Effect of thyroid hormone replacement therapy on cognition in long-term survivors of aneurysmal subarachnoid hemorrhage

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Abstract. Aneurysmal subarachnoid hemorrhage (aSAH) is a recently identified risk factor for chronic hypothyroidism. Patients with hypothyroidism often exhibit cognitive dysfunction. The aim of the present study was to determine the effects of thyroid hormone replacement therapy on cognition in aSAH survivors with hypothyroidism. A study population of 135 patients was recruited and subjected to the Montreal Cognitive Assessment (MoCA) and Beck Depression Inventory. Among the study population, 52 patients exhibited cognitive dysfunction. Thyroid hormone levels were measured in these patients using an electrochemiluminescence immunoassay in order to elucidate possible deficits in the thyrotrophic hormonal axes, and hypothyroidism was confirmed in 31 patients. Among these 31 patients, 22 patients consented to be randomized into groups and were administered levothyroxine replacement or a placebo treatment for 3 months. The MoCA and Wechsler Adult Intelligence Scale-Chinese version (WAIS-RC) testing were performed prior to and following the replacement therapy or placebo treatments. All subjects completed the study with no negative side effects. After 8-12 weeks of oral levothyroxine administration, it was observed that the serum concentration of thyroid-stimulating hormone was restored to normal levels. Furthermore, neuropsychological test results improved following the replacement therapy. A significant improvement was observed in the MoCA scores of the replacement group following therapy, with the exception of the score for abstraction. Additionally, significant improvements in the WAIS-RC were observed in the replacement group, with the exceptions of the information comprehension and letter-number sequencing scores. Thus, the present study has demonstrated the partial normalization of cognitive impairments in patients with hypothyroidism following aSAH as a result of appropriate levothyroxine replacement therapy.

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Introduction

Ruptured intracranial aneurysms are the most common cause of subarachnoid hemorrhage (1). Numerous patients achieve good outcomes with embolization therapy, and exhibit no severe neurological dysfunction [Glasgow Outcome Scale (GOS) grades 4 and 5] (2). During the chronic stage of the disease [12 months after aneurysmal subarachnoid hemorrhage (aSAH)], however, certain patients continue to exhibit cognitive dysfunctions, including diminishment in memory, attention, thinking and language cognitive function. A previous study on the long-term outcome of patients with aSAH demonstrated that there are numerous types of cognitive dysfunction in long-term survivors of aSAH following embolization therapy (3). In addition, a retrospective matched cohort study assessed neuropsychological functioning at least 12 months after aSAH treatment. The patients were treated with endovascular coiling or surgical clipping. The patients provided written consent and comprehensive neuropsychological test. Both treatment groups exhibited cognitive impairments in memory, attention and speed of information processing (4). Previous clinical studies have indicated that long-term survivors of aSAH frequently exhibit hypothyroidism (5,6). Furthermore, cognitive dysfunctions in these patients resemble the disruptions observed in patients with hypothyroidism. A previous study indicated that thyroid hormones are closely associated with cognition in adults (7). Thyroid hormone replacement therapy for elderly patients with subclinical hypothyroidism has positive effects on the improvement of mild cognitive impairment. The patients exhibited statistically significant improvements in a clock drawing test, iconic memory, block design, complex graphics recall and delayed recall, trail making A, word list learning, recall and recognize, forward and backward digital span, verbal fluency, and digital symbol from WAIS-RC (8). Based on these findings, we hypothesize that hormone replacement

Table I. Demographic and clinical data of the study population.

Parameter	Placebo group, n=11	Replacement group, n=11
Age (years)	56.27±6.29	52.27±8.13
Hunt-Hess score	1.81±0.75	1.90±1.04
Fisher score	2.27±0.46	2.63±0.67
Time since rupture (months)	24.09±13.07	22.72±12.65
GOS score	4.63±0.50	4.54±0.52
Education (years)	8.72±0.90	9.18±1.53

Groups were compared for age, Hunt-Hess score, Fisher score, time since rupture, GOS score and years of education when starting participation in the study. No significant differences were observed. GOS, Glasgow Outcome Scale.

may have an effect on cognition in long-term survivors of aSAH. To the best of our knowledge, there are no published studies investigating hormone replacement in this patient population. Considering this deficit in the literature, the aim of the present study was to observe the possible effect of thyroid hormone replacement on cognition in survivors of aSAH.

Materials and methods

Clinical materials. A total of 152 consecutive patients with aSAH that had survived following endovascular treatment, with mild or no neurological dysfunction (GOS grades 4 and 5), were screened in the Department of Neurosurgery of Guizhou Provincial People's Hospital (Guiyang, China) between January 2008 and March 2012. Approval was obtained from the Medical Ethics Committee of the hospital. The diagnosis of aSAH was verified using computed tomography scanning and the location of the aneurysm was confirmed using digital subtraction angiography. The patient inclusion criteria were as follows: i) Patients in whom aSAH occurred 12 months prior to the study; ii) patients aged 18-65 years; iii) completion of emobilization therapy, with little to no neurological dysfunction (GOS grades 4 and 5); and iv) provision of informed consent by the patient or next of kin. The patient exclusion criteria included any history of the following: i) Previous neurological and/or endocrine diseases other than mental disorders; ii) neurosurgery prior to ictus; iii) hormone therapy; and iv) severe chronic diseases and/or organ failure.

On the basis of the 152 records screened, 135 patients were invited to participate in the present study. Patients were assessed using the Montreal Cognitive Assessment (MoCA) and Beck Depression Inventory (BDI), and cognitive dysfunction was confirmed in 52 patients without depression. Thyroid hormone blood plasma levels were subsequently determined in these 52 patients. Hypothyroidism was confirmed in 31 subjects, and 22 of these patients consented to be randomly allocated to receive either 3 months of levothyroxine sodium replacement or a placebo treatment.

Among the 22 subjects, there were 5 men and 17 women, with a mean age of 54 years (range, 36-63 years). Hunt-Hess grading scores (9) ranged between 1 and 4 (1 in 9 subjects, 2 in 8 subjects, 3 in 4 subjects and 4 in 1 subject). Fisher grading scores (10) ranged between 2 and 4 (2 in 13 subjects, 3 in 8 subjects and 4 in 1 subject). The GOS scores ranged between 4 and 5, with 4 in 9 subjects and 5 in 13 subjects. The mean interval between the onset of the primary disease and the onset of hormone examination was 22.95 months (range, 12-46 months), and the duration of patient education ranged between 7 and 10 years (mean, 8.63 years). Aneurysms affected the anterior communicating artery (n=4), the internal carotid artery bifurcation (n=2) and the posterior communicating artery (n=16). All subjects were right-handed. The details of the two groups are presented in Table I.

Neuropsychological tests. The MoCA and BDI were conducted on the patients with hypothyroidism. Additionally, assessment based on the Wechsler Adult Intelligence Scale-Chinese version (WAIS-RC) was performed prior to and following the replacement treatment. In the MoCA, various cognitive domains are evaluated, including attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculation and orientation. The maximum score is 30 points, and a score ≥26 is considered normal. An extra point is added to the final score if the patient has received ≤12 years of education (11). The BDI is a questionnaire, with ratings ranging between 0 and 16. The standard scoring of the BDI is as follows: ≥0 and ≤4, no depression; ≥5 and ≤7, mild depression; ≥8 and ≤15, moderate depression; and ≥16, severe depression (12). The WAIS-RC assesses various cognitive domains, including vocabulary, similarities, arithmetic, digit span, information comprehension, letter-number sequencing performance, picture completion, digit symbol-coding, block design, matrix reasoning picture arrangement and symbol searching (13).

Thyroid hormone testing. Endocrine testing was performed at 8:00 a.m., prior to eating, and included measuring the levels of total triiodothyronine (TT3), total thyroxin (TT4), free T3 (FT3), free T4 (FT4) and thyroid-stimulating hormone (TSH). Hormone levels were determined using an electrochemiluminescence immunoassay (Shanghai Roche Pharmaceuticals Ltd., Shanghai, China).

The reference ranges of the hormones in healthy volunteers are as follows: TT3, 1.3-3.1 nmol/l; TT4, 66.00-181.00 nmol/l; FT3, 2.80-7.10 pmol/l; FT4, 12.00-22.00 pmol/l; and TSH, 0.270-4.200 mIU/l.

Table II. Hormone levels prior to and following replacement treatment.

Parameter	Baseline		After therapy		Reference
	Placebo group, n=11	Replacement group, n=11	Placebo group, n=11	Replacement group, n=11	
TT3 (nmol/l)	1.83±0.28	1.92±0.31	2.08±0.33	1.99±0.22	1.3-3.1
TT4 (nmol/l)	95.79±19.26	94.57±16.43	94.28±19.36	94.52±14.94	66.00-181.00
FT3 (nmol/l)	5.57±1.08	5.03±1.06	4.94±0.94	5.31±0.79	2.80-7.10
FT4 (nmol/l)	18.62±1.59	17.22±2.39	17.86±1.44	16.83±1.97	12.00-22.00
TSH (nmol/l)	5.55±1.05	5.43±0.76	4.89±0.93	2.40±0.58	0.270-4.200

Prior to treatment, the serum levels of TSH were significantly higher than the reference value. Following 3 months of hormone therapy, the serum levels of TSH were significantly improved (P<0.01). TT3, total triiodothyronine; TT4, total thyroxin; FT3, free triiodothyronine; FT4, free thyroxin; TSH, thyroid-stimulating hormone.

Table III. MoCA and BDI assessment prior to and following replacement treatment.

Test	Baseline		After therapy	
	Placebo group, n=11	Replacement group, n=11	Placebo group, n=11	Replacement group, n=11
MoCA				
Visuospatial/executive	3.81±0.75	3.27±1.10	3.81±0.87	4.72±0.46
Naming	1.63±0.50	1.72±0.46	1.81±0.40	2.36±0.50
Attention	4.18±0.75	3.90±0.70	4.54±0.52	5.18±0.60
Language	2.00±0.44	1.90±0.53	2.18±0.40	2.63±0.50
Abstraction	1.36±0.67	1.45±0.52	1.54±0.52	1.63±0.50
Delayed recall	3.36±0.67	3.72±0.64	3.81±0.75	4.81±0.40
Orientation	4.54±0.93	4.36±0.50	4.18±0.75	5.54±0.68
Total	20.90±1.30	20.36±1.36	22.00±1.67	26.90±0.70
BDI	1.81±1.07	1.90±1.13	2.00±0.89	2.00±1.00

No statistically significant differences were observed in the BDI score or the abstraction score of the MoCA. Subjects in the replacement group showed significant improvements in visuospatial/executive function, naming, attention, language, delayed recall, orientation and total scores following 3 months of hormone therapy (P<0.05). MoCA, Montreal Cognitive Assessment; BDI, Beck Depression Inventory.

Hormone replacement therapy. Subjects were randomly divided into two groups: Placebo (3 men and 8 women) and replacement (2 men and 9 women). Graded doses of levothyroxine sodium (Merck Millipore, Darmstadt, Germany) were administered to the replacement group. The daily levothyroxine sodium dose was initially 25 μg, and was increased by 25 μg every week. The maintenance dose was 25-100 μg/day, and was administered until serum TSH levels returned to normal (14). The placebo group received starch tablets. All subjects completed the study with no negative side effects.

Statistical analysis. Data are presented as the mean ± standard deviation. Analysis of variance was performed to analyze the results of the MoCA, BDI and WAIS-RC using SPSS software, version 19.0 (IBM SPSS, Armonk, NY, USA). P<0.05 was considered to indicate a statistically significant difference.

Results

Serum hormone levels. In the present study, 22 subjects consented to be allocated at random into one of two groups, receiving 3 months of levothyroxine sodium replacement or starch placebo. All subjects completed the study with no untoward side effects. All subjects exhibited normal serum hormone concentrations of FT3, FT4, TT3 and TT4, and higher concentrations of TSH at baseline. After 8 weeks of oral levothyroxine tablets, the serum concentrations of TSH were restored to normal levels in 8 of the patients (72.7%). In 3 cases, the serum concentrations of TSH were restored to normal levels after a 12-week period of oral levothyroxine treatment. Levothyroxine replacement therefore effectively reduced the serum concentration of TSH in the patients, with a significant difference observed prior to and following treatment (P<0.01). The serum hormone levels are presented in Table II.

Table IV. Wechsler Adult Intelligence Scale-Chinese version results prior to and following replacement treatment.

	Baseline		After therapy	
Parameter	Placebo group, n=11	Replacement group, n=11	Placebo group, n=11	Replacement group, n=11
Information	9.09±1.22	9.36±1.74	9.90±1.22	10.45±1.75
Comprehension	8.81±1.40	7.81±0.75	8.36±0.92	9.90±1.75
Arithmetic	9.63±1.56	10.00±2.40	9.72±1.34	11.63±1.12
Similarities	9.63±2.06	9.63±1.80	8.27±1.27	11.36±1.43
Digit span	8.45±1.43	8.54±1.43	8.72±1.27	10.00±1.18
Vocabulary	8.36±1.68	8.63±1.96	8.72±2.14	11.00±2.09
Letter-number sequencing	7.72±1.10	7.90±1.04	7.36±1.02	8.27±1.42
Picture completion	8.00±1.78	7.54±1.12	7.81±1.07	9.45±2.11
Block design	7.63±0.92	7.81±1.07	7.90±1.04	9.81±1.88
Digit symbol-coding	9.09±1.37	9.18±1.88	9.18±1.83	11.00±1.67
Matrix reasoning picture arrangement	9.18±1.72	8.36±1.20	8.81±1.16	10.09±1.51
Total	95.63±6.50	94.81±3.45	94.81±4.89	113.00±3.94

Significantly improved scores for vocabulary, similarities, arithmetic, digit span, picture completion, digit symbol coding, block design, matrix reasoning picture arrangement and symbol search domains were observed in the replacement group following 3 months of hormone therapy ($P<0.05$). No significant differences were found in the information comprehension and letter-number sequencing following the hormone replacement therapy.

Neuropsychological test results. Prior to hormone replacement, the total MoCA scores were <26 points, indicating that all subjects exhibited a certain degree of cognitive dysfunction. The BDI scores were <4 points, indicating no depression in either of the two groups. No statistically significant difference was observed between the BDI scores obtained prior to and following replacement therapy. By contrast, significantly improved MoCA scores were observed in the replacement group following treatment, with the exception of the abstraction score. Additionally, significantly improved WAIS-RC scores were observed in the replacement group following treatment, with the exceptions of the information comprehension and letter-number sequencing scores. The results of these tests are presented in Tables III and IV.

Discussion

With the development of embolization therapy, it is possible for patients with aSAH to completely recover neural function; however, it has previously been reported that, in the chronic stage of the disease (12 months after aSAH), certain patients continue to exhibit dysfunctional memory, attention, thinking and language cognitive function (15-17). In the current study, comparable results were obtained regarding the cognition of patients with aSAH, with 52/135 subjects exhibiting cognitive dysfunction (38.52%).

Previous studies have demonstrated that patients with aSAH exhibit pituitary hormone deficiencies in the acute and chronic stages, including deficits in gonadotrophin, somatotropin and T4 (18-22). In the present study, 31 subjects exhibited hypothyroidism, with elevated levels of TSH and normal levels of FT3, FT4, TT3 and TT4 in the chronic stage. The mechanism underlying thyroid dysfunction in the chronic stage of aSAH remains unclear. The dysfunction may be the result of compression of the hypothalamic-pituitary-thyroid axis by the aneurysm, or by post-hemorrhagic local tissue pressure alterations. In addition, the toxic effects of the disintegration of blood cells, ischemia as a result of vasospasm, elevated intracranial pressure, hydrocephalus or local injury during surgery may be involved in thyroid dysfunction. With disease rehabilitation, the function of the hypothalamic-pituitary-thyroid axis may be restored to normal; however, inadequate compensation of the hypothalamic-pituitary-thyroid axis may lead to abnormal thyroid hormone levels, including elevated TSH and normal levels of FT3, FT4, TT3 and TT4. Thus, hormonal changes are similar to those observed in subclinical cases of hypothyroidism. The results of the present study suggest that the follow-up period after aSAH should be extended in order to monitor thyroid hormone levels, and that replacement therapy should be considered, where appropriate.

It has been reported that thyroid hormone replacement therapy is able to improve cognition in patients with hypothyroidism (23). In the present study, the results of the MoCA and the WAIS-RC test indicated that patients possessed improved memory, attention, logical and abstract thinking, generalization and visuospatial/executive function following hormone replacement therapy; therefore, cognitive impairments in patients that exhibit hypothyroidism following aSAH may be reversible with appropriate levothyroxine replacement therapy.

One limitation of the current study was that the sample population size was relatively small, and the data used relatively crude metrics for the assessment of the experimental results. Despite this, the present study indicated that levothyroxine replacement may improve cognitive impairments associated with hypothyroidism following aSAH. Future studies will require a larger sample size in order to systematically examine

this issue. Another limitation of the present study was that it only examined the effects of the thyroid hormones on cognition. In the chronic stage of aSAH, patients typically exhibit other pituitary hormone deficiencies, including disruptions to gonadotrophin, somatotropin and growth hormone. We will therefore aim to investigate the replacement of other affected hormones in a future study. In conclusion, the results of the present study suggest that a number of the cognitive impairments observed in patients with hypothyroidism in the chronic stage of aSAH may be partially reversible via the application of levothyroxine replacement therapy.

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