Tuberculose

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Às portas do novo milênio, a tuberculose rapidamente se apresenta, lembrando-nos que a longa luta, travada pela humanidade contra ela, encontra-se longe da vitória final.

As esperanças de erradicá-la, a partir da década de 40, oriundas da descoberta de medicamentos eficazes, frustraram-se ao apagar das luzes do século XX. A principal causa disto, a pobreza, a fome, frutos da desigualdade social, têm permitido a sua manutenção e disseminação, levando a uma situação em que praticamente todos se encontram sob risco. Assim, com um terço da população mundial infectada pelo bacilo de Koch, aproximadamente oito milhões de casos novos a cada ano, afetando principalmente jovens e adultos, uma elevada mortalidade correspondente a 25% dos óbitos preveníveis entre jovens, a declaração da Organização Mundial da Saúde – OMS – de que nos encontramos sob estado de emergência mundial é muito pertinente. Agrega-se a essa situação o vírus da imunodeficiência humana – HIV – que sozinho tem contribuído para o aumento de 10 a 20% dos casos de tuberculose.

Como mais de 90% dos casos e das mortes por tuberculose ocorrem em países economicamente deficientes, com baixa capacidade de organização sanitária, ela se perpetua. Também em países ricos, quando esta organização foi deficiente, a tuberculose mostrou sua força, emergindo na forma de cepas resistentes a múltiplas drogas.

A OMS preconiza a estratégia DOTS *(directly observed treatment short course)* como uma das mais eficazes para o controle da TB. Devido à lenta implantação desta estratégia, e com o intuito de acelerar sua implantação, criou-se um movimento – *Stop TB iniciative* – que congrega, além da OMS, a *International Union Against Tuberculosis and Lung Diseases*, a *Royal Netherlands Tuberculosis Association*, a *American Lung Association*, a *American Thoracic Society*, a *US Centers for Disease Control and Prevention* e o *World Bank*. O Brasil encontra-se entre os 22 países que concentram 80% dos casos de tuberculose – na décima posição do mundo, e que serão alvo prioritário dessa iniciativa.

Dentre as estratégias definidas, será criado um programa mundial de pesquisa que tente superar as limitações operacionais, a curto prazo, buscando o desenvolvimento de novos meios diagnósticos, medicamentos e vacinas. O movimento buscará facilitar a colaboração para o aumento da capacidade de investigação de países com poucos recursos e alta prevalência de TB.

No Brasil, a luta contra a tuberculose, sempre presente, foi marcada por altos e baixos, como conseqüência do nível de priorização governamental do momento. Após o desastre da extinção da Campanha Nacional Contra a Tuberculose, pelo governo Collor, novamente o programa de combate foi ativado, a partir de 1994, com o lançamento do Plano Emergencial, que priorizou 230 municípios e concentra 85% dos casos do país. Mais recentemente foi apresentado o Plano Nacional de Controle da Tuberculose, que tem como metas: implementar o programa em 100% dos municípios; em três anos (2001) diagnosticar, pelo menos, 92% dos casos estimados; curar, no mínimo, 85% dos casos diagnosticados; em nove anos reduzir a incidência em pelo menos 50% e a mortalidade a dois terços.

O Plano incorporou a estratégia de criação de Rede Nacional de Luta Contra a Tuberculose denominada "Centro de Excelência de Combate à Tuberculose". Este modelo propõe a formação de extensas redes de parcerias estratégicas, a execução de trabalhos conjuntos; a otimização do todo através da manutenção de trabalho em rede; a busca de incorporação da inteligência nacional aos processos, produtos, serviços e gestão nacionais.

No capítulo da tecnologia, aponta-se para a pesquisa de novas drogas, vacinas e processos de diagnóstico, estudos nas áreas de biogenética, farmacologia e engenharia biomédica, gerando novos métodos e processos, tanto na análise quanto nos equipamentos e terapias. Também busca-se a inovação em padrões de atendimento e de suplementação alimentar.

Identifica-se que há pouca correlação, em geral, entre as necessidades de pesquisa para controle da TB e as efetivamente realizadas, além do próprio desconhecimento do que vem sendo realizado. Com a concentração dos recursos, hoje dispersos, poder-se-ia através de uma política organizada atingir-se melhor eficácia no direcionamento das linhas de pesquisa.

O alto nível dos trabalhos aqui apresentados, resumidamente, denota a capacidade e a qualidade do pesquisador brasileiro. O que nos deixa a esperança de que possamos, ainda, vencer a tuberculose no próximo milênio...

SERUM ADENOSINE DEAMINASE ISOFORM 2 (ADA2) ACTIVITY IN HIV SERONEGATIVE PATIENTS WITH PULMONARY TUBERCULOSIS (PTB).

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Introduction: the serum value of ADA2 is increased in patients with infection for intracellular microorganisms. Objective: to determine the ADA2 activity in HIV seronegative patients with PTB. Material and Methods: the patients assisted in HUCFF/UFRJ for investigation of PTB from July 1st, 1996 to January 31, 1998 were evaluated prospectively. ADA2 activity in serum was determined in 340 individuals (all seronegative for HIV), being 187 with PTB (178 with bacteriological diagnosis and 9 with diagnosis of probability), 41 with lung disease other than TB (23 inespecific bacterial infection, 8 virus infection and 10 cases of lung cancer), 93 healthy individuals PPD negative and 19 with previous anti-TB treatment according to the method of Giusti and methodology of Gakis for isoenzymes differentiation. The cut off point for PTB (25 IU/L) was obtained through receiver operator curves (ROC). Results: the serum ADA2 in PTB patients (29.2 IU/L) was significantly ($p < 0.001$) elevated compared with

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healthy group (PPD negative – 12 IU/L – and previous anti-TB treatment –20.0 IU/L) and with lung disease other than TB group (18.3 IU/L). The sensitivity for PTB diagnosis was 54.5%, the specificity 98.0%, the positive predictive value 97.1% and the negative predictive value 63.8%. Conclusion: serum ADA2 activity is increased in HIV seronegative patients with PTB. Additional studies are necessary to confirm these results.

PREVENTIVE THERAPY FOR TUBERCULOSIS IN HIV SEROPOSITIVE INDIVIDUALS UNDER FIELDS CONDITIONS IN RIO DE JANEIRO CITY. PRELIMINARY RESULTS.

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Background: In 1995, Brazilian National AIDS and Tuberculosis Program recommended the preventive therapy for TB (PT-TB) with isoniazid-INH (400 mg/day), during 6 months) among HIV seropositive individuals. Since then, there is no information regarding the PT-TB results under field conditions. Objective: to evaluate the PT-TB with INH among HIV seropositive individuals under field conditions. Methods: 144 HIV seropositive individuals consecutively received INH for PT from Jan to Dec, 1997, in Rio de Janeiro city. Retrospectively, medical charts were reviewed by trained personnel. Results: one hundred and three (72%) were male, 71 (61%) white, 93 (74%) single and median age of 35 years old (range from 19 to 70). In 22 (30%) individuals previous liver disease was detected. The PT was given among individuals with PPD > 5 mm in 60 (45%), with PPD < 5 mm in 68 (51%) and close contacts of pulmonary TB case in 4 (3%). Before the start of PT, chest x ray was evaluated in 102 (71%) and serum AST/ALT in 48 (33%). Among 75 individuals older than 35 years old, serum AST/ALT was evaluated in only 22 (29%). Adverse effects on PT were detected in 13 (11%) cases, and the PT was stopped in 6. Eighty three (57%) individuals had completed their treatment, 35 (24%) were lost of follow-up, and 22 (15%) were under treatment. Among those completed the PT, 2 (2%) develop active TB. Comments: high proportion of PT initiated without an adequate workup and high proportion of default highlight the necessity of improving the interaction between TB and AIDS Program.

HEPATOTOXICITY IN PATIENTS SUBMITTED TO ANTITUBERCULOSIS THERAPY (ATT) IN A HOSPITAL REFERENCE FOR ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS) IN RIO DE JANEIRO, BRAZIL.

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Introduction: the rate of hepatotoxicity in patients submitted to ATT in a hospital reference for AIDS is not well established. Objective: to assess the rate of hepatotoxicity of ATT and possible factors associated to this in a hospital reference for AIDS. Methods: cases of hepatotoxicity associated to ATT with rifampin (R), isoniazid (H), pyrazinamide (Z) and ethambutol (E) from January 1st, 1994 to December 31, 1995 were analyzed in a retrospective case-control study. The control group consisted in patients without hepatic alterations during the ATT. There was no significant difference in gender; age and initial ATT among cases and controls. The control-to-case ratio was: 5:1. Results: among 588 patients submitted to ATT with RHZ (with or without E) the hepatotoxicity was referred in 6.8% (40/588). In 85% (35/40) was need the suspension of the ATT. Sixty-six percent (23/35) of these received alternative ATT, 26% (9/35) restarted the same drugs and 8% (3/35) died. The diagnosis of AIDS, the unfavorable evolution, the disseminated form of TB, the presence of reticular infiltrated and/or hilar adenomegaly on chest X ray and the presence of viral hepatitis B and/or C were associated significantly with hepatotoxicity ($p < 0.05$). Conclusion: the hepatotoxicity in patients submitted to ATT was high (6.8%) and occurred more frequently among patients with AIDS, viral hepatitis and disseminated TB.

DRUG RESISTANCE PATTERNS AND OUTCOMES AMONG TUBERCULOSIS (TB) CASES IN BRAZIL.

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Introduction: drug resistant TB is a concern in many countries. In Brazil, little is known about the epidemiology and outcomes of drug resistant cases in outpatient settings. Methods: we enrolled and prospectively followed 187 culture-confirmed cases of pulmonary tuberculosis with resistance to isoniazid, rifampin, and at least one other anti-TB drug. In three clinical outpatient centers in Brazil from April 1995 through December 1997. Information was collected about the patients' sex, age and clinical characteristics. Voluntary, confidential HIV counseling and testing were offered. Patients treated during 12-18 months with four or more second-line anti-TB drugs and treatment outcomes were determined. Cultures and drug susceptibility testing were performed at enrollment, 6 months and 12 months thereafter using Lowenstein Jensen and Bactec System. Results: there were 20 patients (10.7%) with primary drug resistance and 160 patients (89.3%) with acquired drug resistance. Patients were resistant to three (HRS, HRE, HRZ), four (HRSE, HRSZ, HREZ), or five anti-TB drugs (HRSZE) upon study enrollment.

Resistance	Cure		Failure		Default		Death		Total
	n = 105	56.1%	n = 54	28.9%	n = 16	8.6%	n = 12	6.4%	187
3 drugs	56	53.3%	17	31.5%	5	41.7%	9	56.3%	87
4 drugs	29	27.6%	23	42.6%	5	41.7%	3	18.8%	60
5 drugs	20	19.0%	14	25.9%	2	16.7%	4	25.0%	40

Few patients were HIV-seropositive (n = 3, 1.6%). Patients with resistance to 3 anti-TB drugs were more likely to be cured than patients with resistance to 4 or 5 anti-TB drugs (OR = 1.89, 95% Cl 1.0, 1.37, p = 0.049). Conclusion: our results show poor outcomes with increasing drug resistance in this population of mainly HIV-seronegative outpatients. Resistance to more than 3 anti-TB drug is a predictor of poor treatment outcomes (failure, default or death).

LEVELS OF CYTOKINES AND REACTIVE NITROGEN INTERMEDIATES (RNI) IN TUBERCULOUS PLEURAL EFFUSION.

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Unlike pulmonary tuberculosis, tuberculous pleurisy generally resolves without specific chemotherapy, suggesting effective local immune responses. In this work, we evaluated the cytokine profile and RNI production in the tuberculous pleural effusion. We selected 48 consecutive patients with pleural effusion. Cytokines present in the pleural fluid was determined by ELISA. The following groups were constituted: pleural tuberculosis (n = 34) and pleural effusions of other causes (NTB, n = 14). The mean age was 43.6 ± 18 (16-79 years) and 21 (39.6%) females and 27 (40.4%) males. Duration of symptoms varied between 7 and 360 days (mean and SD 62.6 ± 77 days), with 72.8% of cases presenting symptoms less than 60 days. Only IFN- was significantly different between TB and NTB. No IFN- was seen in pleural effusions of the other origin, against 59% in the pleural effusion of TB origin ($p < 0.01$). We found a statistically significant correlation between the levels of cytokines and RNI in the pleural effusion with the time of duration of the symptoms. Pleural effusions with less than 45 days of symptoms had higher IFN- and RNI levels compared with those with more than 60 days of symptoms (P, 0.05). The inverse relationship was seen with IL-10, showing low levels in patients with less than 45 days of symptoms and higher levels in those with more than 60 days. The data suggested that IL-10 may interfere with the protective immune responses, leading to a chronification of the process through inhibition of the nitric oxide pathway.