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————— Original Article —————

GENDER DIFFERENCE IN INDEX AND SECONDARY PATIENTS WITH OR WITHOUT HOUSEHOLD CONTACT

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Abstract [Objectives] To investigate gender difference in index and secondary patients with or without household contact.

[Subjects and Methods] The subjects of this retrospective study were 3,174 pulmonary TB patients registered in Aichi prefecture between 1989 and 2003. All recorded files were reviewed to identify epidemiologically-related TB patient clusters. In case of epidemiologically-related patients registered within less than 10 years interval, the first registered patients was defined as the index case of the cluster. The other patients in the cluster were defined as secondary cases. Therefore, all pulmonary TB patients were classified to index, secondary, or unclustered cases. An index patient with sputum smear positive was defined as the source of transmission in the cluster. The male/female ratio was calculated separately in the sources and secondary patients with or without household contact.

[Results] A total of 100 source patients were identified. Of these, 77 were male and 23 were female, and the male/female ratio was 3.3. The secondary patients were 153, of whom 77 were male and 76 were female, and the male/female ratio was 1.0. The difference of the male/female ratio was statistically significant ($p < 0.001$).

The male/female ratio in the source patients was 2.5 for 78 clusters with household contact and 21.0 for 22 clusters without household ($p < 0.05$), while the ratio in the secondary patients were 0.8 and 2.2 respectively ($p < 0.01$). Of the 111 secondary patients with household contact, the relations to the

source patients were wife-husband in 32, parent-child in 55, brother or sister in 12, grandparent-grandchild in 8, and the others in 4. In the 32 wife-husband transmission, most secondary patients were female (male/female=9/23) while in other 67 transmissions with household contact, male and female secondary cases were almost same (male/female=39/40). The male/female ratios in these two settings were significantly different (0.4 vs 1.0, $p < 0.05$). Of the 42 secondary patients without household contact, transmission were occurred in working places in 24, schools in 11, religion circles in 4, hospital in one, and others in 2. The male/female ratio of secondary cases was 7.0 for transmission at working places, and 0.8 for transmission at the other places ($p < 0.01$).

[Conclusion] These findings suggest that the male/female ratio of secondary patients with household contact is significantly lower than that of those without household contact.

Key words: Gender difference, Male/female ratio, Smear-positive pulmonary tuberculosis, TB transmission inside and/or outside household

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LIVER DAMAGE IN TREATMENT OF LATENT TUBERCULOUS INFECTION BY ISONIAZID

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Abstract [Purpose] To study the frequency and degree of liver damage as adverse effect of isoniazid (INH) preventive therapy in Japanese people.

[Object and Method] Chart review of Japanese persons who started isoniazid preventive chemotherapy in the two clinics in Tokyo, from 2003/1/1 to 2004/12/31.

[Result] There were 779 cases who did not transiently or completely stop INH preventive therapy because of adverse effect, and 26 cases who stopped INH transiently or completely because of liver damage as adverse effect (total 805 cases). In 371 cases, of those 779 cases, AST (aspartate aminotransferase) and ALT (alanine aminotransferase) was measured after starting INH at least once. In 14.9% (59/397) of these 391 cases (=371+26), liver damage as adverse effect was found. In 1.51% (6/397), liver damage with AST and/or ALT higher than 400 IU/L was found. Clinical hepatitis, associated with

clinical symptom of hepatitis, was seen in 0.37% (3/805). Hepatitis with liver failure was seen in 0.12%. There was no death due to liver damage.

[Conclusion] Liver damage as adverse effect of isoniazid (INH) preventive therapy in Japanese people is not rare.

Key words: Isoniazid, Treatment of latent tuberculous infection, Preventive chemotherapy, Adverse effect, Liver damage

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A CASE OF TUBERCULOUS PSOAS ABSCESS SUCCESSFULLY TREATED WITH SURGERY DURING ANTITUBERCULOSIS THERAPY FOR MILIARY TUBERCULOSIS

Naoya KATSURAGI, Yuji SHIRAISHI, and Hidefumi KITA

Abstract A case of tuberculous psoas abscess complicated during antituberculosis therapy for miliary tuberculosis and successfully treated with surgery was reported. A 20-year-old man visited our hospital because of fever lasting for 3 months. Chest radiography showed miliary nodules in both lungs and transbronchial lung biopsy revealed granuloma. Magnetic resonance imaging of the head showed small lesions in the brain. Computed tomography of the abdomen showed an enlarged paraaortic lymph node and a nodule in the spleen. Needle biopsy of the lymph node revealed necrotic tissue. *Mycobacterium tuberculosis* was not isolated; however, miliary tuberculosis was highly suspected based on clinical and radiographic findings. Once antituberculosis therapy was initiated with isoniazid, rifampicin, streptomycin, and pyrazinamide, the fever subsided. In spite of improvement of general radiographic findings, a new abscess was found in the right psoas major muscle after 8 months of therapy by computed tomography. A sample of the abscess showed a positive smear, negative culture, and positive PCR test for *M. tuberculosis*. Although antituberculosis therapy continued

for another 6 months, the abscess enlarged to 7 cm and new retroperitoneal lymph nodes also appeared. Surgical drainage and curettage of the abscess was performed. Intra- and post-operative specimens were negative for bacteria, fungi, and *M. tuberculosis*. The patient was treated with isoniazid, rifampicin, and ethambutol for one year postoperatively. The disease disappeared without any evidence of relapse for 2.5 years after surgery.

Key words: Tuberculous psoas abscess, Miliary tuberculosis, Psoas abscess, Tuberculosis, Surgery

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Case Report

**A CASE OF DISSEMINATED TUBERCULOSIS COMPLICATED WITH
TUBERCULOUS MENINGITIS WHILE INVESTIGATING
AN ABDOMINAL LYMPHADENOPATHY**

Junichi TSUYUSAKI, Yuka SASAKI, Fumio YAMAGISHI, Takenori YAGI,
Tomohiro HASHIMOTO, Rei BEKKU, and Makako YAMANAKA

Abstract In February 2005, a 33-year-old man visited A hospital complaining of fever. The blood screening test revealed the liver dysfunction, then computed tomography showed swelling of abdominal lymph nodes. In April, headache and disorientation appeared. He was diagnosed as disseminated tuberculosis and tuberculous meningitis based on chest X-ray and computed tomography findings and examination of cerebrospinal fluid. After admission to our hospital, anti-tuberculous drugs were prescribed, but the cerebral infarction happened. The disturbance of consciousness and the left half of his body paralysis appeared. They did not improve and hydrocephalus was complicated in August, though he was treated by steroids. He needed all helps because of the left half of his body paralysis and an advanced sequelae was left. It was thought that the abdominal lymph adenopathy preceded as one of symptoms of the disseminated tuberculosis in this case. It is said to be rare that abdominal lymph node swelling

is seen in the early stage of disseminated tuberculosis. But, we think that it is necessary to keep in mind that the possibility of disseminated tuberculosis as one of the diseases in differential diagnosis, when we examine enlargement of abdominal lymph nodes with symptoms suggesting the presence of infection such as fever.

Key words: Tuberculous meningitis, Abdominal lymph node tuberculosis, Disseminated tuberculosis

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THE COMPARISON OF TREATMENT BETWEEN TB, AIDS, AND MALARIA FROM PUBLIC HEALTH PERSPECTIVE

Arata KOCHI

Abstract Millions of people, mostly in Africa and Asia, die of the main infectious diseases such as tuberculosis, AIDS and malaria every year. In this talk, based on my experience in addressing global public health issues of the infectious diseases, I summarized key points to a successful international health initiative, and outlined achievements and problems in the global control strategy of tuberculosis, AIDS and malaria.

Key words: Tuberculosis, AIDS, Malaria, Public health

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Memorial Lecture by the Imamura Award Winner

CHARACTERISTICS OF A DIAGNOSTIC METHOD OF TUBERCULOSIS INFECTION
BASED ON WHOLE BLOOD INTERFERON- γ ASSAY

Nobuyuki HARADA

Abstract It is assumed that about 10% of individuals infected with *M. tuberculosis* (Mtb) develop tuberculosis (Tb), and the remaining 90% suppress contain Mtb through their immune systems, but have a latent tuberculosis infection (LTBI). To effectively control Tb, it is essential to detect individuals with LTBI in a Tb outbreak and provide chemoprophylaxis for them.

Until recently, the tuberculin skin test (TST) has been the only diagnostic method for LTBI. However, the specificity of TST is low, because the purified protein derivative (PPD) used for TST contains numerous Mtb antigens that are almost identical to BCG antigens or similar to non-tuberculous mycobacterium (NTM) antigens. For this reason, TST may produce positive results in BCG-vaccinated individuals or NTM-infected individuals without Mtb infection. Therefore, it is very difficult to diagnose LTBI in Japan, where BCG vaccination is widely administered. In addition to this, TST has other defects, such as technical variations for injecting PPD or measuring the TST response, the necessity of a return visit to the doctor to measure the TST response 2 days after PPD injection, and the booster effect through reinjection of PPD.

More recently, a new diagnostic method that can overcome these defects in TST, QuantiFERON[®]TB-2G (QFT-2G), has been developed. In QFT-2G, two Mtb-specific antigens, ESAT-6 and CFP-10, are used to stimulate whole blood, and based on produced interferon- γ (IFN- γ), Mtb infection is diagnosed. Since ESAT-6 and CFP-10 are absent from all *M. bovis* BCG substrains and most of NTM including *M. avium*, *M. intracellulare*, but are present in tuberculosis complex (*M. tuberculosis*, *M. bovis*, *M. africanum*) and only a few strains of NTM, QFT-2G is not affected by prior BCG vaccination nor most of NTM infections. Moreover, as measurement of IFN- γ can be carried out by machines on the next day following the blood draw, more objective results are obtained more quickly than with TST. It is not necessary to consider the booster effect in QFT-2G as PPD is not injected, nor to revisit the doctor. Thus, QFT-2G overcomes the defects of TST described here.

From a clinical trial of QFT-2G in which the subjects were smear-positive, untreated Tb patients and BCG-vaccinated healthy individuals, it has been demonstrated that the specificity and sensitivity of QFT-2G are 98.1% and 89.0%,

respectively, and QFT-2G is an excellent diagnostic method. Furthermore, many contact investigations have shown that QFT-2G detects not only active Tb but also LTBI. Several data indicate that frequency of contact with Tb patients correlates well with QFT-2G positive rates in contact investigations. The validity and usefulness of diagnosing LTBI by QFT-2G have been suggested in other countries.

In many contact investigations, it has been shown that most contacts who had been diagnosed as LTBI based on TST results were QFT-2G negative, suggesting that as a result, many unnecessary chemoprophylaxes were indicated. On the contrary, many QFT-2G positives were identified in those who were diagnosed to be uninfected with Mtb based on TST. Therefore, as the wide spread of QFT-2G testing in contact investigations would prevent unnecessary chemoprophylaxes and detect true infected individuals more accurately, we hope that more effective Tb control could be performed.

Although QFT-2G is an excellent diagnostic method, it is still new, and some questions remain to be answered. For example, the period of converting QFT-2G positive after Mtb infection, alteration of long-term QFT-2G responses after Mtb infection, and the effects of treatment for Tb or LTBI are not fully understood. The behavior of QFT-2G in infants or children is not understood either. Especially in infants, the problem of the blood volume required for the QFT-2G test is the major issue. We are working on these issues to provide more appropriate directions for QFT-2G users, and hope that we can contribute to Tb control.

Key words: Diagnosis of tuberculosis infection, Tuberculin skin test, QuantiFERON[®]TB-2G, Latent tuberculosis infection, Contact investigation

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————— The 81st Annual Meeting Educational Lecture —————

PROTECTIVE IMMUNITY AGAINST *MYCOBACTERIUM TUBERCULOSIS*

Ikuo KAWAMURA

Abstract *Mycobacterium tuberculosis* (MTB) is a facultative intracellular pathogen with which over a billion people have been infected and 3 million people die annually. The bacterium induces vigorous immune responses, yet evades host immunity, persisting within phagosomes of the infected macrophages. Thus, it is necessary to delineate that the virulence-related intracellular survival mechanism and the host immune responses to eradicate *M. tuberculosis* on the molecular basis. In this regard, recent findings clearly indicated that Toll-like receptors (TLRs) play an essential role in the recognition of MTB components by macrophages and dendritic cells, resulting in not only activation of innate immunity but also development of antigen-specific adaptive immunity. It has been also reported that induction of early death of the infected cells may be one of the strategy of host defense against MTB because macrophages go into apoptosis upon infection with MTB, resulting in suppression of the intracellular replication. Furthermore, recent report has shown that autophagy is induced by IFN- γ and suppress intracellular survival of mycobacteria, suggesting that activation of autophagy pathway is required to overcome phagosome maturation arrest induced by MTB. In addition, it is known that IFN- γ

plays an important role in protection. The cytokine that is produced from NK cells and dendritic cells at the early period of infection strongly induces not only macrophage activation but also development of antigen-specific IFN- γ -producing CD4⁺T cells. Since antigen-specific CD8⁺ T cells and CD1-restricted T cells are also reported to contribute to the protective immunity, cooperation of these T cells is essential for the host resistance. In this paper, I am going to summarize the recent progress of the understanding of protective immunity against MTB.

Key words : *Mycobacterium tuberculosis*, Macrophages, Toll-like receptor, T cells, Apoptosis, Autophagy, IFN- γ

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A NEW ERA OF MOLECULAR EPIDEMIOLOGY OF TUBERCULOSIS IN JAPAN

Chairpersons: ¹Tetsuya TAKASHIMA and ²Tomotada IWAMOTO

Abstract Molecular epidemiology of tuberculosis (TB) is a science to study TB transmission dynamics and to enhance our understanding of the epidemiology of TB by utilizing molecular typing methods as an adjunct to classical epidemiological approach. Before the era of molecular epidemiology, it was quite difficult to ascertain the source of the infections since *M. tuberculosis* is spread by air-borne droplets of respiratory secretions expelled by an infectious person to a susceptible host and it can remain latent as an asymptomatic infection for years. Now a day, our understanding of TB transmission dynamics has been refined by genotyping of *M. tuberculosis* strains.

The methods of molecular epidemiology, especially IS6110 RFLP of *M. tuberculosis*, were first introduced to outbreak investigations and then gradually been expanded its application to population-based study in Japan. IS6110 RFLP is obviously a powerful tool for strain differentiation of *M. tuberculosis* but its labor-intensiveness limits the achievable throughput and makes it less useful for long-term prospective studies. Recently, apart from IS6110 RFLP, DNA amplification-based method, i.e., variable number of tandem repeats (VNTR) has appeared as a substitute for or adjunct to the IS6110 RFLP.

In this symposium, we have invited four opinion leaders in molecular epidemiology of TB from different fields: Mycobacterium reference center, basic science, clinical practice, and public health practice. We, as the chairpersons of this symposium, hope that this symposium would trigger the

development of molecular epidemiological network of TB in Japan.

1. Achievement and problem of molecular epidemiologic study with IS6110-RFLP analyses of tuberculosis in Okinawa: Shinji MAEDA (Mycobacterium Reference Center, The Research Institute of Tuberculosis, Japan Anti-Tuberculosis Association)

The long-term RFLP analyses of tuberculosis in Okinawa showed that endemic *M. tuberculosis* might be present. This is one of the achievements of our project study. On the other hand, for more effective examination of contact persons, information of molecular epidemiology should be used actively. Therefore because the analysis report needs to be sent back quickly, the PCR-based VNTR method should substitute for the RFLP analysis.

2. Basic knowledge and application of Variable Numbers of Tandem Repeats: Kei NISHIMORI (Department of epidemiology, National Institute of Animal Health)

Genomic loci of Variable Numbers of Tandem Repeats (VNTR loci) in *Mycobacterium tuberculosis* complex and *Mycobacterium avium*, the history of analysis of VNTR loci, the hypothetical mechanisms of increase or decrease of number of repeats, the structures of the loci, and the necessity of standardizing the VNTR typing were introduced.

3. Clinical application of VNTR: Tomoshige MATSUMOTO,

and Hiromi ANO (Department of Clinical Research and Development, Osaka Prefectural Hospital Organization Osaka Prefectural Medical Center for Respiratory and Allergic Diseases)

Tuberculosis genotyping was first introduced to outbreak investigations and population-based studies. The advent of Variable Numbers of Tandem Repeats (VNTR) can be applied to clinical fields of not only *Mycobacterium tuberculosis* but also of *Mycobacterium avium*. In Osaka Prefectural Medical Center for Respiratory and Allergic Diseases, clinical application of VNTR was first introduced in Japan to determine whether *Mycobacterium tuberculosis* or *avium* disease was caused by reactivation or reinfection when relapsed. We showed some examples about usefulness of the clinical application of VNTR.

4. Molecular epidemiology of tuberculosis to improve TB prevention and control activities : Tomotada IWAMOTO (Department of microbiology, Kobe Institute of Health), Riyo FUJIYAMA, Noriko TANAKA, Yasuto KAWAKAMI (Kobe City Public Health Center), Chika SHIRAI (Hyogo-ku Health and Welfare Department, Kobe)

M. tuberculosis isolates in Kobe have been characterized as :

a) Beijing family strains are highly prevalent (77%), b) two major MIRU profiles in Beijing family were found, one is globally pandemic genotype and the other is locally prevalent strains, c) six strains belonged to T3-Osaka family, and d) Manila family strains made cluster consisting of 3 strains. Kobe VNTR Database which consists of 12-loci MIRU and 9 additional VNTR loci has been developed. The basis for the selection of these supplemental 9 VNTR loci and the application of VNTR database in TB control program were introduced.

Key words: Molecular epidemiology of tuberculosis, IS6110 RFLP, VNTR

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