EGYPTIAN ACADEMIC JOURNAL OF

BIOLOGICAL SCIENCES

PHYSIOLOGY & MOLECULARBIOLOGY

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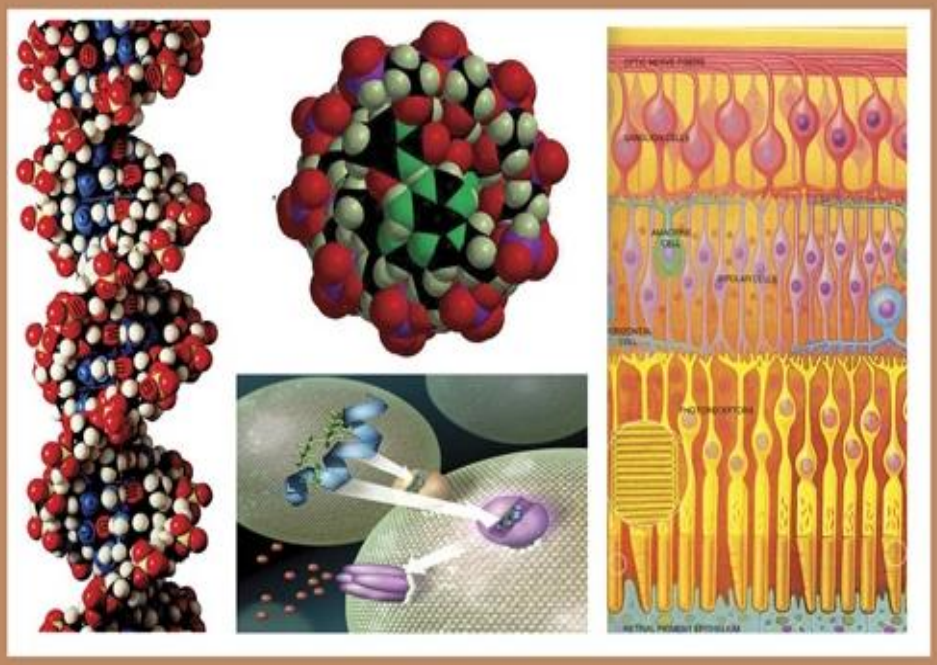

ISSN
2090-0767

WWW.EAJBS.EG.NET

Vol. 13 No. 1 (2021)

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Citation: *Egypt.Acad.J.Biolog.Sci. (C.Physiology and Molecular biology) Vol. 13(1) pp149-157 (2021)*
DOI: 10.21608/EAJBSC.2021.178245

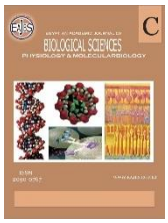
Egypt. Acad. J. Biolog. Sci., 13(1):149-157 (2021)

Egyptian Academic Journal of Biological Sciences

C. Physiology & Molecular Biology

ISSN 2090-0767

www.eajbsc.journals.ekb.eg



Multi-Resistant Tuberculosis in Western Algeria: about 36 Cases

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ARTICLE INFO

Article History

Received:6/4/2021

Accepted:8/6/2021

Keywords:

Tuberculosis, primary multi-resistant, secondary multi-resistant, Western Algeria

ABSTRACT

Multi-drug resistant tuberculosis (*MDR-TB*) is defined by the loss of susceptibility of *Mycobacterium tuberculosis* complex strains to the two major anti-tuberculosis drugs: isoniazid (H) and Rifampicin (R). This resistance may be acquired or primary. The aim of our study was to describe the epidemiological, clinical, bacteriological and evolutionary profile of *multi-resistant tuberculosis* patients in Western Algeria. To do so, a retrospective analytical study, which included 36 patients, was carried out in the pneumo-phthisiology department (B) of the Oran University Hospital (West Algeria) from January 2010 to December 2014. Our result showed an average age of 33.7 years. The risk factors for *MDR-TB* highlighted were tobacco (*n=12*; 33.3%), alcoholism (*n=1*; 2.8%) and family history of *MDR-TB* (*n=3*; 8.33). Primary *MDR-TB* was present in 11.11% of cases and secondary *MDR-TB* in 88.89% of cases. There was resistance to H and R in 13.8% of cases (n=5); to H, R and Streptomycin (S) in 50% of cases (*n=18*); to H, R and Ethambutol (E) in 5.6% of cases (*n=2*). The percentage of patients who had lost the sensitivity of the *Bacillus* to the four first-line anti-tuberculosis drugs (H, R, S, and E) was 25% of all patients tested (*n=9*) and H, R, S, and Ofloxacin (O) in one case. Five patients died. The rate of primary resistance found in this study constitutes a threat to efforts to control *MDR tuberculosis* in Algeria. It is therefore important to update the results and assess the extent of the problem.

INTRODUCTION

The World Health Organization (WHO) estimates that 2 billion people are infected with *Mycobacterium tuberculosis* (*TB*), of whom 7-9 million become ill and 3 million die each year (Aka Danguy, 2007). The highest per capita incidence rate is in the African region with 340 per 100 000 inhabitants (Bagdadi *et al.*,1997). The human immunodeficiency virus (HIV) and the spread of *TB* cases with drug-resistant *Bacilli* are the main causes (Aka Danguy, 2007). The dual resistance to rifampicin and isoniazid, the two major anti-*TB* drugs, also known as multi-drug resistance (*MDR),* is particularly worrying because of the difficulty of treating patients, its high mortality rate, and its potential impact on the epidemiology of the disease (Baough *et al.*,2007).

In 2012, the WHO estimates that 410 *multi-drug resistant tuberculosis* worldwide and that one-third of them died from it (Baough *et al.,* 2007). *MDR-TB* exists in all regions of the world but is particularly common in countries with a high incidence of *tuberculosis* and *HIV* co-infection, where, moreover, the management of patients is uncertain (Caminero, 2006; Dominique, 2007). Resistance has already been described in certain African countries such as Côte d'Ivoire 2.5% (Dye, 2006) and Algeria 9.2 % (Hawken *et al.*,2001). At the national level, two prospective surveys were carried out on representative samples of patients, in 1988 and 2002 respectively; 8 and 22 years after the introduction of rifampicin in the associated form in first-line chemotherapy regimes. The prevalence of primary resistance was 8.6% in 1988 (of which 1.2% was due to primary resistance to isoniazid and rifampicin) and 5.9% in 2002 (of which 1.4% was due to primary resistance to isoniazid and rifampicin). The prevalence of bacterial resistance to anti-tuberculosis drugs among previously untreated patients (or primary resistance) is the epidemiological index that reflects the quality of chemotherapy applied in a national program (Holmes *et al.,* 1998). In view of the need for reliable data on tuberculosis drug resistance and more particularly on multidrug-resistant cases, the aim of this study was to describe the epidemiological, clinical, bacteriological and even evolutionary profile of multidrug-resistant tuberculosis patients in western Algeria.

MATERIALS AND METHODS

This was a retrospective analytical study from January 2010 to December 2014 carried out in the Pneumo-phthisiology department (B) of the Oran University Hospital (Western Algeria). The study concerned patients with *multi-drug resistant tuberculosis* confirmed by sensitivity testing to anti-tuberculosis drugs. The study material came from the different hospital services of the UHC and from the different public health sectors of the states of the Western Algeria region. Statistical processing and data analysis were carried out using SPSS version 20 software.

RESULTS

During the study period from January 2010 to December 2014, 36 cases of *multi-drug resistant tuberculosis* were recorded. We noted a male predominance with 23 men (63.9%), 13 women (36.1%) and a sex ratio of 1.76 (Table. 1).

According to the year of recruitment, the distribution of patients with *MDR-TB* showed that the year 2013 recorded the highest annual frequency with 33.3% of cases (*n=12*), followed by the year 2011 (22.2%; *n=8*), the year 2012 (19.4%; *n=7*), the year 2010 (13.9%; *n=5*) and the year 2014 (11.1%; *n=4*). The disease affected both sexes in different proportions (Fig.1).

The average age of our patients was 33.7 years (extreme: 18-53 years). The distribution of *MDR-TB* cases according to age showed that the most affected age groups were 28-37 years (47.2%; *n=17*), (22.2%; *n=8*) for the age groups 18-27 and 38-47 years and (8.3%; *n=3*) for 48-53 years (Table.1).

Two-thirds, or 66.66% (*n=24*) of the patients were single. Whereas nearly 33.34% were married, making it difficult to isolate these patients during the period of contagiousness, as the risk of contamination of the member of the direct family circle was manifest (Table.1).

The standard of living was average for 72.2% of tuberculosis patients but was estimated to be lower for 19.4% of cases. 8.3% of the patients responded that they had a good standard of living.

In our analyzed cohort, 12 patients were chronic smokers, i.e., 33.3% and one patient out of 36 was an alcohol user (Table.1). The presence of diabetes could potentiate the adverse effects of anti-

tuberculosis drugs, including kidney dysfunction. One (01) patient had diabetes, which accounted for 2.8% of all recorded cases (Table.1). Testing for *HIV* infection was recommended and only one patient was co-infected, a 50-year-old man (Table.1).

Table 1: Socio-demographic and clinical characteristics of *MDR-TB* cases.

Variable	Work force		Frequency (%)	
Age groups				
18-27	8		22,2	
28-37	17		47,2	
38-47	8		22,2	
48-53	3		8,3	
Total	36		100	
Sex				
Female	13		36.1	
Male	23		63.9	
Total	36		100	
Marital status	**Female**	**Male**	**Female**	**Male**
Single	9	15	69	65
Married	4	8	31	35
Total	13	23	100	100
Socio-economic level				
Good	3		8,3	
Medium	26		72,2	
Low	7		19,5	
Total	36		100	
Toxic habits	**Smoking**	**Alcoholism**	**Smoking**	**Alcoholism**
Yes	12	1	33,3	2,8
No	24	35	66,7	97,2
Total	36	36	100	100
Comorbidities	***HIV***	**Diabetes**	***HIV***	**Diabetes**
YES	11		2,8	2.8
NO	35		97,2	97,2
Total	36		100	100
Location				
TBP	34		94,4	
TBP+TBEP	2		5,6	
Total	36		100	
Family history of *MDR-TB*				
0	33		92	
1	2		5	
4	1		3	
Total	36		100	

TBP: Pulmonary tubeculosis, TBEP: Extrapulmonary tuberculosis

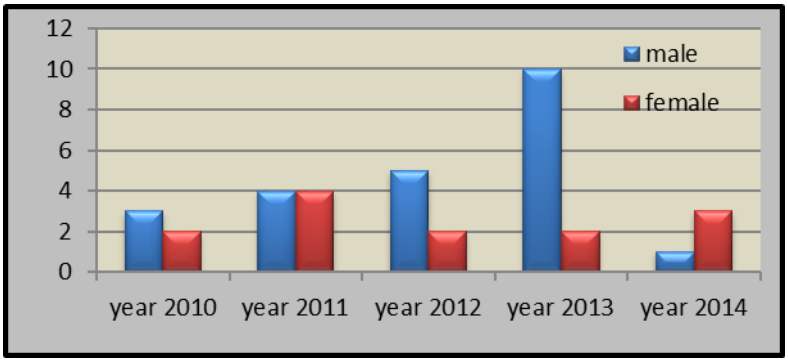

Fig .1: Distribution of *MDR tuberculosis cases* by year and sex.

The majority of the patients had an isolated thoracic localization of *tuberculosis*; however, two patients had a double thoracic and extra-thoracic localization (Table.1). Extra-thoracic tuberculosis noted were pot-sickness and meningo-encephalitis. No isolated extra-thoracic locations were observed. 100% of the multi-resistant patients registered did not have a *tuberculosis* patient in their family circle. Similarly, for the family history of *MDR-TB*, 92% of cases had no *MDR-TB* patient in the family, but in the remaining cases (8% of patients) there was at least one *MDR-TB* patient; two patients had one *MDR-TB* in the family, while for another patient we noted the presence of four *MDR-TB* patients in the same family (Table.1). One patient highlighted one death from *multi-resistant tuberculosis* in his family circle and four deaths for another case.

Resistance can be primary or acquired. In our analyzed cohort, primary resistance was recorded in four cases, i.e., 11.11% of the total number of cases, these patients had never been treated before for pulmonary tuberculosis. On the other hand, acquired resistance was detected in 32 patients, i.e. 88.89%. These patients have already been treated for *tuberculosis*.

Multi-drug resistance was confirmed in all patients. It was resistant to H and R in 13.8% of cases (*n=5*); to H, R and Streptomycin (S) in 50% of cases (*n=18*); to H, R and Ethambutol (E) in 5.6% of cases (*n=2*). The percentage of patients who had lost the sensitivity of the *Bacillus* to the four first-line anti-tuberculosis drugs (H, R, S, and E) was 25% of all patients tested (*n=9*) and H, R, S, and Ofloxacin (O) in 2.8% of cases (*n=1*). One patient had ultra-resistant *TB (XDR),* i.e., 2.8%. No mono-or poly-resistance was recorded (Table .2).

Table 2: Antibiogram Results

Resistance to anti-tuberculosis drugs	Number	Percentage %
H+R	5	13.8
H+R+E	2	5.6
H+R+S	18	50.0
H+R+S+E	9	25
H+R+S+O	1	2.8
All ATBs : *XDR* case	1	2.8
Total	36	100.0

Regarding problems with third-line treatment, almost half of the patients (47.2%; *n=17*) experienced side effects. One case showed non-compliance unrelated to another problem (5.6%), the same percentage was recorded in another patient with non-compliance related to side effects. No information was mentioned for the patient with ultra-resistant *tuberculosis (XDR).* Thus for 14 patients (38.8%), no problem could be highlighted (Table.3).

When analyzing the treatment outcome of the multi-resistant tuberculosis episode, the cure was noted for 10 cases, i.e., 27.78%, five patients had died, i.e., 13.88%.11.11percentage of patients (*n=4*) were lost to follow-up and 17 patients or 47.33% were still being treated (Table .4).

Table 3: Distribution of Cases by Reprocessing Problems

Problems of reprocessing	Number	Percentage %
Lack of Compliance	2	5.6
Failure to Comply+ Side Effects	2	5.6
Side Effects	17	47.2
No Problem pointed out	14	38.8
Not mentioned	1	2.8
Total	36	100

Table 4: Treatment Outcome of *MDR-TB* Episode

Treatment Outcome	Number	Percentage %
Death	5	13.88
Processing in progress	17	47.23
Healing	10	27.78
Lost in sight	4	11.11
Total	36	100

DISCUSSION

The fight against tuberculosis is based on interrupting the chain of transmission by rapidly detecting cases and treating them appropriately (Horo *et al.*, 2011). Mycobacterial resistance to *TB* drugs is a worldwide phenomenon. It is also a determining factor in the eradication of tuberculosis (Houndonougbo and Yélognissè, 2011).

During the study period from January 2010 to December 2014, 36 cases were recorded. The male sex was predominant in 63.9% of the cases with a sex ratio of 1.76. The male sex was predominant in 63.9% of the cases with a sex ratio of 1.76. Our results are similar to those of (Ouardi,2013), who in his study conducted in the same department, noted a male predominance and a sex ratio of 1.4 (Kabedi *et al.*,2007). In terms of *TB* epidemiology, male predominance has also been reported in other studies. Indeed, (Kashongwe *et al.*, 1995 and Kir *et al.*, 2006) had found a clear male predominance in 83% and 83.9% of cases, with a sex ratio of 4.87 and 5.2 respectively. Similarly, (Sangaré *et al.*,2010) found a male predominance (68%) in a series composed mainly of young adults (Kouassi *et al.*, 2004), which could be the result of differences in exposure between men and women in their societal role, i.e., in relation to their activities (Kuaban *et al.*,2000). Indeed, men occupy different sectors of activity, which facilitates the transmission of the *tuberculosis Bacillus*. On the other hand, (Shean and Willcox ,2006) found a female predominance with sex ratios of 2.5 and 3.5 respectively in favour of women (Moutaouakkil, 2014).

According to (Dominique ,2007), in his study on the resistance of *Mycobacterium tuberculosis*, tuberculosis primarily affects 75% of patients aged between 15 and 45 years (WHO ,1997). In our series, the 28-37 age group was the most affected with 47.2% of cases. This result agrees with those of (Ouardi ,2013) and Houndonougbo and Yélognissè, 2011**,** who found that the age groups 25-34 years and 21-40 years were the most represented with 45.3% and 53.20% of the cases respectively. An average standard of living was highlighted for 72.2% of patients.

This result is consistent with (Ouardi, 2013), finding in his survey that 59.8% of patients felt they had an average standard of living. 66.7% of patients were single compared to 33.3% married. Similarly Ouardi, 2013 noted 54.6% of single patients, while Moutaouakkil, 2014 noted only 25% of single patients versus 75% of married patients.

The risk factors for *MDR-TB* highlighted in our series were tobacco (*n=12*; 33.3%), alcoholism (*n=1*; 2.8%), family history of *MDR-TB* (*n=3*; 8.33%), diabetes (*n=1*) and *HIV*=one equals 2.8% for each. The low rate of *HIV* co-infection among *tuberculosis* patients shows that the global *HIV* epidemic in Algeria has no practical impact on the incidence of *tuberculosis* or on the results of treatment. It proves that *HIV* circulates little and is currently limited to populations (Holmes *et al.,* 1998).

In Tunisia, Snène *et al.,* 2014 found in their study of fifty-four patients that the risk factors were: tobacco (*n=42*), incarceration (*n=4*), drug addiction (*n=6*), family history of *MDR-TB* (*n=4*) and co-morbidities *(n=4).* In the Moutaouakkil,2014 study in Morocco, smoking accounted for 36.11%, diabetes 20.58% and asthma 02.79%. No *tuberculosis* patients were *HIV*-positive in this series.

A primary resistance rate of 11.11% was highlighted in our study. This result is much lower than that of Kabedi *et al.,* 2007 who noted a primary resistance rate of 43.5% and that of Kashongwe *et al.*, 1995 (31.6%); as well as those of other African countries, such as Morocco (23.9%), Cameroon (31.8%), Benin (18.5%) and Kenya (14.4%). On the other hand, this rate is close to that noted in Malawi (11.8 %) but higher than that recorded in South Africa (6.9 %) (Park *et al.,*1998; Robert and Jarlier,2002**;** Sabai *et al.,* 2003**;** Sangaré *et al.,*2010**;** Schaaf *et al.,*2000; Shean *et al.,*2006).

In our cohort of 36 *TB* patients, multidrug resistance was confirmed in all patients. Resistance was to H and R in 13.8% of cases (*n=5*); to H, R and Streptomycin (S) in 50% of cases (*n=18*); to H, R and Ethambutol (E) in 5.6% of cases (*n=2*). Resistance to the four first-line anti-tuberculosis drugs (H, R, S and E) was recorded in 25% of all patients tested (*n=9*) and to H, R, S, and Ofloxacin (O) in 2.8% of cases (*n=1*). One patient had ultra-resistant *TB (XDR)* at 2.8%. Our results are in agreement with those noted by (Ouardi ,2013), who found in his study that resistance of the R+H+S association type was the most frequent with 32% of cases followed by R+H+S with 16.8%. In the Snène *et al.,* 2014 cohort, it was resistant to H and R in 33% of cases; H, R and Streptomycin (S) in 15% of cases; H, R and Ethambutol (E) in 10% of cases; H, R, S and E in 20% of cases and H, R, S, E and Pyrazinamide (Z) in 20% of cases.

Among the 36 patients, seventeen (17) or 47.23% of the patients continued their treatment, while Sidibé, 2009 and Houndonougbo and Yélognissè, 2011 had reported, in their series, a rate of 54.8% and 66% respectively (Kir *et al.,* 2006**;** Kashongwe *et al.,*1995).

A rate of the abundance of treatment by patients was noted at 11.11%, while Sidibé, 2009 had recorded a rate of 25.8% Kir *et al.,* 2006; Houndonougbo and Yélognissè, 2011 and Ouardi,2013 recorded a lower rate of 6.4% and 6.25% respectively. We recorded a death rate of 13.88% among the population studied. This result is lower than that reported in the series of Houndonougbo and Yélognissè, 2011 (14.9%), Sidibé, 2009 (16.1%), (Horo *et al.,* 2011) (15.2%); **(**Ouardi,2013) (15%).

A cure rate of 27.78% was highlighted in our series. This result is far from that reported by (Ouardi,2013), i.e., a cure rate of 61.25%. Houndonougbo and Yélognissè, 2011 had not recorded any cases of recovery. In Côte d'Ivoire, Horo *et al.,* 2011, reported a cure rate of 5.1%. Yew *et al.,* 2000**,** reported a cure rate of 81.00% in China. The researchers reported

a cure rate of 83 percent in a cohort of 75 patients. Treatment success ranged from 50% in Taiwan (Trébucq *et al.*,1999) to over 80% in Korea (Trébucq *et al.,* 1999) and Turkey (Tahaoğlu *et al.*,2001). The strong therapeutic success in these countries is due to the early diagnosis of *MDR-TB.*

The side effects of the treatments were polymorphic and represented the major problem in the course of third-line treatment. Sidibé, 2009 and Horo *et al.*, 2011, reported the same results.

CONCLUSION

Despite the improvement in the performance of the culture and sensitivity test, efforts still need to be made in the management of patients with *MDR* strains. The rate of primary and even secondary resistance found in this study constitutes a threat to efforts to control *MDR tuberculosis* in Algeria. It is therefore important to update the results and assess the extent of the problem.

Acknowledgments

We would like to thank the staff of the Pneumo-phthisiology department (B) of the University Hospital of Oran (Western Algeria) for their invaluable support.

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