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DRUG RESISTANCE OF *M. TUBERCULOSIS* ISOLATED FROM PATIENTS WITH HIV INFECTION SEEN AT AN AIDS REFERENCE CENTER IN SÃO PAULO, BRAZIL.

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SUMMARY

M. tuberculosis-positive cultures were obtained from 228 patients seen in our service and drug sensitivity assays were carried out from January 1992 to December 1994. A survey of the medical records of these patients showed resistance to one or more drugs in 47 (20.6%), 25 of whom (10.9%), who reported previous treatment, were considered to have acquired resistance. Among the antecedents investigated, only previous treatment and alcoholism were the factors independently associated with the occurrence of resistance. The survival of patients with resistant strains was lower than that of patients attacked by non-resistant *M. tuberculosis*. We conclude that in the present series *M. tuberculosis* resistance to tuberculostatic agents was predominantly of the acquired type.

KEYWORDS: Tuberculosis; Tuberculosis treatment; AIDS; Multidrug resistance; Drug resistance; HIV infection.

INTRODUCTION

Tuberculosis is endemic in Brazil, where several studies on the resistance of *M. tuberculosis* to tuberculostatic agents have been performed, most of them before the advent of acquired immunodeficiency syndrome (AIDS) or, even today, focusing on the question of resistance among non-HIV-infected patients [11, 15, 17]. Studies carried out in other countries have indicated the possibility that HIV-seropositive patients are among those at higher risk to develop disease induced by a multiresistant bacillus [2, 6].

In Brazil, the cumulative incidence of cases of AIDS is 45.9/100,000 inhabitants and among patients with AIDS, approximately 12.8% manifest different forms of tuberculosis at the time of notification [3]. However, few cases of multiresistance have been recorded thus far, perhaps because the interest in evaluating the problem of resistance to tuberculostatic agents among patients with AIDS is very recent[12, 14, 20].

São Paulo is one of the Brazilian states in which the impact of tuberculosis/HIV co-infection is higher since the cumulative incidence of AIDS cases is 120.6/100,000 inhabitants[3]. In our service, approximately 33.3% of patients with AIDS present tuberculosis [13]. These data demonstrate the relevance of studies related to this co-infection.

The present study was conducted jointly by the

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Mycobacteria Sector of the Adolfo Lutz Institute (IAL) and by the Sexually Transmissible Diseases and AIDS Reference and Training Center (CRT DST/AIDS-SP) in São Paulo in order to determine: 1) the frequency of drug resistance, 2) the pattern of resistance, and 3) the factors predisposing to resistance in the series of HIV-infected patients with tuberculosis registered at the CRT DST/AIDS-SP.

MATERIALS AND METHODS

In March 1995, the medical records of all patients presenting positive culture results from the period of January 1992 to December 1994 (n=228) were surveyed. In all cases, the strains isolated had been submitted to a sensitivity test. No changes in the criteria for patient referral to the service or in laboratory methods occurred during these years.

The survey was conducted using a standardized form to obtain information about the following variables: category of exposure to HIV, history of alcoholism, homelessness, permanence in support homes, work as a health professional, previous history of tuberculosis, regular or irregular use of tuberculostatic agents, previous treatment and hospitalization for a period of two years or less, follow-up time, and survival. The patients who reported risk sexual behavior and the use of intravenous drugs were assigned to the category of intravenous drug users.

Laboratory methods: 1 - culture - sputum specimens, bronchial lavage, gastric lavage, feces, urine, biopsies, secretions, pleural and peritoneal fluids were submitted to decontamination by the method of Petroff and later plated onto Löwenstein-Jensen medium [10]. Blood specimens (5 ml) were inoculated directly into biphasic culture medium consisting of liquid Middlebrook 7H9 medium (Difco) containing sodium polyanetol sulfonate as an anticoagulant (0.25 g/ml), polymyxin B (200 U/ml), amphotericin B (10 µg/ml), carbenicillin (50 µg/ml), and trimetoprim (20 µg/ml), and of solid Löwenstein-Jensen medium (approximately 0.2 ml). After plating, the culture media were incubated in an oven at 37°C and inspected weekly until the growth of BAAR colonies was observed, or for a period of 60 days when, in the absence of growth, they were considered negative. The biopsies were also incubated at 28°C and 37°C. **2** -identification of mycobacteria - BAAR colonies with a rugose aspect without pigmentation, growing in Löwenstein-Jensen medium only at 37°C for a period of more than seven days (slow growth), which produced niacin and were nitrate reducers, which were sensitive to para-nitrobenzoic acid and resistant to 2-thiophenocarboxylic acid, were identified as *M. tuberculosis* [4, 18]. **3** - drug sensitivity test - The following drugs were tested by the proportion method [4]: rifampicin (RMP), isoniazid (INH), pyrazinamide (PZA), ethambutol (EMB), streptomycin (SM) for all strains, and ethionamide (ETH) and cycloserine (CS) for some of them.

Resistance was defined as primary (R1) for strains isolated from patients who denied a previous use of tuberculostatic agents, and secondary (R2) for strains isolated from patients who confirmed the previous use of these drugs. We decided to call resistance "undefined" for strains isolated from patients with an inconclusive history of use of tuberculostatic agents.

The sample was stratified into two groups: patients with strains sensitive to all drugs tested or sensitive group (SG), and patients with strains resistant to one or more drugs or resistant group (RG). The groups were compared in terms of the frequency of the variables mentioned earlier.

The chi-square test was used to compare proportions in the contingency tables, respecting the limitations imposed by the expected frequencies. Univariate analysis was used to determine the association of each relevant variable with the occurrence of *M. tuberculosis* resistance to the medications. For multivariate analysis we chose logistic regression, considering the occurrence of resistance to be the dependent variable and the nine antecedents in the medical records to be independent variables.

To compare the survival pattern of the patients infected with a resistant agent to that of patients infected with a sensitive agent we used the actuarial method, constructing the Kaplan-Meier curves and using the KMSURV software.

The date of collection of the first specimen from which *M. tuberculosis* was isolated and submitted to the sensitivity test was considered to be time zero. The date of death was recorded for the patients who died, and the time of observation and follow-up to the last medical visit within the study period (which ended in May 1995) was considered for the patients who did not die.

The level of significance used in all statistical analyses was 0.05.

RESULTS

Of the 228 patients studied, 201 (88.2%) were males. Age, which was determined for 222 of them, ranged from 16 to 58 years (mean $\pm$ SD = 31.8 $\pm$ 0.88). The distribution by category of exposure was 36.4% for homosexuals, 5.7% for bisexuals, 17.1% for heterosexuals, 33.3% for intravenous drug users, and 7.5% for other or undefined categories. Of these patients, 7.5% were health professionals, 18.9% alcoholics, 6.1% homeless, 21.1% reported previous tuberculosis, 21.5% reported previous treatment, and 21.9% reported previous hospitalization. Follow-up ranged from less than one day to 44.6 months, with a mean of 7.7 months. Survival ranged from 1 day to 25.1 months, with a mean of 5.1 months.

Among the 228 cases, the strains were sensitive in 181 (79.4%) and resistant in 47 (20.6%). There was no significant correlation between the occurrence of resistant strains and category of exposure (Table 1). The distribution of SG and RG cases was also homogenous with respect to the following variables: work as a health professional, living in a support home, homelessness, and regular use of tuberculostatic agents.

There was a significant positive correlation between the occurrence of resistant strains and the following variables: alcoholism (p = 0.01), previous history of tuberculosis (p = 0.000005), previous treatment (p = 0.0000002), and previous hospitalization (p = 0.008) (Table 2).

TABLE 1

Distribution of patients with sensitive and resistant *M. tuberculosis* strains by category of exposure to infection with human immunodeficiency virus

Category of exposure	No.	SG(%)	RG (%)
Homosexuals	83	77.1	22.9
Bisexuals	13	76.9	23.1
Heterosexuals	39	76.9	23.1
Intravenous drug users	76	82.2	15.8
Others/undefined	17	76.5	23.5

SG = Patients with susceptible strains; **RG** = Patients with resistant strains.

Multivariate analysis showed a significant correlation with the occurrence of resistant strains only for the variables alcoholism (p = 0.047) and previous treatment (p = 0.005) (Table 3).

Resistance pattern: Of the 228 cases studied, 12 (5.3%) presented strains with R1, 25(10.9%) strains with R2 and 10 (4.4%), strains with undefined resistance (Table 4).

Information about the previous use of tuberculostatic agents was available for 151 patients,of whom 114 (75.5%) had strains sensitive to all drugs tested and 37 (24.4%) had resistant strains; 102 denied previous treatment and 49 reported previous treatment. Of the 102 patients who denied previous treatment, 12

Table 2

Factors associated with resistance to tuberculostatic agents among 228 patients with tuberculosis and AIDS (chi-square test).

Antecedents	No.	SG (%)	RG (%)	Chi- square	p
alcoholism	43	62.8	37.2		
no alcoholism	104	82.7	17.3	8.96	0.01
undefined	81	84.0	16.0		
previous tuberculosis	48	54.2	45.8		
no previous tuberculosis	102	88.2	11.8	24.28	0.000005
undefined	78	83.3	16.7		
previous treatment	49	51.0	49.0		
no previous treatment	102	87.3	12.7	30.60	0.0000002
undefined	77	87.0	13.0		
previous hospitalization	50	64.0	36.0		
no previous hospitalization	112	84.8	15.2	9.49	0.008
undefined	66	81.8	18.2		

SG = Patients with susceptible strains; **RG** = Patients with resistant strains;

TABLE 3

Factors associated with resistance to tuberculostatic agents in 228 patients with tuberculosis and AIDS considering the occurrence of resistant *M. tuberculosis* strains as dependent variable (logistic regression)

Variable	Standard deviation	p	Odds ratio	Int.	Conf
Category of exposure	0.130	0.417	0.900	0.697	1.161
Profession +	0.553	0.930	1.050	0.355	3.108
Support Home	0.615	0.866	0.902	0.270	3.014
Homeless	0.657	0.418	0.587	0.162	2.131
Alcoholism *	0.265	0.047	0.592	0.352	0.995
Previous tuberculosis	0.570	0.123	2.410	0.787	7.374
Previous treatment*	0.593	0.005	0.189	0.059	0.604
Regular use	0.234	0.575	1.141	0.720	1.806
Previous Hospitalization.	0.269	0.234	0.726	0.428	1.230

+ = working as a health professional ; * = p< 0.005

had primary resistance (11.7 %) and of the 49 who reported previous treatment, 25 (51.0 %) presented secondary resistance. Among the 77 patients (33.8%) for whom no information was available about the use of tuberculostatic agents, 67 (87%) had sensitive strains and 10 (13%) had resistant strains (undefined resistance).

Considering the resistance patterns as a whole, 5.6% of cases presented resistance to one drug and 15.1% to two or more drugs, and resistance to combined RMP and INH was observed in 11.8% (27/228) of the patients and in 57.4% (27/47) of the resistant strains.

In 1.7% of the patients there was primary resistance (R1) to one drug and in 3.4% there was R1 to two or more drugs. Primary resistance to combined RMP and INH was observed in 2.6% of the patients.

Analysis of the survival curves showed that the survival of patients with resistant strains was signifi-

TABLE 4

Distribution of the 47 cases of tuberculosis with resistant strains in relation to the total number of 228 patients according to resistance profile

Drugs	Primary Resistance	Secondary Resistance	Undefined Resistance	Total
Resistance to one drug				
INH	1 (0.4)	1 (0.4)	2 (0.9)	4 (1.7)
RMP	1 (0.4)	1 (0.4)	1 (0.4)	3 (1.3)
PZA		2 (0.9)	1 (0.4)	3 (1.3)
EMB				0 (0.0)
SM	2 (0.9)		1 (0.4)	3 (1.3)
ETH				0 (0.0)
Multiresistance				
INH/RMP	4 (1.7)	8 (3.5)	1 (0.4)	13 (5.6)
INH/PZA	1 (0.4)			1 (0.4)
INH/ETH	1 (0.4)	2 (0.9)		3 (1.3)
PZA/SM		1 (0.4)		1 (0.4)
INH/RMP/PZA	2 (0.9)	7 (3.1)	2 (0.9)	11 (4.8)
INH/RMP/SM		1 (0.4)		1 (0.4)
INH/PZA/EMB			1 (0.4)	1 (0.4)
INH/EMB/SM			1 (0.4)	1 (0.4)
INH/RMP/SM/ ETH		1 (0.4)		1 (0.4)
INH/RMP/PZA/ EMB/SM		1 (0.4)		1 (0.4)
TOTAL	12 (5.3)	25 (10.9)	10 (4.4)	47 (20.6)

INH = Isoniazid; RMP = Rifampin; PZA = Pyrazinamide; EMB = Ethambutol; SM = Streptomycin; ETH = Ethionamide.

cantly shorter (p = 0.01) than that of patients with non-resistant *M. tuberculosis* (Figure 1).

DISCUSSION

The distribution of the present patients by sex, age range and category of exposure to HIV agrees with the AIDS data observed in Brazil as a whole[3], except that the percentage of drug addicts (33.3%) exceeds that reported for national cases, perhaps because of the higher incidence of tuberculosis in this group.[9] The tuberculosis and previous hospitalization factors, that were shown to be correlated with resistance by univariate analysis, did not present a correlation by multivariate analysis, probably because they were closely linked to the previous treatment factor, which is associated with resistance in these patients and is recognized as the major factor predisposing to resistance to tuberculostatic agents [6, 7, 16, 21] .Patients with AIDS present characteristics that can lead to lack of compliance with treatment, such as neuropsychiatric alterations and the concomitant use of other drugs. Alcoholism and drug dependence may also lead to non-compliance [5, 8, 19].

Although we did not detect a correlation between drug addiction and resistance, we would like to emphasize that the study carried out by VITTI [19] in Santos (State of São Paulo) in 1992 demonstrated a rate of abandonment of tuberculosis treatment as high as 40% among intravenous drug users, indicating that drug addition may become a factor predisposing to the acquisition of secondary resistance.

The present results differ from those reported by FRIEDEN et al.[6] who, in a study of 518 patients that were HIV positive or not, 32% of whom were alcoholics, did not detect a correlation between resistance and alcoholism. We cannot conclude that in our patients the resistance was directly related to alcoholism since alcoholism is known to predispose the patient to non-compliance, which in turn predisposes to resistance. We believe that this analysis was impaired because of the difficulty in obtaining data about the regular or irregular previous use of drugs, since in general health professionals do not record details about previous medication in the patient's medical records. Nevertheless, in view of these results, we judge it important to point out that alcoholism may be an additional factor that should always be investigated in the anamnesis of these patients.

The rates of secondary resistance detected in the present sample are apparently lower than those detected in patients not infected with HIV in our State[15,17] although it should be pointed out that these investigators worked with data obtained from laboratory material [17] or from material obtained from patients not responsive to treatment[15]. In a review of the sensitivity pattern of 1668 strains isolated at Public Health laboratories from 1986 to 1990 in the State of São Paulo, SILVA et al.[17] detected resistance to one or more drugs in 660 (46.6%) of the 1414 samples obtained from patients under treatment.

The presence of an 10.9% rate of secondary resistance in our sample emphasizes the need to always

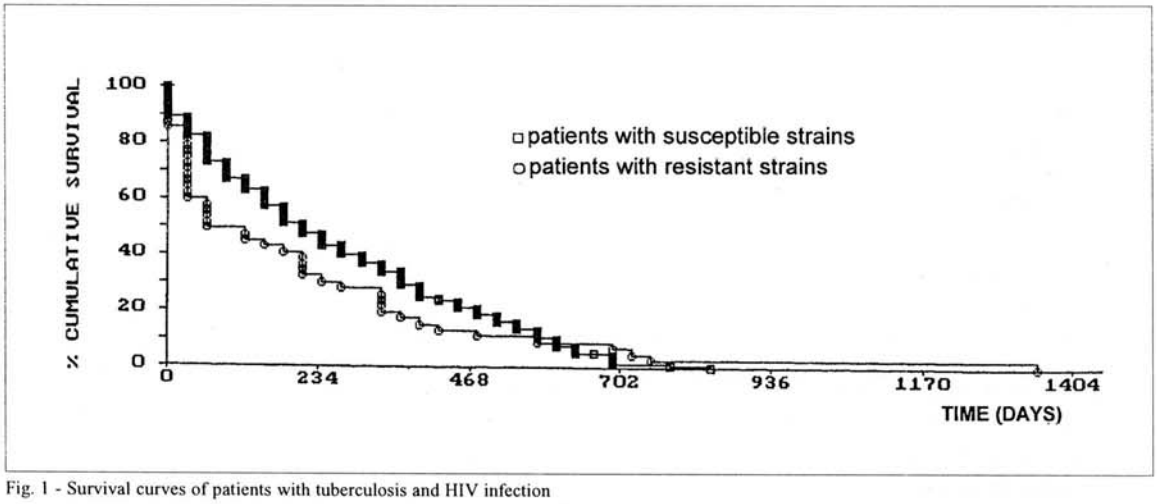

Fig. 1 - Survival curves of patients with tuberculosis and HIV infection

obtain information about tuberculosis and previous treatments for AIDS patients since this information may be useful for the decisions about the treatment of cases that do not respond to standard treatment until the result of the sensitivity test is obtained.

As to primary resistance, the question is whether the rates detected in the present study are excessively high or similar to those observed in other groups of patients with tuberculosis in Brazil. Among the most recent data that are suitable for a comparison are those obtained in a retrospective study by MELO et al. (personal communication) at a tuberculosis reference center located in the same metropolitan region as the STD-AIDS Reference Center. The authors evaluated patients with tuberculosis older than 14 years with negative anti-HIV serology and not previously treated who were seen from 1986 to 1989 and detected a 7.4% rate of primary resistance, i.e., a higher rate than the 5.3% value obtained in the present study. However, the primary resistance profile of the patients studied by MELO et al. differed from that observed in our series since 5.6% were resistant to one drug and 1.5% presented multiple resistance (two or more drugs). Among our patients, 1.7% (4/228) presented resistance to one drug and 3.4% (8/228) multiple resistance (Table 4). If, for comparative purposes, we considered the percentages of primary resistance in this series only with respect to the 102 patients who denied previous treatment, these rates would even be higher: 11.7% primary resistance, 3.9% with resistance to one drug and 7.8% with multiple primary resistance.

The factors found to predispose to resistance in the present study (alcoholism and previous treatment) are usually associated with acquired resistance and differ from those that are usually associated with primary resistance such as drug addiction and time of permanence in shelters, hospitals or prisons[6, 21]. The higher frequency of primary resistance among HIV-positive patients and patients with AIDS may be due to a greater possibility of progression to active disease among these patients compared to immunocompetent patients infected with resistant strains, recently infected patients with more rapid progression to disease or greater exposure to resistant bacilli[6].

Since most of the studies approaching the question of primary resistance among HIV-positive patients were carried out in other countries, reflecting a different epidemiologic reality, we cannot state that these are the factors causing the rates of multiple primary resistance observed in our patients. We did not detect a correlation between resistance and previous hospitalization, a result that reflects the lack of reports of hospital outbreaks of multiresistant tuberculosis in Brazil. On the other hand, considering the limitations of a retrospective study in terms of determining time of previous hospitalization for each case, we cannot rule out the hypothesis that a longer permanence in hospitals or in support centers may have been associated with the occurrence of primary resistance in some individual cases.

The wide range of follow-up periods and survival may be explained by the characteristics of the service that admits both patients with AIDS in the initial phase and patients in an advanced clinical phase. Indeed, it is known that tuberculosis can manifest in HIV-positive patients at different times during the course of HIV infection [1]. Furthermore, because of the nature of our medical care structure, many patients are followed up for short periods of time at an outpatient service and are admitted to other institutions, thus becoming lost to follow-up.

Because of the difficulty in precisely determining the beginning of AIDS symptoms in a retrospective study, we did not evaluate the time of AIDS evolution in the two groups. The determination of immunologic parameters such as CD4 lymphocyte counts for all patients may contribute to a better analysis of survival time, but this procedure was not available for the present series. Even so, the lower survival time of RG patients (Figure 1) agreed with literature data[6] and suggests that the occurrence of resistance may have contributed to the shorter survival.

The present results reflect the reality of patients seen at a public service. In São Paulo, many patients with AIDS have a different socioeconomic profile and many are followed up on the basis of other medical care models including home care. However, we wish to emphasize that these multiple primary resistance rates may represent a tendency that may become more evident in the future. Furthermore, based only on epidemiological data, it seems that in our State the resistance of patients with AIDS to tuberculostatic agents is predominantly acquired, a significant phenomenon that could be controlled by improving the services specializing in the care of patients with tuberculosis and infected with HIV.

RESUMO

Resistência a drogas de *M. tuberculosis* isolados de pacientes com infecção pelo HIV atendidos no Centro de Referência e Treinamento DST/AIDS, São Paulo, Brasil.

No período de janeiro de 1992 a dezembro de 1994, foram obtidas culturas positivas para *M. tuberculosis* e foram realizados testes de sensibilidade a drogas em 228 pacientes atendidos no Centro de Referência DST/AIDS-SP. Através da revisão dos prontuários de todos os casos verificamos resistência a uma ou mais drogas em 47(20.6%), dos quais 25(10.9 %),que relatavam tratamento pregresso, foram considerados como portadores de resistência adquirida. Dos antecedentes investigados, somente os fatores tratamento prévio e alcoolismo foram independentemente associados à ocorrência de resistência. A sobrevivência dos pacientes portadores de cepas resistentes foi menor que a dos pacientes acometidos por *M. tuberculosis* não resistentes. Concluimos que nesta casuística a resistência do *M.tuberculosis* aos tuberculostáticos foi predominantemente do tipo adquirida.

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