Original Article

TUBERCULOSIS AMONG NURSES IN AICHI PREFECTURE, JAPAN

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Abstract [Objectives] To elucidate TB transmission among nurses.

[Subjects and Methods] The subjects of this retrospective study were 1,283 TB women aged 20−59 years registered in Aichi Prefecture between 1989 and 2003. All registration files were reviewed to identify their occupation and working places.

[Results] A total of 80 nurses were found among TB registers. Their age distribution was 45 (56.2%) in 20−29 years, 15 (18.8%) in 30−39 years, 14 (17.5%) in 40−49 years, and 6 (7.5%) in 50−59 years. The proportion of nurses aged 20−29 years decreased from 74.2% in 1989−93 to 24.0% ($p<0.001$) in 1999−2003, while those aged 40−49 years increased from 2.9% to 32.0% ($p<0.01$). Regarding working places, 19 (23.8%) were in 4 TB hospitals, 54 (67.4%) in other 35 hospitals, 6 (7.5%) in 6 clinics, and one (1.3%) was in a home. The proportion of nurses in TB hospitals decreased from 31.4% in 1989−1993 to 4.0% ($p<0.05$) in 1999−2003. Out of 73 nurses working in hospitals, 58 (79.5%) were working in hospitals with more than 250 beds with an emergency department. TB incidence were 49.1 per 100,000 population among 73 nurses working in hospital, and 14.3 among 6 nurses working in clinic, 39.5 among total 80 nurses, and 13.2 among 1,203 women other than nurses. The relative risk was 3.7 for hospital nurses, 1.1 for clinic nurses, and 3.0 for whole 80 nurses.

[Conclusion] These findings suggest that TB incidence for nurses is 3-fold higher than age-matched women other than nurses, and that hospital nurses are infected with TB more frequently than clinic nurses.

Key words: Nurse, Tuberculosis, Incidence rate, Occupation risk, Relative risk

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Original Article

USEFULNESS OF QuantiFERON®TB-2G IN A SUSPECTED CASE OF DRUG RESISTANT TUBERCULOSIS OUTBREAK IN A UNIVERSITY

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Abstract [Objective] To diagnose *M. tuberculosis* infection and select subjects for chemoprophylaxis in a contact investigation, we used the whole blood interferon-γ response test, QuantiFERON®TB-2G (QFT), and examined the usefulness of QFT.

[Subjects and Methods] The index case (heavily positive for sputum smear, at grade 6 by Gaffky system, the duration of coughing being 8 months; hence the infectious risk index is 48) was found at a periodic mass health examination before proceeding to the second grade in a university. Since TB outbreak was suspected based on the results of tuberculin skin test (TST) in the contact investigation, QFT test was carried out to determine the subjects for chemoprophylaxis and to define the target of further contact investigations.

[Results] In the first TST, 57 contacts showed erythema of more than 30 mm in diameter, and these contacts would have been indicated for chemoprophylaxis based on TST results. Thus, this case would have been designated as a TB outbreak, and further investigation should be necessary for less close contacts. However, twice QFT tests revealed that only five contacts were positive for QFT (three showed erythema diameter of more than 30 mm, and two less than 29 mm). These five contacts were indicated chemoprophylaxis. Thus, the number of the secondary infections did not fulfill the criterion defined as a TB outbreak, and therefore an extended contact investigation was stopped. No contact has developed TB so far.

[Conclusion] QFT test was shown to be useful for determining subjects for chemoprophylaxis and selecting the range of the contact investigation.

Key words: Tuberculin skin test, QFT, Contact investigation, Latent tuberculosis infection, Chemoprophylaxis

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DRUG-INDUCED HEPATOTOXICITY CAUSED BY ANTI-TUBERCULOSIS DRUGS IN TUBERCULOSIS PATIENTS COMPLICATED WITH CHRONIC HEPATITIS

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Abstract [Objectives] To investigate retrospectively the incidence of drug-induced hepatitis (DIH) caused by anti-tuberculosis drugs including isoniazid (INH), rifampicin (RFP), with and without pyrazinamide (PZA), and to evaluate risk factors for DIH in tuberculosis patients complicated with chronic hepatitis (CH).

[Materials] One hundred and seven tuberculosis patients with CH (M/F＝96/11, mean age±SE, 60.8±1.4 yr) admitted to our hospital during 1998−2006, whose laboratory data had been followed before and at least 2 months after starting anti-tuberculosis chemotherapy, were enrolled in this study. Of these, 58 were being treated with anti-tuberculosis chemotherapy consisting of INH, RFP and PZA (HRZ group) and the remaining 49 with INH and RFP (HR group). For a case-control study, patients admitted to the hospital during the same period and without CH were selected to each CH patient (n＝107) of the same gender, the same treatment regimens, and the same age. Clinical diagnosis of CH was based on laboratory data and in some cases pathological findings; etiology of CH was C-CH (CH caused by hepatitis C virus) in 68 patients, B-CH (CH caused by hepatitis B virus) in 23, and alcoholic CH in 16.

[Methods] DIH was defined by elevation of serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) at 1 or 2 months after starting anti-tuberculosis chemotherapy. For patients with serum levels of AST or ALT already abnormally high before starting chemotherapy, an increase of ＞1.5 times from the initial serum level was defined to indicate DIH, whereas for patients with AST and ALT within the normal range, and increase of ＞3× the normal upper limit was defined to indicate DIH. The incidence of DIH was calculated separately in the groups HRZ and HR for patients with and patients without CH (control). In the HRZ group, the severity of DIH was defined by the maximum serum levels of AST and ALT, and their mean values were compared between CH patients and the control. Risk factors for DIH were examined by comparing patients with and without CH. The clinical course after development of DIH was also followed.

[Results] The incidence of DIH in the HRZ group was 13/58 (22.4%) for CH patients and 10/36 (27.8%), 2/13 (15.4%) and 1/9 (11.1%) for C-CH, B-CH and alcoholic hepatitis patients, respectively, which was significantly ($p<0.05$) higher than that in the control [4/58 (6.9%)]. Confining to the C-CH patients, the incidence of DIH was 10/36 (27.8%) compared with the control 2/36 (5.6%) ($p<0.05$). In contrast, the incidence of DIH in the HR group was not significantly different between CH patients and the control, [2/49 (4.1%) vs 2/49 (4.1%)], respectively.

The severity of DIH in the HRZ group estimated by the maximum level of serum AST and ALT was not significantly different in CH patients and the control (176.6±28.1 vs 311.0±154.5 IU/L for AST and 187.8±19.1 vs 277.8±72.4 IU/L

for ALT).

Of the 13 CH patients suffering from DIH caused by anti-tuberculosis chemotherapy containing INH, RFP and PZA, 3 were continued treatment without altering the regimen, and 9 were continued treatment after changing the regimen to INH and RFP, omitting PZA.

The one remaining patient was re-treated using INH, RFP and ethambutol (EB), but this again resulted in development of DIH, and he was ultimately treated with INH, EB and levofloxacin, with a successful outcome. Thus, at least 12 out of the 13 CH patients who developed DIH in the HRZ group could be treated by an anti-tuberculosis chemotherapy regimen containing INH and RFP excluding PZA.

In C-CH patients who were treated with INH, RFP and PZA, the incidence of DIH was significantly higher when the daily alcohol intake was ＞20g [8/18 (44.4％)] compared with those ＜20g [0/10 (0％)] ($p < 0.05$), indicating that alcohol is a risk factor for DIH in C-CH patients treated with INH, RFP and PZA.

[Conclusions] In CH patients, anti-tuberculosis chemotherapy containing INH and RFP without PZA can be used safely. The inclusion of PZA in the regimen does substantially increase the incidence of DIH but nonetheless it can be used with caution, especially bearing in mind that daily alcohol intake of ＞20 g is a significant risk factor for C-CH patients.

Key words: Chronic hepatitis, Hepatitis C virus, Drug-induced hepatotoxicity (DIH), Anti-tuberculosis chemotherapy, Anti-tuberculosis drugs, Tuberculosis

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A CASE OF MULTI-DRUG RESISTANT TUBERCULOSIS SHOWING PSYCHIATRIC ADVERSE EFFECT BY CYCLOSERINE

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Abstract A 45-year-old man with multi-drug resistant tuberculosis were referred to our hospital for treatment. We started chemotherapy with cycloserine (CS), ethionamide (TH), kanamycin (KM), pyrazinamide (PZA), para-aminosalicylic acid (PAS) and gatifloxacin (GFLX). Two months later, psychosis and seizure occurred and worsened day after day. We suspected that these symptoms were due to CS. After stopping CS, psychosis and seizure disappeared. After surgical operation, positive tubercle bacilli in sputum converted to negative both on smear and culture. He was successfully discharged from our hospital. We should take care on side effects with second-line drugs that are often used in treating multi-drug resistant tuberculosis.

Key words: Multi-drug resistant tuberculosis, Cycloserine, Adverse effect, Seizure, Psychiatric symptom

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A CASE OF *MYCOBACTERIUM INTRACELLULARE* PLEURISY WITHOUT ACTIVE LUNG LESION

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Abstract Pleural effusion without occurrence of active pulmonary lesion due to nontuberculous mycobacteria is extremely rare. We report a case of *Mycobacterium intracellulare* pleurisy in an 84-year-old woman. The patient was admitted to a nearby hospital because of dyspnea. Massive right pleural effusion was observed on chest roentgenogram. Bacteriological examinations, smear and culture of the sputum or pleural effusion were negative. First we thought pleurisy was caused by *M. tuberculosis* as pleural effusion showed predominant lymphocyte count and high adenosine deaminase level. However, *M. intracellulare* was identified by the polymerase chain reaction method from pleural effusion. Based on clinical findings and laboratory data, we suspected pleurisy was due to *M. intracellulare* infection. Clarithromycin, kanamycin, rifampicin and ethambutol were administered. After four months of treatment pleural effusion disappeared without accompanying the active pulmonary lesion. Therefore, we diagnosed this case as pleurisy without pulmonary lesion due to *M. intracellulare*.

Key words: Nontuberculous mycobacteriosis, Pleurisy, *Mycobacterium intracellulare*

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The 82nd Annual Meeting President Lecture

THE QFT-TEST, A NEW TOOL FOR CONTROL OF NOSOCOMIAL INFECTION OF TUBERCULOSIS

Mitsunori SAKATANI

Abstract In Japan, nosocomial transmission of tuberculosis from patients to hospital workers is not rare yet. The morbidity rate of tuberculosis among workers in national hospitals is higher (45.7 in 2003−2005) than the Japanese average rate (24.8 in 2003). The rate is especially high among nurses, indicating 73.2 in 3 years from 2003 to 2005.

Although the indivisuals with latent tuberculosis infection (LTBI) are usually detected by tuberculin skin test in contact investigation, determination is not strict in BCG-vaccinated indivisuals. A novel diagnostic method (QFT-2G; QFT-test) can detect TB infection regardless past history of BCG vaccination. The tuberculin skin test and QFT-test were concurrently studied with 259 workers in National Hospital Organization Kinki-chuo Chest Medical Center. It is conjectured from the study-results that the QFT-test is a more accurate tool for detecting LTBI. Similar studies as 3 contact investigations in Kobe-city also came to the same inference.

Although QFT-test is still new, and some questions remain to be answered, that is a useful test in medical examination for hospital workers, providing a new tool for control of nosocomial infection of TB.

Key words: Measures against nosocomial transmission of tuberculosis, Tuberculin test, QFT test

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The 82nd Annual Meeting Educational Lecture

MULTI-DRUG RESISTANT TUBERCULOSIS (MDRTB)

Katsuhiro SUZUKI

MDRTB has been made by treatment failure and has also spread by its contagiousness. I tried to explain how to make MDRTB clinically, and also tried to propose how to prevent it from spreading in a hospital. At first, a principle of modern chemotherapy against tuberculosis was elucidated, i.e. "bi-phase method of treatment." Danger of mono-therapy, particularly functional one, was warned through a case report. Thus acquired drug-resistance was made, single at first, multi-drug thereafter. According to the increase of patients of acquired MDRTB, primary MDRTB patient has emerged through the direct contagion. We reported nosocomial outbreak cases of MDRTB, including re-infection to patients with pan-sensitive tuberculosis. Therefore, strict isolation of MDRTB with smear-positive sputum must be instituted in a tuberculosis ward. All smear-positive tuberculosis patients should be isolated in a room against air-borne infection just in case of MDRTB. There are, however, not enough isolation rooms in tuberculosis ward in Japan. Rapid detection of rifampicin-resistance through the gene analysis must be done in this situation.

Key words: MDRTB, Chemotherapy, Prevention of nosocomial infection

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MYCOBACTERIAL TESTS

Chairpersons: [1]Tetsuya TAKASHIMA and [2]Takeshi HIGUCHI

Abstract Tuberculosis is a bacterial disease caused by organisms of the *M. tuberculosis* complex, which is transmitted primarily by airborne droplet nuclei. Rapid and accurate detection of the bacilli is crucial for breaking the chain of transmission. Therefore, mycobacteriology laboratories have a major role to play in it. In this year, "the guideline for testing of *M. tuberculosis*, 2007" has been published. Here, it is emphasized that mycobacteriology laboratories must optimize their procedures for reporting results on the basis of current CDC recommendation: (i) reports of acid-fast examination of specimens within 24 hours of specimen collection, (ii) identification of *M. tuberculosis* within 21 days of specimen collection, and (iii) reports of drug susceptibility tests within 30 days of specimen collection. However, rapid mycobacteriology practices using liquid culture medium have many aerosol-generating handlings. Safety procedures, using a class Ⅱ biological safety cabinet and so on, must be enforced for protecting laboratory personnel. As the improved technology available for use in mycobacteriology laboratories, such as nucleic acid amplification tests and others, are quite complicated, quality control is much more important than before.

In this symposium, the 6 writers of "the guideline for testing of *M. tuberculosis*, 2007" have described the revised points of each chapters. We, as the chairpersons of this symposium, hope that this symposium would move a step forward toward rapid and accurate mycobacteriology practices in Japan.

1. Mycobacterial examinations and quality assurance: Satoshi MITARAI

It is well recognized that the mycobacterial examinations require careful quality assurances to perform highly reliable and safe laboratory examinations. As of 2003, a questionnaire survey was conducted to investigate the real state of laboratory examinations for mycobacterium. A total of 579 laboratories (291 of 390 hospitals and 288 of 397 private commercial laboratories) sent the replies, and the results were analysed from the points of quality assurance. Many laboratories adopted the sample concentration method and liquid culture methods. Meanwhile, the quality assurance activities for all examinations were not good enough to keep the quality and reliability. An effective quality assurance system should be necessary to maintain the good laboratory performances.

2. Revised "The guideline for testing of *M. tuberculosis*, 2007": Chiyoji ABE

Rapid detection, species identification, and testing for drug resistance are necessary to control tuberculosis among patients and populations. Tuberculosis control officials and clinicians need access to prompt and reliable tuberculosis laboratory services.

3. The value of proper sputum collection instruction in detection of acid-fast bacillus: Takeshi HIGUCHI

Modern techniques including molecular biology have been applied to routine laboratory works for rapid detection, identification, and drug susceptibility testing of mycobacteria. Even in using such techniques, however, poor quality specimens yield only poor results. To get a high quality specimen, particularly sputum samples, is very important. Therefore, laboratory technicians in our hospital have directly taught each patient how to expectorate good quality sputa since 2001. The teaching of patients has improved the rate of P1 samples from 21.5% to 36.6% by Miller and Jones visual score of sputum. The teaching has also improved the rate of smear positive P1 samples from 11.4% to 28.8%. To teach patient how to get good sputa seems for useful for keeping the laboratory quality high.

4. The latest information for culture and the identification of

acid-fast bacillus: Hajime SAITOH

Culture methods are much more sensitive than smear ones to detect mycobacteria in the specimens. However, the duration of isolation by solid mediums is considerably long. Contemporary liquid culture methods allow for the rapid detection of *M. tuberculosis* complex, especially in smear positive samples. Therefore, in "the guideline for testing of *M. tuberculosis*, 2007", we recommend the routine use of liquid medium such as MGIT (Mycobacteria Growth Indicator Tube) or KRD in clinical laboratories. We also recommend the use of a simple immunochromatographic assay, Capilia TB, for rapid confirmation of the *M. tuberculosis* complex in liquid cultures.

5. The present condition of molecular detection and identification, and a future view: Mitsuaki NAGASAWA

"The guideline for testing of *M. tuberculosis*, 2007" and the present condition of genetic screening, and a future view were described. It described about the kind of molecular detection and identification kit of Mycobacteria, results, an inspection request and extraction of a sample, preservation, and the measure against a biohazard. Moreover, it described also about quality assurance and the interpretation of a result.

6. Susceptibility testing of *Mycobacterium tuberculosis*: Toyoko OGURI

Included below is a summary in susceptibility testing. The 9 methods that are used in the susceptibility test of *Mycobacterium* are in Table 1. The Committee for Mycobacterial Examination considered that a susceptibility test was attached great importance to rapidly reporting. (1) The target of organism for susceptibility test is *Mycobacterium tuberculosis* complex only. (2) The standard method is proportion methods using ogawa medium. (3) The inoculum suspension is recommended subculture growth in broth. (4) Rapid broth methods for susceptibility testing of *M. tuberculosis* are recommended susceptibility results for *M. tuberculosis* complex could be reported within 28 days of receipt of the specimen in the laboratory. (5) The detection of *rpoB* gene is added to the new method.

Key words: Rapid detection, Quality assurances, Sputum collection instruction, Identification, Molecular detection, Susceptibility test

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