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ORIGINAL ARTICLE

Parathyroid Hormone and Fatigue after Spontaneous Non-Aneurysmal Subarachnoid Hemorrhage.

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ABSTRACT

Background: Spontaneous non-aneurysmal subarachnoid hemorrhage (NASAH) is debilitating, and survivors often complain of fatigue. Fatigue and diffuse musculoskeletal pain are also common symptoms of elevated parathyroid hormone (PTH) levels. A possible association between fatigue and PTH in subarachnoid hemorrhage (SAH) survivors has not yet been established. The aim was to study the relation between PTH and fatigue after NASAH in a period over six months.

Methods: A single-center observational study was conducted among 56 NASAH survivors and 60 healthy people as the control group. Fatigue was measured with the Arabic version of the Chalder Fatigue Scale and its relationships with other clinical variables were examined.

Results: Among the enrolled NASAH survivors, 46 (82%) exhibited pathological fatigue one month after SAH and 33 (59%) enrolled patients exhibited pathological levels of fatigue at follow up after six months of illness**.** PTH was significantly high in NASAH than in the control group. High PTH (>49 ng/L) is associated with an increased risk of fatigue after SAH and was an independent risk factor of fatigue directly after SAH (P = 0.02). **Conclusion**: In patients with NASAH, fatigue worsened functional outcomes. An elevated serum PTH level may be an independent risk factor for fatigue after NASAH.

Keywords: fatigue, parathyroid hormone, subarachnoid hemorrhage**,** outcome

INTRODUCTION

Subarachnoid hemorrhage (SAH) accounts for 5% of all cases of stroke. In about 10% of the SAH cases no aneurysm is found. The mean age of SAH onset is 50 years, which is relatively low compared to the other types of stroke, and approximately 55% of patients survive SAH and regain independent functioning **(1).** Therefore, any adverse long-term deficits affect survivors' ability to continue their previous social roles, including returning to work **(2).**

Fatigue is one of the major consequences after SAH at frequencies from 31% to 90% depending on the type of SAH and timing post-SAH **(2,3).** There are several putative pathological mechanisms that might, theoretically, trigger fatigue after SAH. Systemic inflammation may alter neurotransmitter signaling in the brain by altering the activity of enzymes such as indoleamine 2,3-dioxygenase, while disruption in fronto-subcortical neurocircuits due to complications of SAH, such as delayed ischemia or hydrocephalus may lead to the subtle impairment of attention, arousal and subsequent fatigue **(4,5).** Neuroendocrine changes may also contribute to fatigue development in SAH patients **(1).**

Parathyroid hormone (PTH), a prohormone, which is secreted by the chief cells of the parathyroid glands as an 84 amino acids polypeptide **(6).** The parathyroid hormone is a principal regulator of calcium and is responsible for the normal functions of bones and the kidney **(7).** Patients who were diagnosed with hyperparathyroidism exhibit a vast number of symptoms including memory and concentration problems, irritability, depression, anxiety, sleep problems, bone/joint pain, and fatigue which was the most common **(8).** Sleep impairment and insomnia significantly detriment the patient's quality of life, have been associated with nearly 44% and 62% of hyperparathyroidism cases **(9).**

To our knowledge, no previous study has investigated the association between fatigue in

spontaneous non-aneurysmal SAH (NASAH) and serum PTH value. Therefore, in this research we tried to further study the reason for fatigue after NASAH by evaluating the level of serum PTH in patients with these complaints at six months follow-up.

METHODS

This prospective observational study was carried out in Intensive Care Units from February 2019 to January 2020. Written informed consent was obtained from all participants or their next of kin, the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

The patient inclusion criteria were: [1] spontaneous SAH with etiology of NASAH confirmed through CT angiography carried out using Philips Ingenuity core 128 TM v3.5.7.25001 (Philips healthcare systems, Netherlands) at Zagazig University Hospital [2] hospital admission within 48 h after ictus; [3] more than 18 years of age; [4] informed consent from the patients or their next of kin. Exclusion criteria were aneurysmal subarachnoid hemorrhage, chronic hepatic or renal disease, previous history of strokes, cardiac disease, and pregnant females. Patients with a known history of psychiatric disorders, autoimmune diseases, blood diseases, cancer or subjects using supplemental calcium or vitamin D in the previous four months or patients on anticoagulant, antihistaminic or sedatives drugs were also excluded. Assuming all cases that met the inclusion and exclusion criteria will be included in the study. During the study period, 56 cases were included as a comprehensive sample. Accordingly, 60 healthy individuals matched for age and gender, selected from the relatives of the patients served as a control group.

Blood samples (2 mL of venous blood) were collected under aseptic conditions from all participants into tubes containing an anticoagulant (EDTA) within 48 h from admission and stored at -80ºC. Serum levels of ionized calcium, parathyroid hormone, and vitamin D were evaluated in all cases. The reference interval of ionized calcium in adult was 4.4 to 5.4 milligrams per deciliter (mg/dL), parathyroid hormone was 10-55 ng/L **(10)**, and that of vitamin D was <20 ng/mL (deficiency), 20–29 ng/mL (insufficient), and 30–100 ng/mL (normal) **(11).**

All patients were assessed by the National Institutes of Health Stroke Scale (NIHSS) **(12)** at the acute stage of SAH.

In the Follow up after one month from the onset of NASAH, the modified Rankin Score (mRS) were collected. The mRS is a scale for measuring the patient's disability post-stroke. It has a score of 0–5, with 0 indicating no limitations or symptoms, and 5 being severe disability indicating constant care **(13).** Fatigue was evaluated according to the Arabic version of the Chalder Fatigue Scale (CFS) **(14)** The CFS is a multidimensional scale that evaluates fatigue in two dimensions, physical and mental fatigue. It is a self-report questionnaire with 11 items (7 physical and 4 mental fatigue items), Items are rated on a 4-point Likert scale (0 = better than usual, 1 = no more than usual, 2 = worse than usual, 3 = much worse than usual), with higher scores indicating greater fatigue. with scores ranging from zero to 11. The CFS scores were used as an ordinal variable to evaluate fatigue severity. Patients with a score of four or more were considered to have pathological fatigue **(15).**

Lawton Instrumental Activities of Daily Living Scale (IADL) scale is used to assess the deficits in the performance of everyday activities of the patient**.** It is composed of eight items: telephone usage, shopping, food preparation, housekeeping, laundry, mode of transportation, responsibility for own medications and managing finances. The score ranges from zero (low functioning:= dependent) to eight (high functioning: = independent). Assistance in IADL was defined as the needing for help with one or more activities (16).

Patients were reevaluated six months after the onset of NASAH for mRS, CFS, and IADL scales.

Statistical analyses of all the tests were done using the statistical package of social science (SPSS version, 22) 4th ed. Chicago: SPSS Inc.2013. Results are expressed as percentages for categorical variables and as medians ± standard deviation (SD) for the continuous variables. The Mann-Whitney U test and Chi-square test were used for comparison among the two groups. The influence of vitamin D and parathyroid hormone levels on functional outcome and fatigue were assessed by odds ratios (ORs) and their 95% confidence intervals (95% CIs). Spearman's correlation analysis was carried out between selected study parameters. To examine the associations between PTH serum levels and the frequency of fatigue, subjects were categorized

according to PTH quartiles Q1-Q4: wherein, Q1: 10-31 ng/L, Q2: >31-39 ng/L, Q3:>39-49 ng/L and Q4: >49-189 ng/L. All statistical analyses were performed with SPSS for Windows, version 22 (SPSS Inc., Chicago, IL, USA). Statistical significance was defined as p <0.05.

RESULTS

A total of 56 patients with non-traumatic SAH were enrolled in this study, in the age group of 40– 67 years, and 35 (62.5%) were males. The mean (±SD) NIHSS score on admission was 16.14 ± (7.85). The profiles of the recruited patients, the control groups, and the results from the laboratory evaluation are shown in **table (1, 2).** Vitamin D was lower in the NASAH group than the control group but with no significant difference (P = 0.1), however, the PTH was significantly high in the patient group (P= 0.03) than that in the control group. On the contrary, the calcium level in the two groups showed no significant difference (P = 0.2).

Parathyroid hormone (PTH) exhibited a significant positive correlation with NIHSS score at time of admission (P < 0.004), and a significant correlation with CFS scale (P = 0.03, P < 0.001), mRS scale (P < 0.001, P = 0.002), and IADL scale score (P = 0.01, P < 0.001), respectively, at one month and six months follow-up. On the other hand, there was a significant negative correlation of vitamin D with the CFS scale (P < 0.001), and a significant positive correlation with IADL score (P < 0.001) only after six-month follow up. Vitamin D level also had a significant negative correlation with mRS scale score but only in the one month follow up after the ictus (P<0.001). Table (3).

In the follow up after 6 months, 58.9% of patients had reported fatigue (CFS ≥4) and had a highly significant increase in PTH level and significant decrease in vitamin D when compare with patients without fatigue (P <0.001, 0.012) respectively. A significant higher percentage of diabetic patients among those with fatigue after NASAH than those without (P= 0.03). table (4)

Among our patients, the incidence of fatigue was 82.1% at one month follow-up after NASAH and 58.9% at the six-month follow-up. The risk of fatigue early after one month follow-up was significantly associated only with serum level of PTH >39 (OR 6.82, 95% CI: 1.29-35.95) (P = 0.02). For the fatigue assessment at follow-up after six months, high risk was associated with; age ≥ 50 years (OR 5.06, 95% CI: 1.38-18.57), (P = 0.01) hypertension (OR 0.11, 95% CI: 0.13-0.91) (P = 0.04), NIHSS score > 15(OR 0.24, 95% CI: 0.07-0.89) (P = 0.03), mRS ≥ 3 at first month after SAH (OR 17, 95% CI: 2.9-99.76) (P = 0.01), and decrease in vitamin D level (OR 6.3, 95% CI: 1.22-31.90) and was highly significantly associated with PTH> 39 (OR15.92, 95% CI: 3.18-79.78) (P < 0.001) **Table (5).**

In this study, patients were categorized into four study groups according to the serum level of PTH. A significant decline in the level of fatigue over time was observed for patients in group Q1, CFS declined by 2.6 points from 4.69±2.07 acute stage of SAH to 2.07±1.61 at six months (P = 0.008). CFS score in the Q2 group also decreased from (5.61±1.65) to (5.5±2.85) at six-month follow up but did not show a significant difference (P = 0.89). The Q3 and Q4 groups exhibited an insignificant increase in the CSF scale score (p = 0.81, 0.15) respectively. **Figure (1)**

Table (1): Demographic data and Clinical characteristics of the patients:

Character	Patients (56)	Control (60)	P
Age	53.3±7.13	52.4±7.8	0.5
gender male Female	35 (62.5 %) 21 (37.5%)	36 (60%) 24 (40%)	0.8
Hypertension	34 (60.7%)	28 (46.7%)	0.13
Diabetes mellitus	29 (51.8%)	33 (55%)	0.7
smoking	28 (50%)	34 (56%)	0.5
BMI (kg/m^2)	32.06±8.64	30.8±7.68	0.41
Ionized calcium (mg/dL)	4.7±0.26	4.5±1.03	0.2
Vitamin D	13.1± 9.51	15.8±6.7	0.1
PTH (ng/L)	43.02±20.62	35.8±15.6	0.03*

BMI: body mass index, PTH: parathyroid hormone

*: statistically significant at P<0.05.

Table (2): clinical data of SAH patients:

	Patients (56)	P
mRS at one month follow up	3.62± 1.17	<0.001*
mRS at 6 months follow up	1.36± 1.12	
The CFS in one month follow up	7.3±2.32	0.03*
The CFS at 6 months follow up	6.2±3.1	
IADL after in one month follow up	5.12± 2.35	0.005*
IADL at 6 months follow up	6.26± 1.93	
NIHSS at admission	16.14±7.85	

SAH: subarachnoid hemorrhage, mRS: modified Rankin Score, CFS: the Chalder Fatigue Scale, IADL: The Lawton Instrumental Activities of Daily Living, NIHSS: National Institutes of Health Stroke Scale.

*: statistically significant at P<0.05.

Table (3): Correlation between the clinical characteristics and scales of patient and serum level of PTH and vitamin D:

		Vitamin D		PTH	
		r	P	R	P
CFS Score	**At one month follow up**	-0.083	0.57	0.31	0.03*
	At 6 months follow up	-0.54	**<0.001***	0.68	<0.001**
IADL score	**At one month follow up**	0.307	**0.03***	-0.34	0.01*
	at 6 months follow up	0.45	**<0.001***	-0.51	<0.001**
mRS score	**one month follow up**	-0.47	**<0.001***	0.59	<0.001**
	at 6 months follow up	-0.297	**0.036***	0.43	0.002**
BMI		0.12	0.39	0.084	0.56
AGE		-0.008	0.96	0.14	0.35
NIHSS at admission		-0.24	0.09	0.402	0.004**

mRS: modified Rankin Score , CFS: the Chalder Fatigue Scale, IADL: The Lawton Instrumental Activities of Daily Living, NIHSS: National Institutes of Health Stroke Scale, BMI: body mass index, PTH: parathyroid hormone.

*: statistically significant at P<0.05

Table (4): comparison between SAH patients with fatigue and those without fatigue after 6 months follow up

	Patients without fatigue (CFS<4) (23 patients, 41.1%)	Patients with fatigue (CFS ≥ 4) (33 patients, 58.9%)	P
	Mean ±SD	Mean ±SD	
Age	52.13±7.43	54.12±7.23	0.3
Gender male **Female**	16 (69.6%) 7 (30.4%)	19 (57.6%) 14 (42.4%)	0.46
BMI	30.1±9.13	32.39±8.65	0.4
Hypertension	14 (60.9%)	20 (60.6%)	0.9
Diabetes mellitus	8 (34.8%)	21 (63.6%)	**0.03***
Smoking	10 (43.5%)	18 (54.5%)	0.4
NIHSS	13.7±7.32	17.84±6.72	**0.03***
Ionized calcium	4.39±0.49	4.21±0.76	0.32
Vitamin D	19.48±10.73	13.45±6.62	**0.012***
PTH	61.48±14.56	76.12±7.24	**<0.0001****

SAH: subarachnoid hemorrhage, CFS: the Chalder Fatigue Scale, NIHSS: National Institutes of Health Stroke Scale, BMI: body mass index, PTH: parathyroid hormone.

*: statistically significant at P<0.05.

Table (5): Risk factors of fatigue among SAH patients:

	Fatigue (CFS ≥ 4) at one month follow up. (46 patients, 82.1%)		**Fatigue (CFS ≥ 4) at 6 months follow up. (33 patients, 58.9%)**	
	OR	P	OR	P
Age ≥50	1.2 (0.25-5.8)	0.82	5.06 (1.38-18.57)	0.01*
Male sex	0.54 (0.097-3.02)	0.48	0.63 (0.16-2.39)	0.5
BMI≥ 25	0.60 (0.09-3.61)	0.58	0.69 (0.13-3.82)	0.67
Hypertension	0.26 (0.03-2.29)	0.22	0.11 (0.13-0.91)	0.04*
Diabetes mellitus	2.71(0.57-12.90)	0.21	1.05 (0.30-3.66)	0.94
Smoking	0.73 (0.15-3.44)	0.69	0.62 (0.17-2.22)	0.5
NIHSS >15	0.33 (0.07-1.59)	0.17	0.24 (0.07-0.89)	0.03*
mRS at one month follow up ≥3	0.28(0.052-1.48)	0.13	17 (2.9-99.76)	0.01*
Ionized calcium	1.04 (0.12 ± 3.22)	0.74	1.23 (0.34 ± 3.25)	0.57
Vitamin D < 30	3.17 (0.47-21.24)	0.24	6.3 (1.22-31.90)	0.03*
PTH >49(ng/L)	6.82(1.29-35.95)	0.02*	15.92(3.18-79.78)	<0.001**

SAH: subarachnoid hemorrhage, mRS: modified Rankin Score, CFS: the Chalder Fatigue Scale, NIHSS: National Institutes of Health Stroke Scale, BMI: body mass index, PTH: parathyroid hormone.
*: statistically significant at P<0.05.

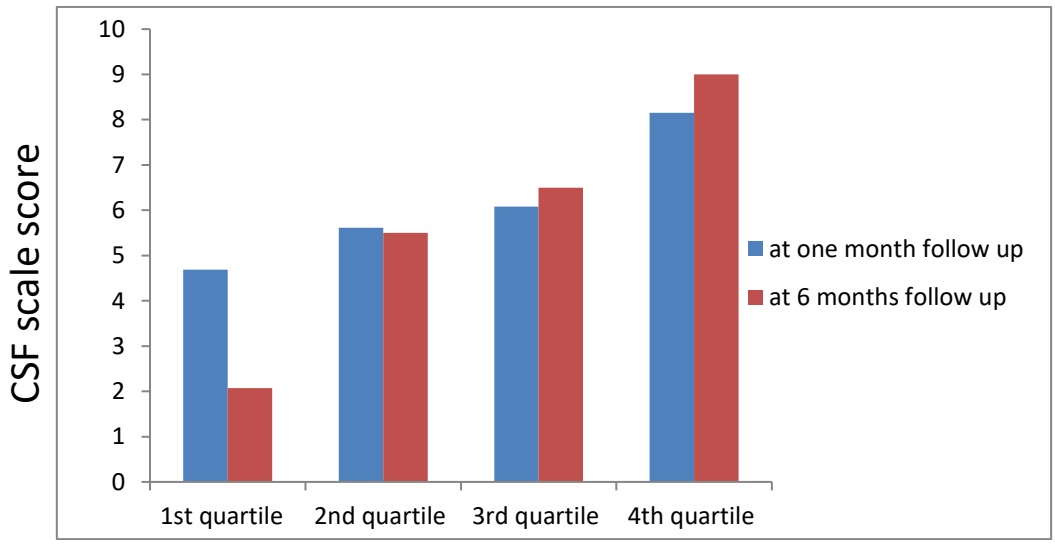

Figure (1): Mean score of the Chalder Fatigue Scale (CFS) and standard error in patients with SAH according to the serum level of PTH in different quartile, measured at the one month and six months follow up after NASAH

DISCUSSION

Fatigue is a common and often debilitating outcome of both ischemic and hemorrhagic stroke. Post stroke fatigue exerts a negative impact on a patient's daily activities, neurological recovery, rehabilitation, and may increase the rate of mortality (17).

The purpose of this study was to determine whether the PTH level can predict fatigue in NASAH, as well as to describe its role in delayed fatigue.

Parathyroid hormone (PTH) levels were found to be significantly elevated in SAH patients. **Macdonald and colleagues, (18)** reported a marked increase in PTH and PTH receptors after SAH. **Randhawa and colleagues (19)** reported a slight elevation, not of statistical significance, in PTH level in SAH patients on admission. These

results were further elucidated by **van den Bergh and colleagues (20)** who indicated that, an increase of the PTH levels after SAH is probably a feature of the acute phase response which was found to be associated with other inflammatory markers, and that its elevation may suggest prolonged persistence of inflammatory processes leading to an overall poorer outcome.

In this study fatigue was reported among our patients according to CFS scale, one month after NASAH (7.3±2.32) and at 6 months follow-up (6.2±3.1). **Rödholm and colleagues (21)** found that fatigue is more common early after SAH and less frequent after one year. However, the studies which followed patients up to seven years after SAH also showed a high frequency of fatigue, indicating that it persists over long time periods after ictus **(22).** Fatigue early after SAH may be attributed to the effect of subarachnoid blood on the cerebral cortex, neuroendocrine and inflammatory changes, while later after ictus it may be associated with mood disorders and other consequences of SAH **(23).**

Although the observable decline in the number of patients with a pathological level of fatigue over time, the proportion of patients with pathological fatigue remained high (58.9%) even after 6 months. Our results are in accordance with **Passier and colleagues (2) and Visser-Meily and colleagues (5)** who showed high levels of fatigue after SAH in a large proportion of subjects.

Our data suggest that serum PTH level was associated positively with the risk of fatigue one month after NASAH independent of vitamin D status. At six months after NASAH, the risk of fatigue increased with a higher PTH serum level. To the best of our knowledge, this is the first survey to elaborate on the relationship of PTH with fatigue in NASAH.

Nilsson and colleagues (24) discovered dysregulation in the cardiac autonomic nerve in patients with hyperparathyroidism. This cardiac autonomic nerve dysfunction may disturb the normal circadian rhythm and alter sleep. Furthermore, there is evidence of a link between PTH level and sleep. Parathyroid hormone (PTH) was found to stimulate osteoblasts to produce the pro-inflammatory cytokine interleukin-6 (IL-6), which was shown to enhance slow-wave non-rapid eye movement sleep **(25),** fatigue was significantly correlated to sleep duration, time spent awake during the night, sleep efficiency, and sleep-related tension and distress **(26).**

Several authors cite hyperparathyroidism as a differential diagnosis of musculoskeletal diseases, and there are reports of cases of primary hyperparathyroidism (PHP) mistakenly diagnosed as fibromyalgia (FM) **(27). Ferrari and Russell (28)** determined a significantly high prevalence of PHP in a sample of patients with FM, in patients with diffuse pain who did not meet criteria for FM, and in a group of patients with localized musculoskeletal pain than that observed in the general population. The results of their study indicated a possible association between PHP and diffuse or localized musculoskeletal pain.

Higher PTH concentrations are associated with increased mortality risk among older populations **(29)**. Parathyroid hormone (PTH) may also increase risk of cardiovascular disease via proinflammatory pathways. Elevated PTH level has been associated with increased cardiac contractility, cardiomyocyte hypertrophy, and impaired endothelial functions **(30)**. Elevated PTH levels are also related to impaired vascular function, increased vascular stiffness, increase carotid and brachial artery intima–media thickness, and increased systolic and diastolic blood pressure **(31)**. Previous studies showed that increased levels of PTH are associated with high risks for cardiovascular morbidity and mortality **(32).** Elevated PTH levels may also be related to nonfatal atherosclerotic in peripheral and central large arteries **(33).**

PTH has also been shown to have direct effects on the brain function. Elevated PTH levels correlate with reduced regional cerebral blood flow and are considered to play a role in decreased cerebral processing speed potentially and cognitive impairment via increased vascular calcification, or endothelial dysfunction **(31).** Excess PTH in animal models has been linked to vasoconstriction by enhance release of vasopressin **(34).** Elevated PTH was also found to cause deterioration in the hippocampal neuronal and glial cells through paradoxical Ca^{2+} overload **(35)**

In our study, patients with SAH were found to have a higher prevalence of vitamin D deficiency as compared to normal individuals, although the difference was not significant. Vitamin D receptors play an important role in the expression of factors, such as vascular endothelial growth factor, and enzymes, such as metalloproteinases, that affect the development and remodeling of vessels **(36).** Vitamin D was found to have anti-proliferative effects on smooth muscle cells in the walls of arteries in addition to potent anti-inflammatory effects **(37).**

According to our results, decrease of vitamin D has a significant effect on fatigue in follow up after six months. Vitamin D appears to be necessary for function of skeletal muscle as well and its deficiency has been associated with nonspecific musculoskeletal pain**,** chronic pain**,** low back pain**,** and myopathy**.** Some researchers have even suggested a link between vitamin D deficiency and all-cause mortality **(38).**

Interestingly, baseline calcemic status had no prognostic value in the present study, probably due to the low number of subjects with PHP. The tight regulation of Ca^{2+} by PTH and vitamin D may also explain the lack of prognostic significance of Ca^{2+} levels in this population. One of the limitations of our study was that although we used an Arabic version for the scale of fatigue, it is still a self -report subjective questionnaire. Also, we measured PTH, Vit D and calcium level once at acute stage. we recommend a longer follow up study with regular evaluation of PTH level.

CONCLUSION

elevated serum PTH (>49 ng/L) level is associated with early fatigue one month after NASAH. This observation was independent and was not explained by Ca^{2+} levels, vitamin D, BMI, or age. It also, associated with delayed fatigue. The request of a laboratory measurement of PTH serum level may be suggested in the evaluation of patients with NASAH. These findings should encourage larger studies to dissect further the involvement of PTH in mechanisms of fatigue in patients with cerebrovascular disease.

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