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Hypothyroidism associated with therapy for multi-drug resistant tuberculosis in Australia

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Background

Efforts to control tuberculosis, the leading cause of death from a single infectious agent, have been challenged in recent years by the global rise of multidrug-resistant tuberculosis (MDR-TB) (1). MDR-TB is defined as tuberculosis (TB) that is resistant to at least isoniazid and rifampicin, the two most effective anti-TB drugs (2). According to Word Health Organization (WHO) estimates, 600,000 people developed MDR-TB worldwide in 2017. MDR-TB is particularly prevalent in comparatively resource-poor countries. Almost half (47%) of incident MDR-TB cases were in India, China and the Russian Federation. Overall, an estimated 4% of all new TB infections and 21% of previously treated cases are multidrug resistant (1). MDR-TB is relatively less prevalent in developed countries: in the United Kingdom (0.16) and USA (0.10) but less than for the Russian Federation (44), India (11) or the African Region (1).

Local data suggest a low burden of MDR-TB in Australia. The national TB incidence in 2016 was 6.1 per 100,000, with an MDR-TB rate of 0.26 per 100,000 (3). Limited evidence suggests the incidence of MDR-TB in Australia is increasing, similar to what has been reported for other developed countries, such as the United Kingdom (4). In Australia, the proportion of TB cases that are multi-resistant has increased from 1.5% in 2005 to 3.5% in

2010 (5). In one retrospective survey, from Western Australia, 16 cases of MDR-TB were notified between 1998 to 2012, 13 from 2006 onwards, compared to only 3 cases prior to 2006 (6).

To overcome resistance and increase cure rates, patients with MDR-TB are treated with multiple drugs. In Australia, the most widely used drugs for MDR-TB include amikacin, cycloserine, moxifloxacin, prothionamide, and para-aminosalicylate sodium (PAS) (2). These drugs are associated with a variety of adverse effects, including vestibular toxicity, hearing loss, hepatitis, nausea and vomiting, psychosis and electrolyte disturbances (2).

Thionamide- and PAS based MDR-TB regimens have also been associated with the development of primary hypothyroidism, but almost exclusively in reports from resource-poor countries, such as India and some African nations, where TB and human immunodeficiency virus (HIV) are endemic and where other risk factors such as anti-retroviral drug use (7), nutritional and iodine deficiencies may potentially contribute to thyroid status. Moreover MDR-TB regimens in these countries include ethionamide, (not available in Australia), where the structurally related prothionamide is used, in which the ethyl group of ethionamide is replaced by a propyl molecule at the alpha position (8).

To date, hypothyroidism in MDR-TB patients in developed countries has not been well described. To our knowledge the largest study from a developed country - the United Kingdom - included only seven patients (9). We therefore conducted a retrospective multi-centre study of academic centres covering TB services in Victoria Australia (2017 population

of six million), to identify predictors and assess the cumulative proportions of subclinical and overt hypothyroidism in patients treated for MDR-TB with prothionamide and/or PAS. We also performed a full literature search to summarize previous pertinent publications.

Methods

In this multi-centre, retrospective study, we identified patients with bacteriologically confirmed MDR-TB and who were treated at any time-point with prothionamide, PAS or both between January 1999 and Jan 2017 from 5 Victorian hospital networks; Alfred Health, Austin Health, Monash Heath, Melbourne Health and Western Health. Patients were identified using each centre's pharmacy department and then cross checked with the Victorian Tuberculosis Program (VTP). Ethics approval was obtained for all participating sites as well as for the VTP database. Patients <18 years, those with pre-existing thyroid conditions or abnormal thyroid function prior to commencing MDR-TB therapy, those with no recorded start and end date of prothionamide or PAS, and those with no or only one set of biochemical thyroid function tests were excluded.

Patients' clinical, investigative and medication data were collected. Subclinical hypothyroidism was defined as a TSH above the assay specific reference interval and overt hypothyroidism was defined as a TSH level above the reference range and a free T4 level below the assay specific reference interval. Patients were required to have at least two sets of abnormal thyroid function tests to be designated as 'hypothyroid', to ensure changes in thyroid function were not transient (e.g. non-thyroidal illness effect)(10).

Statistical Analysis

Statistical analyses were performed using IBM PASW Statistics Package Version 23 (Armonk, NY). Continuous variables were presented as median (interquartile interval) while categorical variables were described as frequencies (percentages). The chi-squared test was used to compare categorical variables and the Mann-Whitney-U test for continuous variables. The cumulative proportions of patients who developed hypothyroidism over time was analysed using the Kaplan-Meier method. The proportion of those who developed hypothyroidism was also compared across different prothionamide dosing regimens (500mg, 750mg, 1000mg) and compared using the log-rank statistic. Univariate Cox regression analysis using the time-period on tuberculosis therapy as a time dependent covariate was performed to determine the association between duration of treatment and development of hypothyroidism. Statistical significance was assumed when $p<0.05$. The relative small sample size precluded the use of multivariable analyses.

Results

A total of 77 individuals with confirmed MDR-TB was identified (Figure 1). Application of exclusion criteria resulted in exclusion of 48 patients, leaving 29 cases available for analysis.

The clinical profile of the 29 cases are presented in Table 1. Mean age was 35 (22-47) years with 38% being male. Patients were mainly of Asian ethnicity, one had a history of autoimmunity (coeliac disease), and only one had a documented family history of thyroid

disorders. No patients had documented HIV infection. Twenty four cases had pulmonary TB with the remaining five having extrapulmonary TB. Twenty one individuals received prothionamide without PAS, and eight individuals were treated with both prothionamide and PAS.

Of the 29 cases, nine developed hypothyroidism, with a cumulative proportion at 5 years of 37% (95% CI: 0-57.8%) (figure 2 and table 2).

The proportion of individuals who developed hypothyroidism at 1 year was not significantly different between the group where PAS and prothionamide were co-administered (n=8) compared to the group prescribed prothionamide without PAS (n=21) (Co-administered 38% (95% CI: 0-71.0) vs. Prothionamide without PAS 37% (95% CI:0-63.5), P=0.57).

The majority of hypothyroidism was identified in the first year after commencement of therapy with eight of the nine patients developing hypothyroidism within this period with the remaining patient developing hypothyroidism at 7 years post prothionamide commencement and was still on PAS treatment at time of hypothyroidism diagnosis. The unusually lengthy course in this patient reflects historical treatment approaches in the setting of failure to convert sputum cultures (11).

When comparing baseline clinical characteristics of the group that developed any thyroid abnormality (n=9) with the group that remained euthyroid (n=20), there were no significant

differences identified (table 1). Only one individual who developed hypothyroidism had positive thyroid-peroxidase (TPO) antibodies (table 2).

The median time on dual therapy for individuals with and without hypothyroidism was 1.7 (1.0-2.7) and 1.7 (0.8-2.5) years respectively. The median times on prothionamide without PAS for individuals with and without hypothyroidism were 1.4 (0.2-1.7) and 1.5 (0.4-1.7) years respectively (P=0.70).

Univariate Cox regression using duration of therapy of prothionamide therapy as a time-dependent covariate did not identify an association between duration and risk of developing hypothyroidism (HR 0.60, 95% CI; 0.12 to 2.98, p=0.53).

There appeared to be a trend towards a higher proportion of hypothyroidism in individuals on higher doses (1000mg and 750mg) of prothionamide when compared to a lower dose (500mg), although this did not achieve statistical significance (P=0.06). There was however, a higher proportion of hypothyroidism in individuals on 750mg of prothionamide when compared to 500mg (P=0.03) figure 3.

Four of the nine individuals with hypothyroidism had a TSH >10mIU/L. Of the seven patients who were commenced on thyroxine replacement, six had overt hypothyroidism with the remaining one having subclinical hypothyroidism. Six of the nine patients with 2 sets of abnormal thyroid function tests had abnormal TFTs over a period of 4 months to 3.5years.

The remaining 3 patients had their two TFTs over a one month period. Two of these three individuals were commenced on thyroxine post the 2nd set of TFTs and subsequent TFTs were normal. The remaining patient developed subclinical hypothyroidism and TSH normalised without treatment within 3 months of rechecking.

Seven individuals had documented symptoms consistent with hypothyroidism at the time of diagnosis. The daily dose of thyroxine ranged from 50-200mcg daily. Two individuals showed normalisation of their thyroid function tests after cessation of MDR-TB therapy and were subsequently able to stop thyroxine replacement. The doses of thyroxine required to normalise thyroid function were 50mcg in one patient and 100mcg in the other. At the time of writing, two patients had not completed MDR-TB therapy and were therefore still on thyroxine replacement therapy. Three patients did not have formal documentation of whether the thyroxine was continued post MDR-TB therapy cessation.

Discussion

Among the 29 MDR-TB patients in our Australian cohort treated with prothionamide and or PAS with sufficient thyroid function data, the cumulative proportion of hypothyroidism at five years was 37% (95% CI: 0-57.8%). In eight of the nine cases, hypothyroidism occurred within the first 12 months of starting MDR-TB therapy. Of note, the one individual who developed hypothyroidism 7 years post initiation of MDR-TB therapy was also the only case to have positive thyroid antibodies suggesting an incidental case of Hashimoto's hypothyroidism rather than MDR-TB drug induced hypothyroidism. Hypothyroidism

appeared to be associated with higher PAS and/or prothionamide doses (p=0.06) and was reversible with the cessation of the anti-tuberculosis medication.

The reported incidence of hypothyroidism in MDR-TB patients varies greatly from 4-69% (12-15) (Table 3). Studies to date have largely investigated the incidence of overt hypothyroidism. Only one previous study reported individuals with subclinical disease (16). Furthermore, reports are limited to developing populations where many confounding factors such as iodine deficiency and HIV status and anti-retroviral use may contribute to thyroid status. Our study is the first Australian study – and the largest from a developed country - to describe thionamide/PAS-treatment associated hypothyroidism. While previous reports largely diagnosed hypothyroidism based on a single abnormal thyroid function test, we required biochemical confirmation by at least one additional set of thyroid function tests.

WHO guidelines recommend thyroid function testing at 6–9 months after initiation of MDR-TB treatment whereas Victorian Tuberculosis management guidelines published in 2012 recommends three-monthly thyroid function tests whilst on PAS or prothionamide (2, 17). In our study just over 50% of cases were excluded from analysis due the absence of any thyroid function tests. Although our study was not designed to evaluate why recommended guidelines have not been followed in individual cases, the apparent lack to do so does suggest the need for a wider recognition of the potential thyroid side-effects of anti-tuberculosis therapy. Greater awareness, and where appropriate, endocrine consultation may facilitate testing for and management of thyroid dysfunction. Biochemical surveillance is essential as

the symptoms of hypothyroidism can be non-specific and may erroneously be attributed to the underlying infection. If confirmed, our data suggest that more frequent monitoring of TFTs may need to be considered in individuals receiving higher doses of prothionamide/PAS treatment.

The mechanisms by which these agents cause hypothyroidism have not been rigorously studied, and evidence is largely provided by historical studies. Prothionamide and ethionamide are structurally similar to methimazole and carbimazole, drugs used for the treatment of hyperthyroidism (18). These drugs inhibit thyroid hormone synthesis primarily by preventing iodine organification of thyroid hormone precursors (19) due to inhibition of thyroid peroxidase (20). In vitro studies in cultured thyroid cells demonstrated that at concentrations seen clinically, ethionamide inhibited organification of iodine with similar potency to methimazole (21). Ethionamide-associated inhibition of thyroid iodine uptake may also contribute (21, 22). Although the evidence for PAS induced hypothyroidism and potential underlying mechanisms are less clear than for thionamides, several studies have demonstrated that co-administration of PAS and a thionamide significantly increases risk of hypothyroidism, suggesting that PAS may impact thyroid function independent of, or at least additional to thionamide-like anti TB drugs (16). In vitro, PAS has been reported to interfere with the normal iodination of thyroid hormone, but at less than one-tenth the potency of anti-thyroid drugs (23, 24). Some (24) but not all (22) experimental studies in humans have reported that PAS reduces thyroidal iodine uptake. PAS has also been associated with

degenerative changes in histological thyroid specimens from PAS-treated rats (25) and human subjects (26).

Interestingly, despite subnormal thyroid hormone levels, TSH levels in our group of participants were not grossly elevated, raising the possibility that non-specific chronic-illness associated central suppression of the thyroid axis may have moderated the degree of TSH elevation.A full literature search using MEDLINE English-language from January 1997 to December 2017 using the search terms "multidrug resistant", "tuberculosis" and "hypothyroidism" identified 6 prospective cohort studies, 2 retrospective cohort studies and 2 case reports reporting thionamide/PAS-treatment based thyroid outcomes (table 3) (9, 12-16, 27-30). The most recent report is a prospective study which investigated 188 euthyroid individuals undergoing treatment for MDR-TB in the state of Karnataka, India over a 6-month period (12). The authors observed that 23% of individuals developed hypothyroidism with the majority (74%) occurring after the initial 3 months of therapy. In the largest prospective study to date (14), 213 MDR-TB participants from Botswana were studied, and 34% of those prescribed ethionamide or PAS developed hypothyroidism.

Compared to previous reports (Table 3), we found a somewhat higher proportion of overt and subclinical hypothyroidism in MDR-TB treated individuals with the cumulative proportion of hypothyroidism occurring in 38% of individuals on combined PAS and prothionamide and 37% of individuals on prothionamide without PAS. This higher proportion is likely due to the inclusion of subclinical hypothyroidism along with overt hypothyroidism. The only other

study reporting individuals with subclinical hypothyroidism observed 78% of their 50-participant cohort to develop either overt or subclinical hypothyroidism, but this study was based on a single abnormal thyroid function test (16). Our study may have overestimated the proportion of hypothyroidism due to selection bias due to clinical indication- rather than protocol-based thyroid function testing. However, hypothyroidism, especially if transient, may have been missed given fifty-one percent of the prothionamide/PAS treated patients had no documented thyroid function tests, despite guideline recommendations (2, 17).

The majority of cases in our study developed hypothyroidism within the first year of drug therapy. This phenomenon may be due to guidelines recommending MDR-TB be treated for approximately 18months then cessation of medications, therefore making diagnosis of hypothyroidism beyond this period less likely. This finding is consistent with previous studies where 50-74% of the MDR-TB-associated cases of hypothyroidism occured within the first 6 months of treatment (12, 13, 15).

Prothionamide dosing is standardised with doses ranging from 250mg twice daily to 500mg twice daily (2). The dose of prothionamide appeared to be associated with hypothyroidism, with a greater number of individuals with high daily doses (1000mg and 750mg) being diagnosed with hypothyroidism compared with those prescribed lower daily doses (500mg). This dose- related effect on thyroid function has not been previously described. These findings however, should be interpreted with caution and be viewed as hypothesis-generating,

as further subgroup analyses between dose categories is limited by diminished statistical power.

Of the nine patients with abnormal thyroid function, most (6/9) patients maintained hypothyroid TFTs over extended periods of time, making the euthyroid sick syndrome a less likely explanation for these abnormalities. The three remaining patients had their TFTs remeasured over a one month interval, and two of these three individuals were commenced on thyroxine. Sick euthyroid syndrome could therefore not be excluded, and may have contributed to the elevation of TSH in the 3rd individual who had self-limiting subclinical hypothyroidism

Of the two patients who completed their MDR-TB therapy and had documentation of thyroxine management, both individuals were able to cease thyroxine therapy and had normalisation of their thyroid function. This suggest that potentially PAS and prothionamide withdrawal may result in normalisation of thyroid function which is consistent with previous mechanistic studies where withdrawal resulted in normalisation of radio-iodine uptake and goitre resolution (21, 23).

Limitations of this study include those inherent in its retrospective nature, the absence of clinical data, and the use of academic centre-based rather than uniform thyroid function assay methodology. However, thyroid function test abnormalities were strictly defined based on assay-specific reference ranges. In light of the fact that MDR-TB is relatively uncommon in

Australia, case numbers were relatively modest. The relative small numbers may reduce the statistical power associated with our regression analyses. Nevertheless, this represents the largest cohort from a developed country.

Conclusions

Prothionamide and PAS, drugs routinely used in the treatment of MDR-TB patients, are commonly associated with the development of hypothyroidism in Australia. Given the expected increase of MDR-TB in Australia awareness of thyroid-associated adverse outcomes of anti-TB treatment among health professionals is important (3, 4, 6). Hypothyroidism most commonly develops during the first 12 months of treatment, but can be delayed. Higher doses of prothionamide may potentially be associated with elevated risk. Routine symptoms screening along with thyroid function testing should be performed in all individuals receiving PAS and/or prothionamide (2, 17). However, prothionamide /PAS associated hypothyroidism is not universal and prospective studies with larger sample sizes are required to fully characterise the incidence of hypothyroidism, and to identify patient-dependent risk factors for the development of hypothyroidism during this treatment. Finally, treatment-associated hypothyroidism may be temporary, and the need for ongoing thyroid hormone replacement if initiated should be re-evaluated once anti-TB treatment has been completed.

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Table 1: Baseline characteristics

	Normal (n=20)	Any abnormality (n=9)	p value
Age (years)	35 (22-47)	34 (30-42)	0.91
Male	8 (40)	3 (33)	>0.99
Ethnicity			
Asian	15 (75)	8 (89)	
African	2 (10)	1 (11)	
Caucasian	2 (10)	0 (0)	
Unknown	1 (5)	0 (0)	0.68
Diabetes	2 (10)	0 (0)	>0.99
Family history thyroid disorder	0 (0)	1 (11)	0.3
Autoimmune disorder	1 (5)	0 (0)	>0.99
TB type			
Pulmonary	18 (90)	6 (67)	
Extra-pulmonary	3 (15)	3 (33)	0.33
Medication			
Prothionamide without PAS	16 (80)	5 (56)	0.21
Median time on therapy	1.5 (0.3-2.0)	1.4 (0.2-1.7)	0.7
PAS and prothionamide	4 (20)	4 (44)	0.21
Median time on therapy	1.7(0.8-2.5)	1.7 (1.0-2.7)	0.11
Interacting agent*	2 (10)	3 (33)	0.14

*Intravenous contrast 6 months prior to baseline thyroid function tests

Values in brackets refer to percentage or (interquartile) range respectively

Table 2: Clinical and biochemical characteristics of the nine hypothyroid cases

Case	Age (years)	Gender	Baseline TSH (mU/L)	Baseline fT4 (pmol/L)	TSH at hypothyroidism diagnosis (mU/L)	fT4 at hypothyroidism diagnosis (pmol/L)	TPO antibody status	Duration on MDR-TB medication prior to diagnosis (months)	Thionamide dose (mg/day)	PAS dose (g/day)
1	44	F	3.11	NA	***8.98**	***7.8**	NA	3.6	1000	NA
2	30	F	1.11	NA	***5.02**	***9.7**	Negative	4.8	750	8
3	35	F	NA	NA	***5.26**	***10**	Negative	6.0	750	NA
4	42	F	1.31	17.6	***5.06**	***10.3**	Negative	6.0	750	NA
5	42	F	2.24	NA	***4.3**	13.4	NA	7.2	750	8
6	26	M	2.22	NA	***5.21**	10.6	NA	8.4	750	NA
7	31	M	1.63	NA	***11.72**	***8.5**	Negative	9.6	750	8
8	32	M	1.21	10.8	***14.8**	***7.6**	Negative	9.6	1000	NA
9	43	F	NA	NA	***40.9**	***7.0**	Positive	88.8	Unclear	8

NA data not available; F female; M male; TPO thyroid peroxidase antibody. While the diagnosis of hypothyroidism was based on two consistent set of thyroid function tests, for clarity only 1 set is shown.

***Outside reference range**

Table 3: Hypothyroidism in adults with MDR-TB and ethionamide, prothionamide and PAS use

Author	Trial type	Number	Country	Drugs	Doses	HIV co-infection	Thyroid function
Munivenkatappa et al, 2016[7]	Prospective	188	India	ETH, PAS	Not specified	No	23% developed hypothyroidism with 74% occurring after 3 months
Bares et al, 2016[11]	Prospective	50	Pakistan	ETH, PAS	Not specified	No	78% developed hypothyroidism, with 48% having subclinical and 38% having overt hypothyroidism occurring over 20months. All individuals that developed hypothyroidism

							were autoantibody negative
Akshata et al, 2015[10)]	Retrospective	484	Egypt	ETH +/-PAS only if drug intolerance	Not specified	No	3.9% developed hypothyroidism with the median time to development being 153days (5 months)
Andries et al, 2013[(16)]	Prospective	69	India	ETH, PAS or both (67% of patients received both)	Not specified	Yes	54% developed hypothyroidism with 62% occurring after 90 days. Co-administration of PAS and ethionamide doubled the risk of hypothyroidism (RR 1.93, 95% CI: 1.06-3.54)
Gupta et al, 2012[(6)]	Prospective	7	United	PTH + PAS	Not specified	No	71% developed

			Kingdom				hypothyroidism over a 2-year period
Dutta et al, 2012[17]	Prospective	52	India	ETH	250mg BD	No	21% developed hypothyroidism, and 3 with goitre. 64% occurring within 3 months of medication initiation. 10 out of 11 patients became euthyroid post cessation of the offending medication
Modongo et al, 2012[9]	Prospective study	213	Botswana	ETH, PAS	Not specified	No	34% developed hypothyroidism

Satti et al, 2012[6]	Retrospective study	186	South Africa	ETH/PTH + PAS (97.3% of patients)	Not specified	Yes	69% developed hypothyroidism with 50% occurring within 93 days, 46 MDRTB patients who underwent urine iodine testing, the median value of urine iodine was 209.1 µg/l (range 32.6–1747.7), indicating adequate iodine intake
McDonnell et al, 2005[29]	Case report	1	America	ETH	250mg BD	No	Severe hypothyroidism

Soumakis et al, 1998[19]	Case report	1	America	ETH + PAS	750mg daily	No	TSH 28U/L, low thyroxine and low fT4-serum level

ETH ethionamide; PAS para-aminosalicylic acid; PTH prothionamide; MDRTB multidrug resistant tuberculosis; TSH thyroid stimulating hormone; FT4 free thyroxine; HIV human immunodeficiency virus

Figure 1: MDR-TB individuals who developed hypothyroidism during the study period

Figure 2: Cumulative proportion of individuals that developed hypothyroidism on MDR-TB therapy

9 out of the 29 cases developed hypothyroidism, with a cumulative proportion at 5 years of 37% (95% CI: 0-57.8%).

Figure 3: Cumulative proportion of individuals on prothionamide that developed hypothyroidism stratified by dose

There was a statistically significant higher proportion of hypothyroidism in individuals on 750mg of prothionamide when compared to 500mg (P=0.03).

Appendix

Figure 4: **Cumulative proportion of individuals on prothionamide that developed hypothyroidism stratified by high or low doses**

There was a trend towards hypothyroidism in individuals on either 1000mg or 750mg of prothionamide when compared to 500mg (P=0.06).

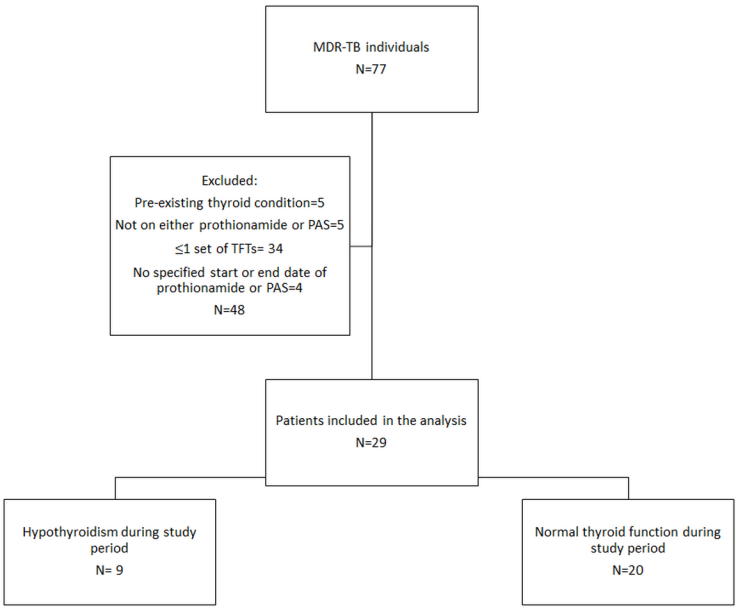

Figure 1 edited.tif

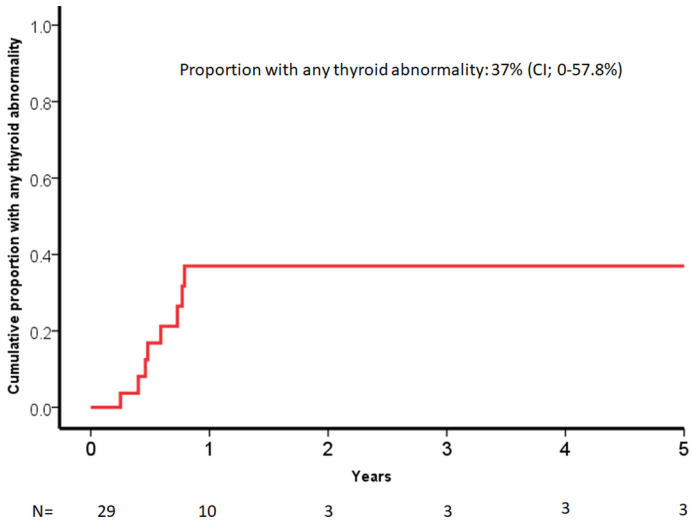

Figure 2 MDRTB.tif

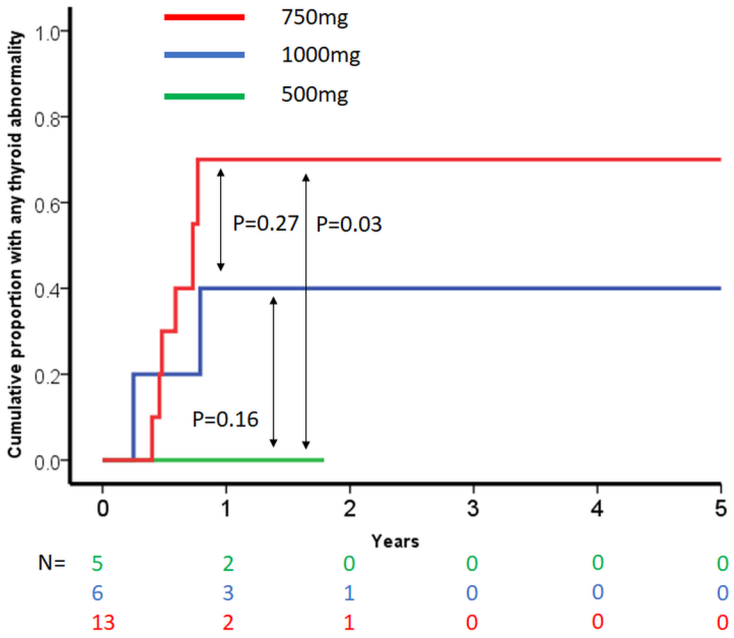

Figure 3 MDRTB.tif

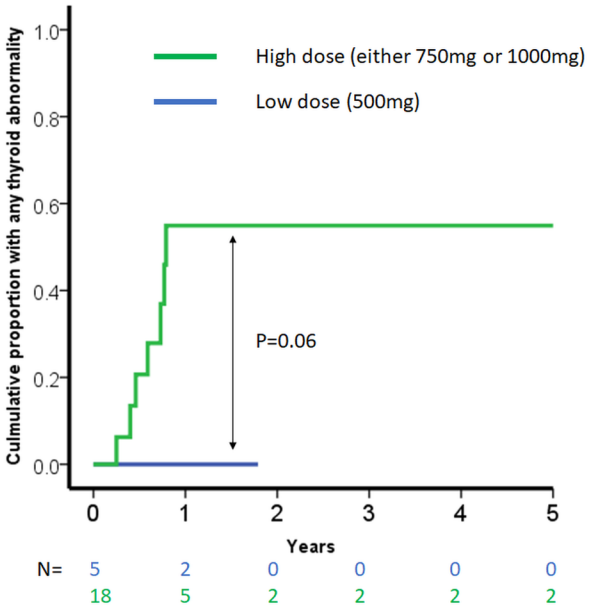

Figure 4 MDRTB.tif

Abstract

Objective: Reports from resource-poor countries have associated thionamide- and para-aminosalicylate sodium (PAS)-based treatment of multidrug-resistant tuberculosis (MDR-TB) with the development of hypothyroidism. We aimed to identify predictors and assess the cumulative proportions of hypothyroidism in patients treated for MDR-TB with these agents in Australia.

Design, Setting and Participants: Retrospective multi-centre study including MDR-TB patients from five academic centres covering TB services in Victoria, Australia. Patients were identified using each centre's pharmacy department and cross checked with the Victorian Tuberculosis Program. Hypothyroidism was categorised as subclinical if thyroid stimulating hormone (TSH) was elevated, and as overt if free thyroxine (fT4) was additionally reduced on two separate occasions.

Main outcome measure: Cumulative proportion of hypothyroidism (at 5 years from treatment initiation).

Results: Of the 29 cases available for analysis, the cumulative proportion of hypothyroidism at 5 years was 37% (95% CI: 0-57.8%). Eight of the nine affected cases developed hypothyroidism within the first 12 months of treatment. Hypothyroidism was marginally ($p=0.06$) associated with higher prothionamide/PAS dosing and was reversible with cessation of the anti-tuberculosis medication.

Conclusions: Prothionamide/PAS treatment-associated hypothyroidism is common in MDR-TB patients in Australia, emphasising the importance of regular thyroid function monitoring during this treatment. Thyroid hormone replacement if initiated, may not need to be continued after MDR-TB treatment is completed.

Hypothyroidism associated with therapy for multi-drug resistant tuberculosis in Australia

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