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Prevalence of Drug-Induced Hypothyroidism in Multi-Drug Resistant Tuberculosis Patients

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Abstract: ***Tuberculosis (TB) existed for long years and still remains a major global health problem in developing countries. It is airborne and caused by Mycobacterium tuberculosis complex. Multi-drug resistant TB (MDR-TB) is caused by drugs used to treat tuberculosis which include isoniazid and rifampicin. This has emerged as a significant threat to TB control in India, with more than 62000 new cases annually. The prevalence of drug-induced hypothyroidism in multi drug-resistant tuberculosis patients is always a dilemma. This review focuses on the detailed data on prevalence of drug-induced Hypothyroidism in MDR TB patients.***

Keywords: Drug-induced Hypothyroidism, Multi-Drug Resistant Tuberculosis, Prevalence

1. Introduction

Tuberculosis (TB) has existed for ages and is one of the ancient diseases which remains a major global health problem. It causes ill-health for approximately 10 million people annually and is one of the top ten causes of mortality worldwide. [1] Overall, a relatively small proportion (5–15%) (approximately 1.7 billion)of people infected with M. tuberculosis will develop TB disease during their lifetime.

Patients with TB can die if they do not get proper treatment but in most cases, TB is treatable and curable. Some patients do not respond to the TB treatment, instead develop MDR - TB where the bacteria become resistant to the drugs used to treat TB. This means that the drug can no longer kill the TB bacteria but can cause harm to the body. [2]

Multi-drug resistant TB has emerged as a significant threat to TB control in India, with more than 62000 new cases annually [1]. Globally, World Health Organization (WHO) reported decreased cases of tuberculosis (TB) patients. However, 20% of previously treated cases and 3.7% of new cases worldwide are estimated to have MDR-TB.

Drug-resistant TB is a persistent threat, with 4,90,000 cases of MDR-TB emerging in the year 2016 and an additional 1,10,000 cases that were resistant to Rifampicin (RR-TB) but susceptible to Isoniazid which are the most effective first-line anti-TB drugs. The countries with the largest prevalence of MDR/RR-TB cases i.e., approximately 47% of the global caseswere China, India, and the Russian Federation. [3] Drug-resistant TB threatens global TB care and prevention, as it is remaining as a major public health concern in majority of countries. Three categories are generally used for global surveillance and treatment which include RR-TB, MDR-TB, and Extensively drug-resistant TB(XDR-TB) [4]

MDR-TB has been defined as tuberculosis, resistant to the most efficacious anti-tubercular medications such as isoniazid and rifampicin, the first line regime [2]. WHO guidelines proposed that four effective drugs which include an injectable drug, are suggested as combination chemotherapy to avoid treatment failure and drug resistance in patients with MDR-TB [3].

Types of Drug Resistance:

1) **Mono-resistance:** Resistance to only one first-line Anti-TB drug.
2) **Poly-resistance:** Resistance to more than one first-line Anti-TB drug, other than either isoniazid and rifampicin.
3) **Multidrug resistance (MDR):** TB is caused by M tuberculosis, a bacteria that is resistant to at least isoniazid and rifampicin, the two most potent and first-line Anti-TB drugs.
4) **Extensive Drug resistance (XDR):** Extensively Drug-resistant TB is a rare type of MDR-TB. This type has resistance to first-line TB drugs i.e., Isoniazid and Rifampin, plus any fluoroquinolone and at least one of three injectable second-line drugs such as Kanamycin or Amikacin or capreomycin. As XDR-TB is resistant to the most potent TB drugs, patients are left with less effective treatment options.
5) **Rifampicin Resistance (RR):** Resistance to Rifampicin alone and not other first-line drugs. It can be either mono resistance or poly resistance and can be detected using phenotypic or genotypic methods. RR has clinical, radiological, and bacteriological evidence. [1]

MDR strain patients require the use of second-line anti-TB drugs and a duration of at least 20 months [2,4-6]. An MDR-TB typically consists of a minimum of 5 drugs which include:

1) Four second-line anti-TB drugs: This may include any first-line medications which are thought to be effective along with one injectable agent.
2) One Fluoroquinolone such as levofloxacin, Moxifloxacin or Gatifloxacin.
3) More than one oral bacteriostatic second-line anti-TB drugs such as ethionamide/prothionamide,p-

aminosalicylic acid, or cycloserine/terizidoneor PAS [6,7].

Second-line anti-TB drugs are relatively known to cause more adverse events (AE's) than first-line anti-TB drugs. One of the known and rare AEs related to MDR-TB treatment is hypothyroidism which is also caused by ethionamide, prothionamide, and p-aminosalicylic acid(PAS) [2,4].

The pathophysiology behind hypothyroidism includes iodine organification inhibition which includes mechanism of inhibition of thyroid hormone synthesis and decreases thyroid hormone production. [1]

Clinical hypothyroidism in MDR-TB patients presents with the following symptoms and signs:

1) Slowing in both mental and physical activities
2) Dry skin and Cold Intolerance
3) Fatigue
4) Muscle cramps
5) Change in voice
6) Constipation
7) Cardiac disease: Bradycardia, Pericardial effusion
8) Slow growth, puffy face, weight gain
9) Hair loss, Goitre, Hyperlipidemia, irregular uterine bleeding, irritability
10) Sexual dysfunction.

For these reasons, the WHO recommends screening hypothyroidism at least per 3 or 6 months in MDR-TB patients on treatment.

Prevalence of Drug-induced Hypothyroidism in Multi-Drug Resistant Tuberculosis Patients:

Studies in the past have reported an incidence ranging from 3.5 to 71.4% [4,5]. However, the reason for this wide variation is unknown, and there is no published data regarding the incidence of hypothyroidism among different countries with MDR-TB patient populations.

Available studies have reported an extremely variable prevalence of hypothyroidism among MDR-TB patients on treatment.

Aristomoandries et al published an on the rate of hypothyroidism in MDR-TB patients and concluded that a high incidence of hypothyroidism was seen in patients who are under 2nd line anti-TB drugs and in patients who are receiving drugs like PAS and ethionamide. [8]

A systematic review and meta-analysis done by Tola et al. in 2019 has compiled data from various studies and provided the prevalence in a table. (Table 1)

Table 1: The below table summarizes the types of studies done earlier and the prevalence of hypothyroidism in respective countries. [9]

Author	Study location	Study design	Sample size	Prevalence of Hypothyroidism (%)
Akshata et al [10]	India	Retrospective cohort	484	19 (3.9)
Andreas et al [11]	India	Prospective cohort	69	37 (54)
Baghaei et al[12]	Iran	Retrospective cohort	80	1(1.3)
Bares et al [13]	Pakistan	Prospective cohort	50	39 (78)
Bhatt et al [14]	Nepal	Prospective cohort	101	6 (6.4)
Brust et al [15]	South Africa	Retrospective cohort	73	26 (36)
Cheung et al [16]	Australia	Retrospective cohort	29	9 (31)
Chhabra et al [17]	India	Prospective cohort	54	6 (11)
Gupta et al [18]	United kingdom	Prospective cohort	5	4 (80)
Hire et al[19]	India	Prospective cohort	110	1(0.9)
Hoa et al[20]	Vietnam	Retrospective cohort	282	3(1.3)
Huerga et al [21]	Kenya	Retrospective cohort	169	31 (18)
Isaakidis et al[22]	India	Prospective cohort	67	21(31)
Jacobs et al[23]	Suth Africa	Retrospective cohort	350	29(8.3)
Kala et al[24]	India	Retrospective cohort	110	12(12.9)
Matveyeva et al[25]	Ukraine	-	30	5 (16.7)
Meressa et al [26]	Ethiopia	Retrospective cohort	612	105 (17.2)
Modongo et al[27]	Botswana	Prospective cohort	213	73 (34.3)
Munivenkatappa et al[28]	India	Prospective cohort	188	43 (23.0)
Nathonson et al[29]	Estonia	Retrospective cohort	818	29 (3.5)
Prasad et al[30]	India	Prospective cohort	98	1(0.8)
Prasad et al[31]	India	Prospective cohort	98	3 (3.1)
Saharia et al[32]	India	Prospective cohort	99	5 (5.1)
Satti et al [33]	Lesotho	Retrospective cohort	186	129 (69)
Shin et al [34]	Russia	Retrospective cohort	244	42 (17.2)
Tag el Din et al[35]	Egypt	Retrospective cohort	107	11 (10.3)
Tag elDin et al[36]	Egypt	Retrospective cohort	138	13 (9.4)
Torun et al [37]	Turkey	Retrospective cohort	263	3(1.1)
Yang et al [38]	South korea	Retrospective cohort	256	6(2.3)
Zhang et al [39]	China	Ambispective cohort	751	148(19.7)

The above table summarizes the prevalence of hypothyroidism in MDR-TB patients which were conducted in various countries. Few studies have reported that 54% – 69% of patients might develop hypothyroidism during treatment for MDR-TB. PAS and ethionamide were mainly

responsible for hypothyroidism in MDR-TB patients. (35,38)

Programmatic Management of Drug-resistant TB in 2011was carried out in India i.e., Karnataka, and patients were treated with following drugs [40]

1) Pyrazinamide, Kanamycin, Levofloxacin, cycloserine, Ethionamide and Ethambutol for 6 – 9 months standard regime.
2) Only pyrazinamide and kanamycin were given in the continuation phase for 18 months apart from the above regime.

This study found an association between ethionamide and hypothyroidism in patients with the MDR-TB regime.

Another study by Modongo in 2012 reported that out of 452 patients included in the analysis, 213 (47.1%) had their TSH levels checked at some point in their treatment: 73 were found to have evidence of hypothyroidism. 260 days was the median time from initiation of MDR-TB treatment to hypothyroidism. [6]Overall prevalence of hypothyroidism in MDR TB patients in African countries (25%) was significantly higher than in Asian (13%) and European (9%). This can be attributed to the presence of autoimmune disease, infections, and food availability, and diversity. [41]

In contrast to positive association of prevalence between hypothyroidism and MDR-TB, a review by Wu et al reported a low prevalence of 3.6%.

MDR-TB patients have serious potential sequelae,i.e., Hypothyroidism (Undiagnosed), increasing the risk for additional mental and physical health problems. Therefore, routine Thyroid Stimulating Hormone testing should be considered for all patients receiving anti-TB treatment for MDR tuberculosis and those receiving regimens containing PAS and ethionamide.

In a study done by Biranu in 2021 [41], the prevalence of hypothyroidism was 19.8% which is moderately higher (17.2%) than the previous study reported from Ethiopia by Meressaet al. [26]

A study reported by Kumar et al in 2020 from China found out that 71.4% of the sample population were significantly associated with hypothyroidism in which prothionamide and para-aminosalicylic acid drugs were given. [42]

The prevalence of hypothyroidism in MDR-TB patients cannot be concluded to a particular percentage as few studies did not define hypothyroidism which can be a source of heterogeneity on the estimated prevalence.

2. Conclusion

This review reported that hypothyroidism is a common adverse event in patients on MDR-TB treatment. Drugs such as Ethionamide and PAS in particular were commonly associated with the occurrence of hypothyroidism. Screening tests for hypothyroidism in MDR-TB patients is essential in patients under ethionamide and/or PASd drugs. Further studies with a large sample size are important to further explore the effect of MDR-TB drugs on hormones of the thyroid.

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