Original Article

SECULAR INCREASE IN THE INCIDENCE RATE OF DRUG-INDUCED HEPATITIS DUE TO ANTI-TUBERCULOSIS CHEMOTHERAPY INCLUDING ISONIAZID AND RIFAMPICIN

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Abstract To investigate the secular change in the incidence rate of drug-induced hepatitis (DIH) due to anti-tuberculosis chemotherapy including isoniazid (INH) and rifampicin (RFP), but not including pyrazinamide (PZA), we retrospectively studied the incidence rates of DIH in patients treated with chemotherapy including INH and RFP in four periods 1980−83, 87−88, 91−92, and 1998−2000. The criteria for selection of the patients were as follows.

1. The serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were measured before, and one month (20−40 days) and 2 months (45−75 days) after starting anti-tuberculosis chemotherapy. When the serum AST and ALT were measured twice or more during period 20−40 days or 45−75 days after starting anti-tuberculosis chemotherapy, the data obtained nearest to 30 or 60 days after were chosen as those of one or two months after starting chemotherapy, respectively.

2. The serum AST and ALT were within normal range before starting anti-tuberculosis chemotherapy. The normal range of serum AST and ALT were ≦40 K-A and ≦35 K-A (in 1980−83) or ≦31 IU/*l* and 34 IU/*l* (in 1987−2000), respectively.

3. Chronic active hepatitis and cirrhosis patients were excluded.

4. All alive after completion of anti-tuberculosis chemotherapy.

The numbers of the subjects who fulfilled the above criteria were 113, 135, 128 and 154 in 1980−83, 1987−88, 1991−92 and 1998-2000, respectively.

DIH was defined serologically by serum AST≧40 K-A and/or ALT≧35 K-A (in 1980−83), or AST≧40 IU/*l* and/or ALT≧40 IU/*l* (1987−2000). The DIH incidence rate of the subjects classified by the year of treatment and age were examined, and the contributions of the risk factors for DIH, such as age, sex, alcoholics, previous liver disease history, HBs ag positivity, anti-HCV ab positivity, and hypoalbuminenia were studied, and none except the age over 80 y.o. was found to be a risk factor to DIH, in our subjects. In patients with the age over 80 y.o., daily doses of antituberculosis drugs RFP, INH and ethambutol (EB) were significantly higher in patients with DIH than those without DIH, but body weight and serum albumin level were not significantly different between these two groups. There was no risk factor to DIH in our patients less than 80 y.o. and this could be explained by the above-mentioned criteria of study patients selection.

To exclude the age dependence of the incidence rate of DIH in our subjects, the incidence rates of DIH were calculated in patients less than 80 y.o. by the period of treatment, and they were 10/111 (9.0%), 23/131 (17.6%), 26/123 (21.1%) and 32/117 (27.4%) in 1980−83, 87−88, 91−92, and 1998−2000, respectively. The secular increase of the incidence rate of DIH was statistically significant ($p=0.01$). It is quite clear that this secular increase was not at all attributable to the above-mentioned risk factors. It is suspected that human liver has become more easily affected with INH and RFP in recent years. It is suggested that the new chemical compounds present in our increasingly complicated human milieu give heavier burdens on human liver, weaken the liver function, and enhance the capacity of INH and RFP to cause DIH.

Key words: Anti-tuberculosis drugs, Drug-induced hepatitis, Secular change, Environment, Rifampicin, Isoniazid

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Original Article

PREDOMINANT LOCATION OF PULMONARY PARENCHYMAL LESIONS OF TUBERCULOSIS PRIMARY COMPLEX IN INFANTS AGED LESS THAN ONE YEAR

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Abstract It is useful to know the distribution of pulmonary lesions in the diagnosis of tuberculosis on radiological examination. The aim of this study was to investigate if there is predominant lung segment or lobe for tuberculous lesions in infants aged less than one year using contrast enhanced CT. We studied 57 infants (40 boys, 17 girls) who were diagnosed as tuberculosis by isolation of *Mycobacterium tuberculosis* or combination of family contact, radiographic findings suggesting tuberculosis, and positive reaction of 5 mm or more induration to PPD tuberculin. All the infants had lesions in mediastinal and/or hilar lymphonodes, and 54 out of 57 infants had parenchymal lesions as well. In the study of the segmental predominance of tuberculous lesions, each infant had a share of 100 points. If an infant had a single focus, all the points were distributed to the corresponding segment. If he or she had multiple foci, the 100 points were equally divided into affected lung segments. There was no significant difference between right (3385 points/10 segments) and left (2005 points/8 segments) lungs. The points in upper lobes (2224 points/5 segments) were significantly higher than the combined points of middle and lingual (896 points/4 segments) and lower (2270 points/9 segments) lobes ($p<0.05$). The points in posterior lung segments (2839 points/7 segments) were significantly higher than the combined points of middle (436 points/3 segments) and anterior (2115 points/8 segments) lung segments ($p<0.05$). These results suggest that upper lobes and posterior segments are predominant parenchymal regions of tuberculosis among infants less than one year, although tuberculous lesions may locate in any lung segment.

Key words : Infants aged less than one year old, Primary complex of tuberculosis, Predominant lung segment of tuberculosis, Contrast enhanced CT, Upper lobes, Posterior lung segments

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PROBLEMS ABOUT THE MANAGEMENT OF ACTIVE PULMONARY TUBERCULOSIS PATIENTS UNDERGOING HAEMODIALYSIS

— Our Experiences and Nation-wide Questionnaire Survey —

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Abstract End-stage renal failure patients on chronic dialysis are high risk groups of tuberculosis due to attenuated cellular immunity. Patients receiving haemodialysis stay prolonged time inside the health-care facilities, thereby increased risk of tuberculosis transmission if a patient has active disease. So management of active pulmonary tuberculosis undergoing haemodialysis is important, however, the number of hospitals which are capable of taking care of such patients is estimated to be few in Japan.

Methods: From August 1994 through July 2002, 1059 active pulmonary tuberculosis patients (mean age; 57 ± 19, male/female=773/286) were admitted to Nishi-Kobe Medical Center, a 500-bed teaching hospital. Out of them, patients undergoing haemodialysis were retrospectively studied to describe the clinical characteristics of such cases. Then we conducted a questionnaire survey regarding the management of active pulmonary tuberculosis patients undergoing haemodialysis for 86 self-governing bodies in Japan.

Results:

(1) Clinical characteristics of active pulmonary tuberculosis undergoing haemodialysis

We encountered 14 cases (mean age; 65 ± 11, male/female= 7/7) of pulmonary tuberculosis undergoing haemodialysis during 8 years. In addition to pulmonary involvement, 3 pleural, one knee joint and one lymph node involvement was detected. Primary renal disease included diabetic nephropathy (n=3), chronic glomerulonephritis (n=3), congenital anomaly (n=1), and unknown (n=7). Nine cases were referred to our hospital from health-care facilities located out of city or prefecture. In five cases it took more than three months from the onset or detection of abnormal chest X-ray findings to the admission to our hospital. Five cases developed pulmonary tuberculosis within the first year after the initiation of dialysis. None of the patients had a past history of tuberculosis. Cavitary lesion on chest X-ray was observed in only one case. Triple antituberculosis therapy was used in 9 patients, and 4 antituberculosis drugs were used in 5 patients. Antituberculosis therapy was successfully done in all cases except two patients who died of apoplexy and cerebral infarction.

(2) The nation-wide questionnaire survey

Of the 86 self-governing bodies we mailed, 66 self-governing bodies replied. Of them, 31% reported that they have experienced difficulties in the management of active pulmonary tuberculosis patients undergoing haemodialysis, and 25% reported the lack of health-care facilities to take care of such cases in their territory. They have referred such patients to hospitals located in the nearby prefectures or they have recommended antituberculosis therapy visiting a local haemodialysis facility.

Conclusion: There are sometimes difficulties to manage active pulmonary tuberculosis patients undergoing haemodialysis in Japan. Health-care facilities to take care of such patients should be arranged and the formation of the network is necessarily.

Key words: Haemodialysis, Tuberculosis, Immunocompromised host

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Short Report

COMPARISON BETWEEN RELATIVE ANALOGY AND HOMOLOGY OF 16S rRNA PARTIAL SEQUENCES BETWEEN *MYCOBACTERIUM SZULGAI* AND *MYCOBACTERIUM MALMOENSE*

Yutaka FUKASAWA

Abstract A lot of nucleotide sequences of some genes, especially 16S rRNA gene, are registered in the public database. In order to identify clinical mycobacterial strains, 16S rRNA gene partial nucleotide sequences from 15 strains of *Mycobacterium malmoense* and 24 strains of *Mycobacterium szulgai* which are stored in the Research Institute of Tuberculosis, Japan Anti-Tuberculosis Association were determined. Then homology of the sequences to the data of type strains submitted to public database were determined. Relative analogy to type strains by ΔDDH was also measured.

In the area of nucleotide position 51−588 corresponding accession number X52930 which is *Mycobacterium malmoense* type strain 16S rRNA gene sequence data, the homology of some partial sequences with *Mycobacterium malmoense* strains to data of accession number X52930 were lower than that with *Mycobacterium szulgai* type strain data, accession number X52926. In the area of nucleotide position 31−568 or nucleotide position 31−588, the homology of all nucleotide sequence data to collect species data of type strains were higher than the homology to another species data. Nucleotide position 38, 40, 47 and 49 might be differential nucleotides conserved between *Mycobacterium malmoense* strains and *Mycobacterium szulgai* one.

These results suggest that homology of about 500bp's 16S rRNA gene nucleotide sequence data may not be enough for differential identification. Nevertheless, database of RIDOM, Ribosomal differentiation of Medical Microorganisms, indentified partial nucleotide sequences between nucleotide position 51−588 corresponding accession number X52930 correctly, though some were lower than 97% homology (data not shown). Therefore quality-controlled 16S rRNA gene nucleotide sequence database could be used for differential identification.

Key words: Microplate hybridization, Relative analogy, 16S rRNA gene, *Mycobacterium szulgai*, *Mycobacterium malmoense*

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Short Report

A NEW METHOD OF SPUTUM PRE-TREATMENT FOR PCR PREPARATION

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Abstract A rapid sputum processing method was developed for PCR. As a protocol prepared for commercial kit is too much simplified, PCR inhibitor is not completely removed from sputum. We developed a new semi-alkaline protease method to dissolve sputum. From April 2001 to August 2001, 261 sputum samples were treated with our new method. Twenty-one cases (8.0%) were PCR positive and all the results perfectly coincided with the results of the conventional culture method.

Key words: TB-PCR, Semi-alkaline protease, Preparation of PCR

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