BRAIN TUMOR AS A PROTOTYPE OF SEVERE BRAIN LESION IN PATIENTS WITH "LOW T_3 SYNDROME"

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SUMMARY – The purpose of our study was to contribute to better understanding of cerebrospinal fluid (CSF) as a valuable biological material in the research of brain tumors within the "low T_3 syndrome", and to discuss the role of thyroid hormones in the central nervous system in subjects with severe cerebral lesions. We studied the levels of total triiodothyronine (tT_3), total thyroxine (tT_4), free triiodothyronine (fT_3), free thyroxine (fT_4), reverse triiodothyronine (rT_3) and thyrotropin (TSH) in serum, and fT_3, fT_4, rT_3 and TSH levels in CSF of patients with brain tumor, and compared the results with control group. Study results indicated a statistically significantly higher level of rT_3 in serum and CSF of brain tumor patients *vs.* control group ($p<0.05$). The rT_3/fT_3 ratio was highest in CSF and serum of brain tumor patients, yielding a statistically significant difference ($p<0.05$). These results could suggest higher permeability of the blood-brain barrier in brain tumor patients. We also assume that rT_3, in the framework of "cerebral low T_3 syndrome", is also generated through local intracerebral conversion. Disruption of this process in severe cerebral lesion can lead to increased rT_3 concentrations, i.e. development of the "low T_3 syndrome".

Key words: *Brain tumor; Cerebrospinal fluid; Low T_3 syndrome; Thyroid hormones*

Introduction

Determination of thyroid hormone concentrations in cerebrospinal fluid (CSF) is of great importance in the research of the interaction of thyroid hormones and development and function of the central nervous system (CNS). There are many researches on thyroid hormone concentrations in serum and CSF of patients with different neurologic disorders. However, little is known about this topic and the pathophysiology of thyroid hormone levels in CSF of patients with brain tumor. CSF thyroid hormone concentrations may indicate pathologic changes in the brain, even earlier and more significantly than serum levels[1]. In some somatic and psychiatric diseases, there is a decrease of total triiodothyronine (tT_3) in serum ("low T_3 syndrome"), accompanied by reverse triiodothyronine (rT_3) increase, which is considered as a severity indicator of a general non thyroid illness. Our aim was to contribute to better understanding of CSF as a valuable biological material in the study of cerebral tissue damage, and to discuss the pathophysiology of thyroid hormones in patients with brain tumors, considered as a prototype of severe cerebral lesion.

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Material and Methods

All patients were Caucasians of European origin, and prior to enrolment in the study an informed consent was signed by all subjects. The study was approved by the local Ethics Committee. Based on hormonal laboratory findings and neck ultrasonography, subjects with known thyroid disorders or thyroid hormone supplementation were not included in our study. The brain tumor group consisted of ten patients and control group of seven subjects (volunteers) matched for age and sex. Brain tumor was diagnosed according to clinical features and standard diagnostic procedure. Histopathology reports confirmed 2 astrocytomas, 2 glioblastomas, 2 meningeomas, 1 glioma piloides, 1 oligodendroglioma, 1 tumor of 3rd ventricle and mesencephalon, and 1 glioma of the cerebellum. At the time of sample collection, patients with proven brain tumor were hospitalized because of headache, dizziness and confusion as the leading symptoms of the underlying disease. The levels of total triiodothyronine (tT_3), total thyroxine (tT_4) and thyrotropin (TSH) were determined by radioimmunoassay, while concentrations of free triiodothyronine (fT_3) and free thyroxine (fT_4) were measured by fluorometric assay (Wallac Pharmacia Company, Turku, Finland). rT_3 concentration was determined by radioimmunoassay utilizing the commercial test of Biodata Company (Horsham, USA). Statistical analysis was done using the MedCalc® statistical software (MedCalc 9.3.9.0, Frank Schoonjans, Mariakerke, Belgium). P values <0.05 were considered statistically significant.

Results

All results are shown in Table 1 (median values). tT_3 serum concentration was lower in patients with brain tumor (1.3 nmol/L) compared with control group (1.4 nmol/L). tT_4 level was higher in patients with brain tumor (110 nmol/L) compared with control group (101 nmol/L). Serum fT_3 concentration median in brain tumor patients was 5.7 pmol/L *vs.* 5.8 pmol/L in control group. fT_3 concentration was lower in CSF (1.3 pmol/L in brain tumor patients and 3.5 pmol/L in control group) ($p<0.05$) than in serum in both groups. Serum fT_4 was higher in brain tumor patients (16.9 pmol/L) *vs.* control group (15.5 pmol/L). CSF concentration of fT_4 was 6.6 pmol/L in brain tumor patients and 3.0 pmol/L in control group, yielding a statistically significant between-group difference ($p<0.05$). The levels of serum TSH were lower in brain tumor patients (1.0 mIU/L) *vs.* control group (1.1 mIU/L), while TSH concentration in CSF was similar in the two groups (0.04 mIU/L in brain tumor patients and 0.10 mIU/L in control group).

Our study indicated a statistically significantly higher level of rT_3 in serum and CSF in brain tumor patients *vs.* control group ($p<0.05$). rT_3 serum concentration was 0.26 nmol/L in control group and 0.39 nmol/L ($p<0.05$) in brain tumor patients. Median CSF concentration was 0.19 nmol/L in control group and 0.29 nmol/L ($p<0.05$) in brain tumor patients. The rT_3/fT_3 ratio was highest in CSF and serum of brain tumor patients, the difference being statistically significant. Median ratio was 6.9 in serum of brain

Table 1. Serum (S) and cerebrospinal fluid (CSF) concentrations (median values) of total T_3 (tT_3), total T_4 (tT_4), free T_3 (fT_3), free T_4 (fT_4), thyrotropin (TSH), reverse T_3 (rT_3) and rT_3/fT_3 ratio (rT_3/fT_3) in the group of patients with brain tumor (TM) and control group (C)

		tT_3 nmol/L	tT_4 nmol/L	fT_3 pmol/L	fT_4 pmol/L	TSH mIU/L	rT_3 nmol/L	rT_3/fT_3
TM	S	1.3	110	5.7	16.9	1.0	0.39 ($p<0.05$)	6.9 ($p<0.05$)
	CSF	/	/	1.3	6.6	0.04	0.29 ($p<0.05$)	15.1 ($p<0.05$)
C	S	1.4	101	5.8	15.5	1.1	0.26	1.1
	CSF	/	/	3.5	3.0	0.1	0.19	3.4

p for Hardy-Weinberg equilibrium, χ^2-test

tumor patients and 1.1 in control group. CSF median was 15.1 in brain tumor patients *vs.* 3.4 in control group ($p<0.05$). When patients were divided into three categories of improvement, fatal outcome and unknown, we found no correlation of serum and CSF rT_3 concentration and rT_3/fT_3 ratio with short-term outcome of the disease (data not shown).

Discussion

The "low T_3 syndrome" indicates alteration in thyroid hormonal status in clinically euthyroid patients with severe non-thyroid diseases. These changes include a T_3 decrease and rT_3 increase[2]. TSH level usually remains normal, but may decrease in severe non-thyroid disorders[3,4]. The etiology of "low T_3 syndrome" is not completely clarified and the common factor still remains unclear. Activity defect of 5'-deodinase type I causes reduced peripheral conversions of T_4 into T_3 and rT_3 clearance with consecutively low T_3 level and high rT_3 level. Some studies predicate that cytokines like tumor necrosis factor play an important role[5]. The "low T_3 syndrome" is not only a secondary adaptation to catabolic state or caloric deprivation as it was believed[6,7], and is more likely actively induced by the disorder from the very beginning in order to prevent extensive catabolism. Transition of thyroid hormones into CSF and their important role in the development, function and nutrition of the CNS have long been a well known fact[8,9]. It is also common knowledge that function of CNS becomes significantly impaired in thyroid disorders, especially in myxedema coma and thyrotoxic crisis. Alterations in thyroid hormone levels in neurologic patients were used as an explanation for some CNS function disorders, which can also appear as symptoms in patients with brain tumor[10-12]. Thompson *et al.*[13] investigated subjects with various neurologic disorders and demonstrated that rT_3 levels were also lower in CSF than in serum, similar to the results of the present study. They also found a lower level of fT_4 in CSF than in serum, which is consistent with our findings, contrary to some other authors who report higher levels of free thyroid hormones in CSF than in serum[14]. The levels of TSH obtained in this study also correspond to the results reported by Thompson *et al.*[13]. The study by Nishikawa *et al.* included patients with meningitis and acute cerebrovascular accident[15]. They found higher levels of rT_3 and lower levels of fT_3 in CSF than in serum, which is consistent with our findings. The group of patients with amyotrophic lateral sclerosis also showed higher levels of rT_3 in CSF[16]. Sampaolo *et al.* report an increased CSF level of 3,3',5'-triiodothyronine in patients with Alzheimer's disease[17]. It appears that some hormone aberrations in stroke are connected to cognitive dysfunction in the early post-stroke phases[18,19]. Spatial disorientation was connected with low TSH level response to thyrotropin-releasing hormone (TRH)[10]. Low response of TSH to TRH was also established in Alzheimer's and depressive disorders[11,12]. It is uncertain whether the secretion of these hormones has a direct impact on mental condition, or there is a common suprapituitary mechanism which affects pituitary and cognitive functions in the early post-stroke phases. Favorable influence of thyroid hormones, together with conventional antidepressant therapy is well known[20]. This can be related to the established thyroid hormone concentration reported in depressive disorders[21]. Kirkegaard and Faber found depression convalescence to be accompanied by a decrease of rT_3 levels in CSF[21]. In normal physiological conditions, electrolytes and small molecules are transported through the blood-brain barrier easily, while the presence of macromolecules in the CSF is much lower. The higher levels of different chemical compounds in the CSF indicate their active concentration in the cells (due to the increased demand for neural tissue metabolism) or their cerebral origin (e.g., neurotransmitters). Various pathologic conditions (e.g., compressive processes) may result in dysfunction of the blood-brain barrier, characterized by higher vascular permeability. At least three different deodinases of iodothyronine contribute to preservation of intracellular level of T_3 and modulate the biological activity of thyroid hormones[6]. Most information about iodothyronine metabolism of the brain were obtained in rat research[5,22,23] and recent studies on T_4 5-deodinases in human brain tumors indicated that human gliomas[24], and probably also malignant skin lymphoma, support T_4 5-deodinases activity. In our findings, the rT_3/fT_3 ratio was highest in brain tumor patients and also higher in CSF than in serum. These results, together with previously cited notions on T_4 5-deodinases activity in the brain, could indicate rT_3 local production in brain tissue, and the importance of

CSF which more explicitly reveals changes within the "low T_3 syndrome" in serious neurologic conditions. Ultimately, the thyroid hormones probably cross the blood-brain barrier up to a certain level; however, we assume that rT_3, in the framework of the „cerebral low T_3 syndrome"[25], is also generated through local intracerebral conversion. Disruption of this process in severe cerebral lesion can lead to increased rT_3 concentrations, i.e. development of the "low T_3 syndrome". Because the present study had a relatively small number of patients, we have only presented our preliminary results. Therefore, our assumptions and results need to be further evaluated.

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Sažetak

TUMOR MOZGA KAO PROTOTIP TEŠKOG MOŽDANOG OŠTEĆENJA U BOLESNIKA SA "SINDROMOM NISKOG T_3"

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Cilj studije bio je doprinijeti boljem poznavanju cerebrospinalne tekućine kao vrijednog biološkog materijala u istraživanju moždanih tumora i "sindroma niskog T_3", te razmotriti ulogu hormona štitnjače unutar središnjega živčanog sustava kod bolesnika s ozbiljnim moždanim oštećenjem. Analizirali smo razinu ukupnog trijodtironina (tT_3), ukupnog tiroksina (tT_4), slobodnog trijodtironina (fT_3), slobodnog tiroksina (fT_4), reverznog trijodtironina (rT_3) i tireotropina (TSH) u serumu i razinu fT_3, fT_4, rT_3 i TSH u cerebrospinalnoj tekućini u bolesnika s tumorom mozga te dobivene rezultate usporedili s kontrolnom skupinom ispitanika. Rezultati su ukazali na statistički značajno veću razinu rT_3 u serumu i cerebrospinalnoj tekućini u bolesnika s tumorom mozga u usporedbi s kontrolnom skupinom ($p<0,05$). Odnos rT_3/fT_3 bio je također statistički značajno veći kod bolesnika s tumorom mozga ($p<0,05$). Naše istraživanje moglo bi ukazivati na veću propustljivost krvno-moždane barijere u bolesnika s tumorom mozga. Također pretpostavljamo da se u bolesnika s tumorom mozga rT_3 pojačano stvara kroz aktivniju intracerebralnu pretvorbu. Svakako, naši rezultati trebaju biti potvrđeni i daljnjim podrobnijim istraživanjima.

Ključne riječi: *Tumor mozga; Cerebrospinalna tekućina; Sindrom niskog T_3; Hormoni štitnjače*