Review Article

PRESENT STATUS OF STUDIES ON EPIDEMIOLOGY AND MOLECULAR EPIDEMIOLOGY OF *MYCOBACTERIUM KANSASII*, IN SPECIAL REFERENCE TO ITS MOLECULAR EPIDEMIOLOGY

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Abstract There appears to be some genetic diversity among *Mycobacterium kansasii* (*M.kansasii*) isolates recovered throughout the world. Restriction analysis of heat shock protein 65-polymerase chain reaction-restriction analysis (*hsp65*PRA) showed that *M.kansasii* contains seven subspecies genetically distinct from *M.kansasii* isolates. *M.kansasii* genotype I is predominant in Japan and shows a very tight clonal structure. Different molecular typing methods including the 16S-23S rRNA spacer (ITS) region, RFLP, and PFGE analysis have been applied to isolates worldwide, and *M.kansasii* genotype I, as defined by *hsp65*PRA, appears to be highly clonal and the most common genotype associated with human disease. However, the identification of *M.kansasii* at the subtype level may possibly be more than just an interesting epidemiological tool; it may be relevant to determining the infectious pathway and clinical management of individual cases, as it allows the differentiation of potentially pathogenic subtypes from non-pathogenic subtypes. This review has been followed by the first review of the epidemiology of *M.kansasii*, and summarizes the evidence of molecular epidemiology and establishes the validity and importance of studies of *M.kansasii*. Further, the more precise definition of various *M.kansasii* isolates herein should provide a significant contribution to the understanding of key aspects of its biology, genotype, and molecular epidemiology.

Key words: *Mycobacterium kansasii*, Molecular epidemiology, Genetic typing, *hsp65*PRA, PFGE

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Review Article

TUBERCULOSIS SCREENING OF FOREIGNERS IN EUROPEAN, NORTH-AMERICAN, AND OCEANIAN COUNTRIES

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Abstract [Purpose] To plan a tuberculosis control program of foreign-born people in Japan, we reviewed the policies of tuberculosis screening on entrance for immigrants and non-immigrant visitors other than refugees and asylum-seekers in European, North American and Oceanic countries.

[Methods] Medical literature review and Internet search for the official governmental web sites.

[Results] In most countries, the main targets of tuberculosis screening programs for foreign-born people are refugees and asylum-seekers. Very few countries have a tuberculosis screening system on entrance for non-immigrant visitors. Such counties include Norway, the Netherlands, UK, Canada, New Zealand and Australia. The USA only screens immigrants who will settle permanently in USA. Screening policies and methods are highly variable, but many of the screening systems are not working well. The effectiveness of mass screening on entrance by chest X-ray, as a tuberculosis control program, is not well analyzed, and the validity of such screening is questionable.

[Conclusion] It is not accurate to think that a tuberculosis-screening program for foreign-born people on entrance to a country is an effective world standard. We must adopt a wider perspective in planning a tuberculosis control program for foreign-born people, including community-based approaches.

Key words: Tuberculosis, Foreign born, Refugee, Screening, Children

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EVALUATION OF GenoType® MTBDR*plus* FOR THE DETECTION OF MULTI-DRUG-RESISTANT *MYCOBACTERIUM TUBERCULOSIS* STRAINS

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Abstract [Objective] To evaluate GenoType® MTBDR*plus* (Hain Lifescience, Germany) for its capacity to detect the resistance of rifampicin (RFP) and isoniazid (INH).

[Method] A total of 44 confirmed multi-drug resistant (MDR) and 67 susceptible *M.tuberculosis* strains were tested for susceptibility to RFP and INH by GenoType®MTBDR *plus*. The core 81bp region of the *rpoB* gene and the 322bp region of the *katG* gene and the *inhA* gene (248bp of which included the promoter and the ORF of the 379bp *inhA*) were directly sequenced for both MDR-TB and susceptible *M. tuberculosis* strains, and the mutations were confirmed. Susceptibility was tested by standard proportion method with 1% Ogawa medium.

[Results] The sensitivities of GenoType® MTBDR*plus* for RFP and INH resistance were 97.7% and 65.9%, respectively. The specificity for RFP and INH was 100%. The sensitivity of GenoType® MTBDR*plus* was almost equivalent to the sequencing method for RFP, but that for INH was slightly inferior to the sequencing without significant difference. Geno Type® MTBDR*plus* detected 97.7% of the mutations of *rpoB* compared with the direct sequencing. It also detected 24 *katG* MUT1 (S315T1) (54.5%) and 5 *inhA* MUT1 (C15T) mutations (11.4%), while the direct sequencing detected an additional 2 (4.5%) *katG* mutants.

[Discussion] The accuracy of GenoType®MTBDR*plus* for the detection of RFP resistance was confirmed to be comparable to that of DST using conventional culture-based methods, while it was less accurate for detection of INH resistance. GenoType® MTBDR*plus* is useful for early diagnosis and infection control for MDR-TB because it has a short turn-around time of approximately 6 hours.

Key words: Line probe assay, Rifampicin, Isoniazid, Multi-drug-resistant *Mycobacterium tuberculosis*, *rpoB*, *katG*, *inhA*

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Original Article

CLINICAL FEATURES OF FOREIGN-BORN TUBERCULOSIS PATIENTS TREATED AT OUR HOSPITAL

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Abstract [Introduction] There has been an increase in the number of foreign-born tuberculosis (TB) patients residing in Japan. The purpose of this study is to clarify the clinical features of the foreign-born TB patients treated at our hospital.

[Materials and methods] This study included foreign-born TB patients treated at our hospital between 2000 and 2009. A comparison was performed with Japanese TB patients in the same age group who were treated in the same period.

[Results] There were 44 patients (17 males and 27 females; mean age: 23.6±5.1). These patients originated from 13 different countries, 12 of which were Asian countries such as China and the Philippines, and 8 of which were WHO-designated high-burden TB countries. The period between the patient's entry into Japan and the onset of TB was less than a year for half of the cases. As compared with the Japanese patients group, the foreign patients group included a significantly higher proportion of students and a significantly large number of cases found by periodic health examination. In terms of clinical findings, no significant difference was observed in the proportion of cavitary cases (37.5%) and of smear positive cases (37.5%); however, the frequency of drug-resistant cases (30.4%) was significantly higher among the foreign patients than the Japanese patients. The cure rate was 75% among foreign-born patients, and there were no defaulters.

[Conclusion] Compared with Japanese patients with the same ages, the foreign-born TB patients treated at our hospital included a high proportion of students from high-burden TB countries who were detected by periodic health examination and a higher proportion of drug-resistant cases. The treatment outcome was satisfactory without any defaulters. Periodic mass health examinations and drug susceptibility tests are important, and careful health examination is necessary for all individuals from high-burden TB countries when they enter Japan.

Key words: Foreign-born TB patients, Foreign student, Periodic health examination, Drug resistance

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Original Article

EPIDEMIOLOGICAL STUDY ON CONTACT EXAMINATIONS DONE BY NISHIO HEALTH CENTER USING QFT FROM 2008 TO 2010

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Abstract [Objective] To elucidate epidemiological significance of contact examination using QFT.

[Subjects and Methods] The subjects of this retrospective study were 110 TB patients registered at the Nishio Health Center between 2008 and 2010, and their contacts who were examined by Nishio HC using QFT in the same period. All registration files were reviewed to identify the index cases and their contacts examined with QFT. An index case, at least one of whose contacts was proven QFT-positive was considered as a source patient. An index case linked to a secondary TB patient whose QFT result was not positive was also considered as a source patient.

A contact examination rate (CER) was defined as following; CER＝*NI*/*NA*, where *NA* is Number of TB patients in a category A, and *NI* is Number of index cases in category A.

A source patient rate (SPR) was defined as following; SPR＝*NS*/*NI*, where *NI*: Number of index cases in a category A, and *NS*: Number of source patients in category A.

A QFT positive rate (QPR) was defined as following; QPR＝*NQP*/*NC*, where *NQP*: Number of QFT-positive contacts in a category A, and *NC*: Number of the contacts in category A.

[Results] A total of 110 TB patients were registered at the Nishio Health Center between 2008 and 2010. Pulmonary TB was found in 79 patients, and 31 had extra-pulmonary TB. Of the 79 patients with pulmonary TB, 37 were smear-positive, 32 were smear-negative but positive for culture or a nucleic acid amplification test, and 10 were bacteriologically negative. The numbers of index cases in these patients according to the bacteriological categories were 23, 2 and none, and the CERs were 62.2%, 6.3%, and 0%, respectively. There were 7 source patients with QFT-positive contacts. Another source patient was associated with a secondary patient who was QFT-negative and diagnosed with tuberculous pleurisy 10 months after the contact. All of these 8 source patients were smear-positive. The SPR was 34.8% for the 23 smear-positive index cases. The ages of the 37 smear-positive patients were 40 to 64 in 15 patients, and 65 or more in 22. 12 of them were female and 25 male. The CERs were 66.7%, for those aged 49 to 64 years, 59.1% for 65 years or older, 75.0% for females, and 56.0% for males. The SPRs were 50.0%, 23.1%, 22.2%, and 42.9%, respectively.

Two smear-negative and bacteriologocially positive index cases were associated with two QFT-negative contacts.

A total of 113 contacts from 22 smear-positive index cases were examined with QFT from 2008 to 2010. The contacts of a smear-positive index case registered late December, 2010 were excluded, since the examination was done in 2011. There were 17 contacts with positive QFT, and the QPR was 15.0%. Of the 7 index cases, one case had 7 QFT-positive contacts, two had 3 QFT-positive contacts, and each of remaining 4 cases had a single QFT-positive contact. The QPRs were 9.1% for 11 contacts aged 10−19 years, 17.2% for 29 twenties, 10.3% for 29 thirties, and 16.2% for 37 forties.

In addition to the 113 contacts, 77 contacts of 8 smear-positive index cases were examined with QFT during the same period. Out of these 8 index cases, 3 were registered in 2005 and 2007, and the other 5 were registered at other Health Centers, but they had social activities in the Nishio HC's service area being in contact with 70 persons in the Nishio area.

[Discussion] The contact examinations are heterogeneous in nature, with cases registered before or after the study period, and with contacts of index cases registered at other Health Centers. Both of them could not be the subjects for the CER calculation, since these contacts are related to the index cases not belonging to the defined case population.

[Conclusion] These findings suggest that the CERs for the male TB patients are lower than those for the female, the SPRs for the male and middle-aged TB patients are higher than those for the elder and the female, and that the CERs and the QPRs are useful parameter to monitor the results of contact examination using QFT.

Key words: TB transmission, Contact examination using Quantiferon, Contact examination rate, Source patient rate, QFT positive rate

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Case Report

PULMONARY THROMBOEMBOLISM WITH PULMONARY TUBERCULOSIS

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Abstract Out of 77 patients who were admitted to our hospital because of pulmonary tuberculosis from January 2007 to October 2009, 3 patients (3.9%) suffered from pulmonary thrombotic embolism (PTE) and/or deep venous thrombosis (DVT).

Case 1: An 80-year-old male with elevated D-dimer was diagnosed with PTE on the basis of an enhanced chest CT showing filling defects in the bilateral pulmonary arteries. Case 2: A 39-year-old male presented with prolonged high-grade fever even after administration of anti-tuberculosis drugs and complained of weakness. His D-dimer was high on admission and became still higher; then, edema was found on his left lower limb, and he was diagnosed with DVT on the basis of lower limb ultrasonography showing isoechoic thrombosis from the IVC to the left popliteal vein. An IVC filter was needed to treat his lesion. Case 3: A 69-year-old female with elevated D-dimer and edema on the right lower limb was diagnosed with PTE and DVT on the basis of chest CT findings. Since anti-coagulation therapy could not be continued due to intestinal bleeding, an IVC filter was placed. All 3 cases presented with no dyspnea and two of the three cases showed no hypoxemia. Even in cases of pulmonary tuberculosis without dyspnea, D-dimer seems to be useful for the early diagnosis of thromboembolism.

Key words: Active pulmonary tuberculosis, Pulmonary thromboembolism, Deep venous thrombosis, D-dimer

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A CASE OF TUBERCULOUS PLEURISY DEVELOPING CONTRALATERAL EFFUSION DURING ANTI-TUBERCULOSIS CHEMOTHERAPY

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Abstract A 55-year-old woman was admitted to our hospital because of chest pain, fever, and right pleural effusion that was exudative and lymphocyte-dominant with a high level of adenosine deaminase (ADA). Since her blood QuantiFERON-TB®3G test (QFT) was positive, she was diagnosed with tuberculous pleurisy. After initiation of anti-tuberculosis chemotherapy with isoniazid, rifampicin, ethambutol, and pyrazinamide, her symptoms improved. Later, liquid culture of the pleural effusion turned positive for *Mycobacterium tuberculosis*. On the 18th day of treatment, her chest X-ray and computed tomography exhibited pleural effusion in a moderate amount in the left thorax, with subsiding pleural effusion in the right thorax. Thoracocentesis demonstrated that the left thorax effusion was also exudative and lymphocyte-dominant, with elevated QFT response and high ADA concentration, suggesting tuberculous pleurisy. *Mycobacterium tuberculosis* was detected in the culture of a left pleural biopsy specimen obtained by thoracoscopy. We assumed that the left pleural effusion was due to paradoxical worsening because (1) on admission no effusion or lung parenchymal lesion was detected in the left hemithorax, (2) on the 14th day of treatment she was afebrile without pleural effusion on both sides, and (3) the bacilli were sensitive to the drugs she had been taking regularly. We performed drainage of the left effusion and continued the same anti-tuberculosis drugs, which led to the elimination of all her symptoms and of the pleural effusion on both sides. In conclusion, paradoxical worsening should be included in the differential diagnosis when contralateral pleural effusion is detected during the treatment of tuberculosis.

Key words: Tuberculous pleurisy, Paradoxical worsening, Contralateral pleural effusion

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THE USE OF NATIONWIDE TUBERCULOSIS SURVEILLANCE SYSTEM DATA TO DETERMINE GEOGRAPHICAL DIFFERENCES IN DRUG RESISTANCE

— Consideration of the Representativeness of the Drug Resistance Rate in Japan —

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Abstract Annual reports of tuberculosis (TB) statistics have been compiled using a database built through the nationwide computerized TB surveillance system in Japan. Using the annual report database for 2007−2009, this study compared the drug resistance rates among eight geographical districts. The proportion of bacteriological test results obtained at public health centers, which enter data into their computers that can then be accessed by the central computer, improved greatly from 2007 to 2009. The proportion of initial culture test results obtained among pulmonary TB increased from 63.8% to 74.8 % and the proportion of drug susceptibility test results obtained among culture-positive pulmonary TB cases increased from 41.8% to 63.5%. As a result, susceptibility test results among 15,425 (26.5%) of 58,198 newly notified pulmonary TB cases during the three-year study period were obtained.

The proportion of multi-drug resistant (MDR) TB among new treatment patients was 0.6% in the whole country. Although there were no particular districts having a significantly high rate of MDR-TB, the Kinki district showed the highest rate at 0.8%. In the case of retreatment patients, the MDR-TB rate was 5.1% in the whole country and there was no statistical difference among the eight districts.

The proportion having resistance to any INH among new treatment patients was 4.5% in the whole country, with the Kinki and Kanto districts showing significantly high rates of 5.3% and 5.2%, respectively. In the case of retreatment patients, the proportion having resistance to any INH was 13.3 % in the whole country, and there was no district where the proportion was significantly high.

The proportion having resistance to one or more drugs among new treatment patients was 12.7% in the whole country, with the Kinki district showing a significantly higher rate of 15.4%. In the case of retreatment patients, the proportion having resistance to one or more drugs was 22.2% in the whole country, and there was no district where the proportion was significantly high.

It is important to monitor drug susceptibility results for a comprehensive TB control program. The results of drug susceptibility tests through the nationwide TB surveillance system revealed a tendency toward higher drug resistance in districts that included large cities. Although many problems remain to be solved in order to optimize the use of results from the nationwide computerized TB surveillance system to represent the drug resistance rates in Japan, this practice is expected to yield great benefits.

Key words: Tuberculosis, Drug susceptibility test, Resistance, Multidrug resistance, District

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Report and Information

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Abstract In 2009 the tuberculosis (TB) incidence rates of the elderly population aged 65−74, 75−84 and 85 or older were 26.5, 63.4 and 98.1 per 100,000 in Japan, respectively. The TB incidence rate of those aged 65−79 showed a substantial decrease compared to 2000, with the rate decrease of those aged 85 or older being less pronounced.

The proportion of TB cases aged 65 or older among all TB patients increased 1.6 times to 58.0% in 2009 from 36.8% in 1987; in particular, the proportion of those aged 80 or older increased 3.6 times to 28.8% from 7.9% in 1987. The proportion of elderly TB cases showed substantial differences between prefectures.

The proportion of extra-pulmonary TB among elderly female TB patients aged 65−74 was 34.3% (22.4% for female TB patients aged 15−64). The proportion of bacillary TB among elderly pulmonary TB (PTB) patients was larger than that of young patients, but the proportion of cavitary PTB among elderly PTB patients was smaller than that of young PTB patients. The proportion of TB patients whose cases did not include respiratory symptoms increased with age. Among this group, the proportions of those aged 65−74, 75−84 and 85 or older were 15.9%, 21.3% and 22.7%, respectively.

The elderly TB "patient's delay" was shorter than young TB "patient's delay", although the "doctor's delay" for elderly TB patients was longer than that for young TB patients. Most TB patients including elderly TB patients were detected upon their visit to a medical institution with some symptoms; in the case of elderly TB, more patients were detected as outpatients or inpatients for diseases other than TB.

The prognosis of newly notified TB patients in 2008 was followed up until the end of 2009. Among TB patients aged 65 or older, 27.6% died within one year and 15.5% died within 3 months. The proportion of death showed a substantial increase with age; the increase was particularly accelerated among those aged 75 years or older.

Key words: Tuberculosis, Incidence, Elderly, Age, Trend, Epidemiological indicator, Death, Prefecture

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A VIEW OF DYNAMICS OF IMMUNE RESPONSES AGAINST TUBERCULOSIS INFECTION THROUGH QFT

Nobuyuki HARADA

Abstract QFT has been approved as a diagnostic test of TB infection in April 2005 in Japan, and further adopted to health insurance in January 2006. QFT is now a necessary tool to diagnose TB infection, especially in contact investigation. Since QFT uses *M.tuberculosis*-specific antigens, which are absent from BCG and most of non-tuberculous mycobacteria, to stimulate blood samples, and Interferon-gamma (IFN-γ) produced with antigen-specific T cells is measured to diagnose TB infection, QFT can specifically diagnose TB infection without influence of BCG vaccination or infection of most of non-tuberculous mycobacteria. There is another diagnostic test, T-SPOT.*TB*, which uses similar antigens to QFT, and these two tests are called as IGRAs (Interferon-Gamma Release Assays). However, as production of IFN-γ is a small part of protective immune responses against TB infection, it is difficult from this point of view to understand the dynamics of protective immune responses against TB infection through IGRAs results. Especially, it is impossible to distinguish between active TB and latent TB infection, to identify time of TB infection, or to detect dormancy TB infection using current IGRAs. Using biomarkers other than IFN-γ or antigens other than antigens used in current IGRAs, development of newer diagnostic tests which have these performances would be awaited.

Key words : IGRAs, QFT, T-SPOT, Interferon-γ, TB immune response

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