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# CLINICAL ANALYSIS ON ALTERATION OF THYROID HORMONE IN ACUTE STROKE PATIENTS AND ITS EFFECT ON CLINICAL OUTCOME

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## ABSTRACT
Background: Thyroid hormone has been found to be significantly altered in critically ill patients. Low T3 and low T4 level has been found to be associated with poor outcome in critically ill patients while elevation of TSH level has been shown to be associated with better outcome in stroke patients. Objective: To determine level of alteration of thyroid hormones in acute stroke patients and its short term effect on clinical outcome. Methodology: Patients without any history of thyroid hormone abnormality who presented with first episode of stroke within 72 hours were studied. Results: Low or low normal T3 (≤0.80 ng/ml) has been found to be the commonest abnormality (49.4% of patients). Patients with low T3 group and low TSH group (thyroid stimulating hormone) showed poor neurological presentation and worse clinical outcome whereas patients with high TSH group showed significantly low short term mortality (7 day mortality rate was 0%). Patients with high T3 and high T4 level in ischemic stroke group also showed poor neurological status at presentation and worse clinical outcome. Conclusion: It is suggested that thyroid hormones measurement after an acute stroke may be an important predictor of stroke outcome. If such a relationship between thyroid function and prognosis of stroke are demonstrated in a randomized controlled trial, thyroid function monitoring can be recommended in all acute stroke patients to optimize furthur treatment measures.

**KEYWORDS:** Alteration of thyroid hormone; acute stroke; clinical outcome.

## INTRODUCTION
Pituitary thyroid axis is significantly altered in patients with acute stroke. Low triiodothyronine (T3) level has been shown to be associated with increase in short term mortality in intensive care unit patients and increased long term mortality in patients with heart disease.[1-4] This is known as nonthyroidal illness syndrome (NTIS) or sick euthyroid syndrome. Abnormalities of thyroid function in NTIS have been classified as low T3 syndrome, low T3-low T4 syndrome, high T4 syndrome and other abnormalities.[5] The most common pattern is a decrease in T3 level with normal level of thyroxine (T4) and thyroid stimulating hormone (TSH).[2,6] This is known as low T3 syndrome. In more severe illness T3 and T4 level are reduced while TSH level does not show expected pituitary thyroid axis reactivity.[2,6] This is known as low T4 syndrome. Serum TSH in NTIS is typically normal or reduced and it is usually not less than 0.05 mU/mL.[6-10] Some patients are found with a TSH level above normal and elevation of TSH above normal commonly occurs if patients recover.[11-13] A decreases in serum T3 level without elevation of TSH level appears to be associated with increase in severity of stroke and worse clinical outcome.[14-16] Whereas an increase in TSH level has been described to be associated with better outcome in stroke patients in some studies.[17,18] The probable correlation between alteration of thyroid hormone and severity of stroke and its outcome needs furthur investigation. The objective of this study is to find out alteration of thyroid hormone level in stroke

patients and its short term effect (7 days) on outcome of stroke patients.

## MATERIAL AND METHODS

### Study population

Between January 2015 to March 2015, 170 patients admitted with acute stroke in Medicine department of Calcutta National Medical College and Hospital were studied. Blood sample were collected in the next morning following admission. Neurological status was monitored by glasgow coma scale from day 1 to day 7. Inclusion criteria were.

1. Any patient with no previous history of thyroid hormone abnormality presented with first ever stroke within 72 hours of symptom onset.
2. Age 18 years or older.

### Exclusion criteria

1. Age < 18 years.
2. Patients with previous abnormal thyroid function or on any medication related to it.
3. Patients with transient ischemic attack, past history of stroke.
4. Severe liver disease (eg. Liver cirrhosis)
5. Severe kidney disease (eg. Requiring dialysis)

### Assessment of T3, T4, TSH

Thyroid function was evaluated by measuring serum total T3, T4, and TSH. T3, T4 and TSH were measured by chemiluminescent microparticle immunoassay. Normal range in our laboratory for T3 is 0.77–1.35 ng/ml; normal range for T4 is 5.4–11.7µg/dl; normal range for TSH is 0.34–4.25 mIU/L. Total T3, T4, and TSH levels obtained in the morning following admission were collected.

### Assessment of other variables

Basic and clinical characteristics including demographic data such as sex, age, blood pressure, concurrent illness, medications related to thyroid disorder were collected. Fasting blood sugar, creatinine, lipid profile were simultaneously measured. eGFR (estimated glomerular filtration rate) was calculated using MDRD (Modification of Diet in Renal Disease) formula. Severity of stroke was assessed and monitored by glasgow coma scale (GCS) from day 1 to day 7 after admission.

### Statistical Analysis

The Statistical Package for Social Sciences (SPSS 16.0) was used for statistical analysis. Continuous data were presented as mean ± standard deviation. Chi-square test was used for testing of significance in case of discrete variables. Indepedent sample t test and bivariate correlation was used for continuous variables. The findings were considered significant if p value was <0.05.

## RESULTS

170 patients meeting the above inclusion and exclusion criteria were studied. 76 patients had hemorrhagic stroke and 94 patients had ischemic stroke. Table 1 shows baseline characteristic of the study population.

**Table: 1 Demographic characteristic of study population**

| Variable | Ischemic CVA group (n=94) | Hemorrhagic CVA group (n=76) | Total population (n=170) |
|---|---|---|---|
| Age | 60.5±11.9 | 55.2±12.5 | 58.1±12.4 |
| Male | 52 (55.3%) | 36 (47.4%) | 88 (51.8%) |
| SBP (mm. of Hg) | 142.8±22.5 | 151.6±20.1 | 146.7±21.8 |
| DBP(mm. of Hg) | 85.7±12 | 88.7±13.9 | 87±12.9 |
| Mortality | 10 (10.6%) | 14 (18.4%) | 24 (14.1%) |
| T3 level (ng/ml) | 0.85±0.2 | 0.91±0.26 | 0.88±0.2 |
| Low T3 population | 12 (12.8%) | 8 (10.5%) | 20 (11.8%) |
| High T3 population | 2 (2.1%) | 6 (7.9%) | 8 (4.7%). |
| T4 level (µg/dl) | 7.7±3.7 | 7.6±1.5 | 7.6±2.9 |
| Low T4 population | 20 (21.3%) | 4 (5.3%) | 24 (14.1%) |
| High T4 population | 8 (8.5%) | Nil | 8 (4.7%) |
| Low T3 and low T4 | 6 (6.4%) | Nil | 6 (3.5%) |
| TSH level (mIU/L) | 5.2±15.5 | 2.1±2.5 | 3.8±11.7 |
| Low TSH population | 6 (6.4%) | 6 (7.9%) | 12 (7.1%) |
| High TSH population | 16 (17%) | 8 (10.5%) | 24 (14.1%) |
| FBS (mg/dl) | 142.1±110 | 103.8±22.3 | 125±85.1 |
| eGFR (ml/min/1.73 $m^2$) | 61.7±19.9 | 69.4±19.7 | 65.2±20.1 |
| Cholesterol (mg/dl) | 189.4±49.3 | 200.2±53.4 | 194.2±51.3 |
| LDL-C (mg/dl) | 138.2±48.4 | 144.8±49 | 141.2±48.6 |
| Triglyceride (mg/dl) | 128.4±64 | 96.1±30.2 | 114±54 |

CVA- cerebrovascular accident, SBP- systolic blood pressure, DBP- diastolic blood pressure, GCS- glasgow coma scale, FBS- fasting blood sugar, eGFR- estimated glomerular filtration rate, LDL-C – low density lipoprotein cholesterol.

In hemorrhagic group patients were younger than ishemic group (p value 0.005), had higher systolic blood pressure (p value 0.009) on the day of admission, lower fasting blood sugar level (p value 0.003), higher eGFR value (p value 0.01) and tend to have a lower TSH value (p value 0.09) and a higher mortality rate (p value 0.15). Patients with low T3 group had significantly higher age group than patients with normal T3 group(p value <0.001).

Prevalence of low T3 was 11.8% in all stroke patients (12.8% in ischemic group, 10.5% in hemorrhagic group). However, T3 ≤0.80 ng/ml was found in 49.4% of all stroke patients (53.2% in iscemic group, 44.7% in hemorrhagic group). High T3 was found in 4.7% patients (2.1% in ischemic group, 7.9% in hemorrhagic group). Prevalence of low T4 was 14.1% (21.3% in ischemic group, 5.3% in hemorrhagic group) and that of high T4 was 4.7% (8.5% in ischemic group, 0% in hemorrhagic group). Low TSH was found in 7.1% patients (6.4% in ischemic group, 7.9% in hemorrhagic group) while high TSH was found in 14.1% patients (17% in ischemic group, 10.5% in hemorrhagic group). Low T3 and low T4 was found in 6.4% of ischemic group only.

Median GCS value was significantly low in low T3 (p value 0.008) and high T3 (p value <0.001) patients in day 1 compared to normal T3 patients. Significantly higher mortality rate was found in low T3 (20%) and high T3 patients (50%) compared to those subjects with normal T3 group (11.3%) (p value 0.007). Patients with low T3 who were alive had significantly lower median GCS at day 7 compared to normal T3 patients (p value 0.012). In hemorrhagic group GCS on day 1 was significantly lower in low T3 patients in day 1 (p value 0.018) and in high T3 group no statistically significant difference in GCS was found compared to normal T3 group (p value 0.52). Mortality rate was also higher in low T3 (25%) and high T3 patients (33.3%) compared to normal T3 patients (16.1%) but not statistically significant (p value 0.51). Low T3 patients who were alive had lower GCS at day 7 compared to normal T3 patients (p value 0.039). In ischemic group GCS on day 1 was significantly lower both in low T3 (p value 0.031) and high T3 group (p value 0.002) of patients compared to normal T3 patients. Mortality rate was higher in low T3 (16.7%) and high T3 group (100%) compared to those subjects with normal T3 group (7.5%) (p value <0.001). Patients with low T3 who were alive had lower GCS at day 7 compared to normal T3 patients (p value <0.001).

T4 level showed negative correlation with GCS value on day 1 (p value 0.01). Patients with high T4 had lower GCS on day 1 compared to normal T4 (p value <0.001) and higher mortality rate (50%) compared to those with normal T4 (15%) and low T4 (9.1%) (p value 0.01). Patients with high T4 who were alive had lower GCS on day 7 compared to normal T4 patients (0.016). In hemorrhagic group however no statistically significant values were found. In ischemic group T4 level also showed negative correlation with GCS value on day 1 (p value <0.001) and patients with high T4 had lower GCS on day 1 compared to normal T4 (p value 0.006). Higher mortality rate was found in high T4 patients (50%) compared to those with normal T4 (6.1%) and low T4 (10%) (p value 0.001). Patients with high T4 who were alive had lower GCS on day 7 compared to normal T4 patients (p value <0.001).

Low T3 and low T4 was found in 6 patients who had ischemic stroke and in these patients neither any significant difference in GCS on day 1 nor any significant difference in outcome was noted compared to other patients.

Patients who had low TSH had significantly low GCS on day 1 (p value <0.001) and higher mortality rate (66.7%) compared to normal TSH (11.9%) and high TSH (0%) patients (p value <0.001). Patients with low TSH who were alive at day 7 had no significant difference in GCS at day 7 compared to normal TSH patients (p value 0.68). In hemorrhagic group similar result was found i.e. low TSH patients had significantly low GCS on day 1 (p value 0.015) and higher mortality (66.7%) compared to normal TSH (16.1%) and high TSH (0%) patients (p value 0.003). In ischemic group also low TSH patients had significantly low GCS on day 1 (p value 0.016) and higher mortality (66.7%) compared to normal TSH (8.3%) and high TSH (0%) patients (p value <0.001).

7 days mortality rate in relation to T3, T4 and TSH value has been shown in bar diagram in figure 1, 2 and 3.

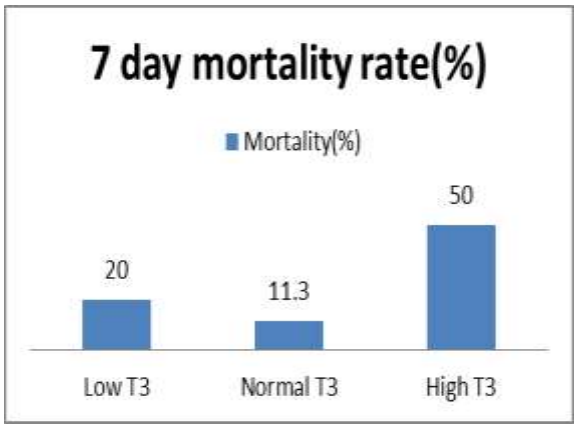


**Figure 1: 7 day mortality rate in relation to T3 level.**

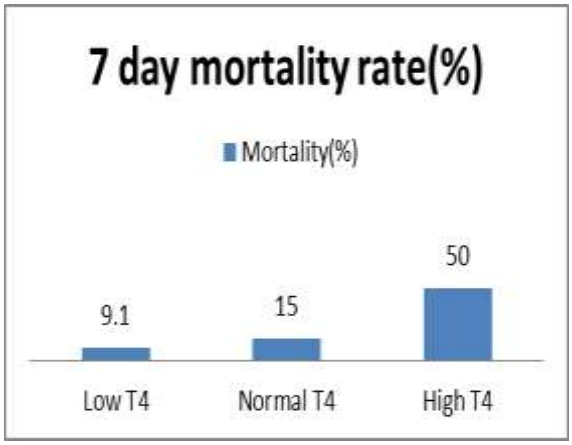


**Figure 2: 7 day mortality rate in relation to T4 level.**

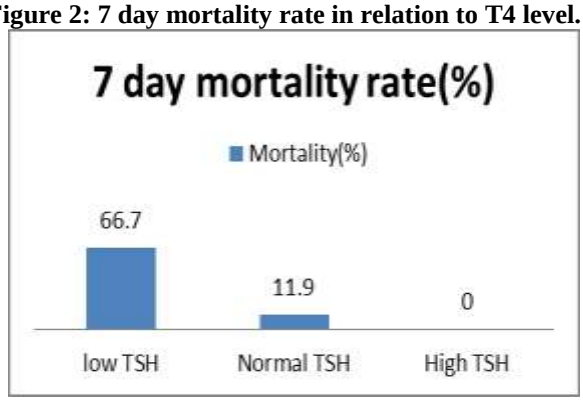


**Figure 3: 7 day mortality rate in relation to TSH level.**

## DISCUSSION

The most common abnormality of NTIS in intensive care unit patients is low T3.[5,16,19] Low T3 accompanying severe illness is considered to be an adaptive response to stress to spare energy as it can be induced in normal person by fasting.[1-4,6,19,20] A reduced level of T3 without elevation of TSH appears to be associated with worse neurological presentation and outcome in stroke patients.[14,15,16,21] A low serum T4 level is also associated with bad prognosis in critically ill patients.[22] Whereas an elevated TSH level has been found to be associated with a favourable outcome in stroke patients which might be due to endogeneous preconditioning, reduced adrenergic tone and hypometabolic state.[17,18] Possible mechanisms of alteration of thyroid hormone are as follows: (1) Carbohydrate deprivation appears to rapidly inhibit deiodination of T4 to T3 by type 1 iodothyronine deiodinase in the liver thus inhibiting the generation of T3 and preventing metabolism of rT3.[23] (2) Effects of proinflammatory cytokines, IL-12 and IL-18 may be involved in alteration of TSH level.[6] (3) A key factor in the fall in T4 level is altered binding to thyroxine binding globulin.[6] (4) Excessive glucocortoid release due to illness or use of corticosteroids, dopamine, anticonvulsants (eg. Phenytoin, carbamazepine) causes inhibition of hypothalamic-pituitary-thyroid axis.[24,25] It remains unresolved whether the hormone responses in NTIS represent part of an adaptive response, which lowers tissue energy requirements in the face of systemic illness or a maladaptive response, which induces damaging tissue hypothyroidism. Use of thyroid hormone therapy in the euthyroid sick syndrome is controversial with conflicting results from small number of trials.[3,26,27]

In our study low or low normal T3 level (≤0.80 ng/ml) was found to be the commonest abnormality (49.4% of patients). Patients with low T3 group showed poor neurological presentation at onset and increased mortality and poor neurological recovery. In patients with ischemic stroke high T3 group showed poor neurological presentation and increased mortality rate. Patients with low TSH group showed poor neurological presentation at onset and increased mortality. In patients with ischemic stroke T4 level showed significant negative correlation with neurological status at presentation and patients with high T4 level showed poor neurological outcome in terms of mortality and recovery. Patients with high TSH group showed a very low mortality rate (0%). Higher age group was found in low T3 group which was consistent with previous studies.[15,16]

## CONCLUSION

In conclusion alteration of thyroid hormone is commonly seen in acute stroke patients and most common presentation is a low or low normal level of T3. Low T3, low TSH in all patients and high T3 and high T4 level in ischemic stroke patients appear to be associated with poor presentation and poor predictor of stroke outcome. Furthur studies involving large number of subjects with longer period of follow up are necessary to recommend assessment of thyroid function test in post stroke patients for monitoring their outcome.

## CONFLICT OF INTERESTS

The authors have no conflict of interests to disclose.

## REFERENCES

1. I. J. Chopra. Euthyroid sick syndrome: is it a misnomer? Journal of Clinical Endocrinology and Metabolism, 1997; 82(2): 329–34.
2. L. J. De Groot. Dangerous dogmas in medicine: the nonthyroidal illness syndrome. Journal of Clinical Endocrinology and Metabolism, 1999; 84(1): 151–64.
3. B. McIver and C. A. Gorman. Euthyroid sick syndrome: an overview. Thyroid, 1997; 7(1): 125–32.
4. G. Van den Berghe, F. De Zegher, and R. Bouillon. Acute and prolonged critical illness as different neuroendocrine paradigms. Journal of Clinical Endocrinology and Metabolism, 1998; 83(6): 1827-34.
5. Chopra IJ, Hershman JM, Pardridge WM, Nicoloff JT. Thyroid function in nonthyroidal illness. Ann Intern Med. 1983; 98: 946 –57.
6. J. L. Jameson and A. P. Weetman. Disorders of the thyroid gland. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J (eds.).

Harrison's principles of internal medicine. 18th Ed., New York; McGraw Hill, 2012; 2911–39.
7. Surks MI, Hupart KH, Pan C, Shapiro LE. Normal free thyroxine in critical nonthyroidal illnesses measured by ultrafiltration of undiluted serum and equilibrium dialysis. J Clin Endocrinol Metab, 1988; 67: 1031–9.
8. Melmed S, Geola FL, Reed AW, Pekary AE, Park J, Hershman JM. A comparison of methods for assessing thyroid function in nonthyroidal illness. J Clin Endocrinol Metab, 1982; 54: 300–6.
9. Chopra IJ, Solomon DH, Hepner GW, Morgenstein AA. Misleadingly low free thyroxine index and usefulness of reverse triiodothyronine measurement in nonthyroidal illnesses. Ann Intern Med., 1979; 90: 905–12.
10. Chopra IJ, Taing P, Mikus L. Direct determination of free triiodothyronine (T3) in undiluted serum by equilibrium dialysis/radioimmunoassay. Thyroid, 1996; 6: 255–9.
11. 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), 1993; 39: 499 – 518.
12. Bacci V, Schussler GC, Kaplan TB. The relationship between serum triiodothyronine and thyrotropin during systemic illness. J Clin Endocrinol Metab, 1982; 54: 1229 –35.
13. Brent GA, Hershman JM. Thyroxine therapy in patients with severe nonthyroidal illnesses and lower serum thyroxine concentration. J Clin Endocrinol Metab, 1986; 63: 1–8.
14. S. Hama, T. Kitaoka, M. Shigenobu et al. Malnutrition and nonthyroidal illness syndrome after stroke. Metabolism: Clinical and Experimental, 2005; 54(6): 699–704.
15. M. Alevizaki, M. Synetou, K. Xynos, T. Pappa, and K. N. Vemmos. Low triiodothyronine: a strong predictor of outcome in acute stroke patients. European Journal of Clinical Investigation, 2007; 37(8): 651–7.
16. Zhang Y, Meyer MA. Clinical analysis on alteration of thyroid hormones in the serum of patients with acute ischemic stroke. Stroke Res Treat, 2010; 2010: 290678.
17. Alevizaki M, Synetou M, Xynos K, Alevizaki CC, Vemmos KN. Hypothyroidism as a protective factor in acute stroke patients. Clin Endocrinol (Oxf), 2006; 65(3): 369-72.
18. Akhoundi FH, Ghorbani A, Soltani A, Meysamie A. Favorable functional outcomes in acute ischemic stroke patients with subclinical hypothyroidism. Neurology, 2011; 77(4): 349-54.
19. J. N. Carter, C. J. Eastman, J. M. Corcoran, and L. Lazarus. Effect of severe, chronic illness on thyroid function. The Lancet, 1974; 304(7887): 971–4.
20. P. M. Rothwell and P. G. Lawler. Prediction of outcome in intensive care patients using endocrine parameters. Critical Care Medicine, 1995; 23(1): 78–83.
21. A. Squizzato, V. E. A. Gerdes, D. P.M. Brandjes, H. R. B¨uller, and J. Stam. Thyroid diseases and cerebrovascular disease. Stroke, 2005; 36(10): 2302–10.
22. Slag MF, Morley JE, Elson MK, Crowson TW, Nettle FQ, Shafer RB. Hypothyroxinemia in critically ill patients as a predictor of high mortality. JAMA, 1981; 245: 43– 5.
23. Harris ARC, Fang SL, Vagenakis AG, Braverman LE. Effect of starvation, nutriment replacement, and hypothyroidism on in vitro hepatic T4 to T3 conversion in the rat. Metabolism, 1978; 27: 1680 – 90.
24. J. Faber, C. Kirkegaard, and B. Rasmussen. Pituitary-thyroid axis in critical illness. Journal of Clinical Endocrinology and Metabolism, 1987; 65(2): 315–20.
25. Spencer CA, Eigen A, Shen D, et al. Specificity of sensitive assays of thyrotropin (TSH) used to screen for thyroid disease in hospitalized patients. Clin Chem, 1987; 33: 1391–6.
26. N. Stathatos, C. Levetan, K. D. Burman, and L. Wartofsky. The controversy of the treatment of critically ill patients with thyroid hormone. Best Practice and Research: Clinical Endocrinology and Metabolism, 2001; 15(4): 465–77.
27. Y. Hiroi, H.-H. Kim, H. Ying et al. Rapid nongenomic actions of thyroid hormone. Proceedings of the National Academy of Sciences of the United States of America, 2006; 103(38): 14104–9.