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RESEARCH ARTICLE

Thyroid Dysfunction in Acute Ischemic Stroke in Medical Intensive Care Unit in Zagazig University Hospitals

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Abstract

Background: Stroke is a serious neurological disease and constitutes a major cause of death and disability throughout the world. It is the leading cause of adult disability in the United States and Europe and the second leading cause of death worldwide. Thyroid disorders can affect different risk factors of ischemic stroke and several studies have reported a high prevalence of thyroid disorders in patients with acute ischemic stroke. **Objectives:** This study was conducted to evaluate prevalence of undiagnosed thyroid disorders in patients with acute ischemic stroke and their relation to age and sex, study effect of thyroid disorders on each of different risk factors and their effect on the outcome of those patients. **Patients and Methods:** Out of 351 patients who were admitted to stroke subunit within 6 months which were diagnosed as stroke clinically and radiological. Only 131 eligible patients with acute ischemic stroke were recruited and followed up during ICU stay. All subjects were subjected to thorough history and general and neurological examination, assessment of severity score system was done in ischemic stroke using GCS and APACHE II score during first 24 hours of stroke onset, routine laboratory investigations, ECG, CT brain and/or MRI brain, arterial blood gases (ABG), TSH, free T4 and freeT3. **Results:** There was a high prevalence of undiagnosed thyroid disorders in patients with acute ischemic stroke (14.5%). Of them 4.6% had overt hyperthyroidism while subclinical hyperthyroidism (SCHyper) was 1.5%, overt hypothyroidism was 6.9% and subclinical hypothyroidism (SCHypo) was 1.5%. The increasing age over 60 years, female gender and smoking increase the prevalence and risk of developing thyroid disorders in patients with ischemic stroke. Overt/SCHyper increased relative risk of AF, fasting hyperglycemia and hypertension by 2.5, 1.3, and 2 folds respectively while overt/SCHypo increased relative risk of hypertension, hypercholesterolemia, high LDL, high TG by 2, 2.6, 2.7, and 2.6 folds respectively. A step wise logistic regression analysis revealed that AF (in overt/SCHyper) and LDL (in overt/SCHypo) were the most important risk factors predicting thyroid disorders in ischemic stroke patients. Thyroid disorders worsen GCS, APACHE II score, increased ICU stay and increased mortality by 1.4, 1.6, 2.4, and 1.7 folds respectively. **Conclusion**: Undiagnosed thyroid disorders was common in acute ischemic stroke patients and can worsen the outcome of acute ischemic stroke, so identification and management of these disorders may reduce recurrence of ischemic stroke and may improve their outcome.

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INTRODUCTION

Stroke is a serious neurological disease, and constitutes a major cause of death and disability throughout the world. The ultimate result of ischemic cascade initiated by acute stroke is neuronal death along with an irreversible loss of neuronal function[(1)]. About 87% of strokes are caused by ischemia and the remainder by hemorrhage. Some hemorrhages develop inside areas of ischemia "hemorrhagic transformation"[(2)]. Ischemic stroke is defined as acute onset, (minutes or hours), of a focal neurological deficit consistent with vascular lesion that persisted for more than 24 hour[(3)]. Subclinical hyperthyroidism is commonly defined as a low serum thyrotropin (TSH) in combination with free thyroxin (T4) and free triiodothyronine (T3) in the normal ranges. When patients with known thyroid disease and/or thyroid treatment are excluded, the prevalence of subclinical hyperthyroidism in the industrialized world averages about 1-4% and increases with age and female gender[(4)]. Atrial fibrillation (AF) is a well-known manifestation of overt hyperthyroidism and is a known risk factor for embolic stroke. Ischemia resulting from increased resting heart rate can increase atrial ectopic activity[(5)]. Subclinical hyperthyroidism predisposes for AF and the risk of developing AF is calculated to increase three-to five-folds in different studies. About 2-5% per year will progress to overt hypothyroidism. Some evidence that subclinical hypothyroidism worsens the cardiovascular risk profile and leads to progression of atherosclerosis [(6)].

Therefore, we performed this study to evaluate the prevalence of different undiagnosed thyroid disorders in patients with acute ischemic stroke, and the effects of age and sex on thyroid disorders in those patients, to clarify the effects of different thyroid disorders on each of different risk factors namely (blood pressure, fasting plasma glucose, lipid profile and AF) and the outcome of those patients regarding GCS, APACHE II score, ICU stay and mortality.

Patients and Methods

This work had been carried out in stroke subunit of medical intensive care unit of Internal Medicine Department Faculty of Medicine, Zagazig University. Our study was observational, cross sectional, analytic cohort study including patients admitted to the stroke unit of medical ICU of Zagazig University Hospital in the period of 6 months during 2013.

Subjects: Out of 351 patients who were admitted to stroke subunit within 6 months which were diagnosed as stroke clinically and radiologically. Only 131 eligible patients with acute ischemic stroke were recruited and followed up during ICU stay. Exclusion criteria included patients with previous attack of ischemic stroke, patients with hemorrhagic stroke, patients with TIA (defined as symptoms for <24h), patients with known possible underlying causes for ischemic stroke such as systemic malignancy, SLE, kidney transplants and patients on estrogen or lipid-altering treatments, patients with preexisting thyroid disorder and patients on thyroxin therapy. The age range of the included subjects was 35-85 years (mean±SD=58.25±10.52y), 48 were females and 83 were males, 49 were hypertensive, 86 were hyperglycemic and 42 patients had AF.

Ethical Clearance: Informed written consents from the patient relatives to participate in the study were taken.

Methods: All subjects of this study were subjected to the following: Full history and thorough physical examination. Complete blood picture (by automated blood counter), liver function tests: serum bilirubin (total and direct), serum albumin, serum alanine transferase and aspartate transferase measured by kinetic method, kidney function tests: serum creatinine, blood urea, bleeding profile: INR, prothrombin time (PT) and Partial thromboplastin Time (PTT), lipid profile (LDL, total cholesterol, serum triglycerides), fasting plasma glucose level, serum uric acid and Arterial blood gases (ABG). Other investigations included: ECG, Neuro-imaging: All patients were examined by CT scan and/or MRI at onset of admission to identify the vascular lesion and to determine the location site of lesion. Severity assessment was done using the most commonly used scoring systems in ICU which are GCS score and APACHE II score. Specific investigation included: Estimation of serum level of FT4, FT3 and TSH within the first 48 hours after admission to avoid non thyroidal illness by ELISA. All data were coded, checked, entered and analyzed using SPSS software version 17; (Levesque, 2010).

RESULTS

Table (1): showed the prevalence of different thyroid disorders among patients with acute ischemic stroke. Total thyroid disorders 14.5%, both overt/SCHyper were 6.1%, overt hyperthyroidism was 4.6%, SCHyper was 1.5%, both overt/SCHypo were 8.4%, overt hypothyroidism was 6.9% and SCHypo was 1.5% of patients with acute ischemic stroke.

Table (2): showed the prevalence of thyroid disorders among patients with acute ischemic stroke: 17.8% in patients ≥60 year old, 10.3% in patients<60 year old, 23.9% in females and 9.4% in males, 17.1% in smokers and 10.9% in nonsmokers.

Table (3): showed relative risk of different clinical and laboratory cardiovascular risk parameters in patients with acute ischemic stroke with and without thyroid dysfunction. Overt/SCHyper increased risk of AF 2.5 folds than euthyroid patients. No increased risk of AF with overt/SCHypo in patients with acute ischemic stroke. Overt/SCHyper increased risk

of hypertension by 2 folds than euthyroid patients. Overt/SCHypo increased risk of hypertension by 2.6 folds than euthyroid patients. Overt/SCHyper increased risk of fasting hyperglycemia by 1.3 folds than euthyroid patients. There was no risk of hyperglycemia with overt/SCHypo in patient. There was no risk of hypercholesterolemia with overt/SCHyper in patient with acute ischemic stroke. Overt/SCHypo increased risk of hypercholesterolemia by 2.5 folds than euthyroid patients with ischemic stroke. There was no risk of increased LDL with overt/ SCHyper in patients with acute ischemic stroke. Overt/SCHypo increased risk of increased LDL by 2.8 folds than euthyroid patients with acute ischemic stroke. Overt/SCHypo increased the risk of increased TG by 2.2 folds than euthyroid patients while there was no risk of increased TG with overt/SCHyper in patients with acute ischemic stroke.

Table (4): Logistic regression of risk factors affected by thyroid disorders in patients with acute ischemic stroke. AF (in overt/SCHyper) and LDL (in overt/SCHypo) were the most important independent risk factors affected by thyroid disorders in patients with acute ischemic stroke.

Table (5): This table showed the relative risk of different prognostic parameters and outcome in patients with acute ischemic stroke with and without thyroid dysfunction overt and subclinical: Thyroid disorders worsen GCS by 1.4 folds than euthyroid patients. Thyroid disorders worsen APACHE II score by 1.7 folds than euthyroid patients. Thyroid disorders increased ICU stay by 2.4 folds. Thyroid disorders increased risk of mortality by 1.6 folds than euthyroid patients.

Table (1): Prevalence of different thyroid disorders among patients with acute ischemic stroke.

	No	Percent
Overt Hyperthyroidism	6	4.6
SCHyper	2	1.5
Overt /SCHyper	8	6.1
Overt Hypothyroidism	9	6.9
SCHypo	2	1.5
Overt /SCHypo	11	8.4
Total thyroid disorders	19	14.5
Euthyroid	112	85.5
Total patients	131	100

Table (2): prevalence and relative risk of thyroid disorders among patients with acute ischemic stroke.

	Thyroid disorders	**%**	Euthyroidism	**%**	Total	**RR**
age≥60	13	**17.8**	60	**82.2**	73	**1.7**
age<60	6	**10.3**	52	**89.7**	58	
Females	11	**23.9**	35	**76.1**	46	**2.5**
Males	8	**9.4**	77	**90.6**	85	
Smoker	13	**17.1**	63	**82.9**	76	**1.6**
Non smoker	6	**10.9**	49	**89.1**	55	

SCHypo: subclinical hypothyroidism, SCHyper: subclinical hyperthyroidism, RR: relative risk.

Table (3): relative risk of thyroid disorders (overt/SCHypo and overt/SCHper) in comparison with euthyroid patients on different risk factors among patients with acute ischemic stroke.

	AF	Sinus	**RR**	B.P≥ 140/90 mmHg	B.P< 140/90 mmHg	**RR**	FPG ≥100 mg%	FPG <100 mg%	**RR**	TC ≥200 mg%	TC< 200 mg%	**RR**	LDL ≥100 mg%	LDL <100 mg%	**RR**	TG ≥160 mg%	TG ≥160 mg%	**RR**
Overt /SCHypo	2	9	**0.6**	9	2	**2.6**	4	7	**0.5**	8	3	**2.5**	10	1	**2.8**	7	4	**2.2**
Euthyroidism	34	78		35	87		75	37		32	80		37	75		32	80	
Overt /SCHyper	6	2	**2.5**	5	3	**2.0**	7	1	**1.3**	2	6	**0.9**	2	6	**0.8**	2	6	**0.9**
Euthyroidism	34	78		35	87		75	37		32	80		37	75		32	80	

AF: atrial fibrillation, RR: relative risk, FBG: fasting plasma glucose, TC: total cholesterol, LDL: low density lipoprotein, TG: triglyceride,

Table (4): Logistic regression analysis of risk factors predicting thyroid disorders in patients with acute ischemic stroke.

Factor in overt/SCHyper	Co-efficient	(95% CI)	P value
AF	6.03± 0.81	14.6(4.5-18)	0.000
Fasting hyperglycemia	9.5±3.1	3 (9.1-12.02)	0.01
Hypertension	4.03±2.81	4.6(2.5-14)	0.03
Factor in overt/SCHypo	Co-efficient	(95% CI)	P value
LDL	1.83±0.51	6.29 (2.27-8.37)	0.000
Cholesterol	13.6±4.39	4(10.05-14.27)	0.04
Hypertension	5.03±2.71	6.6(2.3-15)	0.02

Table (5): Relative risk of thyroid disorders on different outcome and prognostic parameters in patients with acute ischemic stroke.

	CCS ≤8	CCS >8	RR	APACHE ≥14	APACHE <14	RR	ICU stay ≥7 d	ICU stay >7 d	RR	dead	alive	RR
Thyroid disorder	6	13	1.4	8	11	1.7	12	7	2.4	11	8	1.6
euthyroidism	25	88		27	85		30	82		40	72	

DISCUSSION

Stroke is a serious neurological disease and constitutes a major cause of death and disability throughout the world. It is the leading cause of adult disability in the United States and Europe and the second leading cause of death worldwide. Thyroid disorders can affect different risk factors of ischemic stroke and several studies have reported a high prevalence of thyroid disorders in patients with acute ischemic stroke[(1).] Our study showed a high prevalence (14.5%) of newly discovered thyroid disorders in patients with acute ischemic stroke, (overt hyperthyroidism was 4.6%, subclinical hyperthyroidism was 1.5%, overt hypothyroidism was 6.9% and subclinical hypothyroidism was 1.5%), these results were in agreement with **Bengtsson et al., 2012,** Who reported a high prevalence (12%) of unknown thyroid disorders in patients with acute ischemic stroke[(7)].

The present study showed that age over 60 year increases the risk of developing thyroid disorders 17.8% in those patients compared with 10.3% in patients less than 60 years in patients with ischemic stroke this was in line with results reported by **Canaris et al., 2000** and **Hollowell et al., 2002**[(8,9)]. There are many theories about the processes that might be involved in aging. The endocrine system is often referred to as being affected, since aging alters the function of many endocrine glands, including the pituitary and thyroid glands[(10)].

Regarding gender in this study, it was found that there was an increasing risk of developing thyroid disorders in patients with acute ischemic stroke being 23.9% in females and 9.4% in males. This was in agreement with results reported by **Canaris et al., 2000 and Bauer et al., 2014**[(8,11)].

On the other hand it was found that smoking increased risk of developing thyroid disorders than non smokers, it was found that thyroid disorders in smokers with acute ischemic stroke being 17.1% in smokers and 10.9% in nonsmokers.

Results were reported by **Tziomalos and Charsoulis, 2004,** smoking has a significant impact on thyroid function [(45)]. Thiocyanate, a major component of smoke, derived from hydrogen cyanide, leads to increased excretion of iodine, inhibits iodine uptake by the thyroid, competes with iodide in the organification process, and inhibits thyroid hormone synthesis[(46)]. There is also substantial evidence that smoking is a risk factor for Graves' hyperthyroidism, and especially Graves' ophthalmopathy. The ophthalmopathy is more severe in those who smoke**.** Smoking may alter the structure of the thyrotropin receptor slightly, so that in a susceptible person it becomes more immunogenic and the resulting antireceptor antibodies are more reactive with retro-orbital tissue. Alternatively, smoking could augment immunologic responsiveness to whatever factor initiates Graves' hyperthyroidism, sensitize retro-orbital tissue to whatever factor causes ophthalmopathy, or both[(47,48)].

Current study showed that overt and subclinical hyperthyroidism increase the relative risk of AF by 2.5 fold than euthyroid patients with acute ischemic stroke which is consistent with results reported by **Sawin et al., 1994**[(12)]**.** Several potential mechanisms could be involved for the effect of thyroid hormones on AF risk, including elevation of left atrial pressure secondary to increased left ventricular mass and impaired ventricular relaxation**.** Ischemia resulting from increased resting heart rate, and increased atria ectopic activity**.** Thyroid hormone potentiates the effect of adrenergic system on heart. Catecholamine levels are either normal or decreased in thyrotoxicosis. Facilitation of action of catecholamines is by

increasing tissue sensitivity by increased transcription of beta adrenergic receptors and structural similarity to catecholamines. Hyperthyroidism is associated with reduced vagal activity and reduced heart rate variability which can persist despite restoration of euthyroidism [5, 13,14].

Current study showed that overt and subclinical hyperthyroidism increase risk of hyperglycemia by 1.3 folds than euthyroid patients with ischemic stroke while there is no risk of increased blood glucose level in patients with overt or subclinical hypothyroidism, which was consistent with results obtained by **Bengtsson et al., 2012** and **Hage et al., 2011**[15,16]. Several potential mechanisms could be involved for the effects of thyroid hormones on blood glucose level. Hyperthyroidism has long been recognized to promote hyperglycemia. In patients with hyperthyroidism, the half-life of insulin is reduced most likely secondary to an increased rate of degradation and an enhanced release of biologically inactive insulin precursors. In untreated Graves' disease, increased proinsulin levels in response to a meal were observed. In addition, untreated hyperthyroidism was associated with a reduced C-peptide to proinsulin ratio suggesting an underlying defect in proinsulin processing. Another mechanism explaining the relationship between hyperthyroidism and hyperglycemia is the increase in glucose gut absorption mediated by the excess thyroid hormones. Endogenous production of glucose is also enhanced in hyperthyroidism via several mechanisms. Thyroid hormones produce an increase in the hepatocyte plasma membrane concentrations of GLUT2 which is the main glucose transporter in the liver, and consequently, the increased levels of GLUT-2 contribute to the increased hepatic glucose output and abnormal glucose metabolism. Additionally, increased lipolysis is observed in hyperthyroidism resulting in an increase in FFA that stimulates hepatic gluconeogenesis. The increased release of FFA could partially be explained by an enhanced catecholamine-stimulated lipolysis induced by the excess thyroid hormones. Moreover, the nonoxidative glucose disposal in hyperthyroidism is enhanced resulting in an over production of lactate that enters the Cori cycle and promotes further hepatic gluconeogenesis. The increase in GH, glucagon and catecholamine levels associated with hyperthyroidism further contributes to the impaired glucose tolerance[17,18]. Diabetes is an important risk factor in ischemic stroke as people with diabetes mellitus may also have a high blood pressure, high blood cholesterol level and are overweight with subsequent increase in incidence of stroke. In addition that hyperglycemia increase blood viscosity and platelets aggregation and decrease fibrinolytic activity[19]. The strong relationship between thyroid hormones and the coagulation system has been appreciated during last decade [20]. Several biological mechanisms were proposed to explain this intriguing association, including effects of thyroid hormones on synthesis of coagulation factors as well as thyroid-related autoimmune processes, involving the hemostatic system[21, 22,23]. Hypothyroid patients may have several hemostatic abnormalities such as modification of the coagulation proteins and a bleeding tendency. Thyroid hormones may affect the metabolism of several factors of the hemostatic system not only in patients with hypothyroidism but also in those within normal range of thyroid hormone levels[24].

Some studies have suggested a hypercoagulable state in overt hypothyroidism seen from the laboratory-analytic point of view, as shown by an increase of some activation marker of coagulation and fibrinolysis[25]. Thyroid hormone is known to play a role in regulating the synthesis, metabolism and mobilization of lipids[26]. Hypothyroid patients exhibit a more atherogenic lipid profile compared with healthy individuals. Therefore, hypothyroidism is also associated with an increased risk of cardiovascular disease[27]. Studies reported that the influence of hypothyroidism on haemostasis is controversial, both hypocoagulable and hypercoagulable states have been reported. They reported that, hypothyroidism has been associated with atherosclerosis; a hypercoagulable state in addition might represent a risk factor for thromboembolic disease. Previous studies have reported that hyperthyroidism is associated with a hypercoagulable state. There are case reports of cerebral thrombosis and deep vein thrombosis in patients with thyrotoxicosis[28,29]. The hypercoagulable state may be multifactorial and be linked to an increase in the activity of factor VIII, Von Willebrand factor (vWF) and tissue plasminogen activator inhibitor-1(PAI-). Several coagulation and fibrinolytic parameters appear to be affected by thyroid dysfunction, however, the net effect on the haemostatic system remains unclear[30,31].

As regard Hypertension in the present study it was found that overt and subclinical hyperthyroidism increase risk of hypertension by 2 folds while overt and subclinical thypothyroidism by 2.6 folds than euthyroid patients with acute ischemic stroke results were obtained by **Michael et al., 2006 and Stella et al., 2010** respectively[32,33]. In hypothyroidism potential mechanisms for reversible diastolic and systolic hypertension include increases in peripheral vascular resistance and arterial stiffness. Vasoconstriction may reflect the absence of demonstrated vasodilatory T3 effects on vascular smooth muscle or be the result of a higher circulating noradrenaline level and a decrease in the number of vascular B-adrenergic receptors[34, 35].

In hyperthyroidism, T3 dilates resistance arterioles, reducing systemic vascular resistance. The decline in systemic vascular resistance stimulates renin release and sodium reabsorption, resulting in an expansion of blood volume by 5.5% and an increase in venous return to the heart. Cardiac output is increased by >1 L/min in patients with hyperthyroidism than in patients without the condition. The net effect of these hemodynamic changes is a rise in SBP and a widening of pulse pressure. Arterial stiffness is increased [36]. Elevated systolic or diastolic blood pressure or both increased stroke risk by accelerating the progression of atherosclerosis and predisposing to small vessel diseases[37]. On the other hand, it was observed that overt and subclinical hypothyroidism increase risk of hypercholesterolemia by 2.6 folds, LDL by 2.7 folds and TG by 2.6 folds in patients with ischemic stroke, while there is no risk of altered lipid profile in patients with overt or

subclinical hyperthyroidism in consistent with results obtained by **Rizos et al., 2011[38].** Although decreased thyroid function is accompanied by reduced activity of HMG-COA reductase, TC and LDL-C levels are increased in patients with overt hypothyroidism**.** This is due to the decreased LDL-receptors' activity resulting in decreased catabolism of LDL and IDL[39]. Moreover, a decrease in LPL activity is found in overt hypothyroidism, decreasing the clearance of TG-rich lipoproteins. Therefore, overt hypothyroid patients may also present with elevated TG levels associated with increased levels of VLDL and occasionally fasting chylomicronemia[40]**.** The VLDL and IDL particles in hypothyroidism are rich in cholesterol and apolipoprotein E, thus resembling VLDL particles of type III hyperlipoproteinemia. Hypothyroid patients may also exhibit elevated levels of HDL- C mainly due to increased concentration of HDL2 particles. Indeed, due to a reduction of HDL activity a decrease in HDL2 catabolism is observed**.** Hypothyroid patients have increased lipoprotein (a) [LP (a)] levels, which are associated with increased CVD risk**.** Subclinical hypothyroidism is associated with increased levels of TC and LDL[39,40,41]**.** In addition, some studies have shown that subclinical hypothyroidism dyslipidemia may also be accompanied by increased TG and decreased HDL-C levels[42,43,44]**.** Dyslipidemia is an important risk factor of atherosclerosis with subsequent increase in incidence of ischemic stroke. From all of the above we had list of risk factors of ischemic stroke. We tried to know what was the risk factor mostly affected by thyroid disorders that can be suspected to decrease recurrence of ischemic stroke, so we made stepwise logistic regression analysis which showed that AF in hyperthyroidism and LDL in hypothyroidism are the most important predictors of thyroid disorders in ischemic stroke patients.

The current study showed that thyroid disorders worsen GCS, APACHE II score , increased ICU stay and mortality by 1.4, 1.7, 2.4, 1.6 folds respectively than euthyroid patients with ischemic stroke. This was in line with results obtained by **Wollenweber et al., 2013,** but was not in agreement with **Fahimeh et al., 2011** that showed a significant protective association of subclinical hypothyroidism with better outcomes and lower mortality after cerebral ischemic stroke. Possible explanations for this association are reduced adrenergic tone, and hypometabolic state. APACHE II score take into consideration various parameters like physiological variables, vital signs, urine outputs, neurological score, along with age related parameters and comorbid condition which may have a significant impact on outcome of ill patients[49,50]**.** Thus thyroid disorders worsen functional outcome in patients with acute ischemic stroke

CONCLUSION

We can conclude that newly discovered thyroid disorders are prevalent in ischemic stroke patients especially in female gender, and the subjects over 60 years old. The presence of AF and elevated level of LDL are considered the most important predictors for thyroid disorders in those patients that increase risk of mortality and morbidity. Thyroid disorders can affect different risk factors of ischemic stroke, so identification and management of these disorders can reduce recurrence of ischemic stroke.

RECOMMENDATION: Screening for thyroid disorders in old patients especially females with elevated LDL or presented with AF could hopefully reduce the incidence of ischemic stroke development. To answer the question whether thyroid abnormalities are associated with cerebrovascular disease and whether restoration of euthyroidism will affect outcome and recurrence of ischemic stroke, there is a need for further studies with longer term follow up to confirm this.

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