ORIGINAL ARTICLE

Low T3 syndrome predicts severe neurological deficits of cerebral infarction inpatients with large artery artherosclerosis in internal carotid artery system

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Abstract

OBJECTIVES: The low triiodothyronine (T3) syndrome indicates poor prognosis for patients with cerebral infarction. It is unknown, however, whether basic conditions or severities in the patients with the low T3 syndrome are different compared to those without the low T3 syndrome.

METHODS: We compared the risk factors and the severity of the disease using the National Institutes of Health stroke scale (NIHSS) score at the worst condition for cerebral infarction in patients with or without the low T3 syndrome in order to better understand the characteristics underlying the worse prognosis in patients with the low T3 syndrome.

RESULTS: We found that cerebral infarction patients with the low T3 syndrome were significantly older ($p<0.001$) and significantly more likely to be female ($p=0.002$) and had hypertension ($p=0.04$) or homocystinemia ($p=0.001$), but less likely to smoke ($p=0.008$), compared to patients without the low T3 syndrome. The proportion of NIHSS score ≥8 in the patients with LAA-ICA-associated cerebral infarction accompanied by the low T3 syndrome was significantly higher than in those without the low T3 syndrome ($p=0.001$).

CONCLUSION: We concluded that increased numbers of risk factors for cerebral infarction and more severe neurological deficits may be important causes for worse prognosis in the patients with the low T3 syndrome which may more likely occur in patients with LAA-ICA cerebral infarction. Intense secondary prevention in cerebral infarction especially in older women are needed.

INTRODUCTION

The low triiodothyronine (T3) syndrome, also known as the euthyroid sick syndrome, is caused by a change in thyroid function associated with severe forms of disease and with stress associated with surgeries. It is also seen in elderly individuals with risk factors of stroke. Thyroid function and thyroid stimulating hormone (TSH) output remain normal in these patients. However, numerous reports have indicated that the low T3 syndrome is an indicator of a poor prognosis for patients with a cerebral infarction (Alevizaki *et al.* 2007; Ambrosius *et al.* 2011) Whether the prognosis is more dire in patients who are hospitalized with various diseases than in those with the same diseases but without the low T3 syndrome remains unknown. To investigate the role of this syndrome in the prognosis for patients with a cerebral infarction, we compared the risk factors for the cerebral infarction observed in patients with or without the low T3 syndrome and in patients with various levels of disease severity, using the National Institutes of Health stroke score (NIHSS) as an indicator of infarction severity.

METHODS

Our study design was approved by the Ethics Committee of Suzhou Hospital, which is affiliated with Nanjing Medical University. We obtained thyroid function data from 76 men and 86 women aged between 48 to 94 years in whom an acute cerebral infarction was identified at the hospital between 2010 and 2012. A diagnosis of an acute cerebral infarction was based on The American Heart Association's (AHA's) *Guidelines for the Early Management of Patients With Acute Ischemic Stroke* (2013). Patients taking medications that affect thyroid function and patients with chronic thyroid disease, a non-acute cerebral infarction, cerebral tumor, encephalitis, head trauma, or severe multiple organ dysfunction were excluded from this study.

Examination and evaluation during hospitalization

Fasting venous blood was drawn within 24 hours admission into the hospital. T3 (1.21–2.29 nmol/l), thyroxine (T4) (62.68–150.84 nmol/l), TSH (0.35–4.94 mIU/l), and free T3 (fT3, 2.63–5.70 pmol/l) and T4 (fT4, 9.01–19.05 pmol/l) levels were determined using radioimmunologic techniques. The diagnosis of the low T3 syndrome was based on a T3 level less than 1.21 nmol/L. Biochemical data were obtained using a fully automatic biochemical analyzer (HITACHI 7600) (Hitachi High Technologies America, Inc.; Schaumburg, IL). Hypertension (blood pressure ≥140/90 mmHg on repeated measurements or taking antihypertensive medication), diabetes (fasting plasma glucose level ≥7.0 mmol/l or plasma glucose level at any time ≥11.1 mmol/l on repeated measurements or taking antidiabetic medication), and atrial fibrillation(a reported history or diagnosed by in-hospital electrocardiograph) were identified based on patient history, and NIHSS scores were obtained at the worst condition of the disease. The NIHSS score equal to or more than 8 was considered as severe neurological deficits. We located the infarctions using magnetic resonance imaging(MRI), magnetic resonance angiography(MRA), computerized tomographic angiography(CTA), or color ultrasonography of the internal carotid artery system (ICA) or the vertebral basilar artery system (VBA) and classified them according to TOAST (Trial of Org 10172 in Acute Stroke Treatment). We then divided the participants into 4 groups according to the type of lesion – large-artery atherosclerosis (LAA), small-vessel occlusion (SVO), cardioembolism (CE) – and stroke of other etiology (SOE). No cases involving in hypothalamus and pituitary were found in this study.

Data analysis

The χ^2 test was used to compare morbidity among patient groups and risk factors. The t test was used to evaluate continuous variables, which are displayed as mean ± standard deviation (x ± SD). The *p*-values of less than 0.05 were were considered to indicate statistical significance.

RESULTS

There were 137 cases scanned by MRI with MRA, 9 cases by CTA and 16 cases by MRI with tof-MRA and color ultrasonography. The patients were divided into 8 groups according to the results of imaging examination and TOAST classification.

Of the 162 individuals enrolled in this study, 29 patients were reported to have an acute cerebral infarction accompanied by the low T3 syndrome(17.9%); 20 (12.35%) patients had a fT3 level lower than the reference range. Mean T4, fT4, and TSH levels were within normal limits for the entire population. In patients with the low T3 syndrome, however, the mean T3, fT3, and TSH levels were significantly lower than in patients without T3 syndrome ($p<0.001$, $p<0.001$ and $p=0.048$, respectively) (Table 1).

Compared with patients with normal T3 levels, those with a cerebral infarction accompanied by T3 syndrome were older (78.21±6.48 vs 70.96±12.85 years, $p<0.001$) and more likely to be women ($\chi^2=9.75$, $p=0.002$) and have hypertension ($\chi^2=4.23$, $p=0.04$) or homocystinemia ($\chi^2=11.68$, $p=0.001$), but less likely to be smokers ($\chi^2=7.10$, $p=0.008$). The same trends were seen for patients with type 2 diabetes mellitus, atrial fibrillation, hyperlipidemia, or hyperuricemia ($p>0.05$) (Table 2).

Using TOAST criteria and differentiating the ICA and VBA system to categorize the lesions, there were no significant differences in constituent ratio of TOAST subtypes in the low T3 syndrome group and the normal T3 group ($p>0.05$) (Table 3).

The proportion of NIHSS ≥ 8 for patients with LAA-ICA in low T3 group was significantly higher than that in normal T3 group (p=0.001). There were no difference found in other groups (p>0.05) (Table 4).

DISCUSSION

The coexistence of severe disease and T3 syndrome has gained widespread attention, but the pathophysiological mechanism underlying this phenomenon is still unknown. Under stressful conditions, the function of the hypothalamic-pituitary axis becomes abnormal and deiodinase activity is altered. These changes could lead to abnormal changes in the pathway through which T4 is converted to T3 in peripheral tissue, and this, in turn, could increase the amount of inactive rT3 (Peeters *et al.* 2003 and 2005; De Groot 2006; Maia *et al.* 2011). Oxidative stress, dystrophia, and the presence of inflammatory factors may also contribute to the decrease in T3 (Boelen *et al.* 2011; Mebis *et al.* 2012; Wajner & Maia 2012).

The low T3 syndrome was an independent predictor of early- and late-stage survival for acute cerebral infarction, which could predict the severity of disability one year after the disease (Alevizaki *et al.* 2007; Ambrosius *et al.* 2011). In one prospective study, the investigators found that patients with low-tertile fT3 levels had higher NIHSS scores, more severe neural damage, and a higher annual mortality than those with high-tertile fT3 levels. The frequency of occurrence of elevated white blood cell (WBC) count and ipsilateral ventricle compression deformation were also higher (Ambrosius *et al.* 2011). Skvortsova *et al.* (2006) administered TSH to patients with acute cerebral infarction within 24 hours of diagnosis and noted significant increasing in thyroxine levels and decreasing in comorbidity with low T3 syndrome; they also observed improvement in the neurological dificits. Experimental data have shown that T3 helps reducing the size of cerebral infarction and improves neurological deficits (Hiroi *et al.* 2006). In studies carried out in patients with cardiovascular disease, investigators have found that cardiopulmonary function and left ventricular diastolic function are worsen in patients with the low T3 syndrome and that this syndrome is an independent predicator of death (Cassetti *et al.* 2009; Pfister *et al.* 2010; Fontana *et al.* 2012). The longer the patient with acute coronary syndrome remains in asystole, the lower the T3 level; however, the T3 level can increase with treatment (Iltumur *et al.* 2005).

Tab. 1. Comparison of thyroid hormones levels in cerebral infarction patients between low T3 group and normal T3 group.

	Low T3 group (n=29)	Normal T3 group (n=133)	*p*-values
T3 (nmol/l)	1.06±0.08	1.46±0.16	<0.001
fT3 (pmol/l)	3.02±0.57	3.79±0.66	<0.001
T4 (nmol/l)	91.91±14.95	92.65±14.68	=0.519
fT4 (pmol/l)	14.78±1.21	14.61±1.23	=0.576
TSH (mIU/l)	1.77±1.19	2.36±1.72	=0.048

Tab. 2. Characteristics of cerebral infarction patients with low T3 and normal T3 values.

	Low T3 group (n=29)	Normal T3 group (n=133)	*p*-values
Age (years)	78.21±6.48	70.96±12.85	<0.001
Sex (female cases)	23(79.3%)	63(47.4%)	=0.002
Hypertension	27(93.1%)	101(75.9%)	=0.040
Diabetes mellitus	16(55.2%)	54(40.6%)	=0.151
Prior TIA/stroke	7(24.1%)	39(29.3%)	=0.575
Atrial fibrillation	7(24.1%)	20(15.0%)	=0.359
Current smoking	8(27.6%)	73(54.9%)	=0.008
Hypercholesterolemia	15(51.7%)	68(51.1%)	=0.954
Hyperhomocysteinemia	19(65.5%)	42(31.6%)	=0.001
Hyperuricemia	4(13.8%)	12(9.0%)	=0.435

Tab. 3. Constituent ratio of TOAST subtypes in patients with or without low T3 syndrome.

	Low T3 group (n=29)	Normal T3 group (n=133)	*p*-values
LAA-ICA	10(34.5%)	35(26.3%)	=0.374
LAA-VBA	1(3.4%)	4(3.0%)	=1.000
SVO-ICA	5(17.2%)	17(12.8%)	=0.737
SVO-VBA	6(20.7%)	39(29.3%)	=0.347
CE-ICA	3(10.3%)	12(9.0%)	=1.000
CE-VBA	2(6.9%)	8(6.0%)	=1.000
SOE-ICA	2(6.9%)	10(7.5%)	=1.000
SOE-VBA	0(0%)	8(6.0%)	N/A

Tab. 4. Proportion of NIHSS ≥ 8 in TOAST subtypes with or without low T3 syndrome.

	Low T3 group (n=29)	Normal T3 group (n=133)	*p*-values
LAA-ICA	7/10	4/35	=0.001
LAA-VBA	0/1	0/4	N/A
SVO-ICA	0/5	4/17	N/A
SVO-VBA	1/6	6/39	=1.000
CE-ICA	2/3	7/12	=1.000
CE-VBA	1/2	0/8	N/A
SOE-ICA	2/2	0/10	N/A
SOE-VBA	0/0	0/8	N/A

In our study, cerebral infarction patients with low T3 syndrome were older, more likely to be female, and more likely to have hypertension and homocystinemia than those without low T3 syndrome. The proportion of NIHSS score ≥8 in patients with an LAA-ICA-associated cerebral infarction accompanied by low T3 syndrome significantly higher than in those without low T3 syndrome group and did not differ significantly among the other TOAST groups in our study. This suggests that patients with a large-artery infarction accompanied by low T3 syndrome are at increased risk for severe neural damage and may point to a reason for a worse prognosis (Eikelboom *et al.* 2000; Wu *et al.* 2010; Forti *et al.* 2013). Similar findings have been reported by Forti *et al.* (2013), who found that patients with low T3 syndrome were older, had more risk factors, and had a poorer prognosis; and by Zargar *et al.* (2004), who found an inverse relationship between the T3 level and the severity of the disease. Eriksson and colleagues also find the prognosis of stroke patients was worse in women and Fitzek *et al.* think the worse outcome in women patients should be owe to older age and serious conditions at the time of stroke (Fitzek *et al.* 2011; Eriksson *et al.* 2012). The fact that the proportion of severe neurological dificits did not differ significantly among other TOAST groups with or without low T3 syndrome in our study suggests that the T3 level has little effect in other types of cerebral infarctions and the worse prognosis may be mainly exsiting in patients with LAA-ICA subtype. The less cases may be responsible for no differences between groups in VBA system. Another possibility is that the validity of NIHSS evaluating neurological deficits in VBA system is not so good as it done in ICA system (Sato *et al.* 2008). Low T3 syndrome did not appear to be affected by the comorbidity of type 2 diabetes, atrial fibrillation, hyperlipidemia, or hyperuricemia. This may indicate that the severity of the infarct in patients with low T3 syndrome is not influenced by these diseases. The number of smokers with low T3 syndrome is very low; this may be due to the greater number of women in our patient populations, given that female smokers are rare in China (Wu *et al.* 2010).

To our knowledge, this is the first report that low T3 syndrome is related to the severity of neulogical deficits in patients with specific categories of cerebral infarction. The differences in the effect of low T3 syndrome among these subgroups point to potential mechanism underlying its effect (Ihle-Hansen *et al.* 2012). However, further study is required to determine the exact mechanism through which low T3 syndrome influences morbidity and prognosis in each group.

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