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Malnutrition and nonthyroidal illness syndrome after stroke

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Abstract

In the present study, nonthyroidal illness syndrome (NTIS), which is characterized by reduction of serum triiodothyronine (T3) without elevation of thyroid-stimulating hormone (TSH), was induced by protein-energy malnutrition (PCM). Protein-energy malnutrition is a common condition and is associated with worse clinical outcome in stroke patients admitted to a rehabilitation service. However, little is known about NTIS in stroke patients. Therefore, we studied the effects of PCM and NTIS on functional dependence in 51 stroke patients. We examined thyroid function by measuring serum free T3 (free T3), free thyroxine (free T4), and TSH. We estimated whether patients had mild NTIS (reduction of only free T3) or serious NTIS (reduction of both free T3 and free T4), examined PCM by measuring serum albumin, calculated body mass index (BMI) from weight and height on admission, and examined disability by obtaining the functional independence measurement (FIM). The 51 patients were divided into 2 groups according to FIM score on admission (low and high). The low-FIM group was divided into 2 subgroups according to the change in FIM score during hospitalization (improved or non-improved). Hypoalbuminemia was observed in 57% of patients, underweight in 22%, and mild NTIS in 82%; serious NTIS was not observed in any patients. Albumin and BMI were significantly higher in the high-FIM group than in the low-FIM group. Serum albumin concentration and BMI significantly positively correlated with free T3. Free T3 (but not albumin or BMI) was significantly higher in the improved subgroup than in the non-improved subgroup. Nonthyroidal illness syndrome after stroke was common and was provoked by PCM, which occurred in a high proportion of functionally dependent patients. It appears that, once stroke patients develop NTIS, it is difficult to achieve functional improvement. Therefore, during the recovery period after stroke, it is important to determine whether NTIS is present and ensure proper intensive rehabilitation and nutritional management.

1. Introduction

Protein-energy malnutrition (PCM) is commonly seen in the context of a wide variety of acute and chronic illnesses that lead to depletion of body fat, muscle wasting, and multiple signs of micronutrient deficiencies [1]. In a previous study, PCM was observed in 49% of the stroke patients admitted to a rehabilitation service, and PCM has been found to be associated with worse clinical outcome in stroke patients [2-6].

Protein-energy malnutrition and a variety of illnesses lead to decreased serum concentrations of triiodothyronine (T3) without causing elevated serum levels of thyroid-stimulating hormone (TSH), a phenomenon known as sick euthyroid syndrome or nonthyroidal illness syndrome (NTIS) [7-11]. The most common hormone pattern in NTIS is a decrease in free T3 level with normal levels of thyroxine (T4) and TSH [7,8]. The magnitude of the fall in T3 correlates with severity of the illness. However, very sick patients may exhibit decreased free T4 and T3 levels without elevation of TSH [7,8]; this condition has a poor prognosis. Although the effect of PCM on functional disability after stroke has been investigated at various institutes, little is known about the effect of NTIS on functional independence of stroke patients.

The aim of the present study was to evaluate the effects of PCM and NTIS on functional dependence in stroke patients. Among the various markers of nutritional status, serum albumin concentration and body mass index (BMI) are highly sensitive indicators of PCM and have been shown to be strongly associated with clinical outcomes of stroke patients [3-6]. Therefore, we used serum albumin and BMI as the markers of malnutrition in this study.

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2. Subjects and methods

2.1. Patients

Institutional ethics committee approval was obtained for this prospective study. Written informed consent for functional and laboratory measurements, including blood testing, was obtained on admission from all patients or those authorized to give consent for them. The subjects were 51 hemorrhagic and occlusive stroke patients without subarachnoid hemorrhage diagnosed using computed tomography and/or magnetic resonance imaging and were admitted to the Nishi-Hiroshima Rehabilitation Hospital less than 110 days after suffering a stroke (range, 12-109 days; mean, 44 ± 23 days). We excluded patients who suffered from thyroidal disease, severe liver disease (eg, liver cirrhosis), severe kidney disease (eg, requiring artificial dialysis or nephrosis), or other diseases causing metabolic abnormality (eg, cancer).

2.2. Data collection and analysis

The functional independence measurement (FIM) is an observer-rated, multi-item, summed rating scale used to evaluate disability in terms of dependency and is widely used as a measure of disability in stroke patients [12,13]. The maximum total FIM score is 126. Lower scores indicate greater disability. All present patients were examined for disability using the FIM within 1 week after admission and within 2 weeks before discharge.

One day after admission, free T3 (free T3) (reference range, 2.60-4.26 pg/mL), free thyroxine (free T4) (reference range, 0.85-1.72 ng/dL), and TSH (reference range, 0.30-3.90 μIU/mL) were evaluated using an electric chemiluminescence immunochemistry assay, and albumin (reference range, 4.0-5.0 g/dL) was evaluated using bromcresol green. We calculated BMI from patient height and weight on admission as follows: BMI = weight (kg)/height^2 (m). Abnormal BMI was defined as follows: underweight, BMI of less than 19; overweight, BMI of more than 25 [1]. We also examined patients for dysphagia (difficulty in swallowing requiring tube feeding) and speech impediment (including aphasia and dysarthria) on admission.

We divided the NTIS group into 2 subgroups (mild and serious NTIS) according to the severity of NTIS. Mild NTIS was defined as a decrease in free T3 with normal free T4 and without elevation of TSH. Serious NTIS was defined as a decrease in both free T3 and free T4 without elevation of TSH. We estimated severity of NTIS at an average of 44 days after stroke.

The patients were also divided into 2 groups according to FIM score on admission: low-FIM group, 20 patients with greater disability and FIM score of 70 or less; high-FIM group, 31 patients with mild disability and FIM score of 71 or more. The 2 groups were matched for age, sex, type of stroke, and the presence of a history of stroke.

The low-FIM group was divided into 2 subgroups according to FIM score on discharge: non-improved group, 8 patients with little functional improvement and FIM score on discharge of 70 or less; improved group, 12 patients with better functional improvement and FIM score on discharge of 71 or more. The 2 groups were matched for age, sex, type of stroke, and the presence of a history of stroke.

2.3. Statistical analysis

Statistical analysis was performed for paired (Spearman rank test) and unpaired (standard t test) groups. For correlative analysis, the Spearman rank correlation coefficient (ρ) was calculated. We also used the Fisher exact test to compare categorical variables. Differences were considered significant at $P < .05$. The Stat View 5.0 (SAS Institute, Cary, NC) statistical package was used for all analyses.

3. Results

Table 1 shows the baseline values. As required by inclusion criteria, patients in the 2 FIM groups (low and high) were matched for age, sex, type of stroke, and the

Table 1
Basal characteristics of baseline, and low- and high-FIM groups on admission

	Baseline (n = 54)	FIM group on admission		
		Low-FIM group (n = 20)	High-FIM group (n = 31)	P
Age (y)	66.7 ± 10.2	69.3 ± 8.0	65.0 ± 11.1	.1429
Sex (male, female)	31, 20	10, 10	21, 10	.2485
Type of stroke (hemorrhage, infarction)	15, 36	7, 13	8, 23	.5393
Presence of history of stroke	5 (9.8)	4 (20.0)	4 (12.9)	.6958
Free T3 (pg/mL)	2.3 ± 0.4	2.1 ± 0.4	2.3 ± 0.4	.0645
Free T4 (ng/dL)	1.2 ± 0.2	1.3 ± 0.2	1.2 ± 0.2	.5600
TSH (μIU/mL)	2.0 ± 1.5	2.0 ± 1.2	2.0 ± 1.6	.8561
Albumin (g/dL)	3.9 ± 0.4	3.6 ± 0.3	4.0 ± 0.3	<.0001
Weight (kg)	55.7 ± 12.1	51.8 ± 10.6	58.2 ± 12.5	.0647
BMI (kg/m^2)	21.5 ± 3.8	20.3 ± 2.9	22.4 ± 4.2	.0538
FIM total (total score: 126)	77.6 ± 30.9	44.6 ± 15.4	98.9 ± 15.6	–
Dysphagia	4 (7.8)	4 (20.0)	0	.0194
Speech impediment	33 (64.7)	16 (80.0)	17 (54.8)	.0802

Continuous values are mean ± SD and categorical values are number of patients (percentage). To test the correlation between the low- and high-FIM groups, Fisher exact test was used to compare categorical variables and standard t test was used to compare continuous variables.

presence of a history of stroke. There were no differences in free T3, free T4, TSH, or speech impediment between the 2 FIM groups at baseline, and there was only a small difference in BMI (P = .0538). The 2 FIM groups were not matched for albumin and dysphagia. The difference in albumin between the 2 FIM groups was highly significant (P < .0001).

3.1. Frequency of PCM and NTIS after stroke

Serum albumin, free T3, and free T4 values below the cutoff limits were observed in 29 (56.7%), 44 (86.3%), and 0 patients, respectively. Thyroid-stimulating hormone was reduced in 2 (3.9%) patients and elevated in 3 (5.9%) compared with normal values. Among the 44 low free T3 patients, 2 patients exhibited elevation of TSH, 42 (82.4%) patients had mild NTIS, and no patient had serious NTIS. Body mass index values indicated that 11 (21.6%) patients were underweight and 8 (15.7%) were overweight, and there was significant positive correlation between BMI values and albumin (Spearman, P = .0303). Thus, hypoalbuminemia (PCM) and low T3 with normal TSH (mild NTIS) were common.

3.2. Effect of dysphagia on nutrition status

At baseline, dysphagia was observed in 4 (7.8%) of the stroke patients (Table 1). To clarify the effect of dysphagia on nutrition status, we examined correlation between the presence of dysphagia and both albumin concentration and BMI using the standard t test. The presence of dysphagia correlated well with albumin concentration (P = .0060), but not with BMI (P = .9501). Albumin concentration was significantly reduced in patients with dysphagia.

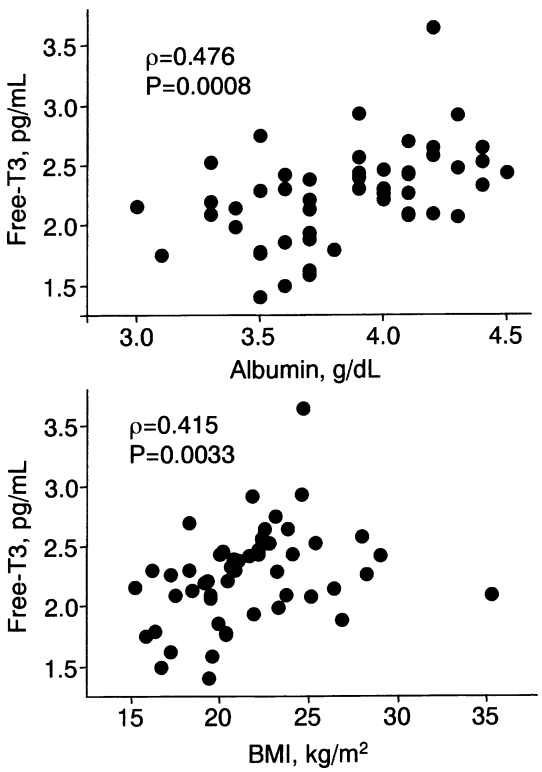

Fig. 1. Correlation between free T3 and both albumin and BMI (Spearman rank tests). Each circle represents a patient.

Table 2
Basal characteristics of non-improved and improved subgroups

	Improvement subgroups of low-FIM group		
	Non-improved group (n = 8)	Improved group (n = 12)	P
Age (y)	73.0 ± 6.4	66.8 ± 8.3	.0873
Sex (male, female)	4, 4	6, 6	>.9999
Type of stroke (hemorrhage, infarction)	3, 5	4, 8	>.9999
Presence of history of stroke	3 (37.5)	1 (8.3)	.2553
Free T3 (pg/mL)	1.9 ± 0.4	2.3 ± 0.3	.0101
Free T4 (ng/dL)	1.3 ± 0.1	1.3 ± 0.2	.7470
TSH (μIU/mL)	2.1 ± 0.9	1.8 ± 1.3	.6128
Albumin (g/dL)	3.5 ± 0.3	3.7 ± 0.3	.2941
Weight (kg)	49.7 ± 11.1	53.3 ± 10.6	.4780
BMI (kg/m^2)	20.0 ± 3.4	20.4 ± 2.6	.7619
Dysphagia	3 (37.5)	1 (8.3)	.2553
Speech impediment	18 (87.5)	9 (75.0)	.6186

Continuous values are mean ± SD and categorical values are number of patients (percentage). To test the correlation between the non-improved and improved subgroups, Fisher exact test was used to compare categorical variables and standard t test was used to compare continuous variables.

3.3. Effect of PCM on thyroid hormonal parameters after stroke

To examine the effect of PCM on thyroid hormone after stroke, we examined relationships between the PCM markers (albumin and BMI) and thyroid hormonal indicators (free T3, free T4, and TSH). At baseline, Spearman coefficient analysis showed significant positive correlation between free T3 and both albumin and BMI (Fig. 1).

Table 3
Serum free T3 concentration (pg/mL) of high- and low-FIM groups (non-improved and improved subgroups) on admission

High-FIM group (n = 31)		Low-FIM group (n = 20)	
		Non-improved group (n = 8)	Improved group (n = 12)
1.63	2.33	1.40	1.79
1.80	2.38	1.50	1.99
1.86	2.39	1.59	2.09
1.89	2.42	1.76	2.14
1.94	2.43	1.77	2.20
2.07	2.44	2.15	2.29
2.08	2.47	2.22	2.30
2.09	2.53	2.53	2.42
2.10	2.56		2.43
2.10	2.58		2.46
2.16	2.64		2.70
2.21	2.64		2.75
2.26	2.92		
2.27	2.93		
2.30	3.65		
2.30			

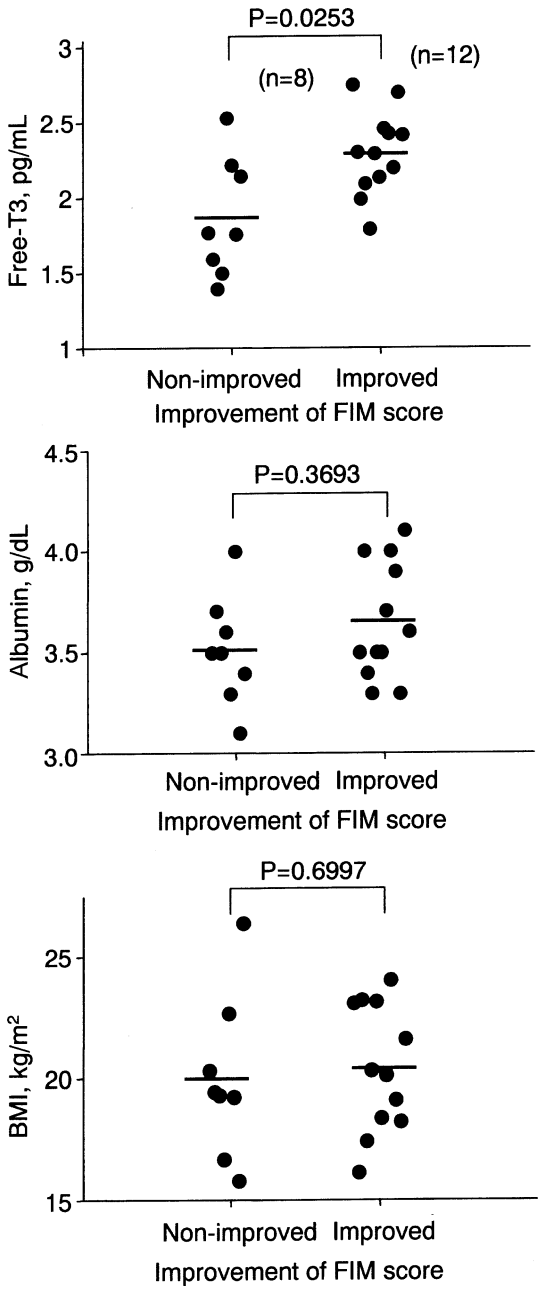

Fig. 2. Scatter diagrams showing differences in free T3, albumin, and BMI between improved and non-improved FIM subgroups. Each circle represents a patient, and the line indicates the median.

However, TSH and free T4 did not correlate with albumin or BMI ($P > .1$).

3.4. Effects of PCM and NTIS on improvement of disability after stroke

Table 2 shows the measurement values of the 2 subgroups (non-improved and improved) of the low-FIM group. As required by inclusion criteria, patients in these 2 subgroups were matched for age, sex, type of stroke, and the presence of a history of stroke. The 2 subgroups correlated with free T3, but not with albumin, BMI, free T4, or TSH (Tables 2 and 3, Fig. 2). The magnitude of improvement of FIM score positively correlated with free T3, suggesting that reduced free T3 (NTIS) on admission is a predictor of poor improvement of disability after stroke.

4. Discussion

The present results demonstrate that PCM and NTIS are common conditions and are associated with functional independence and improvement of disability after stroke. The present study is a prospective study specifically designed to examine both thyroid function and nutrition status in stroke patients. To our knowledge, this is the first stroke study that addresses the influence of malnutrition on thyroid hormonal indicators and the effect of NTIS on functional improvement.

In the present study, low serum albumin, which indicates PCM, was observed in 57% of subjects. This finding is consistent with a previous report, in which PCM was found in 49% of the stroke patients admitted to a rehabilitation service [2]. Stroke patients are at particularly high risk for malnutrition because cognitive deficit and hemiparesis often lead to an inability to feed oneself [2-6]. In a previous study, dysphagia (diagnosed as difficulty in swallowing and chewing using modified barium swallow or swallowing team assessment) was observed in 47% of stroke patients and was associated with malnutrition [2]. In the present study, dysphagia (diagnosed as difficulty in swallowing and chewing and the need for tube feeding) was observed in 4 (7.8%) patients and correlated with the concentration of serum albumin (PCM). Moreover, numerous studies have shown a strong association between serum albumin concentrations and clinical outcome of stroke patients [2-4]. In the present study, serum albumin was significantly higher for the high-FIM group than for the low-FIM group on admission. Thus, stroke-associated disability, including dysphagia, may result in insufficient food intake, leading to PCM.

Protein-energy malnutrition is characterized by loss of body cell mass, as indicated by BMI [4]. In previous studies, BMI has been found to be a good predicting factor for stroke outcome [5,6]. In the present study, BMI significantly positively correlated with albumin ($P = .0303$) and was lower for the low-FIM group than for the high-FIM group ($P = .0538$). Immobilized individuals lose muscle mass irrespective of nutritional intake because of the reduced synthesis of protein and the unchanged rate of breakdown of protein [4,5]. Greater immobility increases the degree of functional dependence, which leads to greater severity of PCM. Therefore, the degree of loss of body cell mass is an indicator of the severity of PCM and is a predictor of unfavorable outcome after stroke.

Starvation, which leads to PCM, is thought to reduce extrathyroidal conversion of T4 to T3 [7-11,14,15]. This leads to decreased serum total and free T3 concentrations, with little change in serum total and free T4 concentrations (low T3 syndrome, mild NTIS). However, there appears to

be a gradual progression from low T3 levels to the most advanced disease condition, which is associated with extremely low T3 and T4 levels (low T4 syndrome, serious NTIS) [7,8]. Starvation also appears to reduce thyroid hormone levels by suppressing thyrotropin-releasing hormone expression in the paraventricular nucleus of the hypothalamus [7,16-19]. Thyroid-stimulating hormone production falls, and simultaneously the glycosylation pattern of newly synthesized TSH is altered, reducing its bioactivity [11]. Thus, as a consequence of starvation, T3 levels fall (NTIS) without elevation of TSH. In the present study, 44 (86.3%) patients exhibited decreased free T3, 42 (82.4%) of whom exhibited normal free T4 without elevation of TSH, indicating that the pathogenesis of reduction of free T3 in the present study involved mild NTIS. Stroke patients have an increased risk of PCM, which can trigger NTIS. Thus, the present findings indicate that mild NTIS is a common condition in stroke patients. However, serious NTIS was not observed in the present study. All present patients were provided with rehabilitation service and nutritional management relatively early after the onset of stroke (average, 44 days), which apparently prevented the disease condition from progressing from mild NTIS to serious NTIS in any of the stroke patients.

In the present study, the magnitude of the decrease in PCM correlated with reduction of free T3 and FIM score on admission. However, although the magnitude of improvement of FIM score correlated with free T3, it did not correlate with albumin or BMI. Thyroid hormones (T3 and T4) act via nuclear hormone receptors to modulate gene expression [8]. They play a critical role in cell differentiation during development and help to maintain thermogenic and metabolic homeostasis in adults [8]. Free T3 may not directly influence protein synthesis. Therefore, NTIS may not provoke PCM, but rather may be induced by PCM. Nonthyroidal illness syndrome appears to be part of normal host adaptation to illness or starvation, perhaps serving to reduce basal energy requirements [8,14,15]. In a rodent model, starvation rapidly suppresses T4 and T3 levels [14,18,20]. Because thyroid hormones set the basal metabolic rate, a drop in thyroid hormone levels should reduce obligatory use of energy stores. However, hypothyroid patients commonly exhibit tiredness, weakness, and cognitive disorder, such as difficulty in concentrating and poor memory [7,8,21]. Once the basal metabolic rate has been reduced by NTIS resulting from prolonged PCM after stroke, disability of the stroke patient is not easily improved by rehabilitation. Therefore, to achieve sufficient improvement of functional disability after stroke, it is important to prevent prolonged PCM (which can provoke NTIS) in stroke patients by providing early rehabilitation (for improvement of immobilization or dysphagia) and supplementing nutrition.

Moreover, because of the difficulty in achieving appreciable improvement in poststroke NTIS patients, such patients should be provided with more intensive nutritional supplementation and rehabilitation as soon as possible. Glass et al [22] reported that serum T3 in undernourished rats depends on the composition of the diet, rather than on total intake of energy or protein. In human beings, several lines of evidence suggest that serum T3 is directly related to the percentage of carbohydrate in the diet [22,23]. These findings indicate that increased total energy or protein intake is not sufficient for improvement of disability in undernourished NTIS stroke patients. Therefore, the composition of the diet should be carefully considered during rehabilitation for NTIS stroke patients. In addition, in some patients with poststroke NTIS and severe disability, administration of thyroid hormone may be a viable treatment option, although treatment of NTIS with thyroid hormone is controversial [7,8,24-28]. During periods of starvation, there is a progressive increase in protein catabolism, as evidenced by reduced urinary excretion of nitrogen and 3-methyl histidine [27,28]. On the other hand, administration of T3 results in increased nitrogen excretion, reflecting increased muscle breakdown [27,28]. Extrapolating this idea to administration of thyroid hormone to critically ill hospitalized patients (such as stroke patients), who are frequently relatively poorly nourished and suffer from NTIS, implies that such treatment can be harmful and may result in increased muscle breakdown, leading to poor improvement of disability [27,28] On the other hand, in previous reports, high mortality rates for patients with T4 levels below 4 μg/dL suggest that such patients comprise a target group for whom thyroid hormone administration should be considered [7,26]. Because of such findings, treatment of NTIS with thyroid hormone (T4 and/or T3) is controversial, but most authorities recommend performing thyroid function tests during recovery without administration of thyroid hormone, unless there is historic or clinical evidence suggesting hypothyroidism [8]. Sufficiently, large randomized controlled trials using thyroid hormone are unlikely to resolve this therapeutic controversy because clinical presentations and outcomes are highly variable. The present results indicate the need to examine thyroid hormonal indicators and carefully select appropriate treatment options for stroke patients, especially those with a high degree of disability.

The diagnosis of NTIS is difficult. Stroke patients often have multiple metabolic derangements. In the present study, useful variables for diagnosis of NTIS included previous history of thyroid disease, medications that may affect thyroid function or thyroid hormone levels, and levels of free T3, free T4, and TSH [8]. However, the present diagnoses of NTIS were frequently presumptive, given the clinical context and pattern of laboratory values. In the present study, we could not exclude the possibility of the presence of other thyroid diseases, such as silent thyroiditis. Diagnosis of NTIS is frequently presumptive, given the clinical context and pattern of laboratory values. Further study is needed to clarify the pathogenesis underlying NTIS and PCM after stroke.

In conclusion, development of NTIS after stroke was a common occurrence among the patients in the present study, and was provoked by PCM, which occurred in a high proportion of the present functionally dependent patients. These findings indicate that, during the recovery period after a stroke, it is important to assess the presence of NTIS by measuring free T3 and to provide proper intensive rehabilitation and nutritional management to help patients gain independence and function.

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