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Thyroid Profile in Patients Admitted with Ischemic Stroke: A Longitudinal Hospital Based Study

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ABSTRACT

Stroke is one of the major causes of morbidity and is the fifth important cause of mortality in the United States. The thyroid hormone level plays as an independent contributing factor for severity and functional outcome in patients of stroke. This study will help in understanding the correlation between the thyroid hormone levels and stroke outcome, which will have a greater impact in reducing morbidity and mortality in stroke patients. Our aim was to study the correlation between baseline thyroid function profile at the time of admission and on follow up days during hospital stay, with the outcome of ischemic stroke in form of functional disabilities and mortality in acute ischemic stroke. This was a longitudinal cohort study, conducted from June 2018-May 2020 at the Department of Medicine, SCB Medical College, Cuttack.100 patients were enrolled with diagnosis of ischemic stroke and thyroid functions were measured at the time of admission, in hospitalisation and on follow up. Functional outcome using Modified rankin scale(MRS) were calculated. Correlation between thyroid status and stroke outcome in terms of functional disabilities were studied with the use of Study specific risk ratios. Low T3 levels were found in 55 number of patients in our study populations. Low T3 syndrome was associated with poor modified Rankin scale scores at 7day,1 and 3 months (odds ratio [OR] 0.023), 95% confidence interval [CI] 0.003-0.177, P=.00 and OR 0.041, 95% CI 0.014-0.177, P=.00 and OR 0.081,[CI] 0.031-0.214,P=0.00, respectively). Poor outcome measured through MRS, was found in acute ischemic stroke patients having low T3 levels. This complex association needs a prospective and interventional study keeping in mind the role of correction of thyroid profile in acute ischemic stroke to improve the mortality and functional outcome.

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Key Words
Ischemic stroke, low T3 syndrome, stroke outcome, thyroid function test

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INTRODUCTION

Stroke affects 15 million people every year all over world, which is the second leading cause of death in people above the age of 60 year and is also the fifth cause of death in the age group of 15-59years[1]. It ranks as the fourth most common cause of death after heart disease, cancer and chronic respiratory disease. India like other countries is in the midst of stroke epidemic. it is one of the leading causes of death and disability in India. The changes in lifestyle, smoking and accompanying urbanization are considered to be the factors for rise in burden of stroke[2].The average life expectancy has gone up from 41.2 years in 1951-1961 to 61.4-68.7 years in 2012-16 in India. The Metabolic Syndrome (MS), consisting of central obesity, high levels of triglyceride and low HDL cholesterol with or without glucose intolerance, is considered to be genetically linked with stroke in India[3].

Hypothalamic-pituitary axis is significantly deranged in patients of ischemic stroke . There are various reports which indicate that low T3 syndrome is an indicator of poor prognosis for patient with cerebral infarction[4]. The worse clinical outcome in ischemic stroke appears to be associated with low T3. Whether the prognosis is more dire in patients of acute ischemic stroke than those with same disease but without low T3 syndrome remains unknown. The role of thyroid hormone in acute ischemic stroke has been controversial as per various several studies in the past because of other component of risk factors modifying the stroke severity[1,5].

Better survival after acute stroke is also found usinghigher cutoff value for the median T3 level in one study. However, the association was not confirmed by other studies[5,6]. Therefore, it is not clear, whether in ischemic stroke patients lower T3 levels especially within the normal range on hospital admission, provide valuable prognostic information or not[6,7]. A better understanding of this prognostic information might be useful for risk stratification of ischemic stroke patients. The basic aim of our Study was to find out the association of any alteration in thyroid hormone levels in patient of acute ischemic stroke and its relation with functional outcome.

MATERIALS AND METHODS

The study was an longitudinal cohort study conducted in PG Department of Medicine, SCB Medical College, Cuttack from June 2018-May 2020. With due institutional ethical committee clearance vide IEC no-27/7.2.2020, a total 100 patients were enrolled in the study, all of whom were radiologically confirmed Ischemic stroke patients who presented to hospital within 07 days of occurrence of stroke.

Inclusion Criteria:

- Those who had thyroid function profile (abnormal or normal) at the time of admission or within two days of admission along with ischemic stroke (embolic, thrombotic, or stenosis) or
- Those admitted within 7 days of onset of stroke or
- Those with a corresponding ischemic lesion on Magnetic Resonance Imaging (MRI) or Computed Tomography scan (CT).

Exclusion Criteria:

- Those with overt thyroid disease or taking medications that could alter thyroid function test (TFT) (eg, levothyroxine, lithium, Amiodarone, etc) at the time of admission.
- Those admitted after 7 days of stroke occurrence
- Those with hemorrhagic lesions on CT or MRI.

Sample Collection:

Patients were first evaluated clinically with detailed history and thorough clinical examination with baseline characteristics including demographic data. Radiological modalities like NCCT /CECT or MRI of brain was used for diagnosis of stroke.

Thyroid function was evaluated by measuring serum Free T3(F T3),Free T4(F T4) and Thyroid Stimulating Hormone(TSH).Thyroid functions were evaluated by chemiluminescence Enzyme immunoassay. (CLEIA)

Normal range of hormones is[2]

TSH	0.27-4.2micro IU/ml
Free T3	3.1-6.8 pg/ml
Free T4	12-22 ng/dl

Blood sample for assessment of thyroid profile was drawn within 24 hours of presentation.

The patients were divided into five categories on the basis of thyroid profile.

Non Thyroidal illness Syndrome (NTIS)/ Sick Euthyroid Syndrome was diagnosed as Low FT3 , low or normal FT4 and low or normal TSH1[3].

Low T3 Syndrome was diagnosed as Low FT3,with normal TSH and FT4 levels[3,5].

Euthyroid was diagnosed as normal FT3, FT4 and TSH[6,7].

Subclinical Hypothyroidism was diagnosed as normal FT3, normal FT4 and high TSH[8,9].

Hyperthyroidism was diagnosed as low TSH with or without high FT4 and FT3[10]

hypothyroidism was diagnosed as high TSH with low FT4 and normal FT3[10].

Functional outcome of the patient in this study was evaluated by using MRS on7th, 30th and 90th day of stroke occurrence. On the basis of this scale, patients were divided into two groups i.e. Poor functional outcome (MRS>2) and good functional outcome (MRS<2).MRS[12].

MRS scale is a commonly used for assessing the degree of disability or dependence in the daily activities of people who have suffered a stroke or other causes of neurologically disability[11,12]. The scale runs from 0-6, running from perfect health without symptoms to death.

- No symptoms,
- No significant disability.
- Mild disability.
- Moderate disability. Requires some help, but able to walk unassisted.
- Moderately sever disability. Unable to walk unassisted.
- Sever disability. Bedridden.
- Dead

RESULTS AND DISCUSSIONS

The mean age of study population was 62.31±12.81 years with maximum age of 85 years and minimum age of 27 years in the study population. Out of the 100 subjects, 49 were female and 51 were male suggesting ischemic stroke was more in male (51%) as compared to female (49%) and male to female ratio was 1.04:1[Table- 1]. Out of 100 patients enrolled in the study group maximum number of patient i.e. 28% were found in 70-79 years age group.

Table-02 represents risk factors in various age groups and their p value was calculated using chi square test. Hypertension (HTN) was more signicant risk factors,found in 58% of study population.Diabetes were found in 32% whereas dyslipidemia were 21% in study group. But nondiabetic and non dyslipidemic patients contribute 68% amd 79% of the stroke patients respectively.

Table-03 illustrated that 68.6% (35) of males and 40.8%(20) of females were in low T3 group.44.9% of females were in euthyroid group of study population.

Table-04 represented that the patients with low T3 level were in 62.67±13.66 years of age with 63.8%(37) of males. Risk factor like Hypertension (HTN) was associated 37(63.8%) with low T3 Group. Patients with low T3 Group of stroke patients were having poor functional outcome in MRS<2 on 7TH ,30TH and 90TH day were 5(8.6%),11(19%) and 16(27.6%) respectively. NB-15 patients also died during follow up. Chi square test was used for calculating p value.

NB: T test was used for calculating P value. FT3 value was low i.e.2.25+-1.35 of MRS >2 in 76 patients.

NB., T test was used for calculating p value. FT3 value were low 1.69 of MRS >2 in 39 patients on30th days of functional outcome.

Table-06,07,08 Represents the correlation of FT3,FT4 and TSH value with functional outcome on 7th,30th,90th days of stroke occurance. FT3 value was low i.e.2.25+-1.35 of MRS >2 in 76 patients on 7th days, but FT3 value were low 1.69 and 1.60 of MRS >2 in 39 and 27 patients on 30th and 90th days of functional outcome. Anova Test was used for establishing the association between thyroid parameters and outcome.

Table 9 shows that there is significant correlation between MRS scores and FT3 level in patients at admission and 7th, 30th, 90th day of discharge.

Table-10 showed that the TSH value was not significantly associated with functional outcome on these days.

In the present study, Ischemic stroke was more among patients of age above 55 years with gender distribution of male to female ratio being 1.02:1, is consistent with Dorr[13] study, where risk of stroke in patients older than 55 years was high and there was no difference between males and female population (p=0.01)[2]. The occurrence of stroke were more in hypertensive patients as compared to non-hypertensive as that of Lewington[14].This above fact can be explained as hypertension is associated with atherosclerosis. The magnitude of Diabetes mellitus as a risk factor for stroke varies widely between studies. R chen *et al* study showed the similar risk magnitude for Diabetes mellitus associated with stroke as in this study[15].

In the present study cohort, no significant statistical relationship was found between age and thyroid hormones (P>0.05).There was no significant difference in risk varies between male and female with TSH, FT3, FT4 levels. These findings were consistent with O Keffe et al study[16].

Out of the 100 patients analysed in this study 66 patients (66%) were found to have abnormal thyroid function test with alteration in atleast one of the thyroid hormones. Only 34 patients (34%) had thyroid hormones within normal range and these patients were included in final analysis of the study.

The cohort was divided into two groups i.e. low T3group and normal T3 group and distribution of risk factors in them were studied. There was no statistical significance between age, gender and vascular risk factors among these two groups. Zhang and Meyer et al6 study observed that the patients with low T3 were older than those with normal T3 levels. However Alverzaki[5] in their study revealed that patients categorized under low T3 group were significantly older. This may be due to the fact that elderly patients usually had low base line thyroid hormone levels which tends to be overt by the stressful events such as stroke.

The median of MRS at 7th ,30th and 90th day of discharge in low T3 were 3,3 and 3 whereas 2,2 and 2 in normal T3 level respectively which were statistically significant (p<0.05). This finding suggested that Low T3 group had higher MRS, so have poor functional outcome, consistent with Zhang *et al* study[6].

Table 1. Age and gender distribution

Age (In years)	Male	Female	Total
<49	8	7	15
50-59	11	10	21
60-69	12	15	27
70-79	13	15	28
>80	7	2	9
Total	51	49	100

Table 2: Distribution of risk factor according to age group

Age (years)	<49	50-59	60-69	70-79	>80	total	pvalue(x2)	Test of significance
Hypertension	HTN	5	18	16	13	6	58	<0.05
	Non HTN	10	3	11	15	3	42	<0.05
Diabetes	diabetes	2	14	6	6	4	32	<0.05
	non DM	13	7	21	22	5	68	<0.05
Dyslipidemia	dyslipid	1	3	6	7	4	21	<0.05
	non dys	14	18	21	21	5	79	<0.05

Table 3: Distribution of thyroid status in study at time of admission

Sex	Euthyroid	Hypo Thyroid	Hyper Thyroid	Low T3	Sub Clinical	Total
Female	22	0	2	20	5	49
%within sex	44.9%	0.0%	4.1%	40.8%	10.2%	100%
Male	12	1	2	35	1	51
%within sex	23.5%	2%	3.9%	68.6%	2%	100%
Total	34	1	4	55	6	100
%within sex	34%	1%	4%	55%	6%	100%

Table 4: Clinicosocial characteristics of acute ischemic stroke patients with low t3 and normal t3 values

Clinical variables	low t3 group (N=55)	Normal t3 (N=42)	p- value(t test)
Age(years)	62.67±13.66	61.81±11.68	.167
Sex(% male)	37(63.8%)	14(33.3%)	.169
History of htn	37(63.8%)	21(50%)	1.902
Diabetes	18(31%)	14(33.3%)	.059
Dyslipidemia	15(25.9%)	6(14.3%)	1.968
TSH	1.59±1.14	3.40±8.31	.019
FT3	1.60±0.72	4.57±0.70	.916
FT4	5.44±5.81	16.47±3.44	.001

Table 5:Distribution of modified rankin scale accorting to thyroid status at the time of admission and outcome observed on 7th,30th and 90th day of discharge.

Thyroid pattern	MRS score at 7th day of discharge(100)			MRS score at 30th day of discharge			MRS score at 90th day of discharge		
	<2	>2	p value	<2	>2	p value	<2	>2	p value
Low t3 syndrome(55)	5	50		10	45		14	27	
Euthyroid(34)	17	17	<0.05	31	3	<0.05	33	1	<0.05
Hypothyroid(1)	1	0		1	0		1	0	
Hyperthyroid(4)	1	3		2	2		2	1	
Sch(6)	5	1		6	0		6	0	
Total	29	71		50	50		56	29	

Table 6: Association of FT3, FT4 and TSH with functional out come on 7th day(fun-7)

Fun-7	MRS<2 (N=24)	MRS>2 (N=76)	p-value t=
FT4	16.39±4.08	8.08±7.05	<0.05
TSH	4.60±10.66	1.65±1.67	<0.05
FT3	4.75±0.73	2.25±1.35	<0.05

Table 7: Correlation of FT3,FT4 AND TSH with function out come on 30TH DAY(FUN-30)

FUN-30	MRS<2 (n=46)	MRS>2 (n=39)	Death (15)	p-value
FT4	14.66±6.01	6.17±6.07	7.92±5.66	<0.05
TSH	3.15±7.97	1.68±1.14	1.73±1.13	<0.05
FT3	4.20±1.14	1.69±0.95	1.22±0.61	<0.05

Table 8: Correlation of FT3,FT4 AND TSH with functional out come on 90TH day(fun-90)

FUN-90	MRS<2 n=56	MRS>2 n=27	Death (2)	p-value (anova test)
FT4	12.91±7.08	5.70±6.23	12.58±9.79	<0.05
TSH	2.83±7.25	1.75±1.22	2.49±1.56	<0.05
FT3	3.93±1.27	1.60±0.82	0.63±0.48	<0.05

Table 9.Correlation between FT3 values on admission and mRS-7 scores.

mRS-7		mRS-7	FT3
	Pearson correlation	1	-0.765
	Sig.(2-tailed)		0.000
	N	100	100
mRS-30		mRS-30	FT3-P
	Pearson correlation	1	-0.594**
	Sig.(2-tailed)		0.000
	N	100	100
mRS-90		mRS-90	FT3-P
	Pearson correlation	1	-0.649**
	Sig.(2-tailed)		0.000
	N	85	85

Table 10: Association of FT3, FT4 and TSH with fun-7, fun-30 and fun-90

	TSH OR (95%CI), P	FT3 OR (95%CI)	TFT4 OR (95%CI)
7TH day out come MRS<2 VS MRS>2 OR Death	0	2.33 (1.646-3.309)	0.023 (0.003-0.177) P<0.05
30TH day out come MRS<2 VS MRS>2 OR Death	0	0.011 (0.003-0.043)	0.041 (0.014-0.177) P<0.05
90TH day out come MRS<2 VS MRS>2 OR Death	0	0.009 (0.001-0.067)	0.081 (0.031-0.214) P<0.05S

In our study we observed that Lower FT3 concentration (odd ratio OR=2.33, 95% confidence interval, p<0.05) remained independently associated with poor functional outcome.(Table-11). This finding indicates worsening of neurological deficit to be related to the degree of decrease in FT3 level.

Thus monitoring of FT3 levels could potentially serve as an easy,quick and prognostic parameter in ischemic stroke for clinicians if confirmed by other studies.This finding was consistent with Zhang[6] and Rothell and Lawler study[17].

Pande[18] in their study,analyzed thyroid dysfunction in ischemic cerebrovascular accidents and reported a negative correlation between FT3 levels and SSS scores and GCS scores on admission among all patients.

The observations in this study were similar to study by Alvezaki[5] which stated that low T3 can be a possible independent predictor for stroke outcome. Table7,8,9 in our study revealed that patients with poor functional outcome (MRS>2) in 7th, 30th and 90th day on follow up had FT3 level of 2.25±1.35 (p<0.05), 1.69±0.95 (p<0.05) and 1.47±0.77 (p<0.05) suggesting poor functional outcome to be associated with Low T3 level. These findings are consistent with Xu and his colleagues.8There was significant negative correlation between FT3 levels at admission and MRS scores on 7th day of discharge (n=100, r=-0.765, p=0.000, 95% Confidence Interval) among all the patients. Poor functional outcome (MRS>2) (n=45, p<0.05) belongs to Low T3 group. Poor functional outcome (MRS>2) and Death (MRS=6) observed in Low T3 group in study population is consistent with pande et al study[18].

During follow up in 90th day we lost 15 patients, as they had died during 30th day of follow up. It was revealed that in this study at 90th day of discharge, out of 85 patients, 56 patients (65.88%) had good functional outcome (MRS<2) and 29 patients (34.11%) had poor functional outcome (MRS>2). Among these patients with poor functional outcome, 02 patients had MRS score of 6 (Death) and they belong to Low T3 Syndrome group. Although levels of TSH and FT4 were not decreased but they were on the lower side of normal range of these hormones. These findings are consistent with findings reported by Xu and his colleagues[8] and was similar to 7Th and 30th day functional outcome. From this study, it was evident that patients with low T3 levels, MRS functional outcome of stroke found out to be poor. Morbidity and mortality in these patients group were more in comparision to patients of normal lebels of thyroid hormone., FT3 Hormone.

Limitation of the Study: As the sample size was less, better inference can be drawn by multiple studies at different places with adequate number of cases.

CONCLUSION

This study concludes that there was alteration in levels of thyroid hormones in patients with acute ischemic stroke. Low T3 level is a predictor of severity and poor functional outcome in acute ischemic stroke. However, the knowledge of Hypothalamic-pituitary-thyroid axis, various factors governing thyroid hormone action at the cellular level and interpretation of different levels in thyroid function test may be beneficial in management of patients with ischemic stroke. Studies involving larger number of patients in future will throw more light in this aspect of Low T3 syndrome for being an independent risk factor for poor functional outcome in ischemic stroke. Prognosis to some extent can be predicted by estimation of thyroid hormone i.e T3 at the time of admission in patient of stroke.

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