Low T_3 Syndrome in Head-Injured Patients is Associated with Prolonged Suppression of Markers of Cell-Mediated Immune Response

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Abstract

Purpose: To clarify the association between disturbed thyroid hormone metabolism (low T_3 syndrome) and release of cytokines and markers of cell-mediated immune response.

Material and Methods: Concentrations of cytokines as well as of thyroid hormones were determined in 32 patients suffering from severe traumatic brain injury: interleukin-(IL-)1, IL-6, IL-10, tumor necrosis factor, transforming growth factor-(TGF-)β, soluble interleukin-2 receptor (sIL-2R), neopterin, and β_2-microglobulin (β2m) in serum and cerebrospinal fluid; triiodothyronine (T_3), free T_3, thyroxine (T_4), free T_4, thyrotropin, thyroxine-binding globulin, and albumin in serum. Additionally, clinical parameters were assessed: Glasgow Coma Score, CT scan, intracranial pressure, Glasgow Outcome Score, and occurrence of pneumonia.

Results: Among 31 patients with a low T_3 syndrome, those with additional low serum T_4 levels (n = 13) showed a prolonged suppression of serum β2m, neopterin, and sIL-2R, and a higher secondary increase of serum β2m, neopterin, and TGF-β, as well as lower T_3 levels (all $p < 0.05$). These patients also had a longer stay in the intensive care unit (34 ± 6 days vs. 22 ± 12 days; $p = 0.008$). Increased levels of β2m correlated with a preceding decrease of thyrotropin (cerebrospinal fluid: $r = -0.53$; $p = 0.004$; serum: $r = -0.41$; $p = 0.029$). Associations of thyroid hormone metabolism with either other cytokines or with clinical parameters were not detected.

Conclusion: These results show that low T3 syndrome is a very common pathophysiological feature after severe traumatic brain injury. The association of a low T_3 syndrome in combination with low serum T_4 levels, with an altered time course of markers of cell-mediated immunity led the authors to hypothesize that a disturbed thyroid hormone metabolism may be interrelated with a prolonged cellular immune dysfunction after traumatic brain injury.

Key Words
Brain injuries · Cytokines · Euthyroid sick syndromes · Human · Immunology · Trauma

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Introduction

Alterations in thyroid hormone metabolism and regulation occur in virtually all patients admitted to the intensive care unit, irrespective of a preexisting thyroidal dis-

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ease. These alterations are mainly characterized by a decrease in serum triiodothyronine (T_3) levels (low T_3), while an additional drop in serum thyroxine (T_4) may occur in the clinically more severe cases (low T_3-low T_4), which is associated with an increased mortality rate [1, 2]. The reduced T_3 and/or T_4 levels are associated with normal or low serum thyrotropin values. The etiology of this disturbance is only partially understood. Changes within the central nervous system (CNS) as well as in the periphery were charged causal, like decreased production of hypothalamic thyrotropin-releasing hormone, decreased generation of T_3 by liver thyroxin deiodinase type 1, altered serum transport capacity by thyroxin-binding globulin (TBG), or a T_3/T_4 tissue transport defect [1, 2]. This endocrine disturbance has been given different names, such as the "low T_3 syndrome", "euthyroid sick syndrome", or "non-thyroidal illness syndrome" and there is still disagreement on the terminology, reflecting the unresolved pathophysiology of these changes and the still open question of a true tissue hypothyroidism [1–3]. In our study, we prefer to use the more descriptive term "low T_3 syndrome", thus avoiding inferences on function or mechanisms.

Cytokines represent a group of locally and systemically released inflammatory proteins held responsible for changes in the hypothalamic-pituitary-thyroid axis equal to those found in low T_3 syndrome (for review see [4]). The list of factors investigated includes pro-inflammatory (tumor necrosis factor [TNF], interleukin-[IL-]1, IL-6) and anti-inflammatory cytokines (IL-10) as well as markers of mononuclear cell activation (soluble interleukin-2 receptor [sIL-2R]) [4–6]. In particular, serum IL-6 concentrations were shown to correlate with low T_3 levels in clinical studies enrolling patients with a large spectrum of disorders [7–9]. However, this issue is questioned by recent studies in which neutralization of cytokine activity failed to prevent the low T_3 syndrome following lipopolysaccharide challenge [10–12]. Many of the clinical studies are cross-sectional and limited to predefined serum sampling, thus possibly missing time effects, and they exclude the central nervous compartment that is pivotal in the regulation of the hypothalamic-pituitary-thyroid axis. Based on these premises, individuals with severe traumatic brain injury (TBI) represent an interesting subgroup of patients for studying the low T_3 syndrome in humans, since they are usually healthy until the defined beginning of the disease at the time of injury, and since the peripheral as well as the central nervous compartment are accessible. The low T_3 syndrome is a common component of the pathophysiology of severe TBI [13–18], and the release of different cytokines such as IL-6, IL-10, TNF or pleiotropic transforming growth factor-(TGF-)β into serum and cerebrospinal fluid (CSF) has previously been shown in these patients [19–21], suggesting a possible physiological link between these cascades.

In the present study we therefore investigated the interrelation of thyroid hormone levels with cytokine levels in serum and CSF as well as with other clinical data in patients suffering from severe TBI. We have se-

Table 1. Epidemiologic and clinical data of 32 patients with severe traumatic brain injury.

Patient #	Sex	Age (years)	GCS[a]	CT[b]	ICP[c] (mmHg)	GOS[d]		Pneumonia[e]
1	Male	21	3	DI IV°	140	1	(5)	
2	Female	59	10	EML	87	1	(7)	
3	Male	42	3	NEML	108	1	(9)	
4	Male	67	5	EML	21	1	(10)	
5	Male	35	8	DI III°	110	1	(10)	
6	Male	23	3	NEML	86	1	(12)	x
7	Male	73	6	DI II°	11	1	(104)	
8	Male	27	3	DI II°	25	3		
9	Male	53	3	DI II°	29	3		x
10	Male	56	5	EML	24	3		
11	Male	22	5	DI II°	19	3		x
12	Male	26	5	DI II°	42	3		
13	Female	51	5	DI II°	35	3		
14	Male	21	3	DI II°	10	4		
15	Male	26	4	DI II°	56	4		x
16	Female	31	5	DI II°	31	4		x[f]
17[g]	Male	45	6	DI II°	29	4		
18	Male	48	8	DI III°	41	4		
19	Male	17	8	DI II°	19	4		
20	Male	31	11	EML	33	4		x
21	Male	48	12	EML	89	4		
22	Male	18	3	DI II°	34	5		x
23	Male	42	3	DI II°	28	5		x
24	Male	55	5	EML	24	5		
25	Female	17	6	DI II°	25	5		x
26	Male	41	10	DI II°	24	5		x
27	Female	35	11	DI II°	12	5		
28	Female	23	12	DI II°	43	5		
29	Female	25	14	EML	30	5		
30	Male	16	14	EML	28	5		
31	Female	34	14	DI II°	26	5		
32	Male	59	14	DI II°	40	5		x

[a] GCS: Glasgow Coma Score [56]
[b] CT: classification of computed tomography of the brain at admission [30]: DI II°–IV°: diffuse injury grade II–IV; EML: evacuated mass lesion; NEML: nonevacuated mass lesion
[c] ICP: maximal intracranial pressure persisting for > 5 min
[d] GOS: Glasgow Outcome Score [31]: 1: dead, 3: severely disabled, 4: moderately disabled, 5: good recovery; numbers in brackets: days of survival
[e] Pneumonia: diagnosis was made if the following criteria were met: pulmonary infiltrates; signs of inflammation (fever, increased serum levels of C-reactive protein, leukocytosis); detection of pathogens in tracheal/bronchial material. This was required for antibiotic treatment. Drugs were not administered on a routine prophylactic regimen
[f] This patient suffered from *Pseudomonas* sepsis
[g] patient without low T_3 syndrome

Table 2. List of assays used for analysis of cytokines/leukocyte activation markers in serum and cerebrospinal fluid. (n) gives the number of brain-injured patients in whom the amount of serum and cerebrospinal fluid was sufficient for a determination throughout the study. β2m: β_2-microglobulin; IL: interleukin; sIL-2R: soluble interleukin-2 receptor; TGF: transforming growth factor; TNF: tumor necrosis factor.

Parameter (n)	Source	Detection limit
β2m (30)	Medizintechnik GmbH, Freiburg, Germany	0.11 pg/ml
IL-1β	R&D Systems, Minneapolis, MN, USA	0.3 pg/ml
sIL-2R (31)	T-Cell Sciences Inc., Cambridge, MA, USA	0.1 U/ml
IL-6 (32)	R&D Systems, Minneapolis, MN, USA	0.35 pg/ml
IL-10 (24)	Biosource, Camarillo, CA, USA	0.2 pg/ml
Neopterin (30)	Ges. für Immunchemie und -biologie mbH, Freiburg, Germany	0.1 ng/ml
TGF-β1 (19)	Genzyme, Cambridge, MA, USA	50 pg/ml
TNF (30)	NBS Biologicals, Cambs, UK	0.09 pg/ml

lected a group of pro- and anti-inflammatory cytokines, some of which have been investigated in previous studies although using serum samples only [4–6]. Since T-lymphocyte-derived sIL-2R has been shown to correlate with the extent of low T_3 syndrome [5, 22] and due to the fact that thyroid hormones themselves influence cellular immune functions [23, 24], we measured further lymphocyte counts and mononuclear cell activation markers (i.e., neopterin, β_2-microglobulin [β2m]). Neopterin is synthesized by stimulated monocytes/macrophages [25], and β2m is released by activated lymphocytes and neutrophils [26, 27].

Material and Methods

Patients and Sampling of Serum and CSF

In this observational study, 32 patients were enrolled with the primary diagnosis of severe TBI (see Table 1). Exclusion criteria were the following: systemic injuries requiring further treatment, i.e., long-bone or spine fractures, and visceral damage; known or suspected preexisting thyroid or pituitary/hypothalamic disorders; general medical conditions requiring drugs known to interfere with thyroid hormone metabolism or regulation; steroid treatment. According to a standardized protocol, all patients received indwelling ventricular catheters for the monitoring and treatment of increased intracranial pressure (ICP) [28]. All patients were enterally tube-fed thus avoiding "fasting", and received low-dose dopamine (3 µg/kg/min) for renal support. Blood and CSF were taken on admission (day 0) and daily between 07:00 and 09:00 a.m. thereafter. Samples were either processed directly (thyroid parameters) or centrifuged at 170×g for 10 min at 4 °C and supernatants were frozen at –80 °C until analyzed. Sample collection was performed up to 3 weeks after trauma or until removal of the intraventricular catheter when ICP remained stable ≤ 15 mmHg for 24 h. Glasgow Coma Score (GCS) [29] was documented on the scene. Computed tomography (CT) of the brain was performed at admission and classified according to Marshall et al. [30]. Maximal ICP levels persisting for > 5 min were recorded daily, and pneumonia was diagnosed as described in Table 1. Total lymphocyte counts were assessed daily using an automatized cell counter (Technicon H*1, Bayer Diagnostics GmbH, Munich, Germany). Time from trauma until discharge from the intensive care unit was recorded, and clinical outcome was assessed at 6 months after injury using the Glasgow Outcome Score (GOS) [31]. The Zurich University Hospital Medical Ethics Board approved the protocol and waived the need for informed consent.

Measurement of Cytokines and Thyroid Hormones

Cytokines and inflammatory mediators as well as thyroid hormones were analyzed using commercially available assays. Thyroid parameters (T_3, T_4, FT_3 [free T_3], FT_4 [free T_4], thyrotropin) were measured by chemiluminescence (ACS:180, Ciba Corning Diagnostics AG, Dietlikon, Switzerland). A radioimmunoassay was used for TBG (CIS bio international, Gif-sur-Yvette, France), and albumin levels were determined by laser photometry (BNA Automat, Behring Werke, Marburg, Germany). Besides neopterin (radioimmunoassay), all cytokines/leukocyte activation markers were measured by ELISA (Table 2). The time course of cytokine concentrations in CSF and serum after TBI has been previously described in detail for IL-6 [20], TGF-β [21], TNF, IL-10 [19], sIL-2R, β2m, and neopterin [32]. Here, these data were complemented by analyzing peak concentrations and the corresponding days of maximal levels for each patient. Due to limitations in the amounts of CSF obtained, complete analyses could not be performed in all patients.

Data Analysis

Statistical analysis was performed using a commercially available data analysis system (StatView®5.0, SAS Institute Inc., Cary, NC, USA). Due to the organization of the data, serial measurements were analyzed using summary measures, i.e., peak values and time to maximum/

minimum response for thyroid hormones and cytokines [33]. Due to different time periods during which measurements were performed for each patient, an area-under-curve analysis was not applicable. Dichotomized outcome variables were GOS (favorable: GOS 4 or 5, vs. unfavorable: GOS 1–3) and low T_3 syndrome state (low T_3 vs. low T_3-low T_4). Data were analyzed using Fisher's exact test, Mann-Whitney U-test, Wilcoxon signed rank test, Spearman rank correlation and multiple regression as appropriate. For multiple logistic regression, patients were grouped into low- or high-level responders according to their maximum cytokine concentrations being below or above the median value, respectively. Values were log-transformed for multiple stepwise backward regression as appropriate. A significance level for $\alpha < 0.05$ was used throughout all tests. Data are given as mean ± standard deviation (SD), unless stated otherwise.

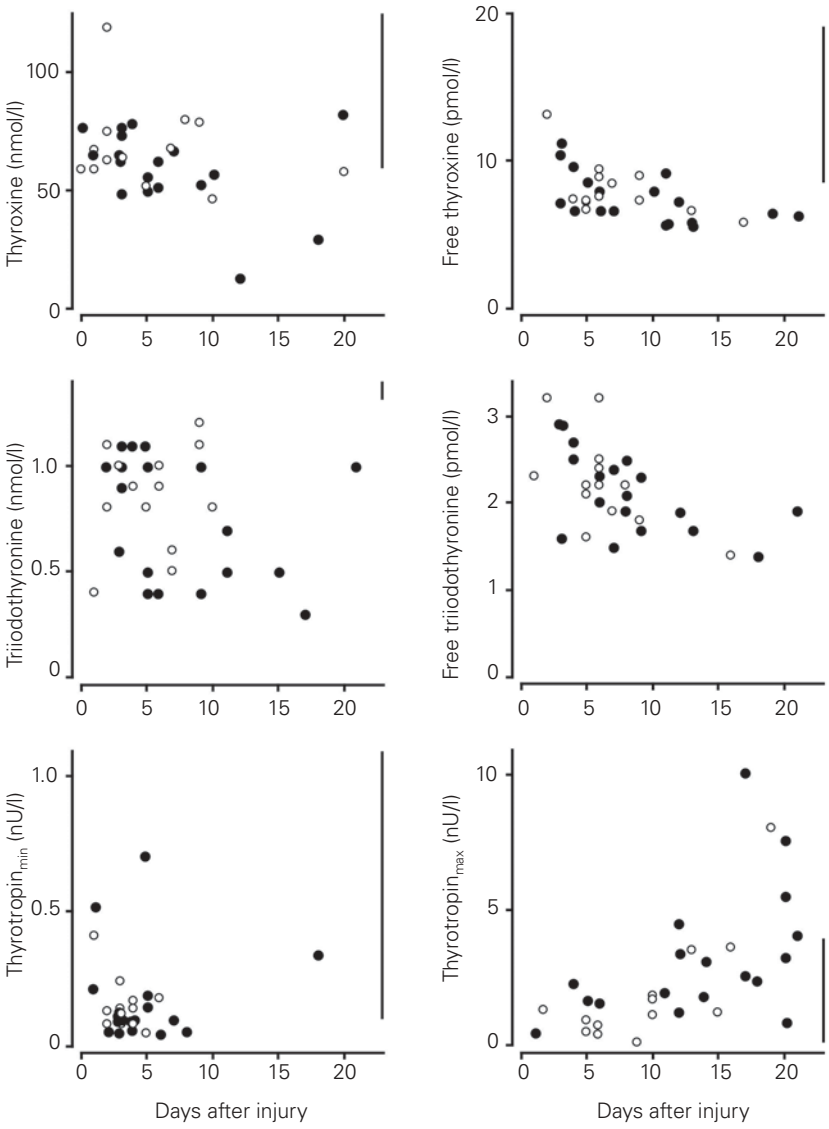
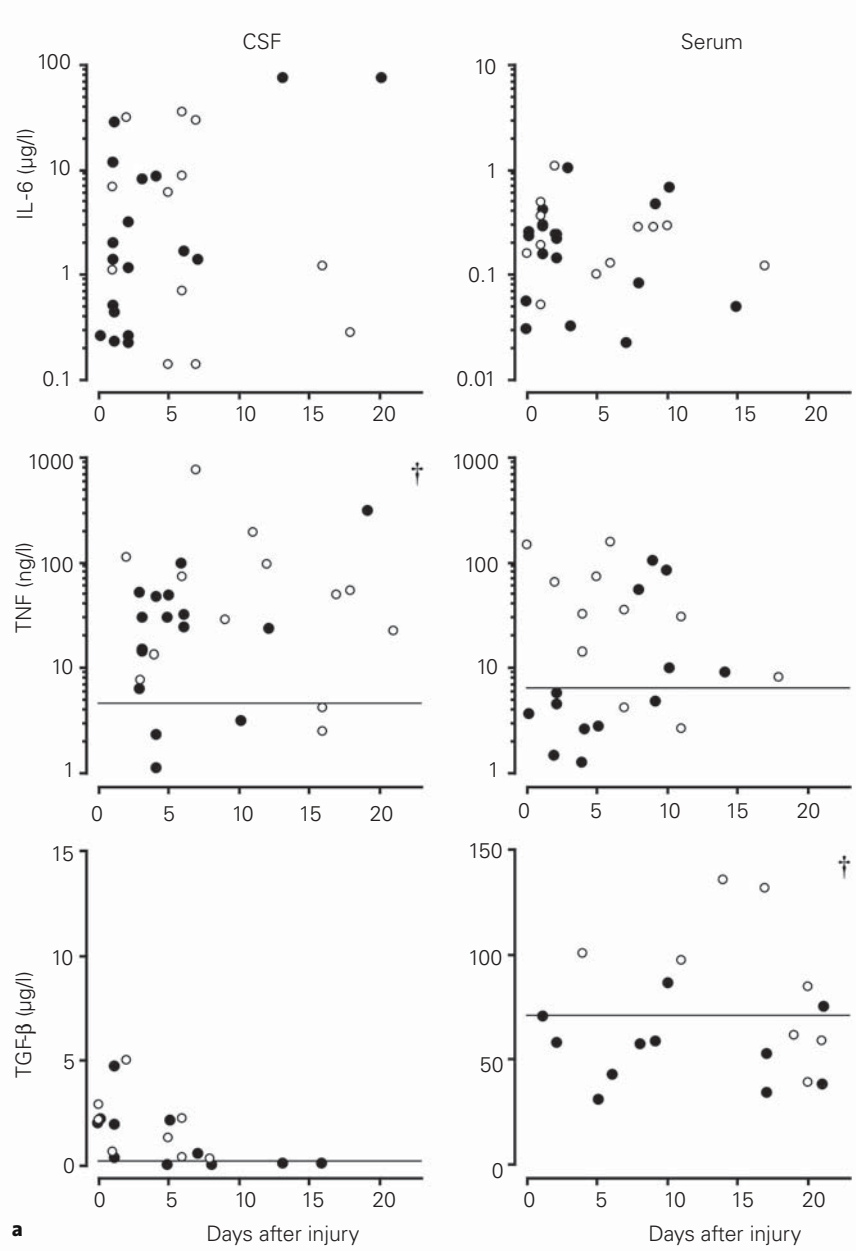


Figure 1. Serum concentrations of thyroid hormones and thyrotropin of 31 patients with low T_3 syndrome up to 3 weeks after traumatic brain injury. Scatter plots show the minimal concentration versus the day of the minimal level of the respective parameter for each patient. For thyrotropin also maximal values after secondary increase are shown (Thyrotropin$_{max}$). One data point is shown for each patient. Normal ranges are outlined by black bars on the right. Levels below the normal range were found for free triiodothyronine in all patients. A more severe low T_3-low T_4 syndrome was detected in 13 patients. Data are split by clinical outcome: closed circles = favorable, i.e., Glasgow Outcome Score 4/5; open circles = unfavorable, i.e., Glasgow Outcome Score 1–3. No significant differences were found between both groups.

Results

Among the 32 patients investigated (37.1 ± 15.8 years; 24 male, eight female), only one showed normal levels for all thyroid parameters besides FT_3 (2.5 pmol/l, normal ≥ 3.5 pmol/l). This individual seemed not to suffer from TBI-associated low T_3 syndrome and was excluded from further analyses in order to obtain a homogeneous study group (low T_3 vs. low T_3-low T_4). All other 31 patients showed T_3 and FT_3 levels below the normal range at any time after TBI (Figure 1). Decreased serum concentrations were observed for T_4 and FT_4 in 13 and 21 individuals, respectively. Elevation of FT_3 concentrations was not observed in the early time period. Patients with low T_3-low T_4 showed lower T_3 concentrations than patients with low T_3 only ($p = 0.005$; Figure 1), while minimal T_3 levels were reached almost simultaneously in both groups. Thyrotropin showed decreased levels in twelve patients, remained normal during the whole study period in 16, and increased later on in six patients. Decreased thyrotropin concentrations were not associated with the lowest T_3 or T_4 levels. Albumin and TBG levels remained within the normal ranges during the whole study period in almost all patients. Lymphocyte counts were below the normal range (1,500–4,000/µl) in all patients investigated with a mean lowest number of 580 ± 200/µl (range 320–1,140/µl) and a nadir at day 4.8 ± 3.2 (range 0–11). A favorable



Figures 2a and 2b. Maximal concentrations of a) cytokines (interleukin-[IL-]6, tumor necrosis factor [TNF], transforming growth factor-[TGF-]β) and b) markers of cellular immune activation (β_2-microglobulin, soluble interleukin-2 receptor [sIL-2R], neopterin) in cerebrospinal fluid (CSF) and serum up to 3 weeks after traumatic brain injury. Scatter plots show the maximal concentration versus the day when the respective parameter reached its maximal level for each patient. One data point is shown for each patient. Lines indicate upper limits of normal ranges. For IL-6, all patients showed increased concentrations at any time. Normal values for this cytokine were below the range depicted in the graphic. Data are divided according to the T_3 state: closed circles = low T_3; open circles = low T_3-low T_4. Parameters showing significant differences ($p < 0.05$) between these two groups are labeled (†); cf. also the Results section.

Figures 2b. See next page.

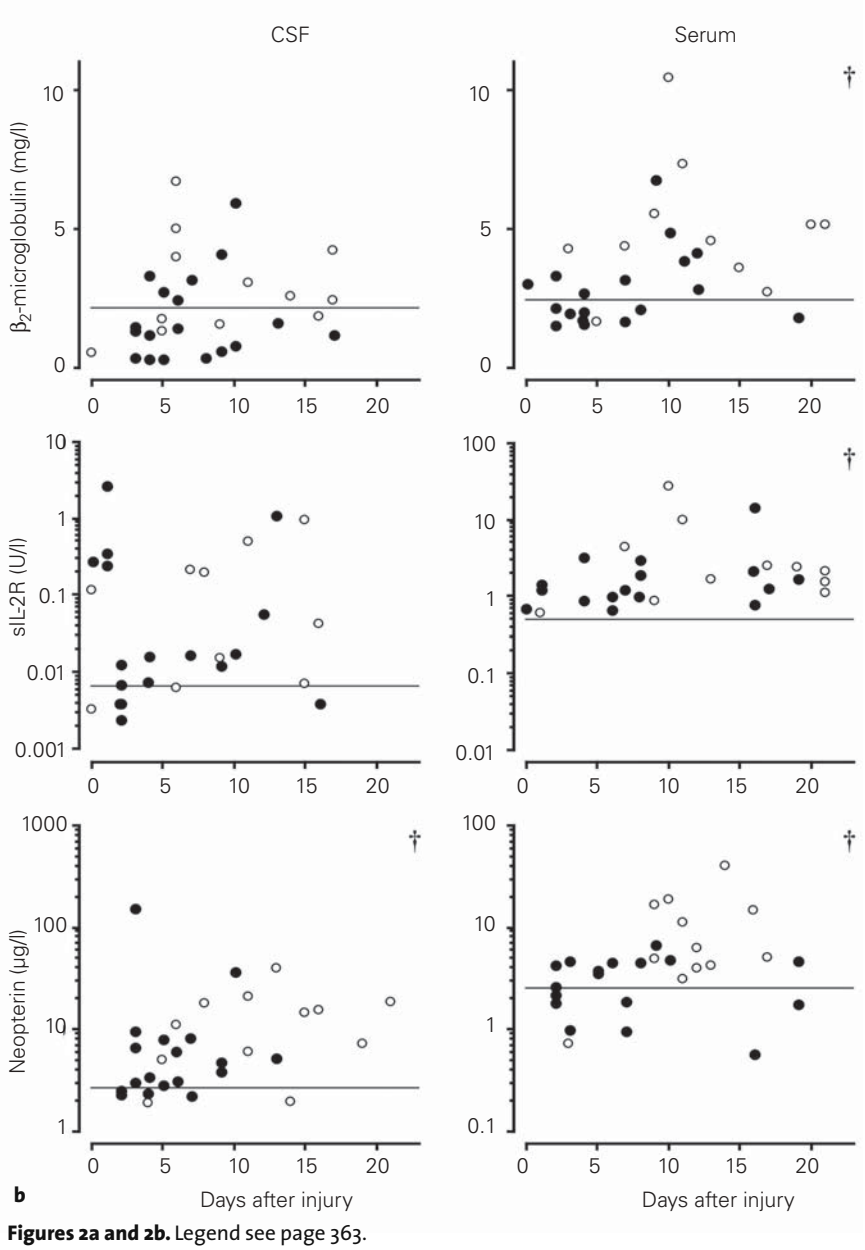
outcome was found in 18 out of 31 patients. No correlation was detected between GCS, or GOS, and low T_3 state. However, considering survivors only, patients with low T_3-low T_4 remained significantly longer at the intensive care unit (33.8 ± 5.6 days) as compared to those with low T_3 only (22.2 ± 12.4 days; $p = 0.008$). Almost all patients (28/31) suffered from increased ICP, and diagnosis of pneumonia as a typical systemic infectious complication was made in one third (11/31) of the TBI victims (see Table 1). Statistically significant associations were absent among these parameters (i.e., ICP, pneumonia) or CT classification and peak values of thyroid hormones or cytokines.

IL-1 concentrations showed no consistent pattern of increase, neither in serum nor in CSF. Only sporadic peaks were observed, and thus this parameter was excluded from further statistical analyses. According to the time of maximal levels, inflammatory markers could be classified as immediate (IL-10 CSF and serum, IL-6 CSF, and TGF-β CSF), prolonged (TNF CSF and serum, IL-6 serum, sIL-2R CSF, β2m CSF, and neopterin CSF), or delayed responders (sIL-2R, β2m, neopterin, and TGF-β, all in serum; Figures 2a and 2b). In particular for the last group, the peak levels appeared significantly later than the minimal levels of T_3, T_4, or thyrotropin, i.e., the cytokines peaked after the minima of the hormone levels ($p < 0.05$). Similarily, thyrotropin reached its minimal levels before β2m, neopterin, and TNF peaked in CSF ($p < 0.05$).

Additionally, we investigated whether a more severe low T_3 syndrome (i.e., low T3-low T_4) may be associated with an increased or prolonged release of pro- or anti-inflammatory parameters. Higher serum levels were observed of β2m, neopterin, and TGF-β in low T_3-low T_4 as compared to low T_3 alone ($p = 0.006$, $p = 0.009$, and $p = 0.023$, respectively; Figures 2a and 2b). Maximum levels were

reached significantly later in patients with low T_3-low T_4 of β2m, neopterin, and sIL-2R in serum ($p = 0.019$, $p = 0.015$, and $p = 0.015$, respectively), and of neopterin and TNF in CSF ($p = 0.016$ and $p = 0.038$, respectively).

To investigate the potential role of cytokines in modulating the onset and severity of the low T_3 syndrome, we only used cytokines peaking early after TBI or simultaneously with thyroid parameters for multiple logistic regression. Neither these calculations nor separately performed Fisher's exact test revealed any association of cytokine release with the low T_3 syndrome. The latter tests were performed to increase the chances to detect any differences. Changes in thyrotropin concentrations could not be associated with cytokine levels in the patients investigated (multiple stepwise backward regression). However, increased levels of β2m correlated with a preceding decrease of thyrotropin (CSF: $\rho = -0.528$; $p = 0.004$; serum: $\rho = -0.414$; $p = 0.029$; Spearman rank). Altogether, there was no independent association between any of the cytokine measurements and the measurements of either circulating thyroid hormones or thyrotropin.



Figures 2a and 2b. Legend see page 363.

Discussion

In this study, we have characterized a group of 32 patients with isolated severe TBI with regard to thyroid hormonal status and to cytokine levels in CSF and in serum from the day of trauma up to 3 weeks post injury. Our data corroborate previous findings, demonstrating altered thyroid hormone metabolism in TBI patients [13, 14, 17, 18]. Only one patient did not present with a low T_3 syndrome. The reason for this single outlier, unfortunately, remains unclear, since none of the clinical and physiological parameters recorded for these patients did explain the absence of an altered thyroid hormonal status in this one patient. Serum T_3 levels were below the normal range in 31 patients and an additional decrease of T_4 was observed in 13 of them. Decreased concentrations of thyrotropin were detected during the first week in twelve patients. Since the mechanisms causing these changes are a matter of debate [1, 2, 4], we monitored cytokine concentrations in CSF and in serum of these patients in order to investigate a putative impact of an intrathecal or peripheral inflammatory response on the low T_3 syndrome.

The major finding of our study was a delayed and marked increase of markers of leukocyte activation, mainly β2m and neopterin, but also of sIL-2R and TGF-β. These markers showed a later or more intense

increase in more severely ill patients (i.e., low T_3-low T_4), even though the time point (day post trauma) of minimal T_3 levels did not differ between both groups (low T_3 vs. low T_3-low T_4). Similarly, β2m showed a stronger increase when thyrotropin was more suppressed at earlier time points.

Head injury is followed by an almost immediate drop of lymphocyte numbers that is accompanied by a deficit in T-cell activation and decreased CD25 expression. These changes seem to persist up to several weeks after TBI [21, 34, 35]. β2m is a small glycoprotein and elevated levels of the soluble form are thought to reflect the release by activated lymphocytes and neutrophils [26, 27]. Neopterin is synthesized and released exclusively by monocytes/macrophages upon stimulation with interferon-(IFN-)γ and is thus considered an activation marker of T-cells in a number of disorders [25]. IL-2R-α is expressed on T- and B-cells as well as on monocytes/macrophages and is shed in a soluble form from the T-cell membrane upon stimulation. It is not only a sensitive and quantitative marker for mononuclear cell activation but may also inhibit effects of IL-2 by scavenging [22].

In part, the increase of these activation markers may be due to a secondary rise in neutrophil granulocyte counts, whereas monocyte numbers showed no significant changes after TBI [20]. At the same time, T-cell numbers and function remain suppressed for up to 3 weeks after injury [21, 34, 35]. However, elevations of sIL-2R and neopterin, representing a sustained activation of the IFN-γ and TNF pathways, are not necessarily synonymous for an efficient immune response [36]. Although our data indicate a negative correlation between serum T_3 and sIL-2R, similarly to the findings by Boelen et al. [5], we disagree with their conclusion implicating the low T_3 syndrome as the consequence rather than the cause of activation of the cytokine network. Our long-term longitudinal study clearly demonstrated that the increase of activation markers occurred after the drop of thyroid hormones. Therefore, it would be more appropriate to hypothesize that a suppression of T-cells was due to lowered T_3/T_4 levels after TBI. Recently, it has become clear that T_3 exerts pleiotropic effects on the thymus by inducing thymocyte proliferation and release from thymic nurse cells [37]. Strong evidence also exists for a modulation of serum sIL-2R levels by thyroid hormones [23, 24]. An action of thyroid hormones on thymic function in head-injured patients was suggested by the observation that low T_3 levels correlated with decreased thymulin concentrations [38]. The molecular associations observed in this study together with previous experimental findings may therefore indicate an endocrinological deficiency (i.e., hypothyroidism) following TBI [1], which may cause abnormalities in cell-mediated immunity and thus a posttraumatic immunodeficiency [21, 34, 35, 38]. On the other hand, low T_3 serum concentrations in conjunction with elevated IL-10 and TGF-β levels [19, 21] may also be part of an anti-inflammatory reaction to TBI, preventing uncontrolled inflammatory tissue damage [39].

We could not detect any statistical correlation supporting a causative role of cytokines for the development of the low T_3 syndrome. Cytokine release within the CNS as well as in the periphery is now an accepted component of the pathophysiology of TBI with IL-6 playing a particularly important role [40]. Experimental investigations and clinical studies demonstrated an interrelation between cytokines such as IL-1, IL-6, or TNF and the low T_3 syndrome [4, 5, 8, 9, 16]. Recently, such a role of cytokines in the pathogenesis of low T_3 syndrome has been challenged. At least the early phase of low T_3 syndrome seemed not to be caused by IL-6, since changes in thyroid hormones preceded increased cytokine levels in surgical patients [41]. Moreover, endotoxin-induced low T_3 syndrome was not attenuated when IL-1, IL-6, or TNF were neutralized [6, 10, 11]. However, in these studies cytokine activity was blocked by systemic administration of inhibitors, which may not cross the blood-brain barrier in a sufficient manner (e.g., antibodies), and thus, immune mediators may promote the low T_3 syndrome at a central level. Since IL-6 receptor and the signal-transducing molecule gp130 are localized in the CNS, particularly in the hypothalamus, and since IL-6 synthesis is upregulated in the brain after TBI [42–45], it seemed reasonable to investigate a putative influence of this cytokine released into CSF on thyroid hormone metabolism. However, our data did not support this hypothesis. Therefore, it may well be that the release of IL-6 and TNF, and the low serum T_3 levels are simultaneous but independent consequences of the acute-phase reaction after TBI, and that a particular, still unknown component of this response may be involved in the pathogenesis of the low T_3 syndrome, as suggested previously [7, 9, 20]. A relationship between IL-10 levels and low T_3 syndrome was also absent in another clinical study [12]. The lack of such correlations may also be due to an independent pathophysiology of low T_3 syndrome occurring after TBI, since some authors described unchanged values of reverse T_3 [17]. However, several other reports found increased concentrations of reverse T_3 suggesting altered

hepatic thyroxin deiodinase type 1 activity similar to other patient groups [13, 15, 18]. Additionally, it cannot be ruled out that statistical significance (especially if the effects to be expected are moderate [7]) was missed due to a limited number of investigated subjects in this special group of patients. Additional mechanisms may also lead to low T_3 syndrome following TBI. Fasting and starvation cause a prompt decline in serum T_3 and FT_3 [1], and are relevant, since malnutrition as well as hypercatabolism are common findings after severe TBI [46]. In a similar group of head-injured patients, treated according to an identical therapy regimen on our intensive care unit [28] during the same study period, an initial temporary hypercatabolism was found. Despite early enteral feeding, positive or neutral nitrogen balance could not be achieved in these patients (unpublished results, personal communication Professor R. Stocker). TBI induces an increase in serum levels of epinephrine, norepinephrine, and dopamine which are suggested to play a role in causing low T_3 syndrome and which may also influence cytokine levels [17, 47–49]. Thus, in this study a disturbed nutritional state and the sympathoadrenal response may both induce or aggravate a low T_3 syndrome in the patients. Therapeutic administration of dopamine requires a special consideration, since thyroid-stimulating hormone (TSH) levels are suppressed during infusion [50, 51]. This was also shown in brain-injured patients [13]. The situation is different for T_3 and T_4. In fact, some authors did not detect a significant decrease of these hormones after initiation of dopamine infusion [13, 50], whereas others have shown a decrease of T_4 during a newly appearing period of shock requiring additional dopamine treatment [51]. Thus, routine administration might confound our results. However, since all patients received the same low dose during the respective study period, we regard the impact on the results as of minor effect, representing a mild but inevitable bias.

The severity of thyroid hormonal disturbance was not predictive of the clinical outcome in severely brain-injured patients, which is contrary to a previous study [17], but is supported by others [13, 15]. However, in an older study, reduction of T_4 was proportional to the severity of coma [14]. This might be reflected by our finding that patients with a low T_3-low T_4 status had to be treated longer in the intensive care unit as compared to those with low T_3 alone. Regarding the putative effects of low T_3 syndrome on the damaged brain, it has been shown that tissue T_3 concentrations in cerebral cortex were significantly lower in a group of low T_3 syndrome patients compared with those in control patients [52]. A global reduction of cerebral blood flow as well as of cerebral glucose metabolism was induced by hypothyroidism of short duration [53]. It might be hypothesized that a reduction in serum T_3 (and T_4) reduces metabolic demands in the brain following injury, which may be a beneficial effect, comparable to the pharmacological concept underlying therapeutic barbiturate coma in TBI patients. On the other hand, since this effect is partly explained by an increased vascular resistance and might also result from an insufficient extraction of oxygen and glucose from the blood [53], these findings could as well represent an inadequate fulfillment of neuronal metabolic requirements. Furthermore, hypothyroidism is known to affect oligodendroglial and neuronal proliferation, apoptosis, migration, and differentiation [54, 55]. Thus, the low T_3 syndrome may negatively influence cerebral recovery after TBI also at that cellular level. Since there is an ongoing debate on the functional effects of the syndrome at a cellular level as well as on its systemic consequences (beneficial adaptation vs. maladaptation), proof for any of these hypotheses is lacking to date. Concerning therapeutic thyroid hormone replacement, it has been stated that there is no clear evidence that T_3 or T_4 treatment of the low T_3 syndrome is disadvantageous, but there is also no certain proof that it is beneficial [1, 2].

Conclusion

Our data show a statistical association between the suppression/recovery of cellular host defense markers and the severity of the low T_3 syndrome after TBI. By contrast, a correlation of cytokine levels with the low T_3 syndrome after TBI was not found in this study. Experimental studies are warranted to further elucidate this possible interrelation at a functional level.

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