

Second-line Anti-Tuberculosis Drugs and Risk of Alopecia: A Retrospective Cohort study

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Abstract

Background: Alopecia is not a well-known adverse effect of second-line anti-tuberculosis drugs. It is however, been frequently reported in Eritrea and 83% of the reports of alopecia associated with second-line anti-TB drugs in the global adverse drug reaction database, as of July 25, 2017, were submitted from Eritrea. It is wondering why this much variation is happening and this study is therefore aimed at quantifying the risk, identifying possible risk factors and elucidating the causal association between alopecia and the second-line anti-TB drugs in Eritrea.

Methods: This was a retrospective cohort study that included all patients with multi-drug resistant tuberculosis (MDR-TB) in Eritrea enrolled to Merhano MDR-TB referral hospital for treatment between June 2011 and December 2016.

Results: A total of 152 eligible MDR-TB patients on treatment were identified with a median observation time of 23 months. Historical longitudinal data of these patients was screened and found 35 cases of alopecia, possibly associated with MDR-TB treatment, with an incidence rate of about 13 cases per 1000 person-months. Majority of the cases (68.6%) developed alopecia after 18 months of exposure to MDR-TB treatment. Patients exposed to treatment for longer period of time (>23 months) were more likely to develop alopecia compared to those exposed for shorter time ($p=0.001$). Patients younger than 45 years of age reported higher rates of alopecia compared to the older age groups (adjusted OR=9.4; 95%CI: 2.41-36.86, $p=0.001$). Females were also more likely to develop alopecia compared to males (adjusted OR=3; 95%CI: 1.24 - 7.34, $p=0.015$).

Conclusion: Alopecia associated with MDR-TB treatment is frequent but its delayed time to onset might be a reason to be missed by several similar studies conducted elsewhere. Even though alopecia is not life-threatening and does not cause physical pain, the cosmetic effects of hair loss can be psychologically devastating.

Keyword: Eritrea; Multi-drug resistant tuberculosis; Treatment; Alopecia

Introduction

Second-line anti-tuberculosis drugs are used to combat multidrug-resistant tuberculosis (MDR-TB); a disease caused by mycobacterium which is resistant to at least isoniazid and rifampicin, the major armament of tuberculosis regimens [1]. It was estimated that about half a million cases per year of patients are diagnosed as MDR-TB and are eligible to start on these medications [2]. The notorious adverse reactions and length of treatment makes them intolerable, which could cause treatment interruptions in several patients [3-5]. A recent study conducted in MDR-TB patients in Eritrea revealed that 92% of the patients experienced at least one serious adverse drug reaction (ADR) while taking second-line anti-TB drugs and 2% of them died of ADRs (unpublished data).

The Eritrean study found alopecia as one of the top ten frequently reported ADRs which is not consistent with previous similar studies that did not report such ADR. Alopecia is abnormal hair loss that occurs before the hair life cycle is completed. It is generally classified into cicatricial (scarring) and nopicatricial (non-scarring) alopecia depending on whether the hair follicles are affected or spared. The causes are myriad; from infectious, endocrine, stress, autoimmune nutritional deficiencies to chemotherapy. Non cicatricial alopecia has been associated with chemotherapy which has shown reversibility after discontinuation of the culprit drugs involved [6].

To the best of our knowledge, there is only one case report of

alopecia associated with ethionamide that is published in medical literature [7], and none of the published studies reported alopecia with second line anti-tuberculosis drugs. Even in the global adverse drug reaction database, as of July 25, 2018, 83% of the alopecia cases associated with MDR-TB drugs are submitted from Eritrea.

Given the small number of MDR-TB patients in Eritrea, it is wondering why this much alopecia cases have been reported from Eritrea. The purpose of this study is therefore, to exactly quantify the risk, identify possible risk factors and elucidate the causal associations between alopecia and MDR-TB drugs.

Materials and Methods

Study design, setting and study population

This study is a continuation of a previous study published by one

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of the authors. It was retrospective cohort study conducted in Merhano MDR-TB national referral hospital. Merhano MDR-TB hospital, a 50-bed facility, is the only hospital for treatment initiation, hospitalization and management of MDR-TB patients in Eritrea. For this study, data was abstracted from patients' longitudinal medical records documented between June 2011 and December 2016. Patients enrolled to the hospital between June 2011 and 31 December 2016 with at least two months of treatment exposure were included in the study irrespective of their age and sex. Patients who lost to follow-up, who died early after admission and newly admitted patients whose cumulative drug exposure was less than two months were excluded. This cut point was chosen because we know from literature that the majority of the ADRs of SLDs manifest beyond two months of treatment [8,9].

Exposure and outcome definition

MDR-TB Treatment has two Phases; the intensive and continuation phase. Patients need to be admitted to the hospital for at least eight months during the intensive phase to receive an injectable drug (Kanamycin) on daily basis and other four oral second-line anti-TB drugs (Levofloxacin, Ethionamide, Pyrazinamide and Cycloserine) as well as Vitamin B6. Once they show sputum culture conversion, they continue the four oral medication for at least 12 months as outpatient in a nearby health facility [10]. All alopecia cases were self-reported from patients and confirmed and documented by the clinicians. Alopecia temporally associated with the use of second-line anti-TB drugs, not present at baseline, were considered as suspected ADR. Hence, cases of alopecia were identified from the notifications made by the clinicians in the medical cards.

Data collection approach and case assessment

Comprehensive longitudinal historical data of patients including demographic information, comorbidities, cumulative exposure time, reaction details, drug details, ADR management and outcome was abstracted from clinical cards. Data was collected between March 15 and March 30, 2017. Patients' clinical records were reviewed critically to identify the notifications of alopecia, to assess seriousness, causality and management of alopecia during the follow-up period.

Causality was assessed using the Naranjo probability scale [11]. Expectedness of alopecia was also assessed by reviewing the updated summary of product characteristics of second-line anti-TB drugs and reliable medical references or published research articles.

Statistical analysis

Data was entered and analyzed using CSPro version 5.0 and SPSS version 20 software packages. To estimate the occurrence of alopecia, incidence rate (IR) was calculated as the longitudinal data was made of a dynamic cohort, admitted at different times. Incidence rate (IR) of alopecia was calculated by dividing the number of cases with alopecia by the total observation time in person-months. Observation time was calculated by subtracting the date of admission (treatment started) from the last date of observation for each patient. Observation time of all patients was added together to get the total person-months. Odds ratio was calculated to measure the associations. Patients were stratified during analysis by age and drug cumulative exposure time to identify risk groups and control confounders. To rule out other possible risk factors of alopecia like psychological problems, thyroid disorder, psychiatric problems, HIV, concurrent use of propranolol, amitriptyline and other drugs known to increase the risk of alopecia were explored individually using chi-square (χ^2) test. To control or adjust potential confounders, the covariates were subjected to multivariate regression

model. P-value and 95% confidence intervals (95% CIs) were used to test statistical significance. Results are presented either as medians, percentile, frequencies, interquartile ranges, odds ratio and incidence rate as appropriate. P-value < 0.05 was regarded as statistically significant.

Ethical considerations

Ethical approval was obtained from the Health Research Ethics and Protocol Review Committee (HREPRC) of the Ministry of Health (letter number: 06/03/17). As this was a retrospective study, informed consent was not obtained from patients and waived by HREPRC. Extensive efforts were made to keep patients' record confidential and thus, patients' identifier anonymized during analysis.

Results

A longitudinal data of 152 MDR-TB patients was retrospectively screened for adverse drug reactions and found 35 cases of alopecia. The prevalence of alopecia during the study period was 23% (n=35) with an incidence rate of 12.67 cases per 1000 person-months. They were 10 males and 25 females with a median age of 35 years. Co-morbidity was reported in seven of the cases. The type of co-morbidities was found to be HIV (n=5), diabetes (n=1) and mental illness (n=1). Of the 35 alopecia cases, 12 were reported as cured, 19 on treatment, three lost to follow-up and one died. Alopecia was recovered in 77.2% of the cases with supportive treatment. Reaction was reported as 'not yet recovered' in six cases and it was 'unknown' in the rest two.

Majority of the cases (88.6%) with alopecia were exposed to MDR-TB treatment for more than 12 months with median exposure time of 23 months. Patients exposed to long-term treatment (>23 months) were more affected by alopecia compared to those exposed to second-line anti-TB drugs for shorter period of time (p=0.001). Of those who developed alopecia, 68.6% experienced this reaction after 18 months of exposure to second-line anti-TB drugs.

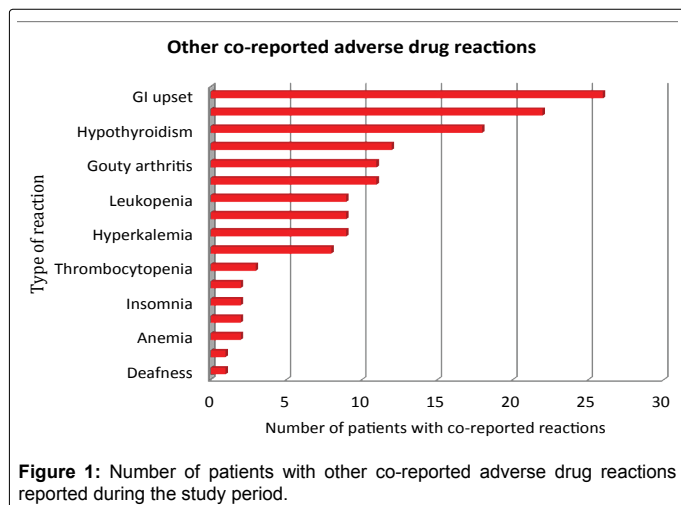
Patients were stratified according to their age and duration of exposure to identify possible risk factors for the occurrence of alopecia. The incidence of alopecia showed significant difference among age groups. Patients younger than 45 years of age reported alopecia about nine times more frequently compared to the older age groups (adjusted OR=9.4; 95%CI: 2.41-36.86, p=0.001). Females were also more likely to develop alopecia compared to males (adjusted OR=3; 95%CI: 1.24 - 7.34, p=0.015).

Naranjo probability score shows that all the alopecia cases were possibly associated with second line anti-TB drugs. GI upset, tachycardia and hypothyroidism were among the commonly co-reported reactions (Figure 1). The effect of hypothyroidism on the occurrence of alopecia was assessed and not found to be significant (p=0.39) in this study population (Table 1).

Discussion

This study found high incidence rate of alopecia associated with second-line anti-TB drugs which is inconsistent with findings of previous studies conducted elsewhere. Studies conducted in Egypt [12,13], Namibia [14,15], South Africa [16], Ethiopia [17], India [18,19], Peru [20], China [21], Russia [22] and Lativa [23] assessed ADRs of second-line anti-TB drugs and did not report alopecia as adverse effect. A Nepalese study [24] however, reported one case of hair loss from 140 patients.

Alopecia was more frequently reported in females, younger age group (less than age of 40) and those exposed to second-line anti-TB



Gender	Developed hypothyroidism	Without hypothyroidism
Male	7	3
Female	11	14
Total	18	17

Table 1: Summary of alopecia cases with hypothyroidism and without hypothyroidism in a contingency table. To rule out the effect of hypothyroidism in development of alopecia, it was tested in two by two table. OR=2.97; (95% CI: 0.6202-14.2201; p-value: 0.173); shows no statistical significance.

drugs for longer duration of treatment. The fact that females were three times more likely to develop alopecia might be explained by differential reporting; females might be more likely to report alopecia as it is associated with self-image. It was unknown why alopecia was about nine times more reported in younger patients compared to older ones. It can however be possibly explained by the fact that hair loss is expected in older people and thus might be left unreported. On the other hand, the high number of patients with alopecia cannot be ignored by the above explanation. As hypothyroidism is a risk factor for alopecia, its contribution was tested and found to be insignificant. Patients who took the second-line anti-tuberculosis for longer periods of time were more likely to develop alopecia. This can be due to either the cumulative effect of the toxic drugs or patients' inability to early recognize hair loss until it is grossly apparent. The longer follow-up duration (median=23 months) in this study might helped us to identify this delayed reaction which could not be identified before with studies employed shorter observation time.

The exact mechanism how second-line anti-tuberculosis drugs cause alopecia is not known. Chemotherapy induced alopecia can, however, be explained by inhibition of mitosis in the hair papilla that could lead to narrowing of the hair shaft with subsequent hair fracture or complete failure of hair formation [25].

Even though alopecia is not life-threatening and does not cause physical pain, the cosmetic effects of hair loss can be psychologically devastating [26]. Recovery generally requires a period of several months to a year, amplifying the psychological impact of the disease and its treatment [27].

The effect of autoimmune disease, the disease by itself, stress and the effect of propranolol tablet (as majority of patients were taking it for tachycardia) were left unmeasured which could partly contributed in explaining the association. Lack of comparator group in our study, which is not possible in MDR-TB patients, also limited us to strengthen

the causal relationship between second-line anti-TB drugs and alopecia. We also did not assess the degree of alopecia which might be helpful in assessing its severity due to the retrospective nature of study.

Conclusion

Alopecia associated with MDR-TB treatment is frequent but its delayed time to onset might be a reason to be missed by several similar studies conducted elsewhere. Longer duration of exposure to MDR-TB treatment, being female and young age are identified as risk factors. Even though alopecia is not life-threatening and does not cause physical pain, the cosmetic effects of hair loss can be psychologically devastating; thus should not be ignored as it may compromise the treatment success rate. Hence, we recommend healthcare professionals working on MDR-TB management need to be conscious of alopecia as adverse effect and to educate patients to be vigilant. We also suggest to do further study to ascertain the degree of alopecia incurred, its reversibility after completion of treatment and to confirm causation. In addition, future studies should try to elucidate the biological mechanism behind the occurrence of alopecia in these patients.

Authors' contributions

Data collection tools were designed and data was collected by Mulugeta Russom. All of the authors played a key role on the analysis, interpretation of the data and write-up of the manuscript.

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Competing Interests

The authors declare that they have no competing interests and no source of funding was used to carry out the study.

Data Availability

The data [SPSS data] used to support the findings of this study are available from the corresponding author upon request via the following e-mail: satiswt@gmail.com or Tel: +291-7197450.

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