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Original Article

광업 이직근로자에서 잠복결핵감염 위험요인 분석

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Risk Factors for Associated with Latent Tuberculosis Infection among Former Mine Workers

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ABSTRACT

Objectives: To identify the positive rate of and the risk factors associated with latent tuberculosis infection(LTBI) in mine workers, the objectives of the present study evaluated those among former mine workers.

Methods: Between January 2015 and May 2017, former male mine workers who had been subjects for epidemiology research for work-related chronic obstructive pulmonary disease(COPD) and had received QuantiFERON-TB® Gold In-Tube(QFT-GIT) from the Institute of Occupation and Environment(IOE) under Korea Workers' Compensation and Welfare Service(KCOMWEL) were selected as the study subjects. To identify significant variables for increased risk of LTBI, logistic regression analysis was performed.

Results: A total of 736 male former mine workers were selected as study subjects. The positive rate of LTBI among subjects was 69.2%(509/736). The current smoking[odds ratio(OR), 2.3; 95% confidence interval(CI), 1.1-4.9], COPD(OR, 1.4; 95% CI, 0.9-2.3), department loading(OR, 1.8; 95% CI, 0.9-3.4) and mining(OR, 1.5; 95% CI, 0.9-2.5), and working duration of over 20(OR, 1.6; 95% CI, 0.9-3.1) and over 30 years(OR, 2.2; 95% CI, 0.9-4.9) were associated with increased risk of LTBI. The interferon-gamma(IFN-γ) level after stimulation with *Mycobacterium tuberculosis*(MTB)-specific antigens showed a significantly negative correlation with age(r=-0.126).

Conclusions: The present study determined that the high positive rate of LTBI among mine workers was associated with not only the host factors but also the occupational exposure to mine dust.

Key words: Chronic obstructive pulmonary disease, latent tuberculosis infection, mine worker, QuantiFERON-TB® Gold In-Tube

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배경: 광업 종사자에서의 잠복결핵감염(latent tuberculosis infection, LTBI) 양성율을 확인하기 위하여, 이번 연구에서는 광업 이직근로자에서 LTBI 양성율 및 위험요인에 대한 연구를 진행하였다.

방법: 근로복지공단에 만성폐쇄성폐질환(chronic obstructive pulmonary disease, COPD)으로 요양 신청하여 2015년 1월부터 2017년 5월까지 근로복지공단 직업환경연구원에서 업무관련성 역학조사 및 LTBI 검사를 받은 남성 광업 이직근로자를 연구대상자로 선정하였다. LTBI 검사는 QuantiFERON-TB® Gold In-Tube (QFT-GIT)를 이용하였고 LTBI 위험요인 분석에는 이분형 로지스틱 회귀분석을 이용하였다.

결과: 전체 736명의 연구대상자의 LTBI 양성율은 69.2%(509/736명)였다. 현재 흡연[odds ratio(OR), 2.3; 95% confidence interval(CI), 1.1-4.9], COPD(OR, 1.4; 95% CI, 0.9-2.3), 적재(loading; OR, 1.8; 95% CI, 0.9-3.4) 및 채탄부서(mining; OR, 1.5; 95% CI, 0.9-2.5), 근무기간 20년대(OR, 1.6; 95% CI, 0.9-3.1) 및 30년 이상 (OR, 2.2; 95% CI, 0.9-4.9)에서 LTBI 위험이 증가하는 것으로 나타났다. 연령의 경우 연령이 증가할수록 LTBI 양성율이 증가하는 경향을 보이고 있지만, LTBI 위험은 감소하는 것으로 나타났다. 연령과 결핵균 특이항원에 감작 후 생성되는 interferon-gamma(IFN-γ) 양은 유의한 음적 상관관계(r=-0.126)를 보여주고 있다.

결론: 광업종사자에서의 LTBI 양성율은 높은 것으로 나타났으며, 연령과 같은 숙주 요인 뿐만 아니라 광업분진 노출과 같은 직업적 요인도 LTBI 위험요인으로 나타났다.

키워드: 광업 종사자, 만성폐쇄성폐질환, 잠복결핵감염, QuantiFERON-TB® Gold In-Tube

I. Introduction

Active tuberculosis(active TB) is not only a major health problem among general population but also serious public problem among mine workers in South Korea. According to the data from the Korea Workers'Compensation and Welfare Service (KCOMWEL), the attack rate of active pulmonary tuberculosis(active PTB) among workers who were received the health examination for diagnosing pneumoconiosis and complications related to pneumoconiosis between 1984 and 2017 was 4.6%(1,744/37,946)(Hwang & Oh, 2018).

The respiratory diseases caused by exposure to mine dust also have a close relation to the development of active TB. Pneumoconiosis is manifested in one of the complications of pneumoconiosis under the act on the prevention of pneumoconiosis and protection, etc. of workers suffering from pneumoconiosis(Park et al., 2014). Among mine workers who were received the health examination for diagnosing pneumoconiosis and complications related to pneumoconiosis between 1981 and 2015, the attack rate of active PTB in patients with pneumoconiosis was 8.7% (1,228/14,183) by the data from the KCOMWEL. And silicosis is also classified as high-risk group of TB according to Korean Guidelines for Tuberculosis(JCRKGT & KCDC, 2017). The risk of developing active TB in patients with silicosis was 2.8(95% CI 1.9-4.1) times high compared to healthy population(Cowie, 1994). Chronic obstructive pulmonary disease(COPD) is also the risk factor associated with developing active TB and one of co-morbidities in patients with active TB (Inghammar et al., 2010; Lee et al., 2013; O'Toole et al., 2015). The risk of developing active TB in patients with COPD was 2.5(95% CI 2.2-2.8) to 3.0 (95% CI 2.4-4.0) times high compared to patients without COPD(Byrne et al., 2015). Accordingly, WHO recommends systemic screening of TB for patients with silicosis and COPD(WHO[b], 2015).

Latent tuberculosis infection(LTBI) is defined as not only a state of being infected with *Mycobacterium tuberculosis*(MTB) but also a state of persistent immune response to stimulation by MTB antigens without any clinical symptoms, radiological abnormality, or microbiological evidence (WHO[a], 2015). With an increased emphasis on the importance of preventive maintenance for TB, diagnostic tests and prophylactic treatment of LTBI are very important to reduce and control the incidence of TB. For this reason, recent global TB management strategy by World Health Organization (WHO) has extended to control LTBI. WHO recommends screening of and prophylactic

treatment for LTBI among high-risk groups of TB including people who are living with human immunodeficiency virus(HIV), people who are contact with of active TB patients, patients with silicosis, patients initiating anti-tumor necrosis factor(TNF) treatment, patients on dialysis, and transplant patients(WHO[a], 2015).

Because mine workers were increased risk of developing active TB by exposure to mine dust and related respiratory diseases, they might have an increased risk of LTBI by them. Therefore, the objectives of the present study were to evaluate the positive rate of LTBI and the risk factors associated with LTBI among former mine workers.

II. Material and Methods

1. Subject selection

The present study was designed to carry out the epidemiology research of occupational lung diseases. Between January 2015 and December 2017, 796 former male dusty workers who were received the epidemiology research for work-related COPD and QuantiFERON-TB® Gold In-Tube(QFT-GIT) test were selected as the study participants. Among these 796 participants, 60 were excluded(4 participants who were diagnosed with indeterminate result in QFT-GIT, 2 participants who had no result of the pulmonary function test(PFT), 9 participants who had no result of smoking status, 13 participants who were diagnosed with active PTB in the past, and 32 participant who worked in non-mining industry). Finally, total 736 former male mine workers selected as the study subjects.

Approved consent was obtained from all study participants. The present study protocol was received and approved by the institutional review board of Institute of Occupation and Environment (IOE), the KCOMWEL(approval no. 219993-201704-HR-03-01). Informed consent was submitted by all participants when they were enrolled.

2. Pulmonary function test

PFT was conducted with a bronchodilator test in accordance with the criteria for the standardization of PFT recommended by the American Thoracic Society/European Respiratory Society(ATS/ERS) using a Vitalograph Pneumotrac 6800(Vitalograph Inc., Lenexa, KS, USA)(Miller et al., 2005). The spirometer was calibrated at the start of each day using the Spirotrac software supplied with the spirometer. Subjects were allowed up to three attempts to provide two reproducible results. The normal predictive values for PFT result were calculated using a reference equation derived from the general population of Korea(Choi et al., 2005).

COPD was defined by the Global Initiative for Chronic Obstructive Lung Disease(GOLD) criterion based on PFT which was a forced expiratory volume in one second/forced vital capacity(FEV_1/FVC) less than 70%(GOLD, 2017).

3.QuantiFERON®-TB Gold In-Tube

MTB-specific antigens stimulation and The inferferon-gamma(IFN-γ) level in plasma were performed using the QuantiFERON®-TB GOLD (QFT) Tube(Cellestis/QIAGEN, Hilden, Germany) and QFT-GIT(Cellestis/QIAGEN, Hilden, Germany). The QFT tube was consisted of the Nil tube which is used for detecting basal level of immune response of peripheral blood cells(negative control), TB antigen tube which is used for detecting MTB-specific immune response of peripheral blood cells(MTB-specific antigens stimulation), and Mitogen tube which is used for detecting immune cell function(positive control). The QFT tube and QFT-GIT were used according to the manufacturer's instructions(Mori et al., 2004).

The QFT-GIT results were interpreted using

QFT analysis software version 2.62. The IFN-γ level of 0.35 international unit(IU)/ml(after subtraction of the IFN-γ concentration level of TB antigen tube from that of Nil tube) after exposure to MTB-specific antigens was considered positive for QFT-GIT and 〈0.35 IU/ml was considered negative. If the IFN-γ level of Mitogen tube was 〈0.5 IU/ml higher than that of the Nil tube or 〉8.0 IU/ml higher than that of the Nil tube, the result was considered indeterminate. LTBI positive defined as the positive results of QFT-GIT test.

4. Statistical analysis

The variables were categorized according by those characteristics and described as the frequency and proportion. Differences between subjects who diagnosed with LTBI positive and those who diagnosed with LTBI negative in the categorized variables were analyzed using chi-square test. To calculate the odds ratio(OR) for each variable and select significant variables for increased risk of the positive result for LTBI, logistic regression analysis was performed. Correlation between the result of QFT-GIT and variables which associated with decreased risk of LTBI was calculated using Pearson correlation coefficient analysis.

Statistical analysis of all outcomes variables was performed using Statistical Package for Social Science(SPSS) version 19.0 for windows (IBM/SPSS Inc., Chicago, IL, USA). Differences were considered significant with p-values less than 0.05.

Ⅲ. Results

All QFT-GIT tests for diagnosis of LTBI were conducted by IOE. Among 736 subjects, 155 (21.1%) did a PFT at IOE and 581(78.9%) obtained PFT data from the health examination results for diagnosing work-related COPD. The median age of total subjects was 71 years(range 59-84 years). 84.3%(620/736) of total subjects were diagnosed with COPD. The positive rate of LTBI among total subjects was 69.2%(509/736). There was a significant difference in smoking status(p=0.036) between subjects who were diagnosed with LTBI positive and those who were diagnosed with LTBI negative. Otherwise, there was no significant difference in age(p=0.053), comorbidities (p=0.191), departments(p=0.184), and working duration(p=0.413) between two groups(Table 1).

The only current smoking was significantly associated with increased risk of LTBI both in the univariate(OR, 2.4; 95% CI, 1.2-4.8) and multivariate logistic analysis(OR, 2.3; 95% CI, 1.1-4.9). Although they did not show significant results, COPD(OR, 1.4; 95% CI, 0.9-2.3), department of loading(OR, 1.8; 95% CI, 0.9-3.4) and mining (OR, 1.5; 95% CI, 0.9-2.5), and working duration of 10s(OR, 1.2; 95% CI, 0.7-2.0), 20s(OR, 1.6; 95% CI, 0.9-3.1), and over 30 years(OR, 2.2; 95% CI, 0.9-4.9) were associated with increased risk of LTBI(Table 2).

The age of 60s(OR, 1.2; 95% CI, 0.5-2.6) was also associated with increased risk of LTBI. However, the age over 70 years was associated with decreased risk of LTBI. The IFN-γ level after stimulation with MTB-specific antigens(TB antigen tube) only showed a significantly negative correlation with age(r=-0.126, p=0.001).

Ⅳ. Discussion

With regard to occupational factors, WHO recommended that screening and prophylactic treatment of LTBI should be performed in patients with silicosis and considered for prisoners and healthcare workers(HCWs)(WHO[a], 2015). Accordingly, the Korean Centers for Disease Control and Prevention(KCDC) also recommended annual screening tests for LTBI in congregate setting

Table 1. Comparison of characteristics between former male mine workers who were diagnosed with LTBI positive and those who were diagnosed with LTBI negative

Characteristics	Total(N=736)	LTBI positive(N=509)	LTBI negative(N=227)	*P*-value
Age categorized, N(%)				0.053
50-59	39(5.3)	28(5.5)	11(4.8)	
60-69	258(35.1)	194(36.1)	64(28.2)	
70-79	360(48.9)	237(46.6)	123(54.2)	
80-	79(10.7)	50(9.8)	29(12.8)	
Smoking status, N(%)				0.036
None	118(16.0)	78(15.3)	40(17.6)	
Former	545(74.1)	37 (72.9)	174(76.7)	
Current	73(9.9)	60(11.8)	13(5.7)	
Comorbidities, N(%)				0.191
None	96(13.1)	62(12.2)	34(15.0)	
Others	8(1.1)	8(1.6)	0(0.0)	
COPD	620(84.3)	432(84.8)	188(83.2)	
Multiple	11(1.5)	7(1.4)	4(1.8)	
Departments, N(%)				0.184
Etc.	79(10.7)	49(9.6)	30(13.2)	
Transport	46(6.3)	28(5.5)	18(7.9)	
Loading	126(17.1)	93(18.3)	32(14.5)	
Drilling	7(1.0)	4(0.8)	3(1.3)	
Pillar	20(2.7)	11(2.2)	9(4.0)	
Mining	458(62.2)	324(63.7)	134(59.1)	
Working duration, categorized, N(%)				0.413
0-9	74(10.1)	49(9.6)	25(11.0)	
10-19	447(60.7)	302(59.4)	145(63.9)	
20-29	158(21.5)	115(22.6)	43(18.9)	
30-	57(7.7)	43(8.4)	14(6.2)	

P-value was calculated by chi-square test for variables between former male mine workers who were diagnosed with LTBI positive and those who were diagnosed with LTBI negative.
LTBI, latent tuberculosis infection; COPD, chronic obstructive pulmonary disease; Multiple, COPD and other diseases

including prisoners, soldiers, students, HCWs, and etc.(KCDC, 2018). The positive rate of LTBI in workplace had the second highest level among congregate setting after correctional facility(Kim & Choi, 2019). It might be necessary to screening testing of LTBI and prophylactic treatment of LTBI positive among mine workers. In order that, it is important to identify the positive rate of LTBI and the risk factors for LTBI among mine workers.

In the present study, the positive rate of LTBI among former male mine workers(mean age 71 years, 69.2%) was higher than that among former male mine workers with pneumoconiosis (median age 67.0 years, 66.4%)(Jin et al., 2018), aged underground hard coal miners(mean age 75 years, 46.6%)(Ringshausen et al., 2013), close contacts of active TB patients(age over 65 years, 37.5%)(Chee et al., 2004), or general population (age over 60 years, 40.0%)(Gao et al., 2015). The positive rate of LTBI among former male mine

Table 2. Logistic regression analysis for factors associated with increased risk of LTBI among former male mine workers

Characteristics	N(%)	Univariate OR(95% CI)	*P*-value	Multivariate OR(95% CI)	*P*-value
Age					
50-59	39(5.3)	1		1	
60-69	258(35.1)	2.5(0.3-19.5)	0.382	1.2(0.5-2.6)	0.663
70-79	360(48.9)	0.8(0.1-6.1)	0.858	0.8(0.4-1.7)	0.508
80-	79(10.7)	0.3(0.0-4.0)	0.327	0.8(0.3-1.8)	0.550
Smoking status					
None	118(16.0)	1		1	
Former	545(74.1)	1.1(0.7-1.7)	0.678	1.1(0.7-1.6)	0.790
Current	73(9.9)	2.4(1.2-4.8)	0.017	2.3(1.1-4.9)	0.023
Comorbidities					
None	96(13.1)	1		1	
Others	8(1.1)	ND	ND	ND	ND
COPD	620(84.3)	1.3(0.8-2.0)	0.316	1.4(0.9-2.3)	0.145
Multiple	11(1.5)	1.0(0.3-3.5)	0.950	1.1(0.3-4.3)	0.846
Departments					
Etc.	79(10.7)	1		1	
Transport	46(6.3)	1.0(0.5-2.0)	0.898	1.0(0.5-2.2)	0.145
Loading	126(17.1)	1.7(0.9-3.2)	0.076	1.8(0.9-3.4)	0.059
Drilling	7(1.0)	0.8(0.2-3.9)	0.799	0.7(0.1-3.8)	0.718
Pillar	20(2.7)	0.7(0.3-2.0)	0.748	0.9(0.3-2.7)	0.908
Mining	458(62.2)	1.5(0.9-2.4)	0.122	1.5(0.9-2.5)	0.121
Working duration					
0-9	74(10.1)	1		1	
10-19	447(60.7)	1.1(0.6-1.8)	0.819	1.2(0.7-2.0)	0.538
20-29	158(21.5)	1.4(0.8-2.5)	0.306	1.6(0.9-3.1)	0.117
30-	57(7.7)	1.6(0.7-3.4)	0.254	2.2(0.9-4.9)	0.060

LTBI, latent tuberculosis infection; OR, odds ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; Multiple, COPD and other diseases; ND, not detected

workers with COPD(69.5%) was also higher than that among aged underground hard coal miners with COPD (40.3%)(Ringshausen et al., 2013). However, there was no significant difference in the positive rate of LTBI between former male mine workers with COPD and those without COPD(69.5% vs. 67.3%).

In the multivariate logistic regression analysis including all variables, current smoking was significantly associated with increased risk of LTBI. comorbidities(COPD), departments(loading and mining), and working duration were associated with increased risk of LTBI. The age was a most important risk factor associated with increased risk of LTBI(Ringshausen et al., 2013; Gao et al., 2016). In the present study, increased age increased the positive rate of LTBI(linear by linear association, p=0.016). The age of 60s was associated with increased risk of LTBI. However, increased age decreased the risk of LTBI after the age of 70. The IFN-γ level after stimulation with MTB-specific antigens showed a significantly

negative correlation with age.

The limitation of present study was that although the positive rate of LTBI among former male mine workers was higher than the previous studies, it was difficult to recommend the screening of LTBI and prophylactic treatment for LTBI positive in mine workers. Because 30% of the people who contact with active TB patients convert to the LTBI and 10% of those develop active TB. In other words, 90% of them do not develops active TB(Lee, 2015). And, due to the side-effects of hepatotoxicity, it was not recommend the prophylactic treatment for LTBI positive among individuals aged over 65 years (JCRKGT & KCDC, 2017). So, it was necessary to follow-up study of the development of active TB among former male mine workers who were diagnosed with LTBI positive. Another limitation of present study, because there is no gold standard of direct test for LTBI in humans, only indirect test using the identification of immune response to stimulation with MTB-specific antigens was used for the diagnosis of LTBI (Inghammar et al., 2010). Although Tuberculin Skin Test(TST) detects cellular immune responses to MTB purified protein derivatives(PPD) which include non-MTB-specific mycobacterial proteins, IFN-γrelease assay(IGRA) detects IFN-γ released after stimulation with MTB-specific antigens. QFT-GIT and T-SPOT.TB(Oxford Immunotec, Abingdon, UK) are developed as commercial IGRA for LTBI diagnosis(Shah et al., 2012). The sensitivity and specificity of commercial IGRA are known to be higher than those of TST(Harada et al., 2008). However, IGRA causes inadequate detection rate and considerable indeterminate results in immunosuppressed patients(Ferrara et al., 2006; Luekemeyer et al., 2007; Menzies et al., 2007; Matulis et al., 2008). Especially, IFN-γ level of coal workers and those with pneumoconiosis was higher than that of normal control(Yao et al., 2018). Therefore, only measuring IFN-γ in IGRA could not represent entire T-cell related immune response to MTB infection among mine workers.

Ⅴ. Conclusion

The positive rate of LTBI among former mine workers was higher than that of previous studies. Although they were not showed significant results, comorbidities, departments, and working duration were associated with increased risk of LTBI. So, the present study determined that the high positive rate of LTBI among mine workers were associated with not only the host factors such as age, smoking status, and etc. but also the occupational exposure to mine dust.

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