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Evaluation of thyroid profile in euthyroid patients taking first line antitubercular drugs in newly detected smear positive pulmonary tuberculosis patient

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Abstract
Background: Pulmonary tuberculosis is a common contagious disease and has a capacity for wide spread dissemination. Present study aims to identify the effect of antituberculous treatment on thyroid profile in new smear positive pulmonary tuberculosis patients. The most common manifestation of thyroid dysfunction in these patients was found to be sick euthyroid syndrome. Many studies were done in MDR TB patients to know the incidence of drug induced hypothyroidism. Even though thyroid function is mandatory test before the initiation of MDR TB drugs, no such protocols exist in new smear positive pulmonary tuberculosis patients. Hence present study was planned to evaluate the effect of first line antitubercular drugs on thyroid function in new smear positive pulmonary tuberculosis patients.
Methods: The present study was planned in Department of General Medicine, ICARE Institute of Medical Science and Research and Dr Bidhan Chandra Roy Hospital, Haldia. The study was planned from Sept 2012 to July 2013. Total 50 cases of the firstly diagnosed smear positive pulmonary tuberculosis patients from our hospital were enrolled in present study. In these selected cases Thyroid function was assessed by measuring free T3, free T4 and TSH value before and after initiating first line 4 drug regimen antitubercular therapy (ATT) and after 3 months of completion of ATT therapy. Patients are started on antituberculosis treatment as per current RNTCP guidelines. Thyroid function testing is repeated at the end of third month and at the end of 6 months and after 3 months of completion of ATT course.
Result: The data generated from the present study concludes that Sick euthyroid syndrome was found to be a temporary reversible condition with highest incidence at the end of three months and was significantly reducing towards the end of treatment and cured after 3 months of stoppage of treatment, however none of these patients were acutely sick during the study and all these patients were euthyroid at the beginning of present study.
Conclusion: The common Thyroid Dysfunction seen during the study period was Sick euthyroid and subclinical hypothyroidism. Anti-tuberculous medication probably Rifampicin would explain the cause for these thyroid dysfunctions noticed during the study time. And author recommend that these patients should be kept under follow up after the diagnosis instead of treating with thyroid supplements. And thyroid supplement should be given in clinically overt hypothyroid cases.

Keywords: anti-tuberculosis treatment, hypothyroidism, thyroid, TSH etc

Introduction

Pulmomary Tuberculosis is an infectious disease caused by mycobacterium tuberculosis. Developing country like India account for one fourth of the global TB burden and it is estimated that TB kills more adults in India more than any other infectious disease.

The most common manifestation of pulmonary tuberculosis involving thyroid gland was found to be sick euthyroid syndrome. Many studies were done in MDR TB patients to know the incidence of drug induced hypothyroidism. Even though thyroid function is mandatory test before the initiation of MDR TB drugs, no such protocols exist in new smear positive pulmonary tuberculosis patients. Therefore, we conducted a study to know effect of first line anti-tubercular treatment on thyroid profile in new smear positive pulmonary tuberculosis cases.

Thyroid function tests (TFTs) is a collective term for blood tests used to check the function of the thyroid gland [1]. TFTs may be requested if a patient is thought to suffer from hyperthyroidism (overactive thyroid) or hypothyroidism (underactive thyroid), or to monitor the effectiveness of either thyroid-suppression or hormone replacement therapy. It is also requested routinely in conditions linked to thyroid disease, such as atrial fibrillation and anxiety disorder.

A TFT panel typically includes thyroid hormones such as thyroid-stimulating hormone (TSH, thyrotropin) and thyroxine (T4), and triiodothyronine (T3), free T3 and free T4 depending on local laboratory policy.

Thyroid-stimulating hormone (TSH, thyrotropin) is generally increased in hypothyroidism and decreased in hyperthyroidism [2], making it the most important test for early detection of both of these conditions [3, 4]. However, when TSH is measured by itself, it can yield misleading results, so additional thyroid function tests must be compared with the result of this test for accurate diagnosis [4, 5, 6].

TSH is produced in the pituitary gland. The production of TSH is controlled by thyrotropin-releasing hormone (TRH), which is produced by hypothalamus. TSH levels may be suppressed by excess free T3 (fT3) or free T4 (fT4) in the blood.

Sick Euthyroid syndrome (also known as nonthyroidal illness syndrome) can be described as abnormal findings on thyroid function tests that occur in the setting of a

nonthyroidal illness (NTI), without preexisting hypothalamic-pituitary and thyroid gland dysfunction. After recovery from an NTI, these thyroid function test result abnormalities should be completely reversible [7-8].

Multiple alterations in serum thyroid function test findings have been recognized in patients with a wide variety of NTIs without evidence of preexisting thyroid or hypothalamic-pituitary disease. The most prominent alterations are low serum triiodothyronine (T3) and elevated reverse T3 (rT3), leading to the general term "low T3 syndrome." Thyroid-stimulating hormone (TSH), thyroxine (T4), free T4 (FT4), and free T4 index (FTI) also are affected in variable degrees based on the severity and duration of the NTI. As the severity of the NTI increases, both serum T3 and T4 levels drop, but they gradually normalize as the patient recovers.

Alterations in thyroid function test findings may reflect changes in production of thyroid hormone by effects on the thyroid itself, on the hypothalamic-pituitary-thyroid axis, on peripheral tissue metabolism of the hormones, or by a combination of these effects.

A general conviction exists that patients with thyroid function test result abnormalities do not have hypothyroidism despite the low serum hormone levels in blood and low T3 in most of the tissues. Many patients with NTI also receive drugs that affect thyroid hormone regulation and metabolism. This discussion does not consider pharmacologic interference an intrinsic part of the spectrum of changes in hypothalamic-pituitary-thyroid function that occur in NTI. Consider pharmacologic interferences as part of the evaluation of a patient who has thyroid function test result abnormalities.

Thyroid hormones have been used in the setting of NTI in various settings with T4 and T3 replacement and still remain controversial. De Groot has supported the notion that nonthyroidal illness syndrome is a manifestation of hypothalamic-pituitary dysfunction, and in view of current evidence, he proposed that treatment should be considered with appropriate replacement therapies such as pituitary hormones, hypothalamic factors in addition to thyroid hormones [9].

First-line anti-tuberculous drug names are often remembered with the mnemonic "RIPE," referring to the use of a rifamycin (like rifampin), isoniazid, pyrazinamide, and ethambutol. U.S. practice uses abbreviations and names that are not internationally convened: rifampicin is called rifampin and abbreviated RIF; streptomycin is abbreviated STM. Other abbreviations have been widely used (for example, the notations RIF, RFP, and RMP have all been widely used for rifampicin, and the combination regimens have notations such as IRPE, HRZE, RIPE, and IREP that are variously synonyms or near-synonyms, depending on dosage schedules), but for clarity, the semistandardized abbreviations used above are used in the rest of this article. In this system, which the World Health Organization (WHO) supports, "RIPE" is "RHZE". (Both have mnemonic potential, as tuberculosis is

Methodology

The present study was an institutional prospective cohort study planned in Department of General Medicine, ICARE Institute of Medical Science and Research and Dr Bidhan Chandra Roy Hospital, Haldia. The study was planned from Sept 2012 to July 2013. Total 50 cases of the tuberculosis found positive in our hospital were enrolled in present study. In the selected cases Thyroid function was assessed by measuring free T3, free T4 and TSH value by electrochemiluminescence method before and after initiating antitubercular therapy (ATT).

Patients are started on antituberculosis treatment as per current RNTCP guidelines. Thyroid function testing is repeated at the end of third month and at the end of treatment and after 3 months of completion of treatment.

Based on thyroid dysfunction, patients were classified as euthyroid (Normal TSH, free T3 and free T4), Primary hypothyroidism (High TSH with low free T4 and free T3), Subclinical hypothyroidism (High TSH and normal free T4 and free T3) and sick euthyroid (low free T3 with normal TSH and free T4 or low free T4 and free T3 with normal TSH).

All the patients were informed consents. The aim and the objective of the present study were conveyed to them. Approval of the institutional ethical committee was taken prior to conduct of this study.

Following was the inclusion and exclusion criteria for the present study.

Inclusion criteria: Cases with newly detected smear positive pulmonary and extra pulmonary tuberculosis and with Age from 18 years- 65 years

Exclusion criteria: Patients who are suspects and diagnosed to have multidrug resistant pulmonary tuberculosis. • Patient with known and newly diagnosed thyroid disorders (Medical and Surgical) • Patients who are acutely ill with possibility of sick euthyroid syndrome. • Patients with HIV seropositive status. • Patients not willing to give informed consent

Results & Discussion

In a series of 50 cases of pulmonary tuberculosis, the youngest was 18 year old and the eldest was 70 year old. Maximum number of patients belonged to the age group between 21-40 years with a mean age of 47±14 years (Table 1).

Out of the 50 patients 38 (76 %) were males and 12 (24 %) were females. Male to female ratio was 3.17:1 (Table 1).

Table 1: Demographic Details of Cases

Age in Years	No. of Cases
Below 20 years	2
21 – 30 years	15
31 – 40 years	9
41 – 50 years	7
51 – 60 years	8
61 and Above	9
Total	50
Sex	
Males	38
Females	12
Total	50

Table 2: Presenting Symptoms

Symptoms	No. of Cases
Fever	41
Cough	38
Breathlessness	5
Abdominal distention	2
Pain abdomen	1
Weight loss	8
Head ache, vomiting	1
Haemoptysis	5

Table 3: Distribution of co-morbidities

Co-morbidities	Present	Absent
Diabetes Mellitus	8	42
Coronary artery disease (stable) Normal LVEF	2	48
Chronic kidney disease	1	49
COPD or ILD	4	46

Table 4: Thyroid Markers

Thyroid parameters	Pre treatment	3 Month Post ATT	6 months post ATT	3 months after ATT course completion
Total Cases	**50**	**50**	**50**	**50**
Free T3 (pg /ml)				
• <0.2.6	0	4	4	0
• 2.6-4.8	50	46	46	50
• >4.8	0	0	0	0
T4 (ng/ml)				
• < 0.75	0	2	2	0
• 0.75-1.95	50	48	48	50
• >1.95	0	0	0	0
TSH (Miu/ml)				
• <0.4	0	0	0	0
• 0.4-5.0	50	43	43	49
• > 5.5	0	7	7	1

On observing the values of free T3 over the study period it was noted that free T3 showed a declining trend. The mean free T3 at the start of study was 2.80 with a standard deviation of 0.54 and It had dropped to 1.74 with a standard deviation of 0.62 at the end of 3 months and finally to 1.61 with a standard deviation of 0.53 at the end of 6 months and after 3 month of completion of ATT course it was 2.70 with a standard deviation of 0.59. The p value during study was found to be <0.001 and was found to be statistically significant.

Free T4 values in study participants also showed a declining trend. The mean free T4 at the start of study before initiation of ATT was 1.32 with a standard deviation of 0.19. At the end of 3 months it dropped to 1.10 with a standard deviation of 0.23 and to 0.99 with a standard deviation of 0.25 at the end of 6 months, after 3 month of completion of ATT course it was 1.31 with a standard deviation of 0.23. The p value during the study period was found to be <0.001 and was found to be statistically significant.

On following up the study subjects over the 9-month study period, TSH was found to show rising trends. The mean TSH at baseline evaluation before initiation of ATT was 3.97. The mean TSH value rose to 4.99 at the end of 3 months and to 5.02 at the end of 6 months study period, after 3 month of completion of ATT course it was 4.4. The chi square value during the study period was 96.63 and p value was found to be <0.001 and was statistically significant.

Antituberculous medication probably rifampicin or isoniazide would be the cause of these thyroid dysfunction noticed during the study time. The need of thyroid supplement would be limited to significant clinical hypothyroidism not sick euthyroid syndrome or subclinical hypothyroidism.

A limitation of the present study was that TSH testing was performed only at the third and sixth months of treatment. It is likely that testing at more regular intervals and throughout the entire length of ATT course would increase the time to detection of hypothyroidism. Future studies are needed to find out the proportion of these patients patients developing hypothyroidism during continuous phase as well, as susceptibility for hypothyroidism may continue beyond IP.

Conclusion

In present study, new smear positive pulmonary tuberculosis can cause thyroid dysfunction at various stages of treatment. Among the thyroid dysfunction, sick euthyroid syndrome and subclinical hypothyroidism was the major thyroid dysfunction observed in present study.

Sick euthyroid syndrome and subclinical hypothyroidism was found to be a temporary reversible condition with highest incidence at the end of three months to 6 months of treatment (75%) and was significantly reducing after 3 months of stoppage of treatment, however none of these patients were acutely sick during the study and all these patients were euthyroid at the beginning of present study. Hence, authors recommend that these patients should be kept under follow up after the diagnosis instead of treating with thyroid supplements.

Among the anti tubercular drugs used, rifampicin and isoniazide which was given for entire six months in all our patients, was probably the cause for thyroid dysfunction noticed during the course of treatment.

Both the drug Isoniazide and Rifampicin, which may have caused thyroid dysfunction in present study, should be continued due to its importance in the treatment of tuberculosis rather than stopping it and starting an alternate drug. Authors recommend thyroid function test to be done in all cases of smear positive pulmonary tuberculosis before initiating treatment, during the course of treatment and if found to be abnormal follow up TFT is advised 6-8 weeks after the stoppage of treatment for better assessment of thyroid function. Thyroid supplenment should be only used in patients with clinical hypothyroidism and thyroid function reevaluated after completion of ATT course and stopped gradually if thyroid function become normal.

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