Thyroid Function Tests in Patient with Ischemic Stroke

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Abstract

Objectives: To analyze thyroid functions tests in patients with ischemic stroke at acute stage and to study the association between ischemic stroke and different types of thyroid dysfunctions.
Methods: A hospital based, cross-sectional, case-control study with trial to cancel the role of age, gender, hypertension and diabetes mellitus as confounding factors was adopted to achieve the aim of this study. A total number of 210 cases (105 as patients group presented with ischemic stroke and another 105 case as control group not suffering from ischemic stroke) were examined for TSH, T4 and T3. The period of data collection was from Jan. 2011 to the end of Jan. 2012. The patients were collected from the wards of neurology while the control group were collected from the out patients clinic, of Baghdad Teaching Hospital, Baghdad, Iraq.
Ischemic stroke was confirmed by their clinical picture and native brain CT scan. Exclusion and inclusion criteria, definition of variables and the consents from all patients were fulfilled.
Results: 8.6% of ischemic stroke patients showed hypothyroid pattern, 8.6% hyperthyroid pattern and 3.8% sick euthyroid pattern and these results were statistically significant as compared with control cases. 7.6% of patients had atrial fibrillation (AF) statistically of significant difference. Most cases of AF registered among patients with hyperthyroidism 60%. 12.7% of patients with hypothyroid pattern had statistically significant obesity and 8% of patients with sick euthyroid pattern had diabetes which was also significant.
Conclusions: Both hyperthyroidism and hypothyroidism might be considered as risk factors for developing ischemic stroke. Atrial Fibrillation may be a predictor for developing ischemic stroke especially in patients with hyperthyroidism. In hypothyroidism, there may be an association of several atherosclerotic risk factors with ischemic stroke. Sick euthyroid is not uncommon in patients with ischemic stroke which reflect the increase in physical stress associated with the insult.
Key words: Ischemic stroke, thyroid function tests, Sick euthyroid, Atrial fibrillation.

Introduction

Stroke is defined by the WHO as the clinical syndrome of rapid onset (usually seconds or minutes) of focal (or global, as in subarachnoid hemorrhage) cerebral deficit, lasting more than 24 hours or leading to death, with no apparent cause other than a vascular one.1

Strokes can be classified into two major categories: ischemic and hemorrhagic. 2 Ischemic strokes are those that are caused by interruption of the blood supply, while hemorrhagic strokes are the ones which result from rupture of a blood vessel or an abnormal vascular structure.3

Disorders of thyroid gland may include: hyperthyroidism, hypothyroidism and euthyroid sick syndrome. Euthyroid sick syndrome can be described as abnormal findings on thyroid function tests that occur in the setting of a nonthyroidal

illness, without preexisting hypothalamic-pituitary and thyroid gland dysfunction. After recovery from a nonthyroidal illness, these thyroid function test abnormalities should be completely reversible.4

Multiple alterations in serum thyroid function test findings have been recognized in patients with a wide variety of nonthyroidal illness without evidence of preexisting thyroid or hypothalamic-pituitary disease. The most prominent alterations are low T3and elevated rT3, leading to the general term "low T3 syndrome". TSH, T4, free T4 (FT4), and free T4 index (FTI) also are affected in variable degrees based on the severity and duration of the nonthyroidal illness. As the severity of the nonthyroidal illness increases, both serum T3 and T4 levels drop and gradually normalize as the patient recovers.5

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, or on peripheral tissue metabolism of the hormones, or by a combination of these effects.4

Hyperthyroidism may cause ischemic stroke by its relation to AF. AF occurs frequently in patients with hyperthyroidism and may be the presenting symptom.6 various studies suggest a prevalence of 10% to 15% in patients with hyperthyroidism, and it is more common in men than in women.7

It is still controversial whether the frequency of stroke and systemic embolism is increased in thyrotoxic AF or not. Some studies have reported a high frequency of stroke and systemic embolism in patients with thyrotoxic AF, but all these studies have methodological flaws.[8] In another study, there was no statistically significant difference between AF patients and age- and sex-matched patients with normal sinus rhythm.[9]

Hypothyroidism may cause ischemic stroke by it tendency to accelerate atherosclerosis. In 1883, Kocher noted that arteriosclerosis occurred commonly after thyroid extirpation and raised the hypothesis of a causal relationship between hypothyroidism and atherosclerosis.[10] Since then, a body of clinical case reports, epidemiological studies, biochemical observations, and case-control and cohort studies have linked hypothyroidism and atherosclerosis. [11] Coronary artery atherosclerosis is twice as common in patients with hypothyroidism compared with sex- and age-matched controls, and adequate thyroid hormone replacement therapy may protect against progression.[12] The aim of this study is to analyze thyroid function tests in patients with ischemic stroke during acute stage.

Patients and Methods

Study setting and design:

The study was conducted in the ward of neurology/ Baghdad teaching hospital, Baghdad, Iraq, from Jan. 2011 to the end of Jan. 2012.

A hospital based cross-sectional, case control study with trial to cancel the role of age, gender, hypertension and diabetes mellitus as confounding factors was adopted to achieve the aim of the present study.

Selection of the study sample:

A total numbers of 105 patients presented with ischemic stroke from both sexes (63 males and 42 females), with age ranged from 45-85 years were examined for TSH, T4 and T3.

Control cases which were collected from neurology outpatient clinic, Baghdad Teaching Hospital were also examined for TSH, T4 and T3. They were 105 cases (65 males & 40 females), with consideration to be matched for age, gender and not suffering from stroke clinically and by a brain CT in selected cases.

Patients and control cases taking drugs that induced thyroid dysfunction like amiodarone, or radio-contrast media were excluded from the study.

Ischemic stroke was confirmed by native brain CT scan.

Definition of variables:

1. The patient was considered diabetic if had history of diabetes in the past (treated with either insulin, oral hypoglycemic agents or not treated), or had a fasting venous plasma glucose (FPG) ≥7.0 mmol/l; or if random venous plasma glucose ≥11.1 mmol/l at two occasions before the onset of stroke.[13]
2. The patient was considered to have cardiovascular risk if he/she had recent or old features of myocardial infarction, valvular heart disease, atrial fibrillation, heart failure, the patients receiving antianginal therapy and carotid bruit.[14-18]
3. Dyslipidemia was considered if one or more of the following had been detected: Total serum cholesterol > 6.2 mmol/L (240 mg/dL), total triglycerides (TG) > 2.26 (200 mg/dL), low density lipoprotein (LDL) > 100 mg/dL, or high density lipoprotein (HDL) < 40 mg/dL in males and <50 mg/dL in females.[19]
4. Hypertension was ascertained if the patient had history of hypertension or ; systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg. [20]
5. Obesity assessed by measurement of Body Mass Index (BMI) calculated as weight in kilograms divided by the square of the height in meters (normal range between18.1-26.5). [21]
6. Patients who had low thyroid stimulating hormone (TSH) levels with or without high thyroxine (T4) levels and triiodothyronine (T3) levels were considered as hyperthyroid pattern while patients who had high TSH with or without low T4 and triiodothyronine (T3) were considered as hypothyroid pattern.
7. Patient who had low triiodothyronine (T3) levels with normal or low thyroxine (T4) levels and normal or low TSH levels or any other patterns that not fit for hypo or hyperthyroid pattern were considered sick euthyroid pattern.

Materials:

Thyroid function has been tested by quantitative measurement of thyroid stimulating hormone (TSH), thyroxine (T4) and triiodothyronine (T3) by ELFA technique (Enzyme Linked Fluorescent Assay), using VIDAS TSH, VIDAS T4 and VIDAS T3.

VIDAS TSH, VIDAS T4 and VIDAS T3 are automated quantitative tests for use on the VIDAS family instruments, for the immunoenzymatic determination of TSH, T4 and T3 in human serum or plasma (lithium heparin) using ELFA technique. The assay principle combines a one-step enzyme immunoassay sandwich method with final fluorescent detection (ELFA).

Range of expected values:

- For thyroid stimulating hormone (TSH): 0.25 to 5 µIU/L
- For thyroxine (T4): 60 to 120 µIU/L
- For triiodothyronine (T3): 0.9 to 2.3 µIU/L

So, we were considered patients with TSH level more than 5.0 µIU/L was high and patients with TSH level less than 0.25 µIU/L was low, patients with T4 level more than 120 µIU/ml was high and patients with T4 level less than 60 µIU/ml was low and patient with T3 level more than 2.3 µIU/L as high and patient with T3 level less than 0.9µIU/L as low.

Statistics:

Analysis of data was carried out using the available statistical package of SPSS-20 (Statistical Packages for Social Sciences- version 20 "PASW" Statistics) for determination of statistical significance among different variables. A descriptive statistics like mean together with analytic statistics, have been done when appropriate. A p-value of less than 0.05 was considered as significant.

Results

The study included 105 patients with ischemic stroke and 105 non-stroke patients served as control.

The frequency of ischemic stroke was more among male patients 63 (60%). The male to female ratio was (1.5:1). The frequency of ischemic stroke was also more frequent among the age older than 55 98(93.3%). The mean age of the patients was (62.73 ± 9.86 SD) years and for control (60.43 ± 8.31 SD) years. The frequency of obesity was more among control group 39 (37.1%) compared to 32 (30.5%) of ischemic stroke patients. The mean BMI was higher in the control group (26.53) than in the ischemic stroke patient (26.26). Also the frequency of ischemic stroke was more in patient with HT (68.8%), DM (40%), current smoking (45.6%), dyslipidemia (17.1%), hypothyroid pattern (8.6%), hyperthyroid pattern (8.6%) and sick euthyroid pattern (3.8%). Table 1

Table 2 shows that there were statistically significant difference among age group older than 55 years with ischemic stroke (p=0.04) but there were no statistically difference between males and females (p=0.77)

Table 3 shows that diabetes and hypertension had caused more ischemic stroke than control, the difference were statistically significant (p=0.001 for both).

Smoking, obesity and dyslipidemia showed no significant differences between case and control groups, as shown in table 3. Table 4 and fig 1 show that there were statistically significant difference among hyperthyroid pattern, hypothyroid pattern and sick euthyroid pattern with ischemic stroke (p=0.010, p=0.030 and 0.04 respectively)

Table 5 shows increase prevalence of atrial fibrillation was seen among patients with ischemic stroke 8 (7.6%) as compared with controlled group 2 (1.9%), these differences were statistically significant (p=0.04). Table 6 show that there were increased prevalence of atrial fibrillation of studied patient with hyperthyroid pattern 6 (60%) as compared with studied patient without hyperthyroid pattern 4 (2%),the difference was statistically significant (P=0.000). Table 7 and fig 2 shows that obesity showed a statistical difference among patients with hypothyroid pattern than patients without hypothyroid pattern of studied patient (p=0.001), while Diabetes, Hypertension and lipid profile shows no statistical difference among patients with hypothyroid pattern than patients without hypothyroid pattern of studied patients.

Table 1: Demographic characteristics of patients and control groups:

Controls		Patients		variables
Percentage	No.	Percentage	No.	
61.9%	65	60%	63	male
38.1%	40	40%	42	female
14.3%	15	6.7%	7	Age < 55 years
85.7%	90	93.3%	98	Age > 55 years
21%	22	68.8%	72	Hypertension
6.7%	8	40%	42	Diabetes Mellitus
36.2%	38	45.6%	48	Current smoking
37.1%	39	30.5%	32	Obesity
1.9%	2	8.6%	9	Hypothyroid pattern
1%	1	8.6%	9	Hyperthyroid pattern
0%	0	3.8%	4	Sick euthyroid pattern
8.6%	9	17.1%	18	dyslipidemia

Table 2: Age and sex distribution among case and control groups

P-value	Controls		Patients		Variables
	Percentage	No.	Percentage	No.	
0.77	61.9%	65	60%	63	**Male**
	38.1%	40	40%	42	**Female**
0.04	14.3%	15	6.7%	7	**Age < 55 years**
	85.7%	90	93.3%	98	**Age > 55 years**

*Significant using Pearson chi-square test at 0.05 level of significance.

Table 3: Risk factors distribution between case and control groups

P-value	Controls		Patients		Variables
	Percentage	No.	Percentage	No.	
0.001	21%	22	68.8%	72	**HT**
0.001	6.7%	8	40%	42	**DM**
0.161	36.2%	38	45.6%	48	**Smoking**
0.307	37.1%	39	30.5%	32	**Obesity**
0.064	8.6%	9	17.1%	18	**Dyslipidemia**

*Significant using Pearson chi-square test at 0.05 level of significance.

Table 4: Thyroid dysfunction distribution between case and control groups.

P-value	Control		case		variables
	Percentage	No.	Percentage	No.	
0.010	1%	1	8.6%	9	Hyperthyroid pattern
0.030	1.9%	2	8.6%	9	Hypothyroid pattern
0.04	0%	0	3.8%	4	Sick euthyroid pattern

*Significant using Pearson chi-square test at 0.05 level of significance.

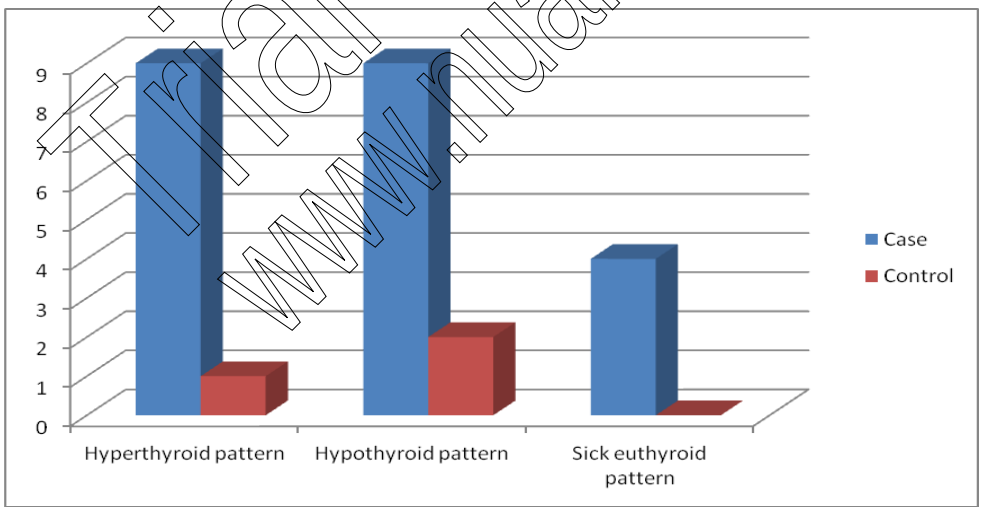

Fig 1: Thyroid dysfunction distribution between case and control groups.

Table 5: Distribution of patients with atrial fibrillation among case and control groups

p-value	Control	Case	AF
0.04	2 (1.9%)	8 (7.6%)	**Yes**
	103 (98.1%)	97 (92.4%)	**No**

*Significant using Pearson chi-square test at 0.05 level of significance.

Table 6: Distribution of patients with atrial fibrillation among studied patients with hyperthyroid pattern.

P-value	Hyperthyroid pattern		AF
	no	yes	
0.000	4 (2%)	6 (60%)	yes
	196 (98%)	4 (40%)	no

*Significant using Pearson chi-square test at 0.05 level of significance.

Table 7: Distribution of patients with some risk factors among studied patients with hypothyroid pattern.

P-value	Hypothyroid pattern		variables
	no	yes	
0.55	86 (91.5%)	8 (8.5%)	HT
0.083	45 (90%)	5 (10%)	DM
0.001	62 (87.3%)	9 (12.7%)	Obesity
0.068	23 (86%)	4 (14%)	dyslipidemia

*Significant using Pearson chi-square test at 0.05 level of significance.

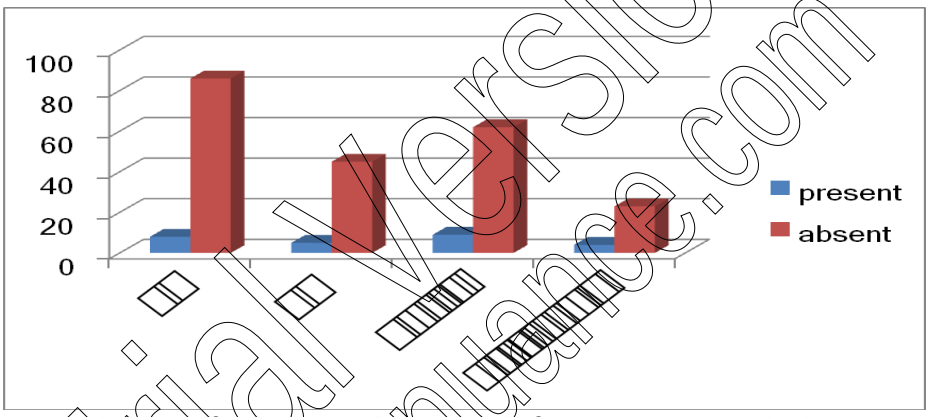

Fig 2: Distribution of patients with some risk factors among studied patients with hypothyroid pattern.

Table 8 shows that DM showed a statistical difference among patients with sick euthyroid pattern than patients without sick euthyroid pattern of studied patient (p=0.001), while hypertension and lipid profile shows no statistically difference among patients with sick euthyroid pattern than patients without sick euthyroid pattern of studied patients.

Table 8: Distribution of patients with some risk factors among studied patients with sick euthyroid pattern.

P-value	Sick euthyroid pattern		variables
	no	yes	
0.219	91 (96.8%)	3 (3.2%)	HT
0.001	46 (92%)	4 (8%)	DM
0.464	26 (96%)	1 (4%)	Dyslipidemia

*Significant using Pearson chi-square test at 0.05 level of significance.

Discussion

This study has analyzed 105 patients with ischemic stroke (cases) and 105 non-stroke people (controls) which reveal that there were statistically significant difference among age group older than 55 years with ischemic stroke (p=0.04) but there were no statistically difference between males and females (p=0.77) with male to female ratio about 1.5:1 .

These results were consistent with Marcus et al [22] study who showed that patient older than 55 years had high risk of stroke ,statistically significance (p=0.001).This is because of the fact that the age is one of the most powerful independent risk factor for atherosclerosis. Also the same study (Marcus et al [22]) showed no statistical difference between male and female especially in age group more than 55 years. This can be explained by hormonal changes after menopause that makes the risk of ischemic stroke equal in both sexes. [23]

This study reveal also that diabetes and hypertension had caused more ischemic stroke than control, the difference were statistically significant (p=0.001 for both). These results were consistent with other studies [24, 22] who showed that patient with hypertension and diabetes had high risk of stroke, statistically significance (p=0.001, p=0.036 respectively). This explains by their link to accelerate atherosclerosis. [25]

In our study the smoking and obesity showed no significant differences between case and control groups. These results were inconsistent with other studies. [24, 22] This might be explained by the nearly equal distribution of both smoking and obesity in both case and control group.

The dyslipidemias in our study show no significant differences between case and control (p=0.064).These results were inconsistent with other studies. [26-30] This could be explained by relatively low cholesterol level during the first few days of acute vascular events due to consumption of lipid after rupture of atheroma plaque. [31]

In our study there is a significant association between AF and ischemic stroke and between AF and Hyperthyroidism which is statistically significant (p=0.04 and 0.00 respectively). These results were consistent with other studies. [22, 32, 32-35]

This could be explained by ineffective atrial contraction in patients with AF which lead to stasis and hypercoagulable state that lead to cardio-embolic stroke. AF may be the presenting symptom of hyperthyroidism in patient with ischemic stroke. [6] Thyrotoxic AF is more common in patients more than 50 years old which indicate high risk of stroke and might require anticoagulation. The factors that increase the risk of ischemic stroke in patients with hyperthyroidism in addition to AF are:

- First, concomitant other risk factors e.g. smoking that leads to hypercoagulable state.
- Second, thyroid hormone cause increase in total body metabolism and oxygen consumption that indirectly increase cardiac work load in addition to direct inotrope and chronotropic effects, they are mediated by effects of thyroid hormones on myosine, calcium activated ATPase, sodium-potassium ATPase and myocardial adrenergic receptors. [36]

In our study, patients with hypothyroidism and obesity have high association with the development of ischemic stroke, and it is statistically significant. These results are consistent with other studies. [38] This can be explained by the following:

- First, obesity may be the presenting symptom of hypothyroidism.
- Second, hypothyroidism may lead to decrease myocardial contractility and heart rate with increase vascular resistance and hypertension particularly diastolic hypertension

- Third, obesity specially truncal increase cerebrovascular and cardiovascular morbidity and mortality, especially if it is associated with other risk factors e.g. hypertension, diabetes and metabolic syndrome .[36]

In our study there is a significant association between ischemic stroke patients and sick euthyroid pattern and sick euthyroid pattern and DM which is statistically significant (p= 0.04 and p= 0.001 respectively). These could be explained by the fact that physical stress associated with ischemic stroke reduce the deiodination process of T4 to T3 and increases the synthesis of reverse T3 without any increase in the TSH level and this physical stress are more in patient with DM.[37]

The thyroid dysfunction have a major impact in ischemic stroke, there were increase incidence of hyperthyroidism and hypothyroidism among studied patients, these results are statistically significant (p=0.010 for hyperthyroidism and p=0.030 for hypothyroidism). These results were consistent with other studies.[22] In conclusion thyroid dysfunction is not uncommon in patients with ischemic stroke. Both hyperthyroidism and hypothyroidism might be considered as risk factors for developing ischemic stroke. Atrial Fibrillation may be a predictor for developing ischemic stroke especially in patients with hyperthyroidism. In hypothyroidism, there may be an association of several atherosclerotic risk factors with ischemic stroke. Sick euthyroid is not uncommon in patients with ischemic stroke which reflect the increase in physical stress associated with the insult. We recommend that thyroid function test must be requested in patients with acute ischemic stroke. Early diagnosis and treatment of thyroid dysfunction may prevent ischemic stroke. We recommend also repeating the thyroid function test after 6 weeks to confirm the suspected cases of sick euthyroid.

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