

Characteristics of pulmonary tuberculosis in HIV seropositive and seronegative patients in a Northeastern region of Brazil

Características da tuberculose pulmonar em pacientes com sorologia positiva e negativa para o HIV em uma região do Nordeste do Brasil

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ABSTRACT

The aim of this study was to analyse the clinical, epidemiological and bacteriological features present in 60 pulmonary tuberculosis patients who were also infected with human immunodeficiency virus (HIV) and to compare these with 120 TB patients who were not infected with HIV. The patients with pulmonary tuberculosis and HIV coinfection were mostly male ($p = 0.001$), showed a higher frequency of weight loss ≥ 10 kilos ($p < 0.001$), had a higher rate of non-reaction result to the tuberculin skin test ($p < 0.001$), a higher frequency of negative sputum smear examination for acid-fast bacilli ($p = 0.001$) and negative sputum culture for Mycobacterium tuberculosis ($p = 0.001$). Treatment failure was more common in those who were HIV positive ($p < 0.000$). No higher frequency of resistance to antituberculosis drugs was found to be associated with TB/HIV coinfection ($p = 0.407$). Association between extrapulmonary and pulmonary tuberculosis was more frequent in those seropositive to HIV than those without HIV virus, 30% and 1.6% respectively. These findings showed a predominance of atypical clinical laboratory features in co-infected patients, and suggest that health care personnel should consider the possibility this diagnosis.

Key-words: Tuberculosis. Tuberculosis/HIV co-infection.

RESUMO

Este estudo teve como objetivo analisar características clínicas, epidemiológicas e bacteriológicas de 60 pacientes com tuberculose pulmonar infectados pelo HIV(+) comparando-as às de 120 pacientes com TB pulmonar/HIV(-). Analisou-se as características em relação ao sexo, idade, hábitos de vida, antecedentes de contato ou tratamento anterior para tuberculose, características clínicas e bacteriológicas e resultado do tratamento. Os doentes co-infectados foram predominantemente do sexo masculino ($p=0,001$), referiram com maior frequência perda ≥ 10 quilos ($p<0,001$), apresentaram maior frequência de teste tuberculínico não reatores ($p<0,001$), baciloscopia negativa ($p=0,001$) e cultura de escarro negativa ($p<0,001$). O insucesso do tratamento foi mais significativa naqueles HIV(+) ($p<0,001$). Não se encontrou uma maior frequência de resistência aos tuberculostáticos associada à co-infecção ($p=0,407$). A tuberculose extrapulmonar associada à tuberculose pulmonar foi mais freqüente nos soropositivos que nos HIV(-), 30% e 1,6% respectivamente. Estes achados evidenciam predominância de características clínico-laboratoriais atípicas nos pacientes com co-infecção, alertando para a possibilidade deste diagnóstico.

Palavras-chaves: Tuberculose. Co-infecção Tuberculose/HIV. AIDS

Tuberculosis (TB) has been known since ancient times, and came very near to being eradicated in developed countries thanks to an effective strategy for combating the disease. However, it once again constitutes a serious public health problem due to its resurgence all over the world. The human acquired

immunodeficiency virus (HIV) epidemic is one of the main factors contributing to the resurgence of the disease. This virus has altered the balance between human beings and the Koch bacillus and has had a noticeable impact on the epidemiology, natural history and clinical evolution of tuberculosis. The greatest impact of the rise

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in TB incidence has been on people between 25 and 44 years of age, since this is the age group predominantly affected by HIV. Kritski⁶ has described a rise in the frequency of TB associated with HIV in Brazil from 8% in 1984 to 19.9% in 1994. Over this period, HIV has ceased to be an infection restricted to male homosexuals of a high socioeconomic status and intravenous drug users and has also spread to low-income groups, among which *M. tuberculosis* infection is more prevalent. The two infections have thus become superimposed with respect to the involvement of the cellular immune system in groups of individuals from the same age group¹¹.

The interaction between the two morbid conditions results in an accelerated development of both diseases. HIV infection amplifies and accelerates the development of TB from infection to the advanced stages of the disease and is the most important risk factor known to be associated with the reactivation of a prior TB infection. In turn TB brings about a reduction in CD4 T lymphocytes, intensifying the immunodepressant effect of HIV and possibly resulting in an increased viral activity^{4,17}.

Pulmonary tuberculosis is the type most frequently found in all patients, whether HIV positive or not⁶. However, there are differences between the clinical manifestations of the disease in the two groups of patients and this has led to a number of studies aimed to describe the procedure to be adopted when attempting to diagnose such a condition. However, there is no consensus on the ways in which pulmonary TB manifests itself when associated with HIV. It is believed that there are two distinct clinical patterns according to the immunodepression stage during which they develop. In the early (pre-AIDS) phase of HIV, the postprimary features of the disease remain the same and clinical and radiological findings are typical. However, in more advanced phases, atypical findings occur more frequently, as a result of the CD4 T lymphocyte depletion (<200), and is reflected in the rise in frequency of extrapulmonary TB associated with pulmonary TB^{15,16}.

So far as risk factors for HIV infection are concerned, these appear to be identical to those already known and independent of the presence of tuberculosis⁶.

The behaviour pattern of TB/HIV association probably differs from region to region and therefore requires different diagnostic approaches⁶. Taking this supposition as our point of departure and given that no analyses of this kind have as yet been carried out in the city of Recife, the present study was conducted with a view to describing and comparing the characteristics of pulmonary TB cases with and without the presence of HIV infection. The study thereby aimed at contributing to the rising suspicion regarding such clinical cases and at facilitating the interpretation of diagnostic results for the investigation of the association between the two disorders.

PATIENTS AND METHODS

This is a prospective case series study with a comparison group. It describes 60 patients diagnosed with pulmonary TB and HIV at the TB outpatients clinic of the Federal University of Pernambuco (UFPE) over the period of December 1996 to December 2000. The clinical and epidemiological features were then compared with

those found in a group of 120 patients with pulmonary TB but without HIV, also attended at the same clinic over the same period. These control cases were chosen randomly using a computer programme at a ratio of two pulmonary TB/HIV(-) cases for each pulmonary TB/HIV(+) case.

Information on the patients was collected using a form specially designed for this study and complemented with investigation of previous medical records.

All the patients underwent three sputum smear tests for acid-fast bacilli performed using the Ziehl-Neelsen technique, the Lowenstein-Jensen method of sputum culture for *Mycobacterium tuberculosis*, a chest X-ray and the tuberculin skin test performed with 0.1ml of PPD RT 23, according to the Mantoux technique. HIV infection was investigated in all patients using a blood test (ELISA I and II with an immunofluorescence test to confirm the result). In exceptional cases, where it was difficult to reach a clear diagnosis, a bronco-alveolar smear test and a histopathological examination involving an open pulmonary biopsy were carried out. All patients were treated according to procedures recommended by the Brazilian Ministry of Health¹⁰, whereby death, non compliance or failure of the tuberculosis treatment are considered to constitute unsuccessful treatment and success is seen in terms of proven cure or the completion of the course of treatment¹¹⁰.

Statistical significance of the differences in characteristics between the two groups was analysed using the χ^2 test and p value < 0.05. The EPI-INFO Version 6.04 software was used both to randomly select the comparison group and to analyse the results.

RESULTS

Table 1 shows that there is a higher frequency of male individuals among pulmonary TB patients in general and that the frequency is even greater among TB cases where HIV infection is also present (p = 0.001). Although it is not statistically significant, it is worth pointing out that there is a higher frequency of individuals under 50 years of age in the HIV seropositive group, whilst the proportion of patients over 50 who are infected with TB but not HIV is 2.28 times greater than the number who are HIV positive. It can be seen that there is no statistically significant difference between the HIV positive and negative groups insofar as the habit of drinking alcohol or a history of contact with other TB patients are concerned.

The statistically significant findings in terms of bacteriological features were as follows: patients who were HIV seropositive had a lower frequency of positive sputum smear tests for acid-fast bacilli and sputum culture for *Mycobacterium tuberculosis* in comparison with those who were HIV negative (Table 2). It was also found that, among patients with the TB and HIV association, there was a higher incidence of non-reacting tuberculin skin tests, whilst a greater proportion of "strong reactions" was found in the TB/HIV negative patients (p < 0.001). The percentage of resistance to one or more drugs did not differ significantly from one group to the other (p = 0.407) (Table 2). Of the five HIV positive patients who showed resistance to anti-tuberculosis drugs, three were resistant to isoniazid alone, one to streptomycin alone, and one to

Table 1 - Biological, social and risk factors for HIV infection characteristics of pulmonary tuberculosis patients, HIV(+) and HIV(-), Recife, 12/1996 - 12/2000.

Characteristics	HIV				total	p value
	positive		negative			
	n	%	n	%		
Sex						
male	49	81.7	68	56.7	117	
female	11	18.3	52	43.3	63	0.001*
Age group (years)						
≤ 14	02	3.3	02	1.7	04	
15-49	51	85.0	86	71.7	137	
≥ 50	07	11.7	32	2.7	39	0.061
Contact with TB						
yes	11	18.3	20	16.7	31	
no	22	36.7	51	42.5	73	
unknow	27	45.0	49	40.8	76	0.754
Alcohol consumption						
excessive	12	20.0	15	12.5	27	
social	18	30.0	34	28.3	52	
no data	30	50.0	71	59.2	101	0.343
Haemophilia						
yes	01	2.2	-	-	01	
no	45	97.8	105	100.0	150	0.304
History of surgery/accident						
yes	19	46.3	35	32.1	54	
no	22	53.7	74	67.9	96	0.153
Use of human blood derivatives						
yes	12	27.9	07	6.5	19	
no	31	72.1	101	93.5	132	0.000*
IV drug use						
yes	05	10.2	00	0.0	05	
no	44	89.8	108	100.0	152	0.002*
Male homosexual relations						
yes	28	68.3	05	8.5	33	
no	13	31.7	54	91.5	67	0.000*
Number of sexual Partners						
≥ 2						
< 2						

*Statistically significant difference (p < 0.05)

a combination of isoniazid, rifampicin and streptomycin. Among the 19 HIV seronegative patients resistant to anti-tuberculosis drugs, five showed combined resistance to isoniazid and rifampicin.

Analysis of the clinical history of the patients showed that, although there was a higher rate of history of previous treatment in TB/HIV(+) patients compared with those who do not carry the HIV virus, this difference was not statistically significant (p = 0.282). It is worth pointing out that there was no statistically significant difference between the two groups in terms of duration of the disease (p = 0.206). Other interesting clinical findings in patients with the TB/HIV association included the higher frequency of a weight loss greater than 10 kilos (p<0.001) and a higher incidence of treatment failure (p<0.001) (Table 2).

The following were found to be positively associated with HIV infection: the use of medical products derived from human blood,

Table 2 - Tuberculin skin test, bacteriological results and clinical characteristics of pulmonary tuberculosis patients HIV(+) and HIV(-), Recife, 12/1996 - 12/2000.

Characteristics	HIV				Total	p value
	positive		negative			
	n	%	n	%		
Acid-fast bacillus in sputum smear						
positive	24	45.3	80	71.4	104	
negative	29	54.7	32	28.6	61	0.001*
Sputum culture for <i>M tb</i>						
positive	19	55.9	80	85.1	99	
negative	15	44.1	14	14.9	29	0.001*
Tuberculin skin test						
non reaction	21	72.4	17	18.9	38	
weak reaction	04	13.8	08	8.9	12	
strong reaction	04	13.8	65	72.2	69	0.000*
Resistance to drugs						
To one or more drugs sensitive	05	31.3	19	25.0	24	
sensitive	11	68.7	57	75.0	68	0.407
Previous treatment						
yes	16	27.1	24	20.0	40	
no	43	72.9	96	80.0	139	0.282
Duration of disease (days)						
≤ 30	18	31.0	26	22.27	44	
> 30	40	69.0	91	7.8	131	0.206
Weight loss (in kg)						
> 10	17	41.5	12	13.5	29	
≤ 10	24	58.5	77	86.5	101	0.000*
Treatment outcome						
failure	10	45.5	12	12.2	22	
success	12	54.5	86	87.8	98	0.000*

* Statistically significant difference (p < 0.05)

the use of intravenous drugs, a number of sexual partners greater than one over the past five years and a history of male to male homosexual relations. Hemophilia and a history of surgery were not found to be risk factors associated with TB/HIV co-infection among the cases studied (Table 1).

A number of patients for whom there was no data on the symptoms under study were excluded from the analysis shown in Table 5. In this case, the study was restricted to 59 HIV positive and 79 HIV negative patients. Of the HIV positive patients the most commonly reported symptoms were fever and weight loss. Other nonspecific symptoms found among TB/HIV(+) patients were chest pain and breathlessness. A dry cough was much more common among HIV seropositive patients (23.7% compared to 6.3% respectively.) On the other hand, among HIV negative patients, the most frequently reported symptom was a cough with expectoration (Table 3).

An important finding was that 18 (30%) of the 60 HIV positive patients showed signs of pulmonary tuberculosis associated with the extrapulmonary form of the disease, whilst only two such cases were found among the HIV negative group. Of the 18 HIV positive cases of extrapulmonary TB, 10 (55.6%) were in the peripheral ganglion, and 7 (38.9%) and 1 (5.6%) respectively, showed signs of the miliary and pleural forms of the disease.

Table 3 - Clinical pattern of pulmonary tuberculosis patients HIV(+) and HIV(-), Recife, 12/1996 - 12/2000

Signs and Symptoms	HIV				total n°
	positive		negative		
	n	%	n	%	
Fever	46	77.9	51	64.5	97
Cough with expectoration	41	69.4	67	84.8	108
Dry cough	14	23.7	05	6.3	19
Haemoptysis	09	15.2	18	22.7	27
Night sweat	09	15.2	14	17.7	23
Chest pains	16	27.1	24	30.3	40
Breathing difficulty	12	20.3	11	13.9	23
Total	59	100.0	79	100.0	138

* 42 no data (1 HIV positive and 41 HIV negative)

DISCUSSION

This study confirms the presence of risk factors that have long been known to facilitate HIV infection. These include a greater frequency of blood transfusions, the use of intravenous drugs, male homosexual relations and a larger number of sexual partners. Such data reinforce the contribution of careful recording of the medical history of patients with tuberculosis in differentiating between the two groups. It should, however, be emphasized that the profile of those infected with HIV is changing in recent years, and a common mistake at present is not to recognize the risk of heterosexuals being HIV positive⁵.

In both groups there were more men than women, but the predominance of the male sex was even greater among the HIV positive group. Although the incidence of HIV infection among women is rising⁸, this is not reflected in the case histories under study, probably because it is a relatively recent phenomenon and the sample population of co-infected patients contains a mixture of those recently infected and those who have carried the virus for some time. It is worth emphasizing that a greater number of patients falling into the 15 to 49 age group were found in the HIV positive group, reflecting the most common age for HIV infection in Brazil⁸.

Analysis of these case histories showed that weight loss and fever were most frequently encountered among patients co-infected with TB and HIV, supporting the hypothesis that tuberculosis as a disease is more difficult to diagnose in HIV positive patients due to changes in its usual clinical pattern^{2 7 15 18}. Over 50% of tested patients were negative for acid-fast bacilli in the sputum, 44.1% had a negative sputum smear culture for *Mycobacterium tuberculosis* and about 70% of the patients were non-reactive to the tuberculin skin test. It should be pointed out that these examinations are easy to perform and readily available within the health services and constitute an important tool in the investigation of patients with suspected pulmonary TB. We should also mention the similarity of its symptoms (fever, difficulty in breathing, dry cough) to those of *P. carinii* pneumonia. All these data reinforce the urgent need to develop and make available new diagnostic methods such as the polymerase chain reaction (PCR) test for *Mycobacterium tuberculosis* in sputum, blood and other organic fluids, especially considering that bronchoscopy and biopsy are risky procedures and not widely available in the regions where

tuberculosis is most prevalent. These new techniques would help to avoid the risk of using the out-dated and questionable strategy of empirical treatment for tuberculosis.

Despite the differences found in the clinical and bacteriological pattern between the two groups of patients, there was no significant difference in terms of disease duration, defined as the period of time from the onset of symptoms to diagnosis (Table 2). This study was carried out in a teaching hospital which could explain the more expeditious manner in which the diagnosis of TB in co-infected patients was undertaken.

With respect to the severity of clinical pattern, our data showed that breathing difficulty was more frequent in patients with concomitant HIV and tuberculosis infection (Table 3). Weight loss was also more pronounced in this group (Table 2) and the spread of tuberculosis (association with extrapulmonary forms) occurred with a much higher frequency, 30% in the HIV positive patients, as opposed to 1.6% in those who were HIV negative.

These results show that tuberculosis and HIV interact not only to produce a combination of the symptoms of the two diseases, but also to exacerbate one another. Tuberculosis is known to intensify the production of proinflammatory cytokines such as TNF- α , which triggers the intercellular reproduction of HIV¹², hence the more dramatic clinical presentation of co-infected patients.

Concerning the final outcome of TB treatment, it should be stressed that the failure rate in HIV seropositive patients was much greater than in HIV negative cohorts, in spite of the use of newer and more effective antiretroviral drugs which were available at the time this research was conducted. Actually, there is no consensus about the role of co-infection with HIV as a risk factor associated with an unfavorable treatment outcome. Rabahi *et al.*¹⁴ found no significant difference in cure rates between TB patients with and without HIV infection. On the other hand, in another series co-infection with HIV was a risk factor associated with an unfavorable treatment outcome¹ and the mortality rate for TB patients with HIV infection was twice as high as for HIV seronegative patients^{3 12 16}. On the other hand, the mortality rate for HIV seropositive patients with tuberculosis is twice as great as for those without HIV³. Illness severity is the major cause of treatment failure among co-infected patients. However lack of compliance to a treatment regime also plays an important role. The simultaneous use of multiple drugs and the common side effects partly explains why patients fail to comply with the treatment. Considering all these causes of treatment failure, emphasis should be placed on development of new strategies for the follow up of these patients.

It should be underscored that the possibility of HIV infection needs to be investigated in all cases of diagnosis of TB. Although this has been recommended for several years now, according Barnes³, only 63% of American patients with tuberculosis are tested for HIV. In Brazil, the Ministry of Health has recently recommended that an HIV test be carried out in the case of patients diagnosed as having TB¹⁰. Recognition of such patients would undoubtedly be easier and more expeditious if quick anti-HIV tests were made readily available (before confirmation by a traditional blood test). This strategy has proven to be quite effective for pregnant women and accidents at work. In these cases the results are available

within hours. Furthermore, a clear distinction should be made between the two groups of patients, and supervised treatment should be the norm in co-infected patients in order to assure compliance and earlier detection of side effects associated with the use of tuberculostatic agents.

Such work could be carried out in collaboration with Family Health Program teams or even with Home Care Programs for people with HIV which are available in some parts of Brazil.

Finally, it has been shown that the resistance of *Mycobacterium tuberculosis* was not greater in the co-infected group, supporting the use of the RIP (rifampicin + isoniazid + pyrazinamide) combination with this group of patients, as recommended by the Brazilian Ministry of Health⁹. This practice differs from that of other countries, where the RIPE (rifampicin + isoniazid + pyrazinamide + ethambutol) combination is always used³. It is, however, not clear whether the use of RIPE combination, would improve the therapeutic outcome in individuals with more serious forms of the disease and with higher degree of immunodepression, or whether this strategy would just be associated with an increase in the toxicity and with the difficulty co-infected patients experience regarding compliance to a prescribed regime.

The present investigation of clinical and epidemiological features of individuals with concomitant pulmonary tuberculosis and HIV infection, compared with patients who have pulmonary TB but not HIV virus has shown that there is a need to develop separate strategies for diagnosis, care and treatment of these two groups if better treatment results are to be obtained.

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