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RESEARCH ARTICLE

THYROID HORMONE ABNORMALITY IN PATIENTS WITH ACUTE STROKE- A HOSPITAL BASED CASE CONTROL STUDY

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Abstract

INTRODUCTION: Stroke or Cerebrovascular accident (CVA) is a major cause of disability worldwide. The estimation of serum Total T3, Total T4 and TSH are very much essential in patients with stroke. Any disturbances in thyroid hormones may have negative influence on the outcome of acute phase of strokes.

AIMS AND OBJECTIVES: Aims and objective was to estimate the Total T3, Total T4 and TSH of patients with acute Stroke and to compare it with age/sex matched healthy controls.

MATERIALS & METHODS: This Hospital Based Case Control Study, consist of total 100 subjects out of which 50 were control ,was carried out in Jorhat Medical College & Hospital, Assam for a period of one year, from July 2017 to June 2018. Age more than 40 years of both sexes was included. Estimation for total T3, total T4, and TSH was carried out in Access 2 ImmunoAssay Systems (Beckman Coulter). Cases were selected randomly .

RESULTS AND OBSERVATIONS: Out of 50 Stroke patients ,the age group of 50 - <60 years constituted the majority of cases(32%) . Greater preponderance of stroke was seen in males (62%) with male to female ratio of 1.63:1. Hemorrhagic stroke was found to be more common than ischemic stroke (54% V/s 46%). Hemorrhagic strokes occurred more in early age than ischemic strokes. The mean ± SD of serum Total T3 levels in stroke patients and controls were 0.960 ± 0.327 and 1.248 ± 0.269 respectively, with statistically significant mean value difference ($p<0.05$) when cases were compared to the controls. A greater number of low T3 was present in ischemic strokes (43.5%) when compared to hemorrhagic strokes (18.5%).

CONCLUTION:. Nonthyroidal illness syndrome (Low T3 syndrome) is observed in the present study with decreased T3 values without alteration of T4 and TSH levels. Further studies with a large sample size should attempt to investigate whether treatment of low T3 syndrome can improve the final outcome.

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INTRODUCTION

Cerebrovascular accident (Stroke) is defined by WHO as "rapidly developing clinical symptoms and signs of focal (at times global) disturbances of cerebral function, lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin" [1]. Due to the consequent high mortality and morbidity rates, stroke has become a major community health problem worldwide and it is the third leading cause of death and long-term morbidity in developed and developing countries [2].Annually, 15 million people worldwide suffer a stroke. Of these, 5 million die and another 5 million are left permanently disabled, placing a burden on family and community [3].Like all developing countries, stroke is fast emerging as a major public health problem in India. Recent community surveys from many regions of India show a crude prevalence rate for stroke presumed to be of vascular origin in the range of 136/100,000 persons (0.136%) [4]. In 2001 it was estimated that cerebrovascular diseases (stroke) accounted for 5.5 million deaths worldwide, equivalent to 9.6 % of all deaths. Two-third of these deaths occurred in people living in developing countries and 40% of the subjects were aged less than 70 years [5].

Conditions such as hypertension, atherosclerosis, diabetes mellitus, and thyroid dysfunction are identified major risk factors in the etiology of stroke. It is not known till date at what extent each one of these risk factors contribute to the pathophysiology of stroke. Neuroendocrine profile is significantly altered in acute stroke; low triiodothyronine (T3) has been associated with increased short-term mortality in intensive care unit patients. Thyroid hormones, mainly consisting of triiodothyronine (T3) and thyroxine (T4) have an irreplaceable role in the development, differentiation and maturation processes of brain tissue A reduction of serum T3 without elevation of thyroid-stimulating hormone appears to be associated with the severity of stroke and a worse clinical outcome.

Keeping in view the above-mentioned observations the present study was undertaken in Jorhat Medical College & Hospital, Jorhat, Assam covering patients from various socio-economic background and ethnic groups with the following aims and objective.

AIMS & OBJECTIVES:

- To estimate the Total T3, Total T4 and TSH in patients diagnosed as Cerebrovascular accidents (Stroke) admitted in JMCH, Jorhat, Assam
- To compare with age/sex matched healthy controls.

MATERIALS & METHODS:

The study was carried out in Jorhat Medical College & Hospital for a period of one year, from July 2017 to June 2018.

Type of study: Hospital Based Case Control Study.

Selection of cases: Random selection.

Sample size: Calculation of right sample size is one of the most important parts for generation of authentic data by performing research works. So to calculate the desired sample size to carry out the present study Epi tools online calculator [10] was used by considering the data of prevalence of stroke in India, which was taken 136/100000 [4]. The sample size was found to be:

No. of cases -50(Fifty) & No. of controls -50(Fifty)

Criteria for selection of study population:

The study was carried out among the patients who attended the medicine OPD as well as emergency service of Jorhat Medical College & Hospital, Jorhat and admitted in the medicine ward as patients of stroke. An informed consent for participating in the study was recorded.

INCLUSION CRITERIA: CASES:

1.Patients diagnosed as cerebrovascular accident (stroke) after performing CT scan and/or MRI of brain.

2. Age 40 years and above.

3. Both male and female sexes

EXCLUSION CRITERIA:

1.Patients with history of fever, renal failure, diabetes mellitus, known thyroid disorder, hepatic cirrhosis, malignancy and psychological abnormality (other acute or chronic illness, other lesions except hemorrhage/ischemia, subarachnoid hemorrhage).

3.Patients with history of head injury.

4.Patients with past history of cerebrovascular accident.

CONTROLS: Age and sex matched healthy controls without any history of cerebrovascular accident.

ETHICAL CLEARANCE:

Permission/clearance from the Institutional Human Ethics Committee, Jorhat Medical College was obtained prior to commencement of the study.

SAMPLE COLLECTION, TRANSPORT AND PROCESSING:

Under all aseptic and antiseptic conditions, 5cc of venous blood was collected from a suitable peripheral vein (preferably antecubital vein) by venepuncture using a sterile disposable syringe in a clot vial. All samples were collected and transported to the laboratory within 2 hours in stoppered containers to avoid contamination and evaporation. For transporting specimen, cold boxes were used so as to avoid fluctuation of temperature and processed according to existing standard laboratory guidelines. The samples were then allowed to clot and later centrifuged at 3000 rpm for 3-5 minutes. Serum was separated and further analysis was done in the Biochemistry wing of Central Clinical Laboratory, JMCH. Estimation was carried out in Access 2 Immunoassay Systems (Beckman Coulter) for total T3, total T4, TSH.

RESULTS & OBSERVATIONS:

The study was conducted on 50 cerebrovascular accident patients and 50 controls. The cases and controls were age and sex matched. The results were compared with controls.

Table 1: Total distribution of study population

Total number of study population	Cases	Controls
100	50	50

It was seen that total number of cases were 50 and total number of controls were 50.

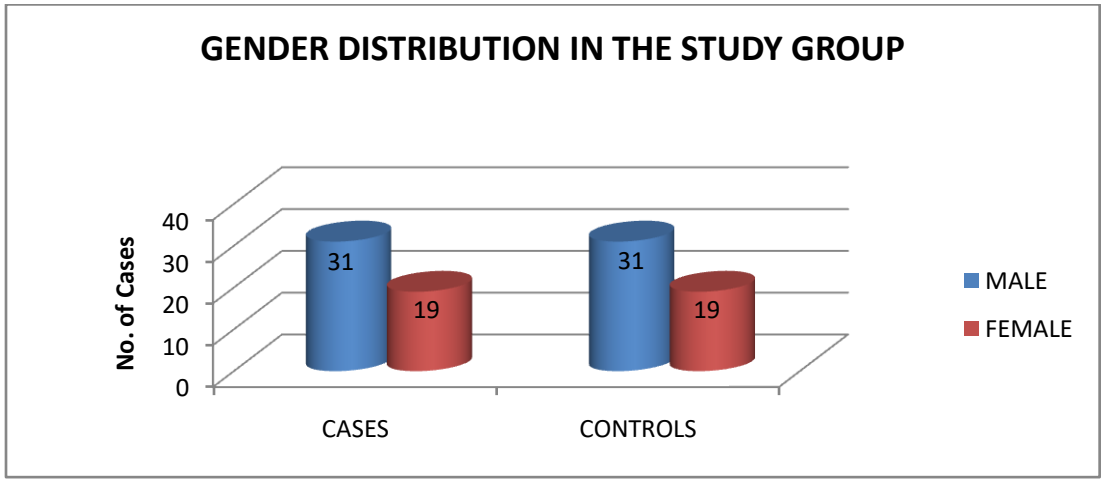
Table 2: Distribution of study population according to age

Age (years)	Case	Control	Percentage
40 - <50	9	9	18 %
50 - <60	16	16	32 %
60 - <70	15	15	30 %
≥70	10	10	20 %

Total	50	50	100 %

As presented in the table the study group was between 40 - ≥70 years and it was further subdivided into four age groups. Those were 40 - < 50, 50 - < 60, 60 - < 70 and ≥ 70. The age group between 50 - < 60 showed the highest number of cases with 16 (32%) of the total study population followed by 60 - < 70 showed 15 (30%) and the least number of cases were observed in the age group between 40 - < 50 showing 9(18%) cases.

Fig 1: Bar diagram showing the distribution of study population according to sex

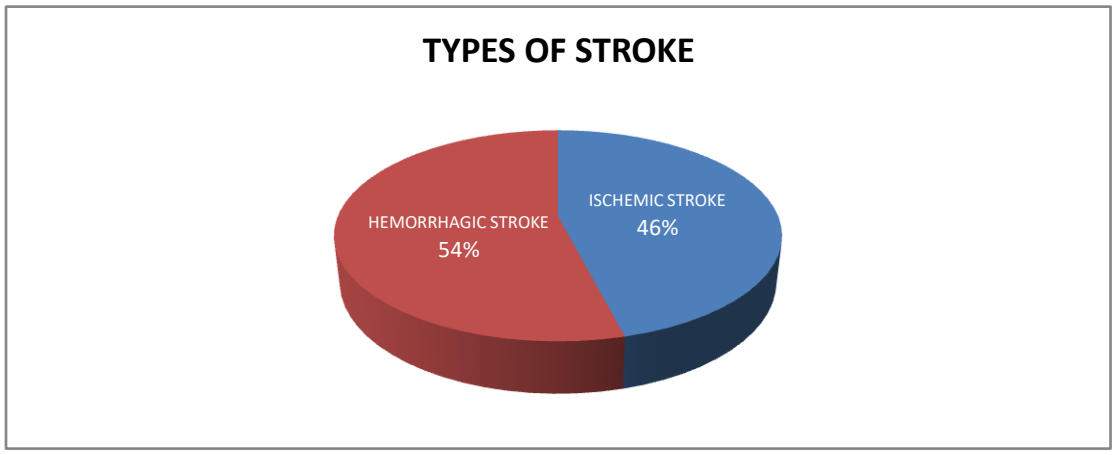


As represented by the above figure; amongst the 50 cases, 31 patients (62%) were male and 19 patients (38%) were female, with male: female ratio of 1.63:1.

Table 3: Distribution of Stroke According to Age

AGE	HEMORRHAGIC	ISCHEMIC
40 - < 50	05	04
50 - < 60	08	08
60 - < 70	08	07
≥70	06	04
TOTAL	27	23

Fig. 2: Pie diagram showing distribution of types of stroke



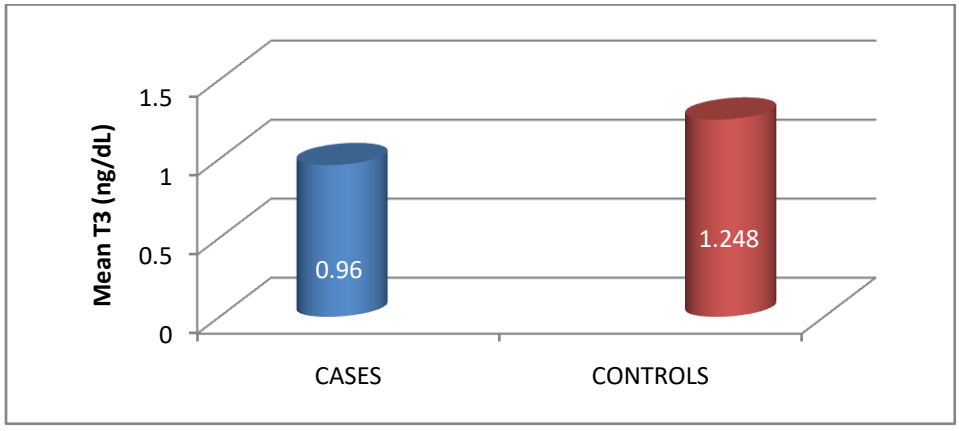
As presented by the above table and figure; amongst the 50 cases, 27 patients (54%) had hemorrhagic stroke and 23 patients (46%) had ischemic stroke.

TOTAL T3 :

Table 5.1: Table showing Mean±SD of Total T3 (ng/mL) value in cases and controls

Cases(ng/mL) Mean±SD n=50	Controls(ng/mL) Mean±SD n=50	t value	P value	Inference
0.960 ± 0.327	1.248 ± 0.269	4.8095	0.0001	Significant

Fig 3: Bar diagram showing mean Total T3 levels (ng/mL) in cases and controls



As presented in the above table and figure, the mean serum Total T3 in acute stroke patients and control groups were 0.960±0.327 and 1.248±0.269 respectively. There was statistically significant mean value difference in the Total T3 value ($p<0.05$) when patients were compared to the control groups.

Table 4: Serum Total T3 level (Mean±SD) in hemorrhagic and ischemic stroke

Hemorrhagic n=27	Ischemic n=23	t value	P value
1.033±0.313	0.873±0.323	1.7753	0.0822

As cited in the above table, the mean Total T3 in hemorrhagic and ischemic stroke was 1.033±0.313 and 0.873±0.323 respectively. It was observed that the mean value of Total T3 in ischemic stroke was lower than the hemorrhagic stroke, but they were not statistically significant (p>0.05).

Table 5: Number of cases with low T3 (<0.87 ng/mL) in hemorrhagic and ischemic stroke

Total number of cases	Hemorrhagic stroke n=27	Ischemic stroke n=23
50	05 (18.5%)	10 (43.5%)

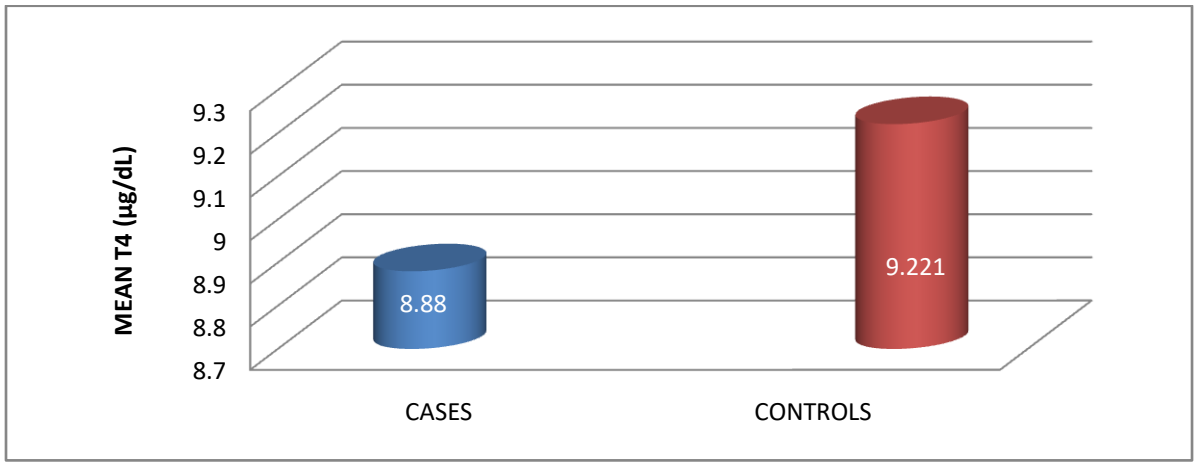
From the above table, it was observed that, low T3 was present in 10 (43.5%) and 5 (18.5%) cases of ischemic stroke and hemorrhagic stroke respectively.

TOTAL T4:

Table 6: Table showing Mean±SD of Total T4 (µg/dL) value in cases and controls

Total T4 (µg/dL) in Cases Mean±SD	Total T4 (µg/dL) in Controls Mean±SD	t value	P value	Inference
8.880 ± 3.501	9.221 ± 1.902	0.6052	0.5465	Not significant

Fig 4: Bar diagram showing mean Total T4 levels (µg/dL) in cases and controls



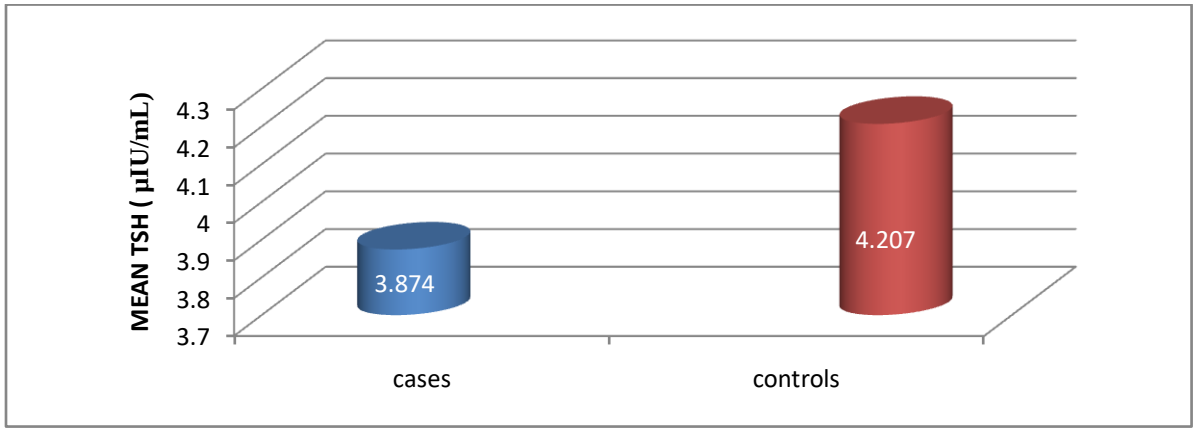
As presented in the above table and figure; the mean of Total T4 in stroke patients and control groups were 8.880±3.501 and 9.221±1.902 respectively. The difference between mean T4 levels of the two study groups were not statistically significant (p >0.05).

TSH:

Table 7: Table showing Mean±SD of Total TSH (µIU/mL) value in cases and controls

Cases (µIU/mL) Mean±SD n=50	Controls (µIU/mL) Mean±SD n=50	t value	P value	Inference
3.874 ±3.182	4.207 ± 2.608	0.5723	0.5684	Not significant

Fig 5: Bar diagram showing mean Total TSH levels (µIU/mL) in cases and control



From the above table and figure; the mean of TSH levels in stroke patients and control groups were 3.874±3.182 and 4.207±2.608 respectively. The difference between the mean TSH levels of the two study groups were not statistically significant (p >0.05).

DISCUSSION:

Stroke or cerebrovascular accident` (CVA) is a major cause of disability worldwide and the second most common cause of death after ischemic heart disease [11,12]. The cause for high mortality is multifactorial like cerebral oedema, infection, deep vein thrombosis, pulmonary embolism, electrolyte imbalance, associated heart disease and metabolic disorders [13]. Among the stroke subtypes, ischemic stroke constitutes around 85-90% of the total stroke in western countries with only about 10-15% patients with cerebral hemorrhage [14]. But contrary to the western population, hemorrhagic CVA constitutes greater percentage of stroke subtype on eastern countries because of poorly controlled hypertension [15].

Study conducted in Dibrugarh (Assam) by Mahanta BN *et al.* in 2017 stated that the possible cause of high hemorrhagic stroke (69.3%) in their study population may be a feature of life style rather than genetics as most of the participants were tea garden worker and they came from a poor or lower middle class family and they had a habit of extra salt intake in their meal and consumption of salted tea [16]. Banerjee TK *et al.* also demonstrated high proportion of cerebral hemorrhage in the Eastern Indian than in Western [17]. **Our study** population was comparable with the population with above studies with near similar food habits and life style showing higher occurrence of hemorrhagic stroke.The strongest determinant factor of stroke is age. In the present study, the age

distribution of the patients was between 40 - ≥70 years. Mean age was 59 years with a standard deviation of ± 10.02. The mean age and standard deviation of hemorrhagic and ischemic strokes were 58.407±9.960 and 60.565±9.845 respectively. The maximum number of patients were in the age group of 50 - <60 years, which constituted 32% of the total patients and greater preponderance of stroke was seen in males as compared to female with male to female ratio of 31:19.

The findings of the present study were in corroboration with a study by Talreja M *et al.* (age distribution 30 – 90 years and mean age 59 years) and another study by Wang *et al*. (mean age 61.01 ± 0.42 for ischemic and 57.58 ± 0.75 years for hemorrhagic stroke) [18,19]. Similarly, risk profile studies from the Framingham Study undertaken by Wolf PA *et al*. have shown that the 10-year probability of stroke was higher in men than in women (9.6% versus 6.5%) [20]. Moreover, Appelros P *et al*. mentioned in their meta-analysis involving 98 studies from 19 countries in 5 continents that male stroke incidence rate was 33% higher than that in females [21]. Wali VV *et al*. found on their study that most common age group affected by stroke was between 45 to 60 years and majority of the patients were males [22]. Pradhan B *et al*. in their study found that out of 100 cases, 58 patients were male and 42 were female and the mean age was 62.52±8.10 years [23].

Men have a higher incidence of stroke as evident from **the present** study. This may be ascribed by several factors; (1) the reason might be the positive effects of estrogen on the cerebral circulation, in case of females [24] and (2) may be due to blood pressure. A study by Reckelhoff JF showed that blood pressure values were higher in men than women of similar ages [25].

***THYROID PROFILE*:**

Thyroid hormones, in addition to their role in cellular metabolic activity also regulate neural development. The central nervous system is particularly dependent on thyroid hormone for normal maturation and function. During critical illness, changes in circulating hormonal levels are a common phenomenon. Hypothyroidism is considered as a possible risk factor for stroke although there are few studies to prove this.

It is not known whether hypothyroidism (either clinical or subclinical) affects outcome in patients with acute cerebrovascular disease.The non-thyroidal illness syndrome (NTIS or 'euthyroid sick syndrome' or 'low-T3 syndrome') is frequently encountered in hospitalized patients, especially those critically ill patients and describes abnormalities in thyroid function tests in the absence of obvious thyroid disease. The most common abnormality is a decrease in triiodothyronine (T3) levels. In the presence of more severe illness, a fall in the level of thyroxine (T4) occurs, while the thyroid stimulating hormone (TSH) levels do not show the expected pituitary thyroid axis reactivity. These changes are associated with disease severity and have been connected with poor short term prognosis [6,7,8].

In the present study, the mean of Total T3 in stroke patients and controls were 0.960±0.327 and 1.248±0.269 respectively. There was statistically significant mean value difference in the total T3 value (p=0.0001) when patients were compared to that of controls. Low T3 was most common among ischemic stroke patients 10(43.5%) followed by hemorrhagic stroke patients 5(18.5%). The mean serum Total T3 in hemorrhagic and ischemic stroke was 1.033±0.313 and 0.873±0.323 respectively. Although the mean of serum Total T3 in ischemic stroke was less than hemorrhagic stroke, but there was no statistical significance (p>0.05). The mean of Total T4 in stroke patients and controls were 8.880±3.501 and 9.221±1.902 respectively. The difference between mean T4 levels of the two study groups were not statistically significant (p value is 0.5465). Similarly, the mean of TSH levels in stroke patients and controls were 3.874±3.182 and 4.207±2.608 respectively. The difference between the mean TSH levels of the two study groups were not statistically significant (p 0.5684).

Pal SK *et al.* in their study observed that a reduced level of T3 without elevation of TSH appears to be associated with worse neurological presentation and outcome in stroke patients. In their study they found 49.4% of all stroke patients had low T3. Low T3 was most commonly found in ischemic stroke (53.2%) following hemorrhagic stroke (44.7%). Patients with low T3 group showed poor neurological presentation at onset and increased mortality and poor neurological recovery [26]. Similarly, Pande A *et al.* in their study concluded that out of the 185 patients, 124 had non-thyroidal illness syndrome (NTIS) accounting 67.03%. This study resemblance with the present study [27].

Alevizaki M *et al.* conducted a study on 737 consecutive patients with acute first ever stroke who presented within 24 hours from symptom onset and concluded that a high proportion of these patients had low T3 values soon after the event. The low-T3 syndrome was an independent predictor of early and late survival in patients with acute stroke. In their study, 417 (56%) had low T3 values and 320 (43.4%) had normal T3 value. The 1- year mortality was 27.34% for low T3 and 19.37% for normal T3 cases (p=0.006). The results showed quite good congruence with the present study [28].

In a retrospective study conducted by Zhang Y *et al.* it was shown that 61% of ischemic stroke patients had lower concentration of Total T3. Patients with low T3 had significantly more severe neurological impairment at presentation ($p<0.05$). They observed that there was a trend of decreased T4 levels but did not yield a significant difference when compared to normal T3 group. TSH levels showed no difference between low T3 and normal T3 groups [6].

Similarly, Xu XY *et al.* stated that a reduction in serum triiodothyronine (T3) level without an elevation of thyroid stimulating hormones (TSH) (i.e. low T3 syndrome) was a common complication in acute cerebrovascular disease setting and reported to be associated with stroke severity and poor clinical outcome. In their study, a total of 637 patients (88.2%) had good functional outcome and 85 patients (11.8%) had poor functional outcome. Lower total T3 concentrations remained independently associated with poor functional outcome [odds ratio (OR) = 0.10; 95% confidence interval (CI), 0.01 – 0.84; p=0.035] [8].

In a study conducted by Boltzmann M *et al.* had shown that reduction of T3 was associated with higher mortality and poor short-term prognosis whereas T4 was not reliably related to outcome [9].

In another study done by Rahman HA *et al.* among 83 stroke patients revealed that 49 patients (59%) had normal T3 level and rest 34 (41%) had low T3 level. Mean total T3 level was 0.4±0.3 ng/mL and 1.8±0.5 ng/mL in low T3 and normal T3 level group respectively. In post stroke follow up, about 63.2% patients with normal T3 level showed favorable neurological functional improvement compared to 38.2% having low T3 level (Chi square = 4.9, $p<0.05$) [29].

From the above discussions, the findings suggested that derangement in thyroid profile are quite common with acute stroke irrespective of types. Prompt identification of such derangements along with their correction can prove to be of tremendous importance in decreasing mortality as well as in dispersing the long-term consequences of stroke

SUMMARY:

The present study comprised of 50 cerebrovascular accident (Stroke) patients and 50 age and sex matched controls. Majority of the cases were from the age group of 50 - <60 years constituting about 32% followed by the age group of 60 - <70 years accounting for 30% and least number of cases were observed in the age group between 40 - <50 years showing only 18% of total cases. A greater preponderance of stroke was seen in males (62%) as compared to female (38%) with male to female ration of 1.63:1. Among the patients of stroke, hemorrhagic stroke was found to be more common than ischemic stroke (54% and 46% respectively) in contrary to other parts of the country. The mean age and standard deviation of hemorrhagic stroke and ischemic strokes were 58.407±9.960 and 60.565±9.845 respectively. Hemorrhagic strokes occurred more in early age than ischemic strokes. The mean ± SD of serum Total T3 levels in stroke patients and controls were 0.960 ± 0.327 and 1.248 ± 0.269 respectively. There was statistically significant mean value difference ($p<0.05$) when cases were compared to the controls. The mean ± SD of serum Total T3 levels in hemorrhagic and ischemic strokes were 1.033±0.313 and 0.873±0.323 respectively. The mean values of Total T3 in ischemic strokes were lower than the hemorrhagic strokes but there was no statistical significance. A greater number of low T3 was present in ischemic strokes (43.5%) when compared to hemorrhagic strokes (18.5%). The mean ± SD of serum Total T4 levels in stroke patients and controls were 8.880±3.501 and 9.221±1.902 respectively. The difference between mean Total T4 of the two study groups was not statistically significant ($p>0.05$). The mean ± SD of serum Total TSH levels in stroke patients and controls were 3.874±3.182 and 4.207±2.608 respectively. The difference between the mean TSH levels of cases and controls were not statistically significant ($p>0.05$).The estimation of serum Total T3, Total T4 and TSH are very much essential in patients with stroke. Any disturbances in thyroid hormones may have negative influence on the outcome of acute phase of strokes. Early detection and timely correction of these important parameters are recommended for an improved outcome of strokes.

CONCLUSION:

From the present study, it is observed that hemorrhagic stroke constitute a larger percentage of stroke subtype in this part of the country. thyroid hormone disturbances are quite common at the time of acute phase of stroke irrespective of the type. Nonthyroidal illness syndrome (Low T3 syndrome) is observed in the present study with decreased T3 values without alteration of T4 and TSH levels .Early detection and correction of these alterations will decrease morbidity and mortality in acute phase of stroke. Further, it will also be helpful in prevention of complications those might arise as a result of such derangements. However, a large sample size with prolonged follow up may be helpful to peer deep into the problem and should attempt to investigate whether treatment of low T3 syndrome can improve the final outcome.

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