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RESEARCH ARTICLE

Tuberculosis Re-Treatment Cases and Factors Associated with Unfavourable Outcome at the Fann University Hospital of Dakar, Senegal between 2011 and 2016: A Follow-Up Study

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Abstract

Introduction: The aim of our study was to describe the socio-demographic, clinical, therapeutic and evolutionary characteristics of patients admitted to tuberculosis re-treatment and managed at the The Infectious and Tropical Diseases Department (SMIT) screening and tuberculosis treatment center (TTC), to determine the factors associated with unfavourable outcome

Methodology: This is a descriptive and analytical retrospective cross sectional study covering all tuberculosis re-treatment cases monitored in the service of infectious and tropical diseases in Fann from 1 January 2011 to 31 December 2016. The Epi-Info software version 7 CDC and SAS (version 9.3, Cary, NC, USA) were used for data entry and analysis.

Results: We collected 83 patients as re-treatment tuberculosis cases during the study period, for an annual average of 14 cases. The average age of the patients was 42.2 years ± 13.6 years, with extremes of 16 and 77 years. There was a male predominance (66.3%) with a sex ratio of 1.96. The majority (95.2%) of our patients came from the Dakar region, 42.2% of them from the suburban area. More than two thirds (77.1%) of our patients were hospitalized. Clinically, the average weight at initiation of tuberculosis treatment was 48.1 kg ± 9.9 kg. The isolated pulmonary form accounted for 63%, followed by the multifocal form 23%. HIV seroprevalence was 73.6% and 92.9% of these patients were on cotrimoxazole chemoprophylaxis and 60.7% on ARV treatment. Relapses (61.4%) and treatment after default (36.1%) constituted the majority of the re-treatment circumstances. The unfavourable outcome was related to provenance in suburban areas and outside Dakar (AOR = 17.5; 95% CI: 3.61 - 85.4).

Conclusion: Compliance and monitoring of retreatment cases is important to avoid TB drug resistance. It is necessary to improve the referral and counter-referral system as well as communication between the different tuberculosis treatment centers.

Keywords

Re-treatment tuberculosis, Outcome, Dakar

Introduction

Progress in tuberculosis (TB) diagnosis has led to an improvement in case detection and a 1.5% reduction in incidence per year between 2014-2015 [1]. These encouraging results must be maintained and even improved in order to end the tuberculosis epidemic by

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2035. In Senegal, TB screening and case follow-up are carried out by tuberculosis treatment center (TTC). Indeed, TB is endemic in these countries. In 2016, the incidence rate was estimated at 140 cases per 100,000 population per year with a case detection rate of 60% and [2] mortality of 25 deaths per 100,000 population per year. The proportion of MDR-TB cases was 0.9% in new cases and 19% in previously treated cases [2]. The Infectious and Tropical Diseases Department (SMIT) of the national Fann University Hospital Center (CHNU) is one of 80 tuberculosis treatment center in Senegal, which treats patients in accordance with the guidelines of the National Tuberculosis Control Program (NTP). Nearly 300 patients are treated there each year [3]. A department of infectious diseases receives patients from other structures, either patients referred to the health centers or the patients who come from them in consultation and then hospitalized.

Previous studies have been conducted on tuberculosis in Senegal [3-5], but only one study looked at the re-treatment cases from January 2008 to April 2012 and found a overall prevalence of 3.86% of these cases [6]. In order to update case follow-up data, we conducted this study to describe the socio-demographic, clinical, therapeutic and evolutionary characteristics of patients admitted to tuberculosis re-treatment and managed at the SMIT- TTC, to determine the factors associated with unfavourable outcome.....

Methodology

Type of study

This was a retrospective descriptive and analytical cross sectional of all TB re-treatment cases, followed by the Infectious and Tropical Diseases Department at Fann university hospital, from January 1, 2011 to December 31, 2016. This is the national reference center for the management of Infectious and tropical diseases.

Study population

We included all patients who received tuberculosis re-treatment protocol and followed in the SMIT-TTC during the study period. Re-treatment patients under 15 years of age were excluded.

Definition of tuberculosis re-treatment cases

Relapse: These patients have previously been treated for active tuberculosis, reported cured at the end of treatment, and is now found to be sputum smear positive.

Treatment after default: These are patients who have been lost to follow-up for 2 months or more and who come back with a positive sputum on examination of the sputum on 2 samples.

Treatment after failure: These are patients who have a positive sputum test at the end of the 5th month of treatment or any time between the 5th month and the end of treatment.

Transfer: Any patient registered in the tuberculosis registry at a TTC and sent to the SMIT for further treatment.

Other: This refers to all negative smear reprocessing. Il cases that do not fit the above definitions, such as patients

- for whom it is not known whether they have been previously treated;
- who were previously treated but with unknown outcome of that previous treatment; and/or
- who have returned to treatment with smear-negative PTB or bacteriologically negative EPTBb [3].

Definition of cases according to treatment outcome:

Cured: This is when the controls of the 5th month and the end of the 6th month are negative.

Completed treatment: TB patient who completed treatment without evidence of failure but with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative, either because tests were not done or because results are unavailable.

Failure: A TB patient whose sputum smear or culture is positive at month 5 or later during treatment.

Default/Lost to follow-up: This is a patient who has interrupted his treatment for 2 consecutive months or more.

Died: A TB patient who dies in the course of treatment, regardless of the cause,

Transferred out: This includes cases “transferred out” to another treatment unit as well as cases for whom the treatment outcome is unknown to the reporting unit.

- Treatment success included both "cured" and "completed treatment".

Data collection

Data were collected from tuberculosis treatment registries, NTP treatment cards. It included socio-demographic aspects (age, sex, residential district), clinical aspects (hospitalization at the time of diagnosis of TB, weight at initiation of treatment, form of TB, location of TB, circumstances of TB in retreatment), paraclinical aspects (confirmation of TB, HIV status) and treatment outcomes.

Statistical analysis

In the descriptive part, the categorical variables were described by the number and frequency in each

class. Concerning the quantitative variables, we specified the mean and standard deviation (SD) after checking the normality (graphical evaluation of the distribution). Variables for which the distribution did not follow a normal distribution are described by the interquartile interval. For the identification of factors associated with unfavourable outcome, we defined the variable of interest "treatment success" and patients were divided into two groups:

- "favourable treatment outcome" group: included both "cured" and "completed treatment" patients; it represented the control group.

- "unfavourable treatment outcome" group: included treatment failure, lost to follow-up, transferred out and died patients.

To look for explanatory factors (age, sex, district, hospitalization at diagnosis, initial weight, form of TB, type of TB, HIV status, type of TB confirmation) associated with "unfavourable treatment outcome", we used a chi^2 test for the categorical variables and a Student's t or Mann-Whitney U test (depending on the distribution of the variable) for the quantitative variables. The logistic regression method was used in multivariate analysis to estimate the Odds Ratio (OR) with 95% confidence intervals (CI). All explanatory variables associated with "unfavourable treatment outcome" in univariate analysis with p value < 0.20 were retained. The analysis was made on the available data, A significance level of $\alpha = 0.05$ was taken into account for statistical significance. Epi Info version 7 and SAS software (version 9.3, Cary, NC, USA) were used for the analysis.

Results

Characteristics of the study population

From 2011 to 2016, 83 patients were recorded for tuberculosis re-treatment out of a total of 1361 tuberculosis cases, representing a prevalence of 6.1% for the entire study duration. More than half of the patients were collected between 2011 and 2012 (54.2%). The average age of the patients was 42.2 years ± 13.6 years and the majority of patients were between 15 and 44 years of age (55.4%). A male predominance was noted (66.3%) with a sex ratio of 1.96 . Almost all (95.2%) of our patients came from the Dakar region, including 42.2% from the suburban area.

Clinically, sixty-four patients were hospitalized at the time of tuberculosis diagnosis. The average weight at the beginning of anti-tuberculosis therapy was 48.1 kg ± 9.9 kg with extremes of 31 kg and 80 kg. Isolated pulmonary tuberculosis was the most common form (63%), followed by multifocal tuberculosis (23%) and extra-pulmonary tuberculosis accounted for only 14% of cases. Neuro-meningeal (16.3%), pleural (5.4%), ganglionic (5.4%) and peritoneal (5.4%) accounted for the majority of extra-pulmonary localizations. Regarding the re-treatment circumstances, relapse cases represented 61.4% of patients followed by treatment after default with 36.1% (Table 1).

Tuberculosis was confirmed in 38 patients with positive BAAR and/or Gene-Xpert sputum, representing 48.1% of cases. BAAR sputum was positive at 37.3% and Gene-Xpert 10.8% of cases. HIV serology was positive in 56 out of 76 patients screened, representing a seroprevalence of 73.7%. Among HIV-positive patients, 60.7% were on ARV treatment and the prescription rate for cotrimoxazole was 92.9%.

Treatment outcomes

In our study, which involved 83 cases of tuberculo-

Table 1: Socio-demographic, clinical, and outcome characteristics of re-treatment of tuberculosis at the department of infectious diseases, Fann Hospital, Dakar, 2011-2016.

Variables	Number	Percent (%)
Year		
2011	20	24.1
2012	25	30.1
2013	10	12.0
2014	7	8.4
2015	8	9.6
2016	13	15.7
Sex		
Male	55	66.3
Female	28	33.7
Age group (year)		
15-44	46	55.4
45-60	29	34.9
≥ 60	8	9.6
Hospitalization		
yes	64	77.1
No	19	22.9
Clinical presentation		
Pulmonary only	52	62.6
Multifocal	19	22.9
Extrapulmonary only	12	14.5
Retreatment circumstances		
Relapse	51	61.4
Treatment after default	30	36.1
Treatment after failure	1	1.2
Others	1	1.2
HIV status (n = 76)		
Positive	56	73.7
Negative	20	26.3
Outcome TB Treatment		
Cured	7	8.4
Completed treatment	24	28.9
Died	21	25.3
Default/Lost to follow up	11	13.3
Transferred out	20	24.1
Failure	-	-

sis re-treatment, 24 patients (28.9%) completed their treatment and 7 patients (8.4%) were reported cured, for a favourable treatment outcome of 37.3%. Lethality was 25.3% and the rate of lost to follow-up cases was 13.3%. No cases of failure were recorded during our study period.

Factors associated with unfavourable treatment outcome

In univariate analysis, the unfavourable treatment outcome was 73.3% in treatment after default and failed patients, while it was 56.9% for patients with relapsed tuberculosis. Nevertheless, this difference was not statistically significant (p = 0.21).

The unfavourable treatment outcome was 84.6% among patients referred by a TTC from suburban/non-Dakar areas compared to 43.1% of patients from TTC located in urban areas (p = 10^{-5}). There was also a correlation between unfavourable treatment outcome and hospitalized patients (70.3% versus 36.8% (p = 0.008) and in patients with a weight between 30-40 kg (p = 0.01).

However, in multivariate analysis, only the health center of origin was associated with unfavourable treatment outcome (AOR = 17.5; 95% CI: 3.61-85.4) (Table 2).

Discussion

The prevalence of re-treatment cases was 6.1%, which is significantly higher than the rate found in 2012 (3.8%) in the same department [6]. This difference could be explained by the increasing use of Gene-Xpert, which has improved case detection. In Senegal, Gene-Xpert is systematically performed in all patients suspected of tuberculosis relapse since 2013 in order to confirm the diagnosis, but above all

Table 2: Factors associated with unfavourable treatment outcome.

Variables	Number	Events* n (%)	Uni Variate analysis	AOR (IC95%)**	p-value
Year of TB diagnosis					
2011	20	11 (55.0)	0.09	1	0.15
2012	25	19 (76.0)		0.63 (0.1-3.5)	
2013	10	9 (90.0)		5.4 (0.4-67)	
2014	7	4 (57.1)		1.29 (0.1-10.3)	
2015	8	3 (37.5)		0.10 (0.008-1.28)	
2016	13	6 (46.2)		0.18 (0.02-1.54)	
Age group (years)					
15-44	46	28 (60.9)	0.48	1	0.50
45-59	29	21 (72.4)		1.5 (0.4-5.67)	
≥ 60	8	3 (37.5)		0.42 (0.05-3.41)	
District residence					
Urban	44	19 (43.2)	10^{-5}	1	**0.0004**
Suburban/out of Dakar	39	33 (84.6)		17.5 (3.61-85.4)	
Hospitalization at TB diagnosis					
Yes	19	7 (36.8)	0.008	1	0.13
No	64	45 (70.3)		3.18 (0.69-14.5)	
Weight at TB diagnosis (kg)					
≤ 45	37	27 (73.0)	0.01	1	0.11
> 45	46	25 (54.3)		0.37 (0.11-1.26)	
HIV status					
Negative	16	8 (50.0)	0.30	1	
Positive	56	38 (67.9)		1.25 (0.5-3.02)	0.13
Unknown	11	6 (54.5)		1.5 (0.18-11.8)	
Re-treatment circumstances					
Relapse	51	29 (56.9)	0.21	1	
others (treatment after default, treatment after failure)	32	22 (73.3)		1.60 (0.46-5.52)	0.4

*Unfavourable treatment outcome; **AOR: Adjusted Odds ratio; CI95%: 95% confidence interval.

to test the sensitivity of the isolated strain to rifampicin. Yet, it should be noted that 45 cases (54.2%) were treated between 2011 and 2012 with a decrease in the number of cases over the years.

The majority of patients in our series (77.1%) were hospitalized at the time of diagnosis of tuberculosis. This result is explained by the fact that patients followed up at SMIT have often been referred for atypical clinical pictures or consulted after a long therapeutic period. The predominance of pulmonary localization reported in our series is comparable to the results of Velavan [7] and Valin N [8]. These data show that regardless of the type of tuberculosis, the lungs remain the main portal of entry.

Regarding the retreatment circumstances, a predominance of relapses (61.4%) followed by treatment after default (36.1%) was noted in our series, this corroborates the results of Diop [6] in Senegal, who had found 49% of relapses and 33% of treatment after default. In Madagascar, Tiaray [9] reported the same trend, with 70% relapses and 16% treatment after default. On the other hand, in Benin, Gninafon [10] had a predominance of treatment after default (47.81%).

In terms of pathophysiology, the occurrence of relapses can be due to two mechanisms, reinfection and reactivation of tuberculosis bacilli. Compared to other authors [6,11], we found only one case of failure (1.2%) as a reason for re-treatment. In 2012 Diop [6] had found again a failure rate of 16% in the same department and Kouamé-N'Takpé [11] in Ivory coast had reported 30.6% failure. The low prevalence of treatment failure (1.2%) in our cohort can be explained by the persistent sensitivity of *Mycobacterium tuberculosis* to standard anti-tuberculosis drugs in the re-treatment regimen and by improved surveillance, including the DOTS strategy.

Across our entire cohort, favourable treatment outcome was achieved in 31 patients (38%), 24 patients who completed treatment (29%) and 7 patients reported cured (9%). Ravahatra [12] reported a rate of 35.84% of favourable outcome. Nevertheless, these rates are much lower than those reported by Saha [13] (75.2%) in India and by Agodokpessi [14] (80%) in Benin.

The rate of people lost to follow-up (13%) was similar to that found in Benin (12%) [14]. Discontinuation of treatment is one of the main reasons for the emergence of multidrug-resistant tuberculosis. In order to remedy this, it is necessary to strengthen surveillance, set up an alert system for patients absent from their appointments and further involve social services in patient follow-up.

The lethality rate was 25%. In two studies conducted respectively in Benin [10] and Madagascar [12] this lethality was 7% and 5.66%. This high lethality in our series could be related to the fact that 77.1% of our patients were hospitalized, 73.6% were co-infected with HIV and had a low average weight of 46 kg at the start of treatment. Indeed, it has been demonstrated that HIV co-infected patients are more likely to die than HIV seronegative patients who are mono-infected with tuberculosis [15].

Regarding success by type of tuberculosis in our series, patients undergoing re-treatment after treatment after default or failure of tuberculosis treatment had more unfavourable outcomes than patients who were relapsing treatment. Saha [13] had found that the rate of unfavourable treatment outcome was more frequent on defaulter also. For Gninafon [10], the therapeutic success rate was comparable between relapses (80%) and failures (85%), but significantly lower ($p < 0.01$) for treatment after default (59%). In another study [16], patients who discontinue their first treatment have a significantly higher and consistent probability of discontinuing a re-treatment regimen compared to relapses. This suggests that the unfavourable treatment outcome is not a priori associated with TB drug resistance, but rather compliance, which remains the main determinant of treatment outcome.

In multivariate analysis, the health center of origin was the only factor associated with the unfavourable treatment outcome. Indeed, patients from suburban areas and outside Dakar were 17.5 times more likely to have an unfavourable treatment outcome than those living in urban areas (AOR = 17.5; 95% CI: 3.61-85.4). This result shows once again to the importance of initiating treatment according to place of residence in order to reduce the transfer rate (24.1%) and the number of people lost to follow-up (13.3%). However, its application sometimes remains difficult, because of the stigma associated with tuberculosis and HIV, some patients prefer to be followed up far from their residential area.

Conclusion

Few cases of failure have been found as re-treatment circumstantial. It is advisable to insist on the observance and follow-up of reprocessing cases to avoid the resistance of anti-tuberculosis drugs. Additionally, in order to have a better estimate of the treatment outcome of our patients, it is necessary to improve the referral and counter-referral system as well as communication between the different tuberculosis treatment center.

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