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Research Article

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Prevalence of Multidrug Resistance Mycobacterium Tuberculosis (MDR-TB) Using GeneXpert; how Serious Is the Situation?

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ABSTRACT

Based on the estimation of World Health Organization (WHO), there were 558000 new cases with resistance to Rifampicin, of which 82% had Multidrug-resistant Tuberculosis (MDR-TB). We aimed to identify the outbreakof MDR-TB in River Nile state, Sudan, and the risk factors contributing to its occurrence. This descriptive cross-sectional hospital-based study involved 200 specimens from patients suspected of having MDR-TB tested using an automated GeneXpert assay. Theresults of the GeneXpert assay showed that the presence of Mycobacterium tuberculosis in 81 (40.5%), and out of 81 positive test results there were 13 (16%) had MDR-TB. Additionally, 7 cases of MDR-TB were previously treated, which represented about (53%) of MDR patients. The remaining 6 MDR-TB patients were new cases and represented (47%) of MDR-TB patients. Moreover, 4 MDR-TB patients had a backgroundof contact with MDR-TB patients. Prevalence of MDR-TB in River Nile State, Sudan was 16%, which is greater than WHO estimation for Sudan (10.1%). The results revealed that the leadingrisk factor in developing MDR-TB was a backgroundof contact with MDR-TB, so adherence to treatment and social awareness about the spread of MDR-TB isa crucial preventive measure.

Key words: *GeneXpert, MDR-TB, Prevalence, River-Nile State, Sudan*

INTRODUCTION

WHO estimated that over 10 million people globally hadTB in 2017 and 2018, although the reported number is only 7 million [1, 2]. TB is considered as one of the top 10 reasonsfordeceasethroughout the world, and in recent studies; WHO estimated the incidence of new cases reaching 4.1% and 19% of formerlytreated cases with MDR-TB [3].

TB is one of the public health concerns in Sudan, as it is accounted among countries with higher TB burden in the Eastern Mediterranean Region/World Health Organization (EMR/WHO) [4-7]. In 2017, there were 21054 cases reported in Sudan [8], and recent WHO reports revealed that tuberculosis-related mortality rate estimated at 25 per 100 000 population [3]. Both Rifampin (RIF) and Isoniazid (INH) resistance are reliable markers of MDR-TB [9]. Drug-resistant TB remainsto be a universalpublic health concern, with nearly580,000 cases worldwide and mortality rates higher than most cancers [1, 10-13]. WHO's surveillance data estimated 600000MDR-TBcasesand deaths of 490000 people with MDR-TB in 2016 [3]. The outbreakof MDR-TB is high in sub-Saharan Africa, speciallyamong patients with a formerbackgroundof TB therapy [14, 15].

In countries with limited resourceslike Sudan, MDR-TB is public health threat because ofshortage of diagnostic centers for MDR-TB, poor adherence to treatment, and delay of treatment [16].

MDR-TB is considered the major obstacleto the control of TB in humans worldwide [17]. WHO established a list of risk factors related to the development of MDR-TB [18]. Furthermore, several researcheshave specifiedthe risk factors associated with MDR-TB, which include inadequate drugs supply, poor adherence to treatment, a short duration of treatment, andimproper dosage [19].

Lately, improvementhas been made in detecting, testing, and treating MDR-TBthat diagnosed 51% of patients with bacteriologically confirmed TB for rifampicin resistance [1]. In spite ofthis improvement, the number of patients treated in 2017 and 2018 was only one-third (32%) of nearly500,000 patients who hadMDR-TB [1, 2].

On the other hand, utilization of the rapid test GeneXpert MTB/RIF had increasedconsiderablysince 2010 when WHO first suggestedusing it. The test revealsTB and the possible resistance to Rifampicin. Diagnosis with this test can be made within 2 hours, and WHO now recommends using the test as an primarydiagnostic test in all patients with symptoms and signs of TB [3].

MATERIALS AND METHODS

The present research was a descriptive cross-sectional hospital-based study conducted in River Nile State, Sudan, between March 2018 and October 2018. River Nile State is one of the northern states of Sudan composed of seven localities with an estimated population of 1.472 million. In Atbara locality, there is a diagnostic center with available GeneXpert assay testing facilities. In this study, we included 200 TB patients suspected to have MDR-TB during the study period. We used a questionnaire with closed-ended questions as a study tool filled by the principal investigators. The questionnaire contained data about the participants' demographic features and questions regarding the risk factors related to the occurrence of MDR-TB and the test results of GeneXpert specimens.

Methods of GeneXpert Assay

Test reagent was included in a 2:1 proportion to untreated sputum and a 3:1 proportion to decontaminate sputum pellets. The extra test reagent in pellets was fundamental to meet the volume necessities for the essay test. The closed sputum holder was manually agitated twice for 15 minutes at room temperature before transferring 2 ml of inactivated fabric to the test cartridge (proportionate to 0.7 ml of untreated sputum or 0.5 ml of purified pellets). Then, the cartridges were embedded into the test platform found within the microscopy room. The test platform (Cepheid, Sunnyvale, CA) is an integrated diagnostic gadget that performs test preparing and heminested real-time Polymerase Chain Response (PCR) examination. It acts in a single hands-free step to diagnose tuberculosis and rapidly detect Rifampicin resistance in the specimens.

Data Analysis

The SPSS version 21 (IBM Corp., Armonk, NY, USA) was used for data analysis. Distributions were summarized using descriptive statistics and were presented as frequencies. Categorical variables were summarized as frequencies and proportions (percentages). We used Chi-Square Test with a p-value less than 0.05 was regardedsignificant.

Ethics Approval and Informed Consent

The present research was carried outbased on the principles of the Declaration of Helsinki. Approval was granted by the Sudan Medical Specialization Board (SMSB) Ethical Committee and the health authorities in the ministry of health in River Nile State, Sudan. Ethical consent to participate in this study was taken from the patients before commencing the study.

RESULTS AND DISCUSSION

We enrolled 200 cases that were suspected of having MDR-TB. Results revealed that most patients were males 142 (71%), whereas the females were 58 (29%). The most common age group was (15-35 years) in 85 (42.5%) of them, and most of the participants, 96 (48%), were residing in the urban areas, as shown in **Table 1**.

Results of the GeneXpert assay showed the presence of mycobacterium tuberculosis in 81 (40.5%) of total patients; however, in the remaining cases (119 (59.5%),mycobacterium tuberculosis were not detected. Out of 81 positive results, 13 (6.5%) had Rifampicin resistant MDR-TB, while the remaining 68 (34%) had mycobacterium tuberculosis drug-susceptible, as shown in **Table 2**.

This study found that 132 (66%) of patients were previously treated with anti-tuberculous medications, and 68 (34%) of them had no previous treatment. Additionally, in patients who had previously been treated with anti-tuberculous medications,125 (94.7%) completed their treatment while 7 (5.3%) of them did not complete it. Of the previously treated patients, 121 (91.7%) were improved, while 11 (8.3%) were not improved. Most of the previously treated patients showed features of improvement in the form of complete resolution of symptoms in 77 (63.6%), sputum convert to negative in 46 (38%), gain weight, and improve in appetite in 59 (48.8%). In comparison, 23 (19%) showed a radiological improvement, as shown in **Table 3**.

The contact history was identified as the majorrisk factor related toMDR-TB development (P-value = 0.000). Moreover, the history of previous treatment is shown to be a protective measure against MDR-TB (P-value = 0.005). Results showed no statistically significant association between HIV infection status and MDR-TB (P-value = 0.6); DM and MDR-TB (P-value = 0.4) as indicatedin **Table 4**.

Table 1. Distribution of Demographic Specificationsof the Participants (N=200)

Character		Frequency (%)
Age	15 – 35	85 (42.5)
	36 – 55	78 (39.0)
	56 – 75	32 (16.0)
	More than 75	5 (2.5)
Gender	Male	142 (71.0)
	Female	58 (29.0)
Residence	Urban	96 (48.0)
	Rural	104 (52.0)

Table 2. The Distribution of Study Group according to GeneXpert Results (N=200)

GeneXpert		N	%
Positive	MDR-TB	13	6.5
	Non-MDR-TB	68	34
Total positive		81	40.5
Negative		119	59.5
Total		200	100

Table 3. The Characteristics of the Patients according to their Treatment and Improvement

Item		N (%)
Previously treated with anti-tuberculous drugs*	Yes	132 (66%)
	No	68 (34%)
Completed their treatment**	Yes	125 (94.7%)
	No	7 (5.3%)
Improved**	Yes	121 (91.7%)
	No	11 (8.3%)
Complete resolution of symptoms***	Yes	77 (63.6%)
	No	44 (36.4%)
Sputum converted to negative***	Yes	46 (38%)
	No	75 (62%)
Gain weight and improvement in appetite***	Yes	59 (48.8%)
	No	62 (51.2%)
Radiological improvement***	Yes	23 (19%)
	No	98 (81%)

* Out of total patients (N = 200). ** Out of patients previously treated with anti-tuberculous drugs (N = 132). *** Out of Improved patients whowere alreadytreated with anti-tuberculous medications (N = 121).

Table 4. The Relationshipbetween Specific Risk Factors and Development of MDR-TB (N=81 Total Positive GeneXpert assay)

Variable		MDR-TB	Non-MDR-TB	P-value
History of Diabetes mellitus	Present	1 (33.3%)	2 (66.7%)	0.406
	Not present	12 (15.4%)	66 (84.6%)	
History of HIV infection	Present	0 (0%)	1 (100%)	0.66
	Not present	13 (16.2%)	67 (83.8%)	
History of previous treatment	Present	7 (10.65%)	59 (89.4%)	0.005
	Not present	6 (40%)	9 (60%)	
History of Contact	Present	4 (80%)	1 (20%)	< .001
	Not present	9 (11.8%)	67 (88.2%)	

To our best available knowledge, there were no previous studies conducted in River Nile State about MDR-TB. The present research aimed to detect the outbreakof MDR-TB among suspected tuberculous patients.

In the present research, most of the study population were males, representing nearly three-quarters, which is close to the result of a similar study that represented 71% [20]. The leading affected group in our study was the young aged group, most properly because they are the working group and are more suspected of having pathogenic bacteria.

Withinthe researchperiod, we identified the outbreakof MDR-TB as16% in River Nile state, Sudan; closer to the findings of the Nigerian study, the outbreakof MDR-TB was 14.7% [21]. The outbreakof MDR-TB in this study is less than that identified in Kassala State, Sudan, where the prevalence was (51.7%) [22] and less than the prevalence rate determined in a meta-analysis study conducted in Ethiopia, which revealed that 2.18% of the newly diagnosed and 21.07% of formerlytreated patients had MDR-TB [23]. On the other hand, the outbreakof MDR-TB in this study is more than another study conducted in Sudan indicatedthe majorityof MDR-TB to be 5% among new cases and 24% among formerlytreated patients [20].

The main identified risk factorrelated toMDR-TB development was a backgroundof contact with MDR-TB patients ($p<0.001$). In contrast, the history of previous treatment was identified as a protective measure against the development of MDR-TB (P-value = 0.005). These findings agree with similar results of a meta-analysis study conducted in Ethiopia using 34 studies among patients with a history of previous treatment [23]. Our findings disagree with the previous research, which determines the lasttreatment as a risk factor with a risk ratio of 5.23 (95% CI:2.30-4.60; $p<0.001$) for MDR-TB [20]. Defaulting from treatment was also recognizedas one of the risk factors for MDR-TB occurrence [24].

CONCLUSION

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Patents

During the study period, the prevalence of MDR-TB among the whole study group was 6.5% and about 16% among all positive results (where M. tuberculosis was detected by using GeneXpert assay). The WHO estimation for Sudan in 2002 was 10.1%, whereas our findings were higher than the WHO estimation. The main risk factors were history of previous treatment and backgroundof contact with MDR-TB patients.

Recommendation

We encourage early detection and proper management of TB cases, which are believed to reduce transmission risk. We recommend providing health services including modern tests to detect the resistant strain at the states level, monitor all cases of MDR-TB, and report any new cases to the federal ministry of health, Sudan, besides increasing social awareness about the risk of the spread of MDR-TB and combating it to control the increasing number of patients with MDR-TB.

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ETHICS STATEMENT : The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of Sudan Medical Specialization Board (SMSB), Ethical Committee, and the health authorities in the ministry of health in River Nile State, Sudan.

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