TRANSMISSION OF TUBERCULOSIS (II)

Masakazu AOKI

Abstract In the previous paper (Kekkaku. 2004 ; 79 : 509−518), the author has made a review on (1) development of droplet nuclei infection theory, (2) experimental basis and (3) epidemiological evidence of droplet nuclei infection, and has discussed about the factors influencing on tuberculosis infection. Various mode of transmission of tubercle bacilli from nonpulmonary sources was reviewed in the present paper, such as (1) infection from cutaneous tuberculosis, (2) infection in the bacteriology laboratory, (3) infection by needle stick, (4) transmission by bronchoscopic examination, (5) tuberculosis infection in the autopsy room, (6) infection followed vaccination and/or cortico-steroid injection therapy, (7) congenital tuberculosis, and (8) other rare transmission of tuberculosis. Moreover, three topics concerning tuberculosis infection were discussed, they are (1) tuberculosis infection risk index, (2) highly infectious case, and (3) virulence and infection. Infection risk index is the product of smear positivity (expressed by Gaffky Grading) by duration of cough (expressed by month). This index is being used widely at the occasion of contact survey at present in Japan so that instructions for use were discussed.

Key words: Tuberculosis infection from nonrespiratory sources, Infection risk index, Highly infectious case, Virulence and infection

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Original Article

VALIDITY OF MEASURING TIME TO DETECT GROWTH OF M. TBC BY BACTEC MGIT960 SYSTEM FOR QUANTITATION AND PREDICTION OF MYCOBACTERIAL GROWTH

Yasushi YAMAMOTO, Satoru FUJIUCHI, Yasuhiro YAMAZAKI, Akinori TAKEDA, Yutaka NISHIGAKI, Yuka FUJITA, Toshiaki FUJIKANE, and Tetsuo SHIMIZU

Abstract [Study design] Time to detect growth of M. tbc by BACTEC MGIT 960 system was examined in sputum specimens collected from 114 patients with active pulmonary tuberculosis before and during antituberculosis therapy. By measuring TTD under chemotherapy, we tried to quantify mycobacterial growth and determine the sensitivity of MGIT system.

[Results] The mean TTD significantly decreased in response to an increment in the range of the quantitation scale for solid media. Moreover, the TTD negatively correlated with colony counts ($\rho = -0.636$, $P < 0.01$). When automated monitoring continued until Day 28 after incubation, MGIT system had been capable of detecting 98% of Ogawa-positive specimens. The receiver operating characteristic (ROC) curve was plotted to determine the sensitivity and specificity in MGIT system, indicating the sensitivity of 98.3% corresponding cutoff level for TTD of Day 28.

[Conclusion] Measuring TTD in MGIT system could allow estimating the mycobacterial growth in similarly quantitative manner. The appropriate endpoint of monitoring could be decided as 4 weeks, accurately reflecting an outcome of cultivation with solid media.

Key words: *Mycobacterium tuberculosis*, Mycobacteria Growth Indicator Tube (MGIT) system, Ogawa medium, Culture

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Original Article

CLINICAL EVALUATION ON CAUSES OF DEATH IN PATIENTS WITH PULMONARY TUBERCULOSIS

Makoto TAKAHARA

Abstract [Purpose] We evaluated the cause of death in patients with active tuberculosis.

[Object and Method] 40 patients (male 32, female 8, mean age 76 years old), died under treatment for tuberculosis during 1999 to 2002 in our hospital, were analized. We compared patients' backgrounds, complications, extent of pulmonary tuberculosis, and outcome of the treatment between 40 died cases and 162 patients who were supposed to be successfully treated by cohort analysis (control group).

[Results] 17 cases died of tuberculosis and 23 cases died of non-tuberculous diseases. Pneumonia occupied the top (9 cases) in the latter group. Died cases were higher in age and showed larger performance status score than the control group. Further, laboratory findings revealed poorer nutritional conditions and higher inflammatory reactions in the died group. The duration of symptoms before admission seemed to be longer in the died group, however, the difference with the control was not significant. All of the died group had complications and the rate of having liver diseases and cerebrovascular diseases was higher than that of the control group. Furthermore, the extent of lung lesions was more extensive in the died group. The frequency of changing drugs due to side effects was higher in the died group, therefore, the proportion of cases completed the standard treatment was lower in the died group.

[Discussion and Conclusion] Impossibility of continuing the standard treatment gave unfavorable impact in the died cases rather than the delay in their admission. Due to the above reasons, negative conversion of their sputum culture was difficult, and they died of tuberculosis directly or indirectly. Some of the patients who died of pneumonia (non-tuberculous death) might be included in cases died of tuberculosis.

Key words: Tuberculous death, Non-tuberculous death, Pneumonia, Standard treatment

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Original Article

PROCESS OF ACQUIRING DRUG RESISTANCE, RETROSPECTIVE REVIEW OF RECORDS OF MDR TB

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Abstract [Purpose] To investigate the reasons of acquiring drug resistance among MDR TB cases and to learn lessons for the prevention of acquiring of drug resistance.

[Method] Retrospective review of 159 MDR TB cases who were treated at Fukujuji Hospital from 1990 January to 2003 August.

[Result] We found that among 159 cases, 48 cases were infected with multidrug resistant *M. tuberculosis* bacilli, 35 cases acquired drug resistance, 7 cases were with the history of tuberculosis treatment before 1970 only, and that remaining 69 cases were difficult to evaluate because of the lack of informations on previous drug susceptibility tests. Among 35 cases that acquired drug resistance, the drug susceptibility test patterns before becoming MDR TB were categorized as follows: 12 HR susceptible, 18 H resistant R susceptible, 3 R susceptible (H unknown), and 2 H susceptible R resistant. The factors that may have influenced to acquire MDR were lack of modification of the regimen after knowing drug resistance among H resistant R susceptible cases, and defaulting among cases that were not evaluated (15/69) and H resistant R susceptible cases (3/18).

[Discussion] Control of MDR TB needs to be strengthened. Proper drug susceptibility test, proper choice of drugs at the beginning of treatment and modification of treatment after knowing drug susceptibility test results are important for the prevention of MDR TB. Ensuring patient adherence to treatment is important in the medical institutions where drug susceptibility test is not properly done, in particular, for H resistant R susceptible cases, and guidance to these institutions by the public health centers should be intensified.

Key words: Multidrug-resistant tuberculosis, Acquired drug resistance, Preventable

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Original Article

BASIC CHARACTERISTICS OF A NOVEL DIAGNOSTIC METHOD (QuantiFERON®TB-2G) OF LATENT TUBERCULOSIS INFECTION WITH A USE OF *MYCOBACTERIUM TUBERCULOSIS*-SPECIFIC ANTIGENS, ESAT-6 AND CFP-10

[1]Nobuyuki HARADA, [1]Kazue HIGUCHI, [1]Yukie SEKIYA, [2]Jim ROTHEL, [3]Takashi KITOH, and [1]Toru MORI

Abstract [Purposes] To determine the optimum cut-off level of a newly developed method for diagnosing tuberculosis infection based on whole-blood interferon-gamma measurement, and to study the basic characteristics of the method.

[Study Subjects] 1) A total of 220 young, healthy individuals having no apparent exposure to tuberculosis infection, most of whom have had a vaccination with BCG vaccine. 2) One hundred eighteen tuberculosis patients who were diagnosed by positive *Mycobacterium tuberculosis* on culture. 3) A group of 75 youngsters exposed to an infectious tuberculosis patient and who showed a strong tuberculin reaction (with erythema diameter of 30 mm or more).

[Method] Whole-blood specimens of donors were stimulated with antigens, i.e., ESAT-6 and CFP-10, and then cultured. Plasma concentrations of interferon-gamma discharged were then determined with QuantiFERON®-CMI. Correlation between interferon-gamma concentrations in response to ESAT-6 and CFP-10, and their correlation with Mantoux test results were analyzed for various categories of donors. The Receiver Operating Characteristics analysis was performed considering the loss due to misclassification.

[Results and Discussion] The optimum cut-off level was determined as 0.35 IU/m*l* for both ESAT-6 and CFP-10. This gave the test a sensitivity of 89.0% and specificity of 98.1% in detecting tuberculosis infection. The correlation of interferon-gamma response with tuberculin tests among BCG-vaccinated individuals was low, which suggested that the test was not influenced by previous BCG vaccination. The low correlation between ESAT-6 and CFP-10 tests suggested that the simultaneous use of the two tests was beneficial. As in the case of clinical tests in general, the cut-off should be set at a lower level when the test is applied to high prevalence situation and vice versa.

Key words: Latent tuberculosis infection, Diagnostics, ESAT-6, CFP-10, IFN-γ, ELISA

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CLINICAL STUDY FOR DEVELOPMENT OF NONTUBERCULOUS MYCOBACTERIAL LUNG DISEASE

Atsuyuki KURASHIMA

Abstract

Developement of MAC lung disease

An increase of nodular bronchiectatic type of MAC lung disease becomes a problem among respiratory physician today. The reason is still unknown, but it seems to be globally recognized that this type of MAC disease is developing particularly in middle-aged woman. Some papers mentioned the existence of such type of MAC lung disease already early in the 70s, in Japan. Yamamoto described that 17 cases of middle lobe type lung disease out of 154 non-photochoromogen cases, and 76.5% were female, in 1970. Shimoide also pointed such type of 39 cases out of 240 MAC lung disease and 84.6% were female, in 1980. Prince reported MAC lung disease seen in old and middle age female of 21 cases including lethality example of 4 cases without a precedent disease in 1989. After his report, the international consensus of this peculiar type of MAC lung disease seems to be spread.

In 1989, we compared 72 cases of nodular bronchiectatic type of MAC lung disease and 56 cases of diffuse panbronchiolitis (DPB) that was a most typical chronic airway disease at that time in Japan. The average age of disease onset of DPB group was 37.0 ± 16.3 years old and that of MAC group was 54.5 ± 16.3 years old. The percentage of female was 32% in DPB group and 87.5% in MAC group. It was highly possible that two groups belong different parent population. We could grasp that nodular bronchiectatic type of MAC lung disease patients is a unique group. We observed the serial films of 21 cases of nodular bronchiectatic MAC lung disease, and divide the progression of the disease to sequential 7 steps as Fig. 1. Small nodules progress to cavities in mean about 10 years.

However, why is MAC which is opportunistic pathogen with weak virulence, able to form a lesion at unimpaired lung parenchyma? Is there really normal site? Why dose it start from lingula? Why is MAC seen a lot in woman? While it is extremely pathognomonic clinical picture, and, is an extremely interesting problem, most are still unidentified.

Study of MAC lung disease treatment

It was known that *Mycobacterium kansasii* lung disease is healed with a chemotherapy like analog of anti-tuberculosis chemotherapy, already in those days. However, the results of MAC lung disease chemotherapy were extremely poor. We tried to express a physicians experience quantitatively as follows, in 1987. The results of 8 weeks sputum culture on Ogawa egg medium were converted semi-quantitatively to CFU numbers based on "Japanese standard guideline of *Mycobacterium tuberculosis* inspection". We exhibit the ratio of post-treatment consecutive 6 months culture yield to pre-treatment culture yield as response rate, about 110 pulmonary MAC cases. Through this study, we clarify the followings.

The results of chemotherapy do not correlate susceptibility test for *Mycobacterium tuberculosis*. Multidrug regimen is more useful. Small extent of lesion is more responsive. Combination with aminoglycoside chemotherapy is more effective. These conclusions were almost same as the ATS guideline of 1990.

New drugs such as, new macrolides and new quinolones appeared for pulmonary MAC treatment through the feedback from systemic MAC complicated AIDS treatments from the latter half of 90's. We measured the sensitive strain ratio at 2 mcg/m*l* of OFLX, CPFX, LVFX about 990 clinical isolates and could expect availability for *M. kansasii* or *M. fortuitum*, but these new quinolones are not enough effective for MAC. Also we examined MIC for various antimycobacterial agent by 50 MAC clinical isolates, and we could expect a certain availability of SPFX, GFLX, CPFX, CAM for MAC. The availability of clarithromycin (CAM) has been established through many randomized clinical trials for disseminated MAC complicated AIDS, but for pulmonary MAC, complete cure is still difficult if we use CAM including regimen.

We performed surgical treatment for relatively young patients with localized lesions. We carry out the adaptation reference such as Table, now. The localization of the lesions become a problem at surgical resection. Through the study of our 55 surgical treatment cases, 8 cases (67%) relapsed out of 12 cases which had destructive airway structure in unresected lung field. On the other, only 1 case relapsed (10%) relapsed out of 10 cases without airway destruction in unresected lung. Therefore, even if there is a little dispersal focus without airway destruction in the other pulmonary lobe except purpose focus of resection, it seems that control is possible by post operational chemotherapy.

Long survival

As overall consequence, we calculate the survival curves of 201 pulmonary MAC patients visited Tokyo National Hospital from 1953. The survival medium value was 7332 days. The prognosis of nodular bronchiectatic type was better than that of post-tuberculosis type. Extent of disease measured by chest X-ray examination at the time of first visit may be a most affecting factor to the survival rate.

Key words: Nontuberculous mycobacteriosis, Nodular bronchiectatic type, Chemotherapy, Surgical treatment

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The 79th Annual Meeting Symposium

NURSING ON TUBERCULOSIS PATIENTS
— Quality Nursing to Support Patient's Compliance to Treatment —

Chairpersons: [1]Ayako NASU and [2]Noriko KOBAYASHI

Abstract Tuberculosis control program in Japan focuses more on completion of treatment. The activities for patients to complete treatment are being actively done with collaboration between nurses of hospitals and public health nurses of the health centers.

In 2000, Ministry of Health Welfare announced DOTS program version Japan. As a result, health centers of big cities implemented DOTS for homeless tuberculosis patients and hospitals DOT for in-patients. In 2003, the government demonstrated the scheme of DOTS strategy Expansion Program version Japan, which includes community DOTS types to be selected depend upon the risk of default with an individual patient. It is necessary to develop and utilize social and human resources in the community to expand surely supporting system for patient's compliance. Mutual understanding and collaboration of the relevant organizations become very important.

In this symposium, four panels from hospital, clinic and public health center discuss on the current situation and challenge of supporting system and the assessment of treatment outcome.

1. DOTS implementation with collaboration on nursing activities between hospital and public health center in Kyoto Prefecture: Ikuyo HIROHATA (National Hospital Organization Minami Kyoto National Hospital)
2. From standpoint of clinical practice: Hidenori MASUYAMA (Japan Anti-Tuberculosis Association Shibuya Clinic)
3. The activities for case support based on DOTS Program in Wakayama Prefecture: Kimiko KAWASAKI (Tanabe Public Health Center, Wakayama Prefecture)
4. Assessment of supporting activities for patient's compliance: Tomoko TAKANO (Uki Public Health Center, Kumamoto Prefecture)

Three speakers gave additional comments and advice on quality supporting and nursing activities for patient's compliance through good coordination between hospitals and publics health centers.

Key words: DOTS, Hospitals DOTS

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