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Low triiodothyronine syndrome as a predictor of poor outcomes in patients undergoing brain tumor surgery: a pilot study

Clinical article

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Object. A low triiodothyronine (T3) state is highly prevalent and is associated with a poor prognosis in critically ill patients. The authors investigated, in patients undergoing brain tumor surgery, the direct association of a perioperative low T3 syndrome with clinical outcomes and also with symptoms of depression and anxiety.

Methods. Ninety consecutive patients (71% women, median age 55 years), on admission for brain tumor surgery, were evaluated for sociodemographic and clinical characteristics. Their thyroid function profile was assessed on the morning of brain tumor surgery and on the morning after brain tumor surgery. Patients with free T3 concentrations of 3.1 pmol/L or less were considered to have low T3 syndrome. The patients were evaluated for symptoms of depression and anxiety using the Hospital Anxiety and Depression Scale (HADS) before and after surgery and for clinical outcomes using the Glasgow Outcome Scale (GOS) at discharge.

Results. After brain tumor surgery, free T3 concentrations decreased ($p < 0.001$) and the proportion of patients with low T3 levels increased from 38% to 54% ($p = 0.02$). Lower preoperative (rho = 0.30, $p = 0.004$) and postoperative (rho = 0.33, $p = 0.002$) free T3 concentrations correlated with low GOS scores at discharge. Preoperative low T3 syndrome (OR 5.49, 95% CI 1.27–23.69, $p = 0.02$) and postoperative low T3 syndrome (OR 8.73, 95% CI 1.49–51.21, $p = 0.02$) both increased risk for unfavorable clinical outcomes (GOS scores < 5) at discharge, after adjusting for age, sex, histological diagnosis of brain tumor, preoperative functional impairment, previous treatment for brain tumor, and depressive symptoms. Preoperative low T3 syndrome increased the risk for preoperative (HADS-depression subscale score ≥ 11; OR 4.12, 95% CI 1.16–14.58, $p = 0.03$) but not postoperative depressive symptoms independently from sociodemographic and clinical factors.

Conclusions. Low T3 syndrome is a strong independent predictor of unfavorable clinical outcomes and depressive symptoms, and its diagnosis and preoperative management should be considered in patients undergoing neurosurgery for the treatment of brain tumors.
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Key Words • **brain tumor** • **thyroid hormones** • **surgery** • **depression** • **clinical outcome** • **oncology**

Brain tumor is a devastating disease associated with significant functional impairment and often with a poor prognosis.[7,17] Surgery remains the most important definitive treatment modality for patients with brain tumors. Hence, early and accurate prediction of postoperative outcomes is vital for the guidance of therapy, defining discharge plans, and optimal use of health care resources. To date, predicting the course of disease in patients with brain tumor rests mainly on clinical disease severity indices, such as histological malignancy, extent of resection, age, and preoperative functional status.[7,25,26] A new generation of genetic and molecular prognostic biomarkers related to brain tumors is emerging, but the routine use of these biomarkers remains limited by high costs, and their prognostic value warrants additional research.[7,20]

Alterations of the hypothalamic-pituitary-thyroid axis are well described in critical illness and in mood disorders.[12,46] Briefly, the activation of this axis involves hypothalamic release of thyrotropin-releasing hormone (TRH), which stimulates the pituitary release of thyroid-stimulating hormone (TSH), which in turn activates the

Abbreviations used in this paper: BI = Barthel Index; GOS = Glasgow Outcome Scale; HADS = Hospital Anxiety and Depression Scale; HADS-A = anxiety subscale of HADS; HADS-D = depression subscale of HADS; IQR = interquartile range; TPO-Abs = anti–thyroid peroxidase antibodies; TRH = thyrotropin-releasing hormone; TSH = thyroid-stimulating hormone; T3 = triiodothyronine; T4 = thyroxine.

thyroid to produce and release the hormones thyroxine (T4) and triiodothyronine (T3).[4,6] The primary secretory product of the thyroid gland is the less metabolically active T4, whereas the majority of the more metabolically active T3 comes from extrathyroidal conversion from T4 via deiodination in different tissues, including brain. The secretion of both TSH and TRH can be inhibited by T3 and T4 via a negative feedback loop.

A typical pattern of altered thyroid hormone metabolism in critical illness is characterized by decreased peripheral concentrations of T3 (that is, low T3 syndrome or euthyroid sick syndrome), due to reduced enzymatic activity of 5′ deiodinase, which is primarily responsible for T4 to T3 conversion and for T3 availability in tissues.[12,46] Low T3 syndrome is highly prevalent and independently predicts a poor prognosis in hospitalized and critically ill patients.[2,34,46] In surgical patients, a number of studies have documented postoperative decrease of T3 concentrations, and lower T3 concentrations were associated with unfavorable outcomes, suggesting that low T3 syndrome can be an important prognostic biomarker in surgical patients.[14,24,36,38,43,48] To our knowledge, however, no studies have investigated the prevalence of low T3 syndrome in the perioperative period and the direct link of low T3 syndrome to clinical outcomes in neurosurgical patients.

Depression and anxiety symptoms are considered important secondary outcomes in neurooncology, are highly prevalent in brain tumor patients, and predict poor clinical outcomes.[3,19,28] Despite the well-established association of thyroid function with psychiatric symptoms in patients with psychiatric and somatic conditions, there are no studies evaluating the association of thyroid axis function with depression and anxiety in brain tumor patients.[4,12] The identification of depression and anxiety biomarkers could potentially improve risk stratification and contribute to the improved care and survival of these patients.

Therefore, the aim of the present report was to evaluate, in patients undergoing brain tumor surgery, the prevalence of perioperative low T3 syndrome and the direct association of perioperative low T3 syndrome with immediate postoperative clinical outcomes as well as with symptoms of depression and anxiety.

Methods

Patients

In the period from March 2010 until June 2011, consecutive patients admitted for scheduled brain tumor surgery at the Department of Neurosurgery of the Lithuanian University of Health Sciences were eligible for this study. Patients were excluded from the study if they were younger than 18 years of age, were pregnant or nursing, had current thyroid disease, or were currently taking thyroid medication or amiodarone.

A total of 114 patients met the inclusion criteria and agreed to participate in the study. However, 24 patients (21%) were excluded because they had elevated titers of anti–thyroid peroxidase antibodies (TPO-Abs), suggesting autoimmune thyroid disease. Hence, our final sample consisted of 90 brain tumor patients without frank thyroid disease (71% women and 29% men; mean age of 55.1 ± 13.9 years). No differences were seen in sociodemographic and clinical characteristics between patients who were excluded and those who were studied ($p > 0.08$ for all comparisons).

Study Design

The study and its consent procedures were approved by the Ethics Committee for Biomedical Research at the Lithuanian University of Health Sciences, Kaunas, Lithuania. Written informed consent was obtained from each study patient.

All study patients were enrolled on admission to the inpatient department and data were recorded for demographic characteristics, education (range from not having finished high school to graduation from college), marital status (living with partner or not living with partner), previous treatment for brain tumor (yes or no), history of psychiatric disorder (yes or no), and current psychiatric treatment (yes or no). During the same visit, patients were evaluated for functional status (Barthel Index, BI)[27] and for symptoms of depression and anxiety (HADS).[49] The final histological diagnosis of brain tumor was established by reviewing the pathology reports, which were obtained from the medical records. Within 3 days after brain tumor surgery, patients were reevaluated using the HADS. At discharge, the clinical outcome was determined according to the score on the GOS.[22] Blood samples for the evaluation of thyroid axis hormone concentrations were drawn on 2 occasions: 1) the morning of brain tumor surgery and 2) the morning following brain tumor surgery.

Functional Status

Functional status on admission was assessed using the BI, which is a 10-item scale designed to evaluate daily functions of dressing, bathing, feeding, grooming, transfers from bed to chair and back, bladder and bowel control, toilet use, mobility, and climbing stairs.[27] Each item is scored as 0, 5, 10, or 15, depending on the person's ability to perform the activity. The global BI score ranges from 0 to 100 points, with higher scores indicating better functional status.

Evaluation for Symptoms of Depression and Anxiety

The HADS is a 14-item self-rating instrument that consists of subscales of anxiety (HADS-A) and depression (HADS-D), which are designed to measure respective symptoms in patients with somatic conditions.[49] Possible scores in both subscales range from 0 to 21, with a higher score indicating more severe symptoms. We also evaluated the total score on the HADS (HADS-total). Scores of 11 or higher on the HADS-D and HADS-A suggest elevated depressive and anxiety symptoms, respectively.[49] A Lithuanian version of the HADS is well validated and widely used on an inpatient and outpatient basis for the evaluation of anxiety and depression in patients with somatic conditions.[10,11]

Evaluation for Clinical Outcome

Clinical outcome at discharge was evaluated by means of the 5-point GOS.[22] In agreement with previous research, patients with GOS scores of 5 (good recovery) were considered as having a favorable clinical outcome and patients with GOS scores ranging from 1 (death) to 4 (moderate disability) were considered as having an unfavorable clinical outcome.[16] The GOS is widely used in neurosurgical clinical practice. It is a well-validated scale with good interobserver agreement.[47]

Thyroid Hormone Assessment

Blood samples for thyroid axis hormone assessment were drawn from an antecubital vein about 8 AM before breakfast and within 10 minutes after patients awoke, following overnight fasting. Blood was rapidly centrifuged and serum was frozen at −40°C. The samples from all patients for each parameter were analyzed in a single batch. Serum concentrations of free T3, free T4, TSH, and TPO-Abs were measured by radioimmunoassay, and serum concentrations of reverse free T3 (rT3) were measured by ELISA method. The reference values for our laboratory were as follows: free T3, 3.1–6.4 pmol/L; free T4, 11.5–20.7 pmol/L; TSH, 0.27–4.2 mIU/L; and TPO-Abs, less than 60 U/ml. We also calculated the free T3 to free T4 ratio, which corresponds to peripheral free T4 to free T3 conversion, with a higher ratio corresponding to greater conversion.

On the basis of free T3 values, patients were dichotomized into 2 subgroups: 1) patients with free T3 concentrations at or below the lower concentration of the free T3 reference interval (≤ 3.1 pmol/L) were considered as having low T3 syndrome and 2) patients were considered to have normal free T3 values if their free T3 concentrations were greater than 3.2 pmol/L.

Statistical Analyses

Data were analyzed with SPSS 17.0 for Windows. Data are presented as mean ± standard deviation and as median (IQR) for continuous variables and as the number (%) for categorical variables. We employed nonparametric statistical tests because, according to the Kolmogorov-Smirnov test, endocrine data and psychiatric data were not normally distributed. All tests were 2-tailed and $p < 0.05$ was considered statistically significant.

First, by using the Wilcoxon signed rank test for continuous data and the McNemar test for categorical data we evaluated the change of thyroid axis hormone concentrations and free T3 to free T4 ratio as well as symptoms of depression and anxiety before versus after brain tumor surgery.

Second, using the Spearman rank correlation, we explored the association of perioperative thyroid axis hormone concentrations and free T3 to free T4 ratios with clinical outcome at discharge. We then evaluated the association of preoperative and postoperative low T3 syndrome with clinical outcome at discharge in univariate logistic regression analyses, and the results are presented as odds ratios and 95% confidence intervals. Significant univariate associations were then adjusted in multivariate binary logistic regression model(s) (forward: LR) for age, sex, preoperative BI score, previous treatment for brain tumor, and histological diagnosis of brain tumor, because these factors were previously shown to be important prognostic factors in patients with brain tumors.[7,25,26] In the final multivariate regression analyses model, the HADS-D score before surgery was included as a covariate.

Finally, the association of preoperative and postoperative thyroid axis hormone concentrations and free T3 to free T4 ratios with preoperative and postoperative HADS-D, HADS-A, and HADS-total scores were explored by using the Spearman rank correlation. The association of preoperative low T3 syndrome with elevated perioperative depressive and anxiety symptoms was evaluated by using univariate binary logistic regression analyses. We then employed multivariate binary logistic regression models and adjusted significant univariate associations (forward: LR) for age, sex, living condition, psychiatric history, current psychiatric treatment, preoperative BI score, previous treatment for brain tumor, and histological diagnosis of brain tumor.

Results

Baseline Characteristics

In 37 patients (41%), the diagnosis was meningioma; in 17 (19%), high-grade glioma; in 12 (13%), pituitary adenoma; in 11 (12%), acoustic neuroma; in 5 (6%), low-grade glioma; and in 8 (9%), other brain tumors, including metastatic tumors (2), hemangiopericytoma (1), germinoma (1), teratoma (1), pineal tumor (1), Rathke cleft cyst (1), and pineocytoma (1) (Table 1). Forty-two percent of patients had graduated from high school, and 76% were living with a partner. Eighteen percent of patients had previously undergone surgery for brain tumor treatment. Six percent of patients had histories of psychiatric disorders, and 8% were receiving psychotropic medication.

Perioperative Thyroid Axis Function and Symptoms of Depression and Anxiety

Thyroid hormone concentrations and ratios and symptoms of depression and anxiety before versus after brain tumor surgery are presented in Table 2. After brain tumor surgery, when compared with respective values before surgery, there was a significant decrease in free T3 concentrations, TSH concentrations, and free T3 to free T4 ratios ($p < 0.001$ for all comparisons). There was also a significant increase in free T4 concentrations after brain tumor surgery ($p < 0.001$). Low T3 syndrome was diagnosed in 38% of patients before surgery and in 54% of patients after surgery ($p = 0.02$).

With respect to symptoms of anxiety and depression, there was a significant decrease in HADS-D scores ($p = 0.003$) and HADS-A scores ($p < 0.001$) after brain tumor surgery (Table 2). There was also a significant decrease in the proportion of patients with elevated HADS-D scores (16% vs 7%, respectively, $p = 0.02$) and a trend for a decreased proportion of patients with elevated HADS-A scores (17% vs 8%, respectively, $p = 0.057$) (Fig. 1).

TABLE 1: Baseline sociodemographic, clinical, and psychiatric data for 90 patients*

Characteristic	Value
sex	
male	26 (29)
female	64 (71)
age in yrs	
mean	55.1 ± 13.9
median	55
IQR	46–66
no. of pts (%) w/ age >50 yrs	62 (69)
education	
not graduated from high school	5 (6)
graduated from high school	38 (42)
some college	24 (27)
graduated from college	23 (25)
marital status	
living w/ partner	68 (76)
not living w/ partner	22 (24)
histological diagnosis of brain tumor	
high-grade glioma	17 (19)
low-grade glioma	5 (6)
meningioma	37 (41)
pituitary adenoma	12 (13)
acoustic neuroma	11 (12)
other	8 (9)
previous brain tumor treatment	
yes	16 (18)
no	74 (82)
Barthel Index	
mean score	94.9 ± 13.6
median score	100
IQR	100–100
history of psychiatric disorder	
yes	5 (6)
no	85 (94)
current psychiatric treatment	
yes	7 (8)
no	83 (92)

* Unless otherwise indicated, values represent numbers of patients (pts) (%). Means are presented with SD.

Association of Thyroid Axis Function With Clinical Outcome

At discharge, the median GOS score was 5, and 18 patients (20%) had GOS scores of 4 or lower, indicative of unfavorable clinical outcomes (including postoperative death in 2 cases).

Correlation analyses revealed that lower preoperative free T3 concentration (rho = 0.30, p = 0.004), lower postoperative free T3 concentration (rho = 0.33, p = 0.002), and lower preoperative free T3 to free T4 ratio (that is, lower T4 to T3 conversion; rho = 0.23, p = 0.03) were associated with lower GOS scores (that is, unfavorable outcome) at discharge (Table 3). Other perioperative thyroid hormone concentrations did not correlate significantly with GOS scores at discharge.

In univariate binary regression analyses, patients with low T3 syndrome before surgery (OR 4.46, 95% CI 1.48–13.40, p = 0.008) and after surgery (OR 5.44, 95% CI 1.45–20.45, p = 0.012; Table 4) were at increased risk for unfavorable clinical outcomes at discharge relative to patients with normal free T3 concentrations. After adjusting for age, sex, preoperative functional impairment, previous treatment for brain tumor, and histological diagnosis of brain tumor, preoperative low T3 syndrome (OR 5.09, 95% CI 1.38–18.78, p = 0.01) and postoperative low T3 syndrome (OR 5.35, 95% CI 1.20–23.90, p = 0.03) were associated with an independently increased risk for unfavorable clinical outcome at discharge. When the preoperative HADS-D score was included as an additional covariate in the multivariate binary regression analyses model, preoperative low T3 syndrome (OR 5.49, 95% CI 1.27–23.69, p = 0.02) and postoperative low T3 syndrome (OR 8.73, 95% CI 1.49–51.21, p = 0.02) remained independently associated with increased risk of an unfavorable clinical outcome at discharge.

Association of Thyroid Axis Function With Symptoms of Depression and Anxiety

Lower preoperative free T3 concentration was associated with greater preoperative HADS-D (rho = −0.22, p = 0.04), HADS-A (rho = −0.25, p = 0.02), and HADS-total (rho = −0.31, p = 0.003) scores, and with greater postoperative HADS-D (rho = −0.22, p = 0.04) and HADS-total (rho = −0.23, p = 0.03) scores. Also, lower preoperative free T3 to free T4 ratio (that is, lower T4 to T3 conversion) was associated with greater preoperative HADS-D (rho = −0.25, p = 0.02) and HADS-total (rho = −0.24, p = 0.03) scores (Table 5). Postoperative thyroid axis hormone concentrations and free T3 to free T4 ratio were not associated with postoperative HADS-D, HADS-A, or HADS-total scores (p ≥ 0.12 for all comparisons; data not shown).

In univariate binary logistic regression analyses, preoperative low T3 syndrome was associated with increased risk for elevated preoperative depressive symptoms (OR 3.60, 95% CI 1.09–11.88, p = 0.035), but not preoperative anxiety symptoms (Table 6). After adjusting for age, sex, living conditions, psychiatric history, current psychiatric treatment, functional impairment, previous treatment for brain tumor, and histological diagnosis of brain tumor, the preoperative low T3 syndrome remained an independent predictor of elevated preoperative depressive symptoms (OR 4.12, 95% CI 1.16–14.58, p = 0.03). Preoperative low T3 syndrome was not associated with increased risk for postoperative depressive and anxiety symptoms.

Discussion

The main findings of the present study were that perioperative low T3 syndrome was highly prevalent in pa-

TABLE 2: Thyroid axis function and scores on the HADS before versus after brain tumor surgery

Variable	Preop*	Postop*	Z/χ^2	p Value†	Increase‡	Decrease‡	No Change‡
thyroid axis hormone concentrations							
free T3, pmol/L	3.5 (3.0–4.1)	3.2 (2.7–3.6)	−4.81	**<0.001**	24	64	0
free T4, pmol/L	12.6 (11.3–14.7)	17.7 (15.4–20.9)	−8.16	**<0.001**	86	4	0
reverse T3, pg/ml	866 (620–1074)	884 (689–1168)	−0.98	0.33	52	38	0
TSH, mIU/L	0.70 (0.36–1.40)	0.32 (0.20–0.57)	−5.99	**<0.001**	16	73	0
free T3/free T4 ratios	0.27 (0.22–0.32)	0.17 (0.15–0.20)	−8.16	**<0.001**	2	86	0
no. of pts (%) w/ low T3 syndrome§	34 (38)	49 (54)	5.28	**0.02**			
HADS scores							
HADS-D	4 (1–7)	2 (1–6)	−3.00	**0.003**	21	37	23
HADS-A	5 (2–9)	4 (1–7)	−4.43	**<0.001**	18	55	8

* Unless otherwise indicated, preoperative and postoperative values represent medians (IQR).
† Bold type indicates statistical significance ($p < 0.05$).
‡ Values represent numbers of patients.
§ Low T3 syndrome is defined by a free T3 (triiodothyronine) concentration ≤ 3.1 pmol/L.

tients undergoing brain tumor surgery and was associated with increased risk for unfavorable clinical outcomes at discharge, and preoperative low T3 syndrome was associated with increased risk for preoperative depressive symptoms.

To the best of our knowledge, this is the first study to examine perioperative thyroid axis function in patients undergoing brain tumor surgery. The preoperative prevalence rate of low T3 syndrome (38%) in brain tumor patients corresponds to low T3 syndrome prevalence rates previously reported in hospitalized cardiac patients (30%)[21] and in acutely ill elderly patients (32%).[41] As expected, median free T3 concentrations decreased and the prevalence of low T3 syndrome (54%) increased within 24 hours after brain tumor surgery. A number of previous studies have documented decreased T3 concentrations within a few hours after major surgery, returning to preoperative levels within a week after surgery.[14,43,48] Comparable prevalence rates of postoperative low T3 syndrome were previously reported after kidney transplantation (52%).[40] It is widely accepted that decreased peripheral 5′ monodeiodinase activity is the chief pathophysiological mechanism underlying the development of low T3 syndrome in critical illness.[44,46] Indeed, we found that the free T3 to free T4 ratio (an index of peripheral 5′ monodeiodinase activity) was significantly decreased after surgery when compared with preoperative levels. A number of factors can interfere with thyroid hormone metabolism; these factors include but are not limited to endogenous stress hormones and proinflammatory cytokines (not evaluated), concentrations of which are expected to elevate after surgery.[1,42,44,46] In line with our results, a decrease in TSH concentration was previously described in critically ill patients and in patients who had undergone surgical procedures.[1,23,46] Decreased TSH secretion results in decreased thyroidal T3 and T4 production and contributes to the development of low T3 syndrome. It was shown that a prolonged low T3 syndrome can be associated with decreased hypothalamic TRH synthesis.[18] Also, postoperative TSH and/or TRH secretion can be suppressed by elevated free T4 concentrations, by postoperative increases in concentrations of proinflammatory cytokines and endogenous cortisol, and by caloric restriction.[1,42,46] The clinical significance of T4 in critical illness remains less clear, and findings regarding postoperative changes in T4 concentrations have been inconsistent, given that it was reported that T4 concentrations may increase,[15] decrease,[48] or remain unchanged[43] after surgery. The postoperative increase in free T4 concentrations found in our study could be due to 1) suppressed conversion of T3 from T4 leading to a build-up of T4; 2) impaired entry of free T4 into cells in patients with low T3 syndrome;[37] and 3) increased release of T4 from thyroid gland stores together with impaired function of thyroid-binding globulin previously described in relation to certain anesthetics, such as isoflurane and enflurane, that are widely used in neurosurgery.[8,15,29]

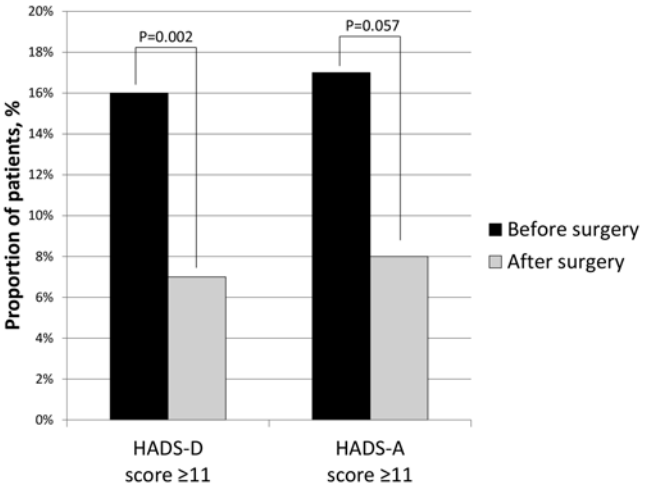

Fig. 1. Proportion of patients with scores of 11 or higher on the depression and anxiety subscales of the HADS before and after brain tumor surgery.

TABLE 3: Association of perioperative thyroid axis function with GOS at discharge*

Hormone Concentration or Ratio	Spearman rho	p Value
free T3 in pmol/L		
preop	**0.30**	**0.004**
postop	**0.33**	**0.002**
free T4 in pmol/L		
preop	0.04	0.70
postop	0.07	0.49
reverse T3 in pg/ml		
preop	0.13	0.21
postop	0.08	0.44
TSH in mIU/L		
preop	0.02	0.85
postop	–0.14	0.20
free T3/free T4 ratio		
preop	**0.23**	**0.03**
postop	0.20	0.06

* Greater scores indicate better clinical outcome. Bold type indicates statistical significance ($p < 0.05$).

Most importantly, we found that perioperative low T3 syndrome was independently associated with a 5- to 8-fold increased risk for unfavorable clinical outcomes at discharge, even after adjusting for age, sex, preoperative functional impairment, previous treatment for brain tumor, histological diagnosis of brain tumor, and preoperative depressive symptoms. It should be noted that inclusion of brain tumor type, including pituitary adenomas, to the models did not change the association between thyroid hormone concentrations and outcomes of brain surgery. In correlation analyses, a lower perioperative free T3 concentration was associated with poor outcomes, suggesting a dose-response relationship between low free T3 concentrations (even within a normal range) and poor clinical outcome. Our results regarding the independent prognostic role of low T3 syndrome correspond to results of previous studies showing that low T3 syndrome was an independent predictor of mortality in different populations of patients, including cardiac patients,[21] stroke patients,[2] and hospitalized elderly patients.[41] A dose-response relationship between low T3 concentrations and poor outcomes was previously described in hospitalized patients[46] and in general surgery patients.[43] Triiodothyronine is essential for proper functioning of the brain and cardiovascular system, and results from preclinical and clinical studies suggest that thyroid hormones can promote plasticity and regeneration in the CNS.[33,39] Further studies should explore mechanisms underlying the negative impact of low T3 syndrome. Nevertheless, clinicians should keep in mind that low T3 syndrome is highly prevalent and independently predicts poor prognosis in brain tumor patients. Patients undergoing surgery for treatment of brain tumors who have perioperative free T3 concentrations at or below the normal range should be considered at high risk for poor outcomes.

An important benefit of low T3 syndrome as a prognostic biomarker is that it can be easily treated by using thyroid hormone replacement therapy. However, the need for thyroid hormone replacement therapy in patients with low T3 syndrome remains controversial.[44,46] For example, in patients with heart failure[32] or in patients undergoing heart surgery,[24,35] thyroid hormone replacement therapy was safe and improved hemodynamic function; however, the benefit with respect to mortality remains less clear. Others have reported that thyroid hormone replacement therapy did not improve clinical outcomes in intensive care unit patients[9] and in patients with burn injuries.[5] Nonetheless, thyroid hormone replacement therapy in low T3 patients undergoing brain surgery is an interesting avenue for future research, because thyroid hormones cross the blood-brain barrier and are critical for proper development, function, and regeneration of the CNS.[6,12,46]

In our patient group, depression and anxiety were prevalent before surgery and improved after surgery. According to the literature, the prevalence of depression in brain tumor patients ranges from 5% for active clinical depression[19] to 40% for elevated depressive symptoms.[3] Lower prevalence rates of depressive and anxiety symptoms in our study can be explained by our having considered patients to have elevated depressive and/or anxiety symptoms if they had moderate to severe levels of respective symptoms if their HADS subscale scores 11 or greater. Gathinji and colleagues[19] reported that preoperative clinical depression independently predicted worse survival of patients with brain tumor, underscoring the fact that depression is an important risk factor that should be promptly diagnosed and treated. In the present study, low T3 syndrome predicted a 4-fold increased risk for el-

TABLE 4: Association of preoperative and postoperative low T3 syndrome with unfavorable clinical outcome at discharge

Variable	Univariate Association			Multivariate Association*			Multivariate Association†		
	OR	95% CI	p Value‡	OR	95% CI	p Value‡	OR	95% CI	p Value‡
predictor: discharge GOS score <5									
preop low T3 syndrome	4.46	1.48–13.40	**0.008**	5.09	1.38–18.78	**0.01**	5.49	1.27–23.69	**0.02**
postop low T3 syndrome	5.44	1.45–20.45	**0.012**	5.35	1.20–23.90	**0.03**	8.73	1.49–51.21	**0.02**

* Adjusted for age, sex, preoperative BI score, previous brain tumor treatment, and histological diagnosis of brain tumor (forward: LR).

† Adjusted for age, sex, preoperative BI score, previous brain tumor treatment, histological diagnosis of brain tumor, and HADS-D score before surgery (forward: LR).

‡ Bold type indicates statistical significance ($p < 0.05$).

TABLE 5: Association of preoperative thyroid axis function with perioperative symptoms of depression and anxiety*

Preop Hormone Concentration or Ratio	Preop HADS Score†			Postop HADS Score†		
	Depression	Anxiety	Total	Depression	Anxiety	Total
free T3 in pmol/L	**−0.22 (0.04)**	**−0.25 (0.02)**	**−0.31 (0.003)**	**−0.22 (0.04)**	−0.14 (0.18)	**−0.23 (0.03)**
free T4 in pmol/L	0.01 (0.95)	−0.21 (0.055)	−0.10 (0.95)	−0.04 (0.74)	−0.17 (0.11)	−0.08 (0.46)
reverse T3, pg/mL	0.17 (0.11)	−0.04 (0.72)	0.06 (0.58)	0.08 (0.45)	0.12 (0.27)	0.12 (0.28)
TSH in mIU/L	−0.01 (0.90)	0.11 (0.29)	0.02 (0.85)	0.06 (0.60)	0.15 (0.17)	0.10 (0.35)
free T3/free T4 ratio	**−0.25 (0.02)**	−0.13 (0.29)	**−0.24 (0.03)**	−0.19 (0.07)	−0.04 (0.74)	−0.17 (0.11)

* Values represent Spearman rho with p value in parentheses. Bold type indicates statistical significance ($p < 0.05$).
† Greater scores indicate more symptoms.

evated preoperative depressive symptoms, independently from age, sex, living condition, psychiatric histories and treatment, functional impairment, previous treatment for brain tumor, and histological diagnosis of brain tumor, including pituitary adenomas. In univariate analyses, lower T3 to T4 ratios were associated with greater depressive symptoms, suggesting that decreased activity of 5′ deiodinase can be related to depressive symptom severity in brain tumor patients. The association of low T3 concentrations with elevated depressive symptoms has been previously reported in medical patients,[13] and it was suggested that elevated hypothalamic-pituitary-adrenal axis activity in depressed patients can suppress 5′ deiodination leading to decreased T3 concentrations.[31] In addition, it is well established that depression is prevalent in hypothyroid patients.[4,12] However, due to the design of our study we could not establish the directional association between thyroid function and depression. Nevertheless, our data suggest that decreased free T3 concentrations can be an important biomarker for the development of depressive symptoms in brain tumor patients; hence, free T3 evaluation should to be considered if patients in this population are depressed.

It should be recalled that we evaluated peripheral concentrations of thyroid hormones. Thyroid hormones undergo significant metabolism, a variety of transporters are responsible for thyroid hormone tissue concentrations, and thyroid hormone receptors have a complex mode of action.[6,12,46] The activity and expression of proteins involved in metabolism, transfer, and binding of thyroid hormones can differ and/or can be differentially modified in response to low T3 syndrome as a function of certain genetic polymorphisms.[30,45,46] These genetic polymorphisms can consequentially result in different clinical and neuropsychiatric outcomes in patients affected by low T3 syndrome. Thus, future studies should explore outcomes of brain tumor patients in relation to genetic polymorphisms of proteins involved in metabolism, transportation, and binding of thyroid hormones. This knowledge could enable more precise identification of high-risk patients based on inherent genetic polymorphisms.

Our study has limitations. First, because of the relatively small sample size, our results should be considered preliminary. In addition, it should be noted that our cohort was heterogeneous in terms of clinical characteristics, such as brain tumor biology and previous treatments for brain tumor; therefore, further studies should explore the impact of low T3 syndrome in more discrete subgroups of brain tumor patients. A larger study evaluating the association of outcomes with low T3 syndrome and with genetic polymorphisms of proteins involved in metabolism and transfer of thyroid hormones is under

TABLE 6: Association of preoperative low T3 syndrome with preoperative and postoperative depressive and anxiety symptoms

Variable	Univariate Association			Multivariate Association*		
	OR	95% CI	p Value	OR	95% CI	p Value
predictor: preop depression†						
preop low T3 syndrome	3.60	1.09–11.88	**0.035**	4.12	1.16–14.58	**0.03**
predictor: preop anxiety‡						
preop low T3 syndrome	2.11	0.39–6.47	0.19	—	—	—
predictor: postop depression†						
preop low T3 syndrome	1.73	0.33–9.14	0.52	—	—	—
predictor: postop anxiety‡						
preop low T3 syndrome	1.28	0.27–6.09	0.76	—	—	—

* Adjusted for age, sex, living condition, psychiatric history, current psychiatric treatment, preoperative BI score, previous brain tumor treatment, and histological diagnosis of brain tumor (forward: LR). Bold type indicates statistical significance ($p < 0.05$).
† Defined as HADS-D score ≥ 11.
‡ Defined as HADS-A score ≥ 11.

way. Also, levels of total (free + bound) thyroid hormone concentrations were not evaluated in our study. However, total thyroid hormone concentration is expected to be a less reliable marker of thyroid status in severe illness because thyroid hormone binding proteins are acute phase reactants.

A strength of this study is that we excluded patients with known thyroid disease, patients taking thyroid medication, and patients in whom autoimmune thyroid diseases was suspected, thus avoiding endocrine bias. Moreover, reliable and widely used instruments were used to measure disease severity, mental symptoms, and outcome, thus fortifying the reliability of our results. However, future studies should investigate the association of low T3 syndrome with more discrete clinical and neuropsychological outcomes.

Conclusions

In conclusion, perioperative low T3 syndrome is highly prevalent in patients undergoing brain tumor surgery and is independently associated with increased risk for unfavorable clinical outcomes and depressive symptoms. Free T3 concentration should be considered as a prognostic biomarker in neurosurgical brain tumor patients.

Disclosure

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