

Sick Euthyroid Syndrome: Thyroid Function Abnormalities in Patients with Non-Thyroid Illness

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ABSTRACT

INTRODUCTION: Non-thyroid illness is accompanied with many severe illnesses like septicemia, renal failure, cirrhosis of liver, Pulmonary Tuberculosis, chronic heart failure, after major surgical trauma, etc. This study was undertaken on first four illnesses, which are common medical problems, and admitted in medical wards in advanced stages. This is to bring awareness amongst clinicians while interpreting TFT abnormalities in severe illnesses.

OBJECTIVE: To assess the thyroid function status in patients with severe illnesses, which are commonly encountered in Medical wards. Interpretation of Thyroid hormones should be cautiously made in such conditions..

DESIGN: Descriptive/Observational, Non-interventional study

PLACE AND DURATION OF STUDY: Medical unit III, Civil Hospital, Karachi. From 1st March 2001 to 1st April 2002. The cases were recorded as and when received, keeping exclusion criteria as mentioned below.

MATERIAL AND METHODS: 50 adult patients of either sex, admitted in the hospital for non-thyroidal illness were tested for the thyroid function status by means of T3, T4 and TSH analysis. Results were evaluated for the presence of Sick Euthyroid Syndrome.

RESULTS: Of the 50 patients, 24 (48%) had a low T3, low T4 or both but with normal TSH.

CONCLUSION: Sick Euthyroid Syndrome should be considered while managing the patients with serious and debilitating illnesses.

KEY WORDS: Sick Euthyroid Syndrome, T3, T4, TSH.

INTRODUCTION

The thyroid gland is important in maintaining the level of metabolism in the tissues that is optimal for their normal function. The principal hormones secreted are Thyroxine (T4), Triiodothyronine (T3) and a calcium lowering hormone Calcitonin. The hormone secretion is controlled by Thyroid stimulating hormone (TSH), secreted by the anterior pituitary^{1,2}. The term " Sick Euthyroid Syndrome" refers to abnormalities in thyroid function that occur in patients with serious illness not caused by primary thyroid or pituitary dysfunction¹. It identifies abnormalities in Thyroid function tests observed in patients with systemic non-thyroidal illness (NTI) and those undergoing surgery or fasting. Severe psychiatric disturbances can also alter the thyroid hormone levels in patients without intrinsic thyroid disease and many other illnesses. The most commonly encountered abnormality is the low T3 level with an increased rT3 and usually low normal TSH and T4 levels. These findings differentiate the Sick Euthyroid Syndrome from true hypothyroidism, in which rT3, T3 and T4 levels would most likely be all low with raised

TSH levels³. In more seriously ill patients, the serum T4 concentration also decreases in the hypothyroid range. The serum TSH concentration, appear normal by conventional assays while the TRH responses are often blunted⁴. Approximately, a mortality rate of 80% was observed in patients having total T4 values of 2µg/dl or less. This rate was reduced to less than 5% if total T4 levels remained at 7µg/dl or greater². The strong association between thyroid function and chronic or severe illness has significant importance while excluding the presence of thyroid disease in an already ill patient.

MATERIAL AND METHODS

The study comprised of 50 adult patients of either sex who were investigated for the presence of abnormal levels of thyroid hormones in the presence of any non-thyroid illness. The study duration was from 1st March 2001 to 1st April 2002. Diagnosis of non-thyroid illness such as Cirrhosis of liver, Chronic renal failure or Pulmonary tuberculosis was made on clinical evidence and relevant laboratory investigations in each case. Patients with Septicemia, irrespective of its cause

were also included in this study. There are many illnesses like Chronic Heart Failure, after Major Surgery can result into this condition, but for limitation of resources (hormonal assays etc) they were not included. Patients already known to have a thyroid disease were not included in the study. In addition to routine investigations, following specific tests were carried out for the confirmation of NTI: Cirrhosis of Liver: Liver function tests, Prothrombin time, Serum proteins and A/G ratio, ultrasound abdomen, Viral markers for HCV and HBV, ascitic fluid analysis and liver biopsy (if required). Chronic Renal Failure: Blood urea Nitrogen, Serum Creatinine, Serum electrolytes and Calcium and Phosphorus, Creatinine clearance and Urinary proteins, Ultrasound kidney and Renal biopsy in doubtful cases. Septicemia: Total and differential Leukocyte count, d-dimers, Fibrin degradation products, blood and other cultures as per requirement. Pulmonary Tuberculosis: Blood complete picture and ESR, Sputum for Acid fast bacilli, Pleural fluid analysis, X-ray chest and Pleural biopsy in certain cases. For the diagnosis of Euthyroids sick Syndrome, T3, T4 and TSH levels were checked in each case by means of immunoradiometric technique.

RESULTS

Out of 50, there were 19 patients with cirrhosis of liver, 15 with pulmonary tuberculosis, 9 with chronic renal

failure and 7 patients with septicemia. (**Table I**) Out of 19 cirrhotic patients, 7 (36.84%) had no thyroid hormone abnormality. T3 was found to be low in 8 (42.10%) while in 1 (5.26%) the levels of both T3 and T4 were low. In all these patients TSH was within normal limits, suggestive of Euthyroid Sick Syndrome. In 3 (15.78%) both T3 and T4 were low but with raised TSH, hence consistent with "true hypothyroidism." Out of 15 patients of pulmonary tuberculosis, 7 (46.66%) had a normal thyroid function test. 5 (33.33%) had a low T3 and 1 (6.66%) had both T3 and T4 in below normal limits. All these patients had a normal TSH (Euthyroid Sick Syndrome). Raised TSH with low T3 and T4 was found in 2 (13.33%) cases. Of 9 patients with chronic renal failure, 4 (44.44%) were found to have hypothyroidism with low T3, T4 and a raised TSH level. Three (33.33%) had a low T3 with normal TSH. Thyroid assays were found to be normal in 2 (22.22%). Out of 7 septicemic patients, 3 (42.85%) had low T3, 2 (28.57%) had low T4 and 1(14.28%) had both T3 and T4 below normal limits. All of these patients had normal TSH. The thyroid function tests were normal in 1 patient. In all, out of 50 patients, the thyroid function tests were suggestive of Euthyroid Sick Syndrome in 24(48%) patients. Of these, 19 (79.16%) had low T3, 7 (29.16%) had both low T3 and T4 and 2 (8.3%) had low T4. (**Table II**)

**TABLE I:
THYROID FUNCTION TESTS IN PATIENTS WITH NON-THYROID ILLNESS**

Non-Thyroid Illness	Total patients	Normal T3	Low T3	High T3	Normal T4	Low T4	High T4	Normal TSH	Low TSH	High TSH
Cirrhosis of Liver	19	7	12	0	15	4	0	16	0	3
Pulmonary TB	15	7	8	0	12	3	0	13	0	2
Chronic Renal failure	9	2	7	0	5	4	0	5	0	4
Septicemia	7	3	4	0	4	3	0	7	0	0

**TABLE II:
PERCENTAGE OF EUTHYROID SICK SYNDROME IN NON-THYROID ILLNESS**

Non-Thyroid Illness	Normal Thyroid level	Hypothyroidism	Hyperthyroidism	Euthyroid Sick Syndrome
Cirrhosis of Liver	36.85%	15.78%	Nil	47.37%
Pulmonary TB	46.66%	13.33%	Nil	40%
Chronic Renal failure	22.22%	44.44%	Nil	33.33%
Septicemia	14.28%	Nil	Nil	85.72%

DISCUSSION

Almost any illness or physiological stress of sufficient severity is capable of inducing changes in one or more aspects of thyroid hormone metabolism⁵. The syndrome is very common and may be found in upto 70% of hospitalised patients¹. Multiple alterations in serum thyroid function test findings have been recognized in patients with a wide variety of NTI without evidence of pre-existing 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, and free T4 index (FTI) are also 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 and gradually normalize as the patient recovers⁶ (rise to normal levels). The types of non-thyroidal illness capable of producing these changes appear diverse, ranging from various acute and chronic illnesses to simple caloric restriction to aging⁷. The abnormal levels thyroid hormones have been noticed in the presence of diseases such as heart failure, chronic renal failure, liver disease, stress, starvation, surgery, trauma, infection, autoimmune diseases as well as with use of a number of drugs such as Phenytoin, Glucocorticoids, Propranolol etc⁸. The exact mechanism responsible for the alterations in thyroid hormone levels, in non-thyroid illness, is not known. The probable factors could be; Decreased T4 to T3 conversion, alterations in serum binding of thyroid hormones, decrease in level of TSH or its effect on the thyroid, increased cytokines and effects of hormones such as cortisol, glucagons etc⁹. Several abnormal patterns of thyroid hormone functions have been observed in patients with non-thyroid illnesses. These include; Low T3 syndrome which is the most common variant, Low T3 and T4 syndrome, unusual variants such as low TSH, T3 and T4 or increased T4 etc. The severity and the nature of changes in thyroid function tests have implications for prognosis of the systemic illness. Thus a low serum T3 level predicts increased mortality from liver cirrhosis, advanced congestive heart failure and possibly several other systemic illnesses. Similarly low total T4 is associated with increased mortality from systemic illness and those patients with low T4 who have very low serum T3 levels have the worst prognosis^{10,11}. Another important clinical issue is the exclusion of primary thyroid disorder in the presence of serious medical illness. Primary thyroid disease is excluded by a normal TSH¹². The distinction between the low T3 and T4 state of non-thyroid illness and true hypothyroidism can be a diagnostic problem¹³. If total T4 and T3 levels are low and the TSH level is above 25-30

$\mu\text{U/ml}$, the problem is most likely primary hypothyroidism. An elevated Reverse T3 (rT3) level argues against the diagnosis of hypothyroidism, when serum TSH level is more than $10\mu\text{U/ml}$ ¹⁴. Therefore a single test is not reliable in the setting of non-thyroid illness and a combination of tests should be considered in separating primary hypothyroid from euthyroid patients with the non-thyroid illness¹⁵. The correction of thyroid hormone deficit is controversial in patients with non-thyroid illnesses.

CONCLUSION

Incidental abnormalities detected in the thyroid function tests, should be thoroughly investigated before initiation of replacement therapy or administration of any other related medication. Sick euthyroid syndrome is a well-recognized medical problem, which should be considered while treating the patients with severe and debilitating illnesses with abnormal thyroid function tests. This is to bring awareness amongst clinicians about Sick Euthyroid Syndrome, while interpreting thyroid function abnormalities in seriously ill patients.

REFERENCES

1. Camacho PM, Dwar Kanthan AA. Sick euthyroid syndrome. What do we do when thyroid function tests are abnormal in critically ill patients: Postgrad Med 1999 Apr; 105(4):215-9.
2. Vandor PT, Romijin JA, Weirsinga WM, Sauerwein HP. Tumor necrosis factor: a putative mediator of the Sick Euthyroid Syndrome. J Clin Endocrinol Metabol 1991. 79: 1342-6.
3. Chestnutt MS, Predergast TJ. Lung. In: Tierney LM, Mc Phee SJ, Papadaks MA, eds. Current medical diagnosis and treatment. 39th ed. New York. Lang medical books/Mc Graw Hill. 2000:301-6.
4. Wartofsky L. Diseases of the thyroid. In: Fauci SA, Braunwald E, Isselbacher JK, Wilson DJ, Martin BJ, Kasper LD, eds. Harrison's principles of internal medicine. 14th ed. New York. The McGraw Hill. 1998: 2019.
5. Braveman LE, Utigar RD. Non-Thyroid illness. In: Werner and Ingbar's The Thyroid. 2000. Lippincott William and Wilkins: 281-95.
6. De Groot LJ. Dangerous dogmas in medicine. The non-thyroidal illness syndrome. J Clin Endocrinol Metab. Jan 1999;84(1):151-64.
7. Zargar AH, Ganie MA, Masoodi SR, Laway BA, Bashir MI, Wani AI, et al. Prevalence and pattern of sick euthyroid syndrome in acute and chronic non-thyroidal illness - its relationship with severity and outcome of the disorder. J Assoc Physicians India. 2004 Jan;52:27-31.

8. Caregarol L, Alberino F, Amodio PO, Merkel C, Angeli P, Pi Ebani M, et al. Nutritional and prognostic significance of hypothyroxinaemia in hospitalised patients with liver cirrhosis. *J Hepatol* 1998 Jan;28(1):115-21.
9. Maldonado LS, Murata GH, Hershman JM, Braunstein GD. Do thyroid function test independently predict the survival in the critically ill? *Thyroid* 1992;2(2):119-23.
10. Hamilton MA. Prevalence and clinical implications of abnormal thyroid hormone metabolism in advanced heart failure. *Ann Thorac Surg* 1993. 56 (1):548-52.
11. Masters PA, Simons RJ. Clinical use of sensitive assays for thyroid stimulating hormone. *J Gen Intern Med* 1996; 11:115.
12. Dillmann WH. The Thyroid. In: Bennett CJ, ed. Cecil text book of medicine. 20th ed. Philadelphia. W.B Saunders company.1996: 1231.
13. Kaptein EM. The effects of systemic illness on the thyroid hormone metabolism. In: Wu SY, ed. Thyroid hormone metabolism. Oxford Blackwell 1991; 211-37.
14. Friedman LS. Liver, biliary tract and pancreas. In: Tierney LM, Mc Phee SJ, Papadkas MA, eds. Current medical diagnosis and treatment. 39th ed. New York. Lange medical books/McGraw Hill 2000: 671-5.
15. Docter R, Krenning EP, de Jong M, Hennemann G. The sick euthyroid syndrome: changes in thyroid hormone serum parameters and hormone metabolism. *Clin Endocrinol (Oxf)*. Nov 1993;39 (5):499-518.



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