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Multidrug resistant tuberculosis (MDR-TB): A lethal risk in Benghazi City, Libya

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ABSTRACT

Anti-tuberculosis (TB) drug resistance is a major public health problem that threatens TB treatment progress made in the inhabitants of countries in Europe, Asia, Africa, and the America. A retrospective study for the pulmonary TB cases admitted to Quefia Chest Hospital Benghazi, Libya, from 1/1/2009 till 1/6/2010 showed that 4 cases out of 430 TB patients were positive for sensitivity culture and didn't respond to the first line anti-TB therapy and therefore were diagnosed as Multidrug Resistant Tuberculosis (MDR-TB). One of these patients was Libyan while others were aliens. The 2nd line anti-TB drugs were given in the form of Amikacin injection, cycloserine, moxifloxacin and pyrazinamide for the first 6 months followed by 18 months therapy with moxifloxacin, cycloserine and pyrazinamide. Follow-up with the patients exhibited clinical-radiological and microbiological improvement.

Keywords: Tuberculosis; multi drug resistance; Libya.

INTRODUCTION

Tuberculosis (TB), one of the oldest diseases known to humankind and it remains one of the world's major causes of illness and death. Two decades ago, TB was declared a global emergency by the WHO. A recent estimates form WHO also indicated roughly 630 000 cases of Multidrug resistance tuberculosis (MDR-TB) worldwide [1, 2] . Despite advances in treatment, TB remains a major cause of illness and death worldwide, especially in Africa and Asia. Every year tuberculosis kills almost 2 million people. Since the 1980s, rates of TB have increased, fueled by the HIV/AIDS epidemic and the emergence of drug-resistant strains of the TB bacteria [3]. In 2009, around 26% of the HIV positive patient died of TB, and MDR-TB, by which the HIV progress faster into sever disease and death [4] which believed to be a real challenge for controlling the disease [5, 6]. MDR-TB shows two types of resistance to the first line potent anti-Tuberculosis drugs (isoniazid and rifampicin), the primary resistance which registered in TB patients with no prior anti-TB treatment, and acquired resistance which attained in TB patients subjected to anti-TB treatment [7]. According to the WHO recent report (2013), about 3.7% of the newly TB infected patients in the world have MDR-TB, and this number increases to 20% among the acquired resistance patients [7, 8]. This increase is a reflection of the mismanagement of TB cases that emerge annually [9] and can be attributed to many factors including health system weakness, lack of sufficient resources and the inadequate treatment and subsequent transmission [10], unlike the eastern Mediterranean countries which are under continues surveillance of the TB and MDR-TB cases [11] Libya has limited records and published studies about the disease status, between 1971 and 1979 the MDR-TB cases in the eastern region of Libya decreases from 16.6 - 33.3% to 8.6 - 14.7%, while in the eighties the Libyan western region was between 11-21.5%, in accordance with the WHO survey the prevalence of the MDR-TB in Libya in 2011 was between 3.4 – 29%. [12].

This study aims to identify the rates of primary and acquired MDR-TB among patients with Pulmonary-TB with description of their clinical profile.

MATERIALS AND METHODS

A one year and six months retrospective study was conducted in the time between the 1st of January 2009 to 31st of May 2010, in Quefia Chest Hospital (QCH). Medical records of the 430 patients whose sputum were positive to pulmonary tuberculosis by direct smear and culture were reviewed to indentify the cases of MDR-TB.

Gram positive Sample Staining: Ziehl-Neelsen method was used to stain three alternative direct sputum smears for each patient. Culture in Lowenstein-Jensen medium and culture sensitivity test for MDR-TB for the first line anti-TB drugs was done by radiometric method (BACTEC-MGIT) [13, 14].

Sample Preparation: Each sample were digested using 4% NaOH (1:2) in water bath for 15 minutes at 37^{o}C, then centrifuged at 3000 r.p.m. for 20 minutes, supernatant were discarded and the pellet washed several times with sterile d.H_2O.

Direct Sputum Smear: Sputum smears were prepared using Ziehl-Neelsen method [14] by placing a droplet from the suspension on a glass slide and leaving it to air dry, 1% of carbol- fuchsin drops were used to stain the smears. After heating and 10 minutes stands for color development, the slides washed with water and decolorized with 25% H_2SO_4 and counterstained with 0.1% methylene blue for 2 minutes then washed and left to air dry before microscopic examination.

Preparation Clinical Isolate: A triplicate from each sputum suspension sample were inoculated in Lowenstein-Jensen medium and incubated at 37^{o}C for 4-6 weeks for optimum growth.

Culture Sensitivity Test: The drug susceptibility of every successful isolate of *M. tuberculosis* was tested using BACTEC MGIT 960 supplemented with isoniazid (0.1 µg/ml), rifampicin (1.0 µg/ml), ethambutol (5.0 µg/ml) or streptomycin (1.0 µg/ml). The isolates confirmed to be multidrug-resistant were then tested for resistance to second-line anti-TB drugs with BACTEC MGIT 960 supplemented with kanamycin (2.5 µg/ml), amikacin (1.0 µg/ml), capreomycin (2.5 µg/ml) or ofloxacin (2.0 µg/ml).
All demographic , clinical, radiological, and other investigations data where re-viewed.

RESULTS

Of 430 admitted patients 91% were males while 9% were females (Figure 1a), 12% were HIV positive and 3% were positive to Hepatitis B or and C, while 85% were merely suffering from tuberculosis (Figure 1b). Culture and sensitivity tests performance to detect MDR-TB were only available for cases admitted after 1 January 2009 and no data regarding drug sensitivity were available for cases admitted before this date.

All admitted cases were initially treated with first-line drug course composed of Isoniazid (INH), Rifampicin, Ethambutol, and Pyrazinamide. 10 cases were defaulters (discontinued medical treatment before course completion), four of them turned to be with MDR-TB (Table 1). One patient was Libyan while the rest were of African origin, these patients details are depicted in Table 2. The patients symptoms varied from cough, night fever, anorexia, weight loss and sweating (Table 3). After the resistance was confirmed, all MDR-TB cases were started with second-line drug regimen composed of Amikacin, Cycloserine, Pyrazinamide, Moxifloxacin or levofloxacin. On treatment with second-line anti-TB drugs course followed by a negative sputum culture test as well as by X-Ray scans, patients were discharged asymptomatic and were advised to continue anti-TB therapy for another 18 months (Figure 2). Though all patients showed considerable cavities in their chest x-ray scans (Figure 2), their blood sample analysis did not exhibit remarkable biochemical data abnormalities as compared to known reference values (Table 4).

DISCUSSION

The health status in Libya generally is changing from a status where morbidity and mortality prevalence were mainly linked to infectious diseases to one associated with non-communicable diseases [15]. According to the department of Tuberculosis, National Center for Diseases Control –Libya (NCDC), the number of newly infected cases of TB is in continues decreasing, almost around 731 TB cases during the period of 2010-2011, 17.5% were TB/HIV co-infection [4, 5, 16] compared to the 13% which addressed globally in the same period of time. Of this world estimate, Africa share goes to as much as 82%. [16]. It is well known that patients with TB/HIV co-infection can progress more rapidly to severe disease and ultimately to death duo to the increased difficulties of the proper diagnosis and treatment delay [17]. There was scarcity in the reported data to WHO regarding MDR-TB, because

of the lack of information regarding the effect of HIV on the prevalence of MDR-TB in the country and all data published by WHO are just estimates of the situation [9]. Few studies were conducted in the 70s and 80s to provide details on the rate of MDR-TB status in Libya. During the period between 1971 to 1976 the prevalence of MDR-TB in Libya declined from 17 – 33% to 9 – 15%, this apparent decline was attributed to the introduction of anti-tuberculosis legislation [18], but in the 80s the prevalence re-increased in the western region of the country to reach 11% and 21.5% within the new and retreatment cases [19]. A major factor which was responsible for these rises was ascribed partly to patients' lack of patient to tolerate the relatively long period of treatment. An apparent decline in the rates of MDR-TB new cases was observed in the first decade of the 21st century as compared to 1970s which was due to improvement in the standard of living, expansion in medical services including TB- immunization programs [9, 15]. Comparing MDR-TB incident rates in Libya which, fell dramatically in recent years to as minimum as 1%, with the sharing boarder countries like Sudan (31%) [20] and Egypt (32%) [21], prevalence of MDR-TB in Libya stands far better. However, with the emphasis on the facts that these countries share large boundaries with Libya and with the current political and economical turmoil in these countries might open the door for more MDR-TB cases to flood to the country.

CONCLUSION AND RECOMMENDATIONS

From this study and the data obtained from previous periodicals, we recommend implementation of advanced new diagnostic techniques for detection of *M. tuberculosis* that involves DNA analysis [22-24] which could be of high efficiency in detecting low bacteria genomic quantities and in short period of time. Medication should be subscribed & followed by health care professionals who are expert in TB management. Maintaining continuous supply of first & second-line drugs as well as the required laboratory materials along with well trained laboratory technicians in every health care centre could lead to dramatic enhancement in reduction and control over the resistance to the disease bacteria.

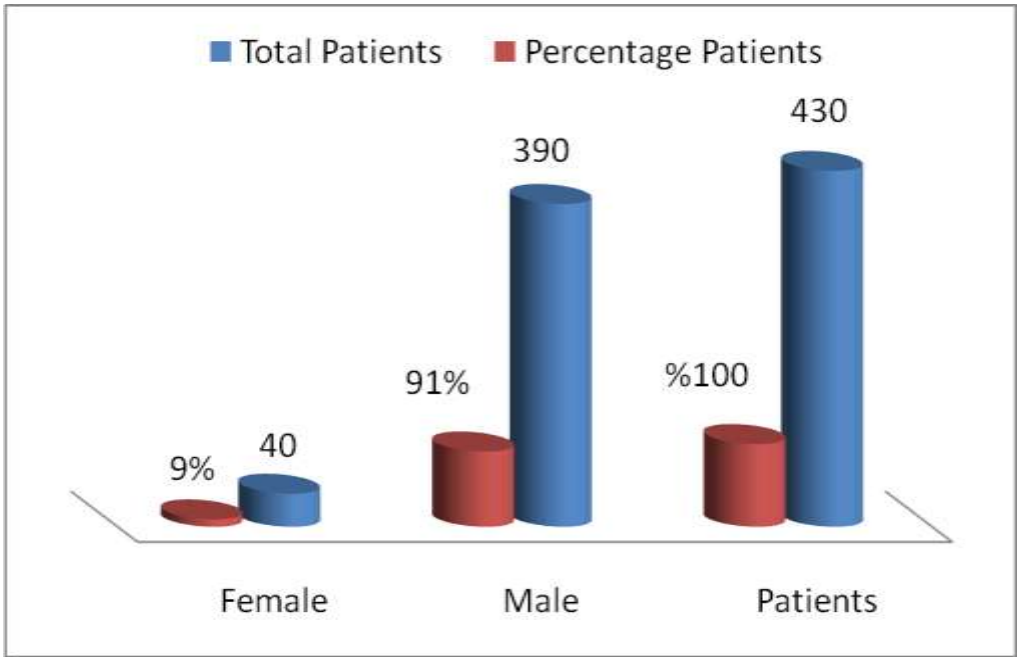

Figure 1a: Gender of total number and percentage of patients

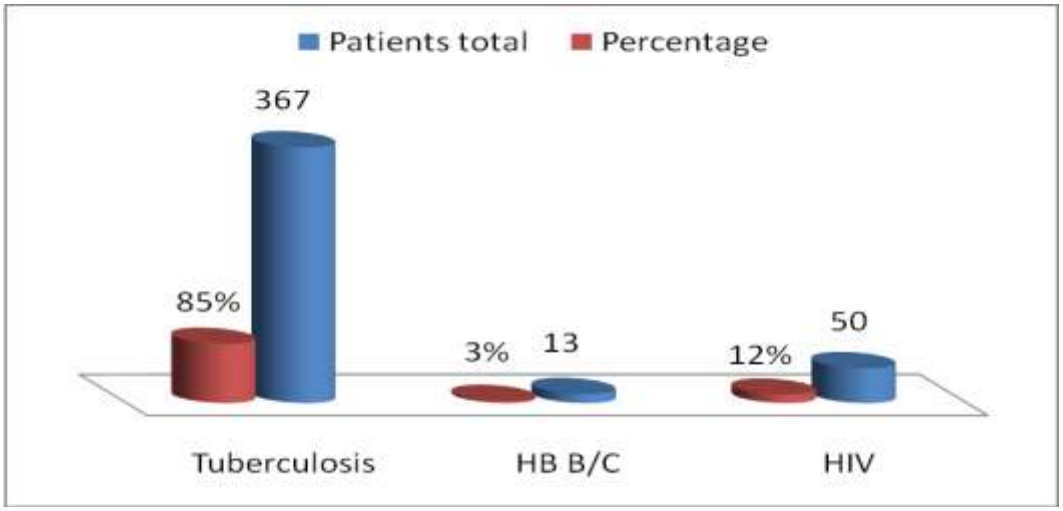

Figure 1b: TB-Patients with co-infection with hepatitis B and or C (HB B/C) and Human Immuno Virus (HIV).

Before Treatment After Treatment

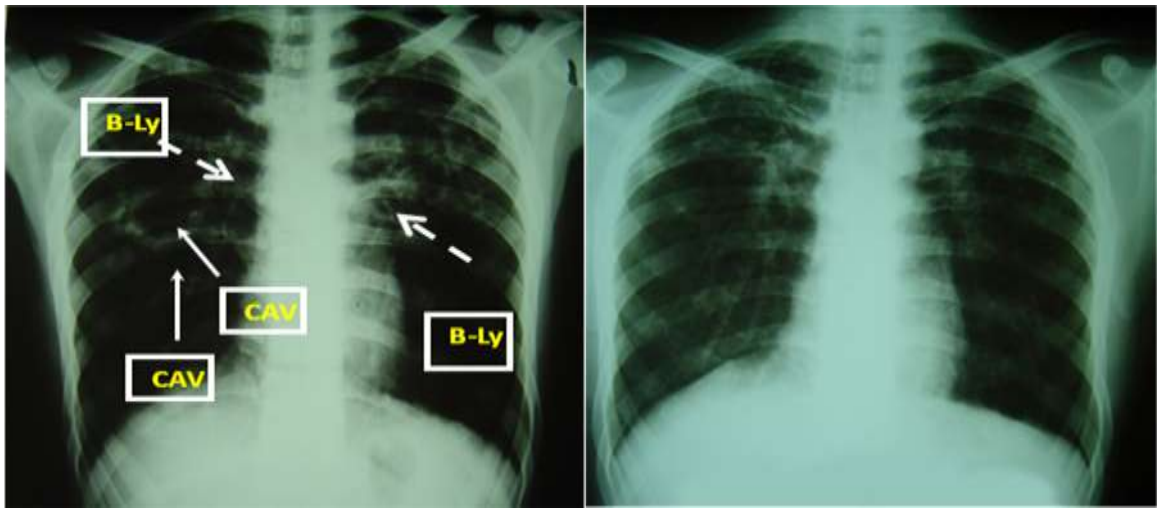

Figure 2: MDR-TB patient's X-ray scans before and after treatment (B-Ly: Bilateral Lymphadenopathy, CAV: Cavity)

Table 1: The four patients (defaulters) who were resistant to streptomycin, isniazid, rifampicin and ethambutol

CASE NO.	ANTIBIOTICS			
	Streptomycin	Isoniazid	Rifampicin	Ethambutol
1	Resistant	Resistant	Resistant	Resistant
2	Resistant	Resistant	Resistant	Resistant
3	Resistant	Resistant	Resistant	Resistant
4	Resistant	Resistant	Resistant	Resistant

Table 2: Defaulters who discontinued treatment without course completion and detected later with development of MDR-TB

	Case 1	Case 2	Case 3	Case 4
Sex	Male	Male	Male	Male
Age	22	30	35	32
Nationality	Libyan	Chadian	Chadian	Sudanese
Residence	Al-Marj	Ejdabia	Sebha	Ejdabia
Date of 1st admission	08/08/2009	23/10/2008	22/12/2007	02/11/2009
Date of detection of MDR-TB	05/11/2009	23/09/2009	02/11/2009	03/12/2009
Date of discharge after conversion to C/S negative	02/02/2010	01/02/2010	14/02/2010	02/02/2010

Table 3: MDR-TB patients' accompanied symptoms

	Case 1	Case 2	Case 3	Case 4
Cough		+ve	+ve	
Sputum		+ve	+ve	
Chest Pain			+ve	
Hemoptysis	+ve	+ve	+ve	
Wheeze				
Night fever	+ve	+ve	+ve	+ve
Night Sweating	+ve	+ve	+ve	+ve
Anorexia		+ve	+ve	+ve
Weight loss		+ve	+ve	+ve
Generalized weakness			+ve	+ve

Table 4: Sputum test, X-ray scans as well as biochemical analysis of the four MDR-TB patients

	Case 1	Case 2	Case 3	Case 4
Chest X-Ray	Cavity	Cavity	Cavity	Cavity
Hemoglobin	13.1	12.7	13.9	10
ESR	29	34	03	12
Urea	17	28	04	NA
Creatinine	0.7	NA	0.3	NA
Bilirubin	0.3	NA	NA	NA
SGPT	NA	105	06	NA
SGOT	NA	NA	NA	NA
Uric Acid	12.8	5.9	12.6	3.9
Direct Sputum for AFB	-ve	-ve	-ve	-ve
Sputum Culture for AFB	+ve	+ve	+ve	+ve

NA: Not Done

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