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ORIGINAL ARTICLE

Frequency and Determinants of Post Stroke Fatigue among Acute Ischemic Stroke Patients: Clinical, Laboratory and Hormonal Predictors

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Background: Post-stroke fatigue (PSF) is a common symptom that can have debilitating effects. Furthermore, it is cited as one of the worse symptoms by up to 40% of stroke survivors. Numerous risk factors for PSF, including clinical, laboratory, and hormonal variables, particularly thyroid hormones, were investigated. We aimed To assess the prevalence and contributing factors of post-stroke fatigue in AIS patients. **Patients and Methods:** This prospective cohort study, which included 70 patients with their first-ever AIS, conducted from August 2022 to January 2023 in the stroke units of the Zagazig neurology department. Patients were evaluated using the fatigue severity scale (scale 7-item version) one month after the stroke's onset. At admission to stroke units, routine laboratory and specialized hormonal assays for thyroid function were performed. **Results:** 16% of our patients reported post-stroke fatigue. Low T3, high TSH, and dyslipidemia were the three most frequently seen predictors. **Conclusions:** Dyslipidemia and altered thyroid function are linked to post-stroke fatigue, pointing to a potential role for neuroendocrine responses in PSF.

Keywords: Thyroid, acute ischemic stroke, post-stroke fatigue

INTRODUCTION

Stroke is described by world health organization (WHO), as 'a clinical condition comprising of quickly emerging clinical indications of focal (or sometimes global) impairment of brain function lasting more than 24 hours or leading to death with no apparent cause other than a vascular origin. A stroke can result in physical disabilities, cognitive, psychological, and behavioral impairments. It is the second leading cause of death worldwide [1-4].

Hyperthyroidism, hypothyroidism, subclinical hypothyroidism, subclinical hyperthyroidism, thyroid illness syndrome, and sick euthyroid syndrome are some of the more common thyroid disorders. Unusual thyroid function test findings that happen without a thyroid gland disease can be used to describe the thyroid disease syndrome. Changes in thyroid function test results can be caused by impacts on the thyroid gland itself, the thyroid axis, the pituitary gland, or the thyroid gland on the hormone metabolism in peripheral tissues, or by combining all of these effects [5].

Pathologic fatigue, or poststroke fatigue (PSF), is a debilitating illness that affects between 23% and 85% of people who have ischemic strokes. It might have a deleterious impact on stroke survivors' long-term and rehabilitation outcomes. However, patients, families, and even healthcare professionals frequently overlook or fail to recognize PSF. Significant weariness has been documented in over 50% of patients upon admission, 59% of patients at 10 days, and 92.3% of patients at one month following ischemic stroke. Its origin is poorly known [6].

For many years, it was believed that fatigue was a sign of post-stroke depression; however, the fact that patients without depression experience fatigue rather frequently has led to the

examination of post-stroke fatigue (PSF) as a distinct illness. Numerous stroke risk variables, such as diabetes mellitus, stroke subtype, various laboratory markers, such as dyslipidemia, and hormonal alterations, such as thyroid hormone, are among the many risk factors for PSF that have been previously examined. The link between the thyroid function profile and PSF in both the acute phase and the follow-up period of cerebral vascular stroke has only been the subject of a few investigations [7].

METHODS

This prospective cohort study was carried out in the stroke sections of the Neurology department from August 2022 to January 2023. Within 48 hours of the first ever AIS onset, we hospitalized 70 (seventy) individuals who were >18 years old.

Exclusion criteria: The study excluded participants with transient ischemic attacks, hemorrhagic strokes, prior stroke histories, traumatic brain injuries, cancer, and pre-existing neuropsychiatric diseases such depression, Parkinsonism, Alzheimer disease, and central nervous system infections.

All patients underwent a thorough medical history review, a thorough neurological assessment, and consideration of stroke risk factors. Initial CT and/or MRI brain scans were performed to determine the topography of AIS and to confirm the diagnosis. ECG, cardiac echocardiography, and carotid doppler were also performed.

Different scales used:

The National Institutes of Health Stroke Scale (NIHSS) measures the severity of a stroke and ranges from 0 to 42. It is tested at day 0 and 30 days after the onset of an ischemic stroke. No stroke symptoms = 0, minor stroke (1-4), moderate stroke (5-15), moderate/severe stroke (16-20), and severe stroke were the classifications used by the NIHSS. (21-42). A change in the NIHSS of plus or minus 4 points or more indicates an improvement or deterioration [8].

Fatigue severity scale (Fss): used to determine post-ischemic stroke fatigue 30 days after the acute ischemic stroke. The nine-item questionnaire includes inquiries on how fatigue affects particular activities, grades its intensity using a self-reported scale, and assigns points to each item on a scale of 1 to 7. Fatigue Severity is measured on a 7-item scale, with 1 being strongly disagree and 7 being strongly agree. (7). Patients with an FSS score of 4 or above were classified as having fatigue, whereas those with a score of 4 or higher had moderate or mild fatigue [9].

Laboratory investigations:

Complete blood count (CBC), Liver function test (LFT) , kidney function test (KFT) , Hemoglobin A1C (HbA1C), lipid profile, calcium and highly sensitive c- reactive protein (CRP).

Special Laboratory Investigations: Serum levels of FT3, FT4 were quantified by RIA (radioimmunoassay) and TSH by IRMA (immunoradiometric assay) at biochemistry laberatory of zazazig university hospitals. Normal range in our laboratory for FT3 is 3.5-6.5 pmol/l. Normal range for FT4 is 11.9-26.0 pmol/l. Normal range for TSH is 0.3-5.0 miu/ml. Blood samples for FT3, FT4, and TSH levels were Collected within 48 hours of acute ischemic stroke onset. Above data collected to classify stroke subtypes according to Trial of Org 10172 in Acute Stroke Treatment (TOAST) **(10)**, into Large-artery diseases, cardioembolic, small-vessel diseases, stroke of other determined etiology and stroke of undetermined etiology was further divided into no cause was found despite an extensive work up (cryptogenic stroke) or two or more plausible cause we're found.

Ethical Considerations:

The study was approved by ethical committee of the faculty of medicine at Zagazig University Written informed consent was obtained from all participants. The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical Analysis:

With SPSS software version 18, data were examined (USA). The parametric data shown as mean SD or as a percentage. Unpaired statistics were used to compare the data from the various groups. For parametric data, use the Student's t-test; for categorical data, use the Fischer exact test and the Chi square test. To find relationships between variables, pearson correlation was used.

The degree of importance will be determined at P<0.05.

RESULTS

In the current study, the mean age of patients was 63.2 ± 12.1, 51% were male. According to TOAST classification, 38.6% of patients had large artery occlusion, 25.7% had cardioembolic, 15.7% had small artery occlusion and 20% had undetermined causes. According to oxfordshire classification, 50% of patients had partial anterior circulation, 20% had total anterior circulation, 17.2% had lacunar syndrome and 12.8% had posterior circulation. The mean NIHSS was 10.8±7.5 and 16% of patients had PSF according to FSS (Table 1, figure 1). There was significant difference between patients with fatigue and those without fatigue regarding NIHSS that was higher in patients with fatigue than those without fatigue, while there was no significant difference regarding TOAST and oxfordshire (Table 2). There was significant difference between patients with and without fatigue regarding cholesterol, LDL and FT4 that were higher in patients with fatigue than those without fatigue. Also, there was significant difference regarding TSH and FT3 that were lower in patients with fatigue than those without fatigue while there was no significant difference regarding other laboratory data (table 3). There was significant negative correlation between fatigue severity scale and TSH and FT3 (Table 4, figure 2, 3). After using multivariate logistic regression analysis, dyslipidemia, NIHSS, TSH and FT3 are predictors for PSF (Table 5).

Table (1): Baseline data of the studied group

Variable	Number Patients= 70	%
Age, y	63.2 ±12.1	
Gender Male female	 36 34	 51% 49%
Stroke subtype according:		
***TOAST :**		
Large artery occlusion	27	38.6 %
Cardioembolic	18	25.7 %
Small artery occlusion	11	15.7 %
undetremined	14	20 %
***Oxfordshire:**		
Total anterior circulation	14	20 %
Partial anterior circulation	35	50 %
Posterior circulation	9	12.8 %
Lacunar syndrome	12	17.2 %
Stroke severity(NIHSS), M±SD	10.8±7.5	
Fatigue frequency (FSS)	11	16%

Table 2: Comparison between those with and without fatigue regarding stroke severity and subtype according to TOAST and Oxfordshire classification.

variable	Pt without fatigue (59)	Pt with fatigue (11)	test	p
NIHSS, M ± SD	**8.4** ±5.6	**13.2**±6.3	**2.36**	**<0.05**
***TOAST:**			**7.3**	**>0.05**
Large artery occlusion	**24**	**3**		
cardioembolic	**11**	**6**		
Small artery occlusion	**10**	**1**		

variable	Pt without fatigue (59)	Pt with fatigue (11)		
undetremined	**14**	**1**		
***Oxfordshire:**				
Total anterior circulation	**12**	**2**	**3.97**	**>0.05**
Partial anterior circulation	**28**	**7**		
Posterior circulation	**11**	**1**		
Lacunar syndromes	**8**	**1**		

Table (3): Comparison between patient with and without fatigue regarding laboratory data.

Variables	Without Fatigue patients (N=59)	Fatigue patients (N=11)	T	P
Hb	13.2 ± 1.67	13.1 ± 1.01	0.3	0.76
WBCs	10.2 ± 3.6	10.2 ± 3.8	0.01	0.98
PLT	230.4 ± 89.4	217.7 ± 75.4	0.44	0.65
ALT	18.7 ± 7.7	18.2 ± 5.5	0.19	0.84
AST	26.2 ± 10.1	25.2 ± 10.06	0.31	0.75
Creatinine	0.89 ± 0.28	1.07 ± 0.27	-1.9	0.05
Hba1C	6.9 ± 1.77	7.34 ± 1.9	-0.59	0.55
Calcium	9.2 ± 0.67	9.2 ± 0.72	-0.05	0.95
HS-CRP	10.1 ± 9.6	9.34 ± 6.9	0.25	0.8
Cholesterol	155.9 ± 37.6	192.2 ± 38.5	2.87	**<0.01***
TG	131.4 ± 71.4	89.5 ± 43.5	1.87	0.06
HDL	40.1 ± 8.9	41.2 ± 8.04	-0.36	0.71
LDL	93.5 ± 35.5	122.09 ± 28.7	2.9	**<0.001 ***
TSH	3.5± 2.89	1.67 ±1.86	2.68	**<0.05***
FT3	6.5± 5.8	3.7±1.5	3.18	**<0.01***
FT4	20.8±18.2	45.1±37.5	2.4	**> 0.05**

Table (4): Correlation between fatigue severity scale results and thyroid hormones.

Variable	R	p
TSH	-0.52	0.01 *
FT3	-0.74	0.001 *
FT4	+0.18	0.24

Table (5): Multivariate logistic regression analysis of factors predicting post stroke fatigue.

Variables	S.E.	Sig.	Exp(B)	95% C.I.for EXP(B)	
				Lower	Upper
Age	0.04	0.895	1.005	0.93	1.087
Gender	1.079	0.9	0.873	0.105	7.236
DM	0.786	0.42	1.884	0.404	8.786

HTN	1.048	0.603	0.58	0.074	4.522
Dyslipidemia	5.7	**0.01***	6.1	3.14	6.15
Cardiac	0.807	0.491	0.573	0.118	2.791
NIHSs	2.88	**0.03***	1.67	2.07	3.18
TSH	-3.5	**0.03***	0.34	0.16	0.67
F T3	2.7	**0.04***	2.71	1.64	4.12
F T4	0.68	0.34	0.91	0.27	2.81

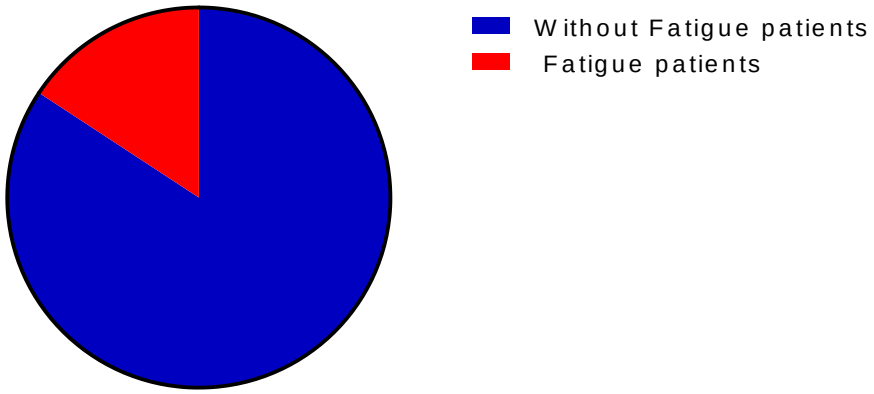

Figure (1): Frequency of fatigue among the studied cohort according to results of fatigue severity scale (FSS).

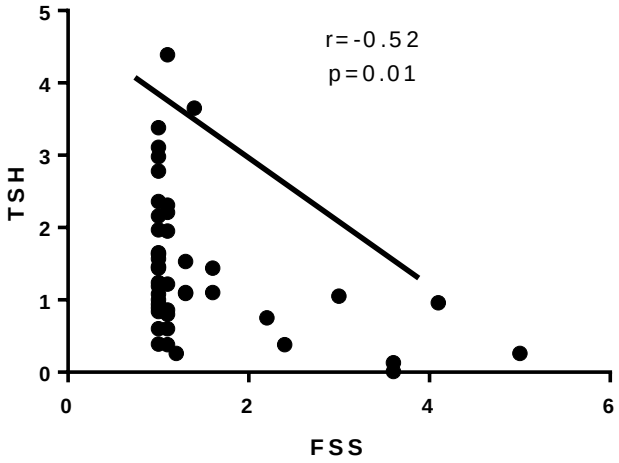

Figure (2): Correlation between fatigue severity scale results and TSH

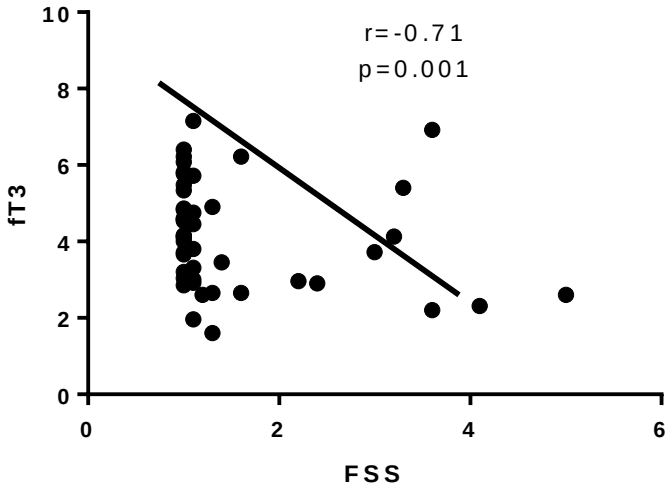

Figure (3): Correlation between fatigue severity scale results and FT3

DISCUSSION

An important issue that requires thorough assessment and quantification of stroke potential risk factors is the examination of "poststroke fatigue" (PSF) in stroke patients who have survived the initial insult. This could help to reduce morbidity in AIS patients, improve treatment, and enhance functional outcome as a specific post stroke [11].One of the largest endocrine glands, the thyroid produces, stores, and secretes thyroid hormones. Recent research from a number of studies has shown that thyroid dysfunction affects post-stroke fatigue [12].

Stroke risk and outcomes are impacted by thyroid disorders. Hypothyroidism can result in heart dysfunction, hypertension, hypercholesterolemia, hypo- and hypercoagulability, all of which are stroke risk factors. Atrial fibrillation, which is a prevalent cause of cardioembolic stroke, and hyperthyroidism are both connected [13]. Thyroid hormones and functional outcomes after stroke have a complicated relationship. According to recent research, low T3 levels are linked to worse functional outcomes, increased stroke severity, and mortality after acute ischemic stroke and PSF [14-15]. The average patient age in the current study was 63.2 12.2, and 51% of the patients were men. 38.6% of patients had big artery occlusion, 25.7% had cardioembolic, 15.7% had minor artery occlusion, and 20% had unknown reasons, according to the TOAST classification. According to the Oxfordshire classification, 12.8% of patients had posterior circulation, 17.2% had lacunar syndrome, and 50% of patients had incomplete anterior circulation. According to FSS, the mean NIHSS score was 10.8 7.5, and 16% of the patients had PSF. Regarding NIHSS, which was greater in patients with fatigue than in those without fatigue in the current study, there was a significant difference between patients with fatigue and those without fatigue, however there was no significant difference with regard to TOAST and oxfordshire. In line with our work, Lee et al [2] demonstrated a significant difference in NIHSS between patients with and without PSF. Regarding cholesterol, LDL, and FT4, which were greater in patients with fatigue than in those without fatigue, there was a significant difference between patients with and without fatigue in the current study. Moreover, patients with fatigue had significantly lower TSH and FT3 levels than patients without fatigue, although other laboratory results showed no significant differences. According to van de Ven et al [16], thyroid dysfunction (either clinical or subclinical) affects stroke fatigue in healthy euthyroid people. This finding is consistent with our own research. Moreover, Wang et al. [6] demonstrated that higher levels of TSH (odds ratio [OR] 0.39, 95% confidence interval [CI] 0.33 -0.46) were associated with a decreased risk of PSF and that total cholesterol (p = 0.015) was substantially different in the acute phase fatigue. Moreover,

Kumral et al. [17] found that dyslipidemia was linked to stroke fatigue and recurrence after a 5-year follow-up in their study of individuals who had ischemic strokes. In contrast to our study, Lee et al [2] demonstrated that while the PSF group had a significantly higher ESR and longer aPTT than the non-PSF group, no variable in the biochemical tests was found to have a significant difference between the groups. The same was true for no variable in the endocrinological tests. A varied sample size could be the cause of this variation. In the current study, there was a strong inverse relationship between the fatigue severity scale, TSH, and FT3, where low levels of T3 were correlated with higher scores and greater levels of TSH were correlated with lower scores. According to recent research, low T3 levels within hours of an acute infarct are linked to increased fatigue, increased stroke severity and mortality, and worse functional outcomes [14-15]. Wang et al [6] demonstrated that whereas FT4 was favourably connected to PSF and reached a significant difference (= 0.10, p = 0.007), TSH was negatively related to PSF (= 0.70, p 0.001).In the current study, dyslipidemia, NIHSS, TSH, and FT3 are predictors for PSF after utilising multivariate logistic regression analysis.In line with our work, Wang et al [6] found that in the multivariate analysis, PSF was independently correlated with both TSH (= 0.34, p = 0.008) and FT3 (= 2.54, p 0.001). They suggested that TSH served as a defence against PSF. Increased TSH in the complete range of thyroid function reduced the risk of PSF by 70%, and increased TSH in the full range of thyroid function reduced the risk of PSF by 60%. Those who had greater TSH levels across the complete spectrum of thyroid function had a 30% lower risk of PSF six months after the first stroke. One possibility is that elevated basal metabolic rate results from aberrant TSH serum levels. The result is the production of too many free radicals and reactive oxygen species, which causes neurotoxic cytotoxicity [18]. Furthermore, the high energy and oxygen demand may compromise ischemia tolerance. A compensatory mechanism between TSH and elevated FT4 may exist, and it played a significant part in the relationship between thyroid function profiles and PSF [19].

CONCLUSIONS

Our findings showed that 16% of patients experienced post-stroke fatigue. Individuals who experienced post-stroke fatigue also had altered thyroid function, indicating a potential role for neuroendocrine responses in PSF.

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