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Short communication

Free thyroxine and TSH interact with secreted protein acidic and rich in cysteine-like 1 in ischemic stroke

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ARTICLE INFO

Article history:
Received 14 December 2017
Accepted 2 January 2018
Available online 6 January 2018

Keywords:
Thyroxine
Thyroid-stimulating hormone
Stroke
Extracellular matrix

ABSTRACT

The role of the thyroid gland in ischemic stroke pathology is not well understood. As thyroid hormones modulate the extracellular matrix, we explored the possible link between them and secreted protein acidic and rich in cysteine like 1 (SC1) – one of the extracellular matrix molecules.

In the 81 patients with acute ischemic stroke, serum SC1 levels were much higher compared with 30 control subjects: 4.47 vs 2.43 ng/mL ($p < 0.001$). Serum levels of free thyroxine (fT4) were higher in stroke subjects compared to those of controls ($p = 0.03$). In stroke patients, TSH concentration was lower than in the control group ($p = 0.03$). SC1 levels positively correlated with fT4 levels ($p = 0.02$) and negatively with TSH ($p = 0.03$) in stroke patients.

Our results confirmed the association between thyroid hormones and SC1 – extracellular matrix protein.

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1. Introduction

Recently, the role of the thyroid gland in the pathophysiology of acute cerebrovascular diseases has been intensively explored. Clinical studies have demonstrated t that thyroid hormones, especially low free triiodothyronine (fT3) are important factors related to ischemic stroke severity and outcome [1,2]. A few studies have also proved the association between TSH (thyroid-stimulating hormone), fT3 and clinical course in subarachnoid hemorrhage [3].

The pathological aspect of thyroid hormones disturbances in acute stroke is not well understood. It is not surprising given the very complex interactions between the thyroid gland and human brain. We know, for a fact, that thyroid hormones participate in brain connectivity by influence on neuronal migration, synaptic plasticity and binding with their receptor on integrin αVß3 which, in turn, affects a large number of extracellular matrix proteins [4]. Secreted protein acidic and rich in cysteine like 1 (SC1) belongs to this family of extracellular matrix molecules presented in the human brain.

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https://doi.org/10.1016/j.pjnns.2018.01.001
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Recently it has been shown that SC1 levels were associated with ischemic stroke severity [5]. It would be interesting if there is a link between thyroid hormones and extracellular matrix (ECM) molecules expression in cerebrovascular disease. Therefore, we investigated the association between TSH, fT3, fT4 (free thyroxine) and SC1 in ischemic stroke patients.

2. Material and methods

We studied ischemic stroke patients consecutively admitted to the Department of Neurology and Cerebrovascular Disorders, within one year of observation. Acute ischemic stroke was defined according to the World Health Organization criteria. We excluded patients with clinical conditions with possible influence on TSH, fT3, fT4 and SC1 levels, such as: a history of thyroid gland disease, recent surgery or trauma, renal insufficiency, malignancy, inflammatory disease, liver failure or recent myocardial infarction. Brain imaging (CT or MRI) was performed routinely within 1 h after admission. Thirty subjects matched for age with confirmed traditional vascular risk factors but without stroke in the history comprised the control group. All study participants gave written, informed consent and the Ethics Committee of our University approved the study.

Baseline characteristics with following variables were recorded: gender, age, history of vascular risk factors and also total cholesterol, HDL cholesterol, triglycerides, white blood cell count (WBC), TSH, fT4, and fT3. Biochemical tests were performed in all patients at the admission. SC1 levels were quantified by commercially available ELISA (Abcam, Cambridge, UK) from blood samples stored at −80 °C until assay.

2.1. Statistical analysis

Most of the continuous variables had non-normal distribution; therefore, results are median with interquartile range (IQR). Categorical variables are presented as counts (with percentage). The differences between the study groups were evaluated using Chi-square tests (categorical variables) and Mann–Whitney tests (continuous variables), as appropriate. Because distributions of thyroid gland markers levels appeared to be left-skewed, they were normalized by log-transformation, and we examined associations between SC1 levels and TSH, fT3, fT4 with Pearson correlation analysis. A p-value <0.05 was considered as statistically significant.

3. Results

At the end of the recruitment period, 81 out of 260 acute stroke patients fulfilled inclusion and exclusion criteria and were enrolled in the study. Apart from matching for age the number of women and men was the same in the control and stroke patient groups. Table 1 shows the basic characteristics of the studied population.

In the 81 patients with acute ischemic stroke, serum SC1 levels were much higher compared with 30 control subjects: 4.47 ng/mL (IQR, 3.34–5.16) versus 2.43 ng/mL (IQR, 1.43–3.16) ($p < 0.001$). The TSH and fT4 levels were also significantly different between studied groups. In stroke patients TSH concentration was lower than in the control group: 1.16 μIU/mL (IQR, 0.48–1.85) versus 1.52 μIU/mL (IQR, 0.92–2.61) ($p = 0.03$). Serum levels of fT4 were slightly higher in stroke subjects when compared to the control group 17.6 pg/mL (IQR, 15–19.4) versus 13.8 pg/mL (IQR, 12.68–17.75) ($p = 0.03$).

SC1 levels positively correlated with (logarithmic) fT4 concentration ($r = 0.26$, $p = 0.02$) in stroke patients (Fig. 1A). SC1 levels showed also modest negative correlation with TSH ($r = -0.24$, $p = 0.03$) (Fig. 1B). We did not find any association between fT4 and SC1.

4. Discussion

The present study showed that circulating SC1 levels in patients with acute ischemic stroke were associated with

Table 1 – The basic characteristics of explored population.

Characteristic	Stroke patients ($n = 81$)	Control group ($n = 30$)	p-value
Female sex (n)	32	16	NS
Mean age (years)	67 ± 14	65 ± 9	NS
Atrial fibrillation, n (%)	28 (34%)	0 (0%)	<0.001
Hypertension, n (%)	60 (74,1%)	25 (83.3%)	NS
Diabetes, n (%)	22 (27%)	9 (30%)	NS
History of stroke or TIA, n (%)	25 (30%)	0 (0%)	<0.001
Coronary heart disease, n (%)	36 (44.4%)	9 (41.8%)	NS
Current cigarette smoking, n (%)	18 (22,2%)	8 (26.6%)	NS
Cholesterol (mg/dL)	205 (160–228)	193 (152–239)	NS
HDL cholesterol (mg/dL)	47 (39.2–62.1)	55 (39.2–62.1)	0.09
Triglyceride (mg/dL)	121 (99.75–165)	113 (82–153)	NS
WBC ($\times 10^9$ L^{-1})	8.48 (7.06–10.71)	5.85 (5.24–6.7)	<0.001
TSH (μIU/mL)	1.16 (0.48–1.85)	1.52 (0.92–2.61)	0.03
fT4 (pg/mL)	17.6 (15–19.4)	13.8 (12.68–17.75)	0.03
fT3 (pg/mL)	4.2 (3.27–4.82)	4.22 (3.88–4.71)	NS
SC1 (ng/mL)	4.47 (3.34–5.16	2.43 (1.43–3.16)	<0.001

All data are presented as number (with percentage) or median (with interquartile ranges).
WBC: white blood cell count; TSH: thyroid stimulating hormone, fT4: free thyroxine, fT3: free triiodothyronine; HDL: high-density lipoprotein; NS, nonsignificant, SC1, secreted protein acidic and rich in cysteine-like 1.

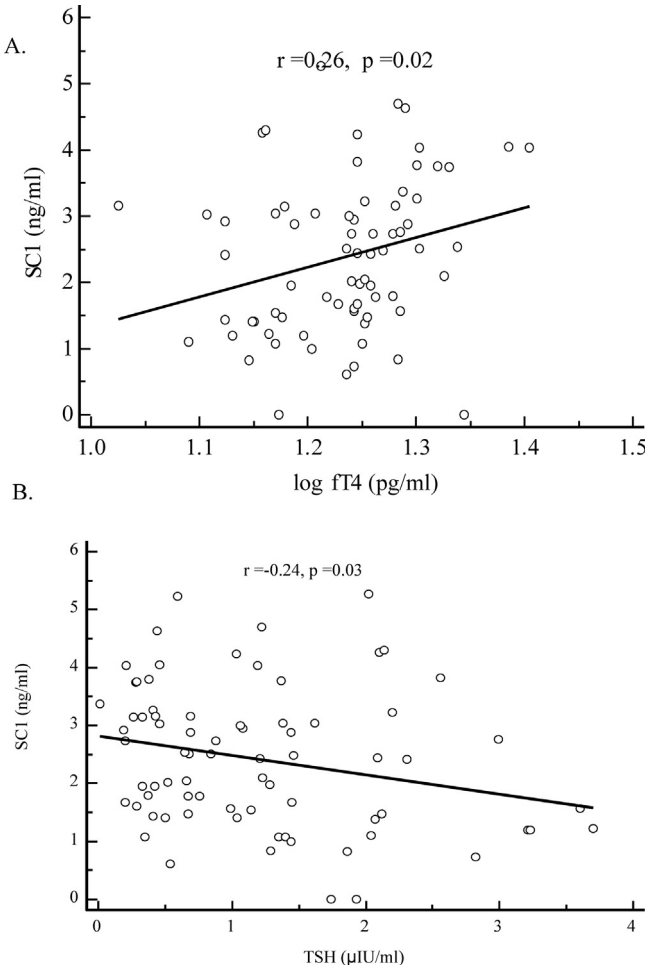

Fig. 1 – Correlations between SC1 and fT4 (A) and TSH (B).

increased fT4 and decreased TSH levels when compared to the control group. SC1 is an anti-adhesive glycoprotein that belongs to the ECM proteins involved in tissue remodeling [6]. The experimental study revealed that after transient brain ischemia SC1 is up-regulated in astrocytes [7]. Clinical studies on the role of SC1 in stroke are spare. As mentioned above, one study proved that high levels of SC1 were associated with moderate and severe clinical status of ischemic stroke patients [5].

A vital source of brain ECM proteins are astrocytes. We know that these cells are not the simple framework for neurons organization but act in many crucial processes, like cerebral blood flow and the glucose homeostasis. A variety of important functions of reactive astrocytes depend on ECM delivered by these cells, such as: regulation of cell migration, survival, differentiation, and axonal pathfinding. It was demonstrated that thyroid hormones (especially T3, the product of T4 conversion) regulate the expression of ECM proteins and induce astrocytes to promote neurite outgrowth in vitro [8]. The favorable effect of T4 treatment on brain ischemic injury was proved in experimental studies [9]. Thus, we can speculate that results of our clinical study (especially the positive correlation between fT4 and SC1) are the additional input to the hypothesis about the neuroprotective effect of thyroid hormones in ischemic stroke, via stimulating acting on ECM proteins. There are few plausible reasons for observing no association between T3 and SC1.

The classic thyroid hormones signaling pathway involves T3 binding to nuclear receptors, T4 has a much lower affinity for them. However, alternative mechanism, called nongenomic or extranuclear, has been recognized and it mainly involves T4 which interact with mentioned above integrin αVß3 within the cell membrane. Probably such thyroid nongenomic action predominates in astrocytes [10].

The major limitation of our report is a low number of patients which could not allow for multivariate statistical analysis. However, it is a pilot study, and we treat these results as preliminary, which is the impulse for conduction the research on the larger group of patients. It is necessary to determine the independent nature of our findings. In conclusion, our data provide evidence about the association between fT4 and TSH and SC1 in stroke patients, which could be a phenomenon encountered in ischemic stroke pathophysiology.

Conflict of interest

None declared.

Acknowledgement and financial support

None declared.

REFERENCES

[1] Neidert S, Katan M, Schuetz P, Fluri F, Ernst A, Bingisser R, et al. Anterior pituitary axis hormones and outcome in acute ischaemic stroke. J Intern Med 2011;269(4):420–32.
[2] Ambrosius W, Kazmierski R, Gupta V, Warot AW, Adamczewska-Kocialkowska D, Blazejewska A, et al. Low free triiodothyronine levels are related to poor prognosis in acute ischemic stroke. Exp Clin Endocrinol Diabetes 2011;119(3):139–43.
[3] Zetterling M, Engstrom BE, Arnardottir S, Ronne-Engstrom E. Somatotropic and thyroid hormones in the acute phase of subarachnoid haemorrhage. Acta Neurochirurg (Wien) 2013;155(11):2053–62.
[4] Cheng SY1, Leonard JL, Davis PJ. Molecular aspects of thyroid hormone actions. Endocr Rev 2010;31(2):139–70.
[5] Ambrosius W, Michalak S, Kazmierski R, Lukasik M, Andrzejewska N, Kozubski W. The association between serum matricellular protein: secreted protein acidic and rich in cysteine-like 1 levels and ischemic stroke severity. J Stroke Cerebrovasc Diseases)2017;(November). pii:S1052-3057(17)30545-1.
[6] Sullivan MM1, Sage EH. Hevin/SC1, a matricellular glycoprotein and potential tumor-suppressor of the SPARC/BM-40/Osteonectin family. Int J Biochem Cell Biol 2004;36:991–6.

[7] Lively S, Moxon-Emre I, Schlichter LC. SC1/hevin and reactive gliosis after transient ischemic stroke in young and aged rats. J Neuropathol Exp Neurol 2011;70:913–29.
[8] Martinez R, Eller C, Viana NB, Gomes FC. Thyroid hormone induces cerebellar neuronal migration and Bergmann glia differentiation through epidermal growth factor/mitogen-activated protein kinase pathway. Eur J Neurosci 2011;33 (January):26–35.
[9] Genovese T1, Impellizzeri D, Ahmad A, Cornelius C, Campolo M, Cuzzocrea S, et al. Post-ischaemic thyroid hormone treatment in a rat model of acute stroke. Brain Res 2013;1513(June):92–102.
[10] Dezonne RS, Lima FR, Trentin AG, Gomes FC. Thyroid hormone and astroglia: endocrine control of the neural environment. J Neuroendocrinol 2015;27:435–45.