8	11	28	17	15	87
Prevalence†	–	–	1,399	720	936	1,447	1,246	1,242	1,127
No. smear and/or culture+	–	–	2 (25.0)	5 (62.5)	5 (45.5)	6 (21.4)	5 (29.4)	4 (26.7)	27 (31.0)
Prevalence†	–	–	350	450	426	310	367	331	350
Sex									
Male	–	–	6 (75.0)	5 (62.5)	7 (63.6)	16 (57.1)	8 (47.1)	7 (46.7)	49 (56.3)
Female	–	–	2 (25.0)	3 (37.5)	4 (36.4)	12 (42.9)	9 (52.9)	8 (53.3)	38 (43.7)
Age yr, median (range)	–	–	38 (28-66)	35 (6-63)	34 (26-58)	35 (15-46)	28 (16-53)	32 (12-45)	35 (6-66)
Site of TB									
Pulmonary	–	–	7 (87.5)	7 (87.5)	11 (100)	24 (85.7)	15 (88.2)	14 (93.3)	78 (89.7)
Extrapulmonary	–	–	1 (12.5)	1 (12.5)	-	4 (14.3)	2 (11.8)	1 (6.7)	9 (10.3)
History of previous TB	–	–	3 (37.5)	6 (75.0)	4 (36.4)	14 (50.0)	9 (52.9)	8 (53.3)	44 (50.6)
Duration of chemotherapy	–	–	3 (0-3)	6 (1-9)	2 (0-5)	2 (0-18)	3 (1-8)	1.5 (0-18)	2 (0-18)
Duration of migration	–	–	32 (2-51)	16 (5-54)	45 (0-67)	15 (3-92)	20 (1-75)	18 (0-93)	21 (0-93)

Data are presented as number (%), median (range).
*From January until August 2006; †per 100,000 population. TB, Tuberculosis; +, positive.

Table 2. Epidemiologic data of TB by age group among the dislocated North Koreans

	0-4	5-14	15-24	25-34	35-44	45-54	55-64	≥65	Total
No. of dislocated North Koreans	77	521	1397	2488	2007	633	325	274	7,722
Prevalence									
Active TB*	–	576	859	1,125	1,495	1,738	615	365	1,127
Smear and/or culture+TB*	–	–	143	402	498	474	615	0	350
No. of tested by TST	12	62	195	419	291	76	39	18	1,112
Sex									
Male	10	29	60	46	58	15	9	4	231
Female	2	33	135	373	233	61	30	14	881
Positive (cutoff 10 mm)									
With BCG scar	1 (33.3)	8 (66.7)	79 (74.5)	264 (86.6)	235 (91.1)	42 (89.4)	10 (79.6)	4 (80.0)	643 (85.8)
Without BCG scar	1 (11.1)	21 (42.0)	61 (68.5)	93 (81.6)	29 (87.9)	28 (96.6)	21 (80.8)	9 (69.2)	263 (72.5)
Positive (cutoff 5 mm)									
With BCG scar	1 (33.3)	8 (66.7)	94 (88.7)	290 (95.1)	250 (96.9)	47 (100)	12 (92.3)	4 (80.0)	706 (94.3)
Without BCG scar	1 (11.1)	25 (50.0)	67 (75.3)	103 (90.4)	32 (97.0)	29 (100)	24 (92.3)	13 (100)	294 (81.0)
No. with BCG scar	3 (25.0)	12 (19.4)	106 (54.4)	305 (72.8)	258 (88.7)	47 (61.8)	13 (33.3)	5 (27.8)	749 (67.4)

Data are presented as number (%).
*per 100,000 population. TB, Tuberculosis; +, positive; TST, tuberculin skin tests; BCG, *Bacille Calmette-Guérin*.

lence of active TB was 1,127/100,000 and that of smear- and/or culture-positive TB was 350/100,000 (Table 1). The prevalence of active TB was higher in men than in women (1,733/100,000 vs. 776/100,000, $p<0.001$). The prevalence of selected age-specific active TB cases is shown in Table 2; 44 (51%) individuals had a history of previous active TB. Thirteen (14.9%) active TB cases were diagnosed at pre-departure screening before final entry into the Republic of Korea.

BCG vaccination scar and latent TB infection

After November 2005, 1,112 subjects were screened for their possible exposure to *M. tuberculosis* as shown by a TST. The survey of presence of BCG vaccination scars were also performed. Of these, 65 (5.8%) subjects had a history of previous active TB and 120 (10.8%) had a history of contacts with patients with active TB. BCG vaccination scars were found in 67.4%. A comparison of TST reactivity with the presence of BCG vaccination scars and cut-off values in the dislocated North Koreans are shown in Table 2 and Fig. 1. BCG vaccination scars were significantly less frequent in those aged under 30 yr than in those older (56.6% vs. 76.0%; $p<0.001$).

The tuberculin positive reaction (≥10 mm in diameter) rate was 81.5%. The positive rate of this TST was higher among participants with BCG scars than among participants without BCG scars (85.8% vs. 72.5%; odds ratio 2.31; 95% CI, 1.70-3.14). We performed an analysis of risk factors for a positive TST. The following factors were associated with a positive TST: a previous history of active TB, odds ratio 3.65

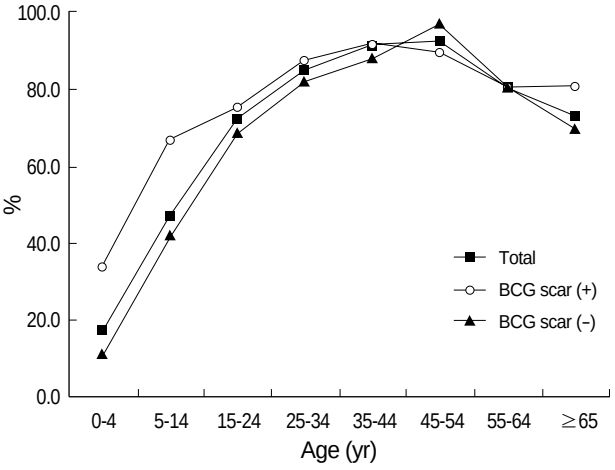

Fig. 1. Comparison of tuberculin skin test reactivity with the presence of BCG vaccination scars among the dislocated North Koreans.

(95% CI 1.31-10.14); contacts with active TB patients, 1.99 (95% CI 1.10-3.61); and the presence of a BCG scar, 2.31 (95% CI, 1.70-3.14). The annual risk of LTBI in the 5-14 yr-old age group without BCG scars (n=50) was 4.6% (mean duration of migration 16 months; mean age 11.1 yr).

Drug resistance

Of 78 active TB patients, there were 22 (40%) culture-positive patients. Of the 22 *M. tuberculosis* isolates obtained from the patients' respiratory specimens, 13 underwent DST. Of these, four (31%) isolates were susceptible to all available anti-tuberculosis drugs. The remaining nine isolates (69%) were resistant to at least one drug in vitro. Among these, six (67%) were resistant only to INH, and three (33%) were multi-drug resistant (MDR); one of these was a primary MDR form of TB and two were acquired MDR forms.

Comparison with statistics of the Republic of Korea

The reported rates of active TB among civilians in the Republic of Korea were 1,842/100,000 in 1990 and 1,032/100,000 in 1995 (6). The PR of active pulmonary TB was 1.29 (95% CI, 1.02-1.61), and the smear- and/or culture-positive PR was 2.03 (95% CI, 1.34-2.95). Among the dislocated North Koreans younger than 30 yr, 56.6% had BCG scars. In the Republic of Korea, 91.8% of individuals had BCG scars in 1995 (6). The LTBI rate of the North Korean refugees younger than 30 yr without BCG scars was 62.3%. In the Republic of Korea, this was 15.5% in 1995 (6). The PR of LTBI was 1.35 (95% CI, 1.12-1.60). The annual risk of LTBI in refugees aged 5-14 yr without BCG scars (n=50) was higher than among civilians of the Republic of Korea (4.6% vs. 0.5%) (6).

DISCUSSION

Since being liberated from Japanese rule in 1945, the Republic of Korea has achieved remarkable economic growth under democracy and a market economy. On the other hand, North Korea has maintained a socialist system and has suffered from economic crisis since the 1990s. Economic status not only directly influences the health level, but also indirectly affects it through influences on nutrition, hygiene, health resources, and other intervening factors (4, 7). During the peak years for public health in North Korea in 1980, the North Korean government claimed that active TB had been "eradicated" in the country (1, 3). However, since the public health crisis in North Korea after 1995, there has been a marked increase in the incidence of smear- and/or culture-positive TB. The abrupt decline in the presence rate of BCG vaccination scar among refugees younger than 30 yr in our study (56.6%) presumably reflects this decay in the North Korean health system. In North Korea, 11,050 cases of active TB were notified in 1997 and this increased to 41,810 in 2003 (184 cases per 100,000 population) (1). This was higher than in the Republic of Korea during the same period (33,888; 71 cases per 100,000 population) (1). Today, TB remains one of the most serious public health problems in North Korea.

By contrast, the government of the Republic of Korea has concentrated its limited resources for public health activities on TB control programmes, whereas the private sector has taken charge of constructing the health delivery system, including health facilities and human resources. The Republic of Korea has performed nationwide active TB prevalence surveys at five-yearly intervals from 1965 to 1995, and the results of the last (the seventh) survey have been reported (6). Over the past 30 yr the prevalence of direct smear-positive individuals has reduced from 683 to 93 per 100,000; that of smear- and/or culture-positive individuals has reduced from 940 to 219 per 100,000 and the prevalence of active TB has gone down from 5,065 to 1,032 per 100,000.

Since 1954, 8,313 North Korean refugees have entered Republic of Korea; 7,722 have entered since 1999 because of the economic crisis. Dislocated North Koreans may carry active TB and LTBI as a result of economic and cultural changes and psychological and environmental stresses (8). In this study, the prevalence of active TB was 1,127 per 100,000 in dislocated North Koreans, which is higher than that of the Republic of Korea in 1995 (1,032 per 100,000; PR 1.29; 95% CI 1.02-1.61). When persons migrate from such nations with poor health care, they often carry LTBI that may reactivate after arrival in the host country. The prevalence of LTBI among dislocated North Koreans aged under 30 years without a BCG scar was 62.3%, much higher than that of the Republic of Korea; 15.5% in 1995 (PR, 1.35; 95% CI 1.12-1.60). Because of the remarkable decline in the incidence of active TB in the Republic of Korea after 1995, the overall PR has been higher recently. Therefore, interventions

that target recent dislocated North Koreans can contribute both to the health of those individuals and to overall TB control in the Republic of Korea. The risk of progression to active TB is greatest soon after arrival; approximately half the active TB cases among immigrants from endemic countries occur during the first five years after immigration (9). Among these dislocated North Koreans, 38 newly active TB cases were diagnosed during the first years after entry into the Republic of Korea, and specialized re-screening programmes for dislocated North Koreans are required.

Outbreaks due to multi-drug-resistant TB (MDR-TB) have occurred in a number of locations, often associated with breakdowns in health care infrastructures. Because of the higher rate of previous treatments for active TB, immigration has been suggested as one factor leading to the increased prevalence of MDR-TB (10). In our study, although DST was performed for only 13 isolates, 69% of these were resistant to at least one drug in vitro and 23% were MDR; higher than those of the Republic of Korea (12.3% and 2.4%, respectively) (11). Rates of drug resistance among immigrant populations reflect the rates in the countries of origin, which are significantly higher in many developing countries than in developed countries (12). Incomplete and inadequate treatment is the most important factor leading to its development, suggesting that it is often a man-made tragedy (13). The high prevalence of MDR-TB among dislocated North Koreans thus reflects the poor infrastructure of the health care system of North Korea.

TB has always been associated with social stigma. Because refugees from North Korea are also at risk of discrimination, the stigma attached to active TB may raise formidable barriers to effective healthcare. Dislocated North Koreans may avoid seeking care for active TB, because of a fear that they will experience discrimination or isolation if they are associated with this contagious illness. The responses of medical providers, whether leaning toward xenophobia or compassion, will have major impacts on societal responses to dislocated North Koreans with active TB. The increased case of international travel has led to increasing recognition that infectious diseases have no borders (8).

This is the first report on the extent of active TB and LTBI in dislocated North Koreans settled in the Republic of Korea. However, there are limitations in our findings. Fewer than 40% of active TB cases were confirmed microbiologically, and few had DST results. The fact that anti-TB medication was initiated after pre-departure screening for active TB among 13 (15%) of the dislocated North Koreans with active TB might explain the lower rate of bacteriologic confirmation of the disease.

In conclusion, our results have documented the prevalence of active and LTBI among dislocated North Koreans. These people bear a disproportionate burden of infectious disease because of the circumstances under which they have migrated to the Republic of Korea. We need to initiate a specific control programme and to plan for the impact and control of TB in the Republic of Korea. In parallel with our efforts to improve the living standards of North Koreans and our consistent pursuit of a policy of reconciliation and cooperation towards the North, we are also trying to reduce or eliminate the causes for their exodus.

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