Endokrynologia Polska
DOI: 10.5603/EP.a2018.0056
Tom/Volume 69; Numer/Number 5/2018
ISSN 0423–104X

Alterations in thyroid hormones in brain-dead patients are related to non-thyroidal illness syndrome

Zmiany stężeń hormonów tarczycy u pacjentów z rozpoznaniem śmierci mózgu mają związek z *non-thyroidal illness syndrome*

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Abstract

Introduction: Alterations in thyroid hormone levels occur in patients with acute neurological disease states. The aim of this study is to study changes in thyroid hormones in patients with brain death (BD).

Material and methods: Eleven brain-dead patients were studied prospectively. Thyroid hormones were measured on admission to the intensive care unit, the day before BD diagnosis (BD before), and the day after BD diagnosis (BD day).

Results: Thyroid stimulating hormone (TSH) and free triiodothyronine (fT3) concentrations were found to be significantly low on admission, BD before, and BD day compared to age-matched healthy controls. TSH levels were shown to be increasing on BD day. Free thyroxine (fT4) levels were within normal limits in all cases except in one case having low fT4 levels with normal TSH levels. No statistically significant changes were encountered between admission thyroid hormone levels and BD-before and BD-day thyroid hormone levels. Six patients were on steroid therapy when BD-before blood samples were drawn, and no difference in thyroid hormone levels was encountered between steroid users and non-users. Correlation analysis showed a positive correlation between GCS and TSH, but a negative association between fT3 and APACHE II.

Conclusion: We have shown that patients with BD have altered thyroid hormones days before BD diagnosis, and these alterations continue until the diagnosis of BD. The changes in thyroid hormones are compatible with non-thyroidal illness syndrome. **(Endokrynol Pol 2018; 69 (5): 545–549)**

Key words: *brain death, critical illness, euthyroid-sick syndrome, neuroendocrine changes*

Streszczenie

Wstęp: Zmiany stężenia hormonów tarczycy występują u chorych z ostrymi chorobami neurologicznymi. Badanie przeprowadzono w celu oceny zmian stężeń hormonów tarczycy u chorych ze stwierdzoną śmiercią mózgu (*brain death*, BD).

Materiał i metody: Prospektywnym badaniem objęto 11 osób z rozpoznaniem BD. Stężenie hormonów tarczycy mierzono przy przyjęciu na oddział intensywnej opieki medycznej (OIOM), dzień przed rozpoznaniem BD (przed BD) i po stwierdzeniu BD (dzień BD).

Wyniki: Stężenia tyreotropiny (*thyroid stimulating hormone*, TSH) oraz wolej trójjodotyroniny (*free triiodothyronine*, fT3) były istotnie niższe przy przyjęciu na OIOM, przed BD i w dniu BD niż u dobranych pod względem płci i wieku osób z grupy kontrolnej. Stwierdzono, że stężenie TSH wzrasta w dniu BD. Stężenia wolnej tyroksyny (fT4) mieściły się w granicach wartości prawidłowych z wyjątkiem jednego chorego, u którego stwierdzono niskie stężenie fT4 i prawidłowe stężenie TSH. Nie zaobserwowano statystycznie istotnych różnic między stężeniami hormonów tarczycy przy przyjęciu na OIOM a stężeniami mierzonymi przed BD i w dniu BD. Sześciu chorych było w trakcie terapii steroidowej w czasie pobierania próbek „przed BD"; nie stwierdzono różnic w stężeniach hormonów tarczycy między osobami leczonymi steroidami a tymi, którym nie podawano leków z tej grupy. Analiza korelacji wykazała dodatnią korelację między oceną w skali GCS a stężeniem TSH oraz ujemną korelację między stężeniem fT3 a oceną w skali APACHE II.

Wnioski: Wykazano, że zmiany stężeń hormonów tarczycy u chorych z BD występują w dniach poprzedzających rozpoznanie śmierci mózgu i utrzymują się do rozpoznania BD. Zmiany stężeń hormonów tarczycy u tych pacjentów są porównywalne ze zmianami obserwowanymi w *non-thyroidal illness syndrome*. **(Endokrynol Pol 2018; 69 (5): 545–549)**

Słowa kluczowe: *śmierć mózgu, stan krytyczny, zespół pozatarczycowy, zaburzenia neuroendokrynologiczne*

Introduction

Neuroendocrine changes occur in critically ill patients, with decreases in thyroid stimulating hormone (TSH), luteinising hormone (LH), follicle stimulating hormone (FSH), and growth hormone (GH) and in their end products of triiodothyronine (T3), testosterone, and insulin-like growth factor [1–3]. These alterations are thought to be related to the inhibitory mechanism of cytokines on the hypothalamic and pituitary hormone synthesis [4]. The hypothalamic-pituitary hormones are also shown to be decreased in patients with brain death

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(BD) [5–7]. These patients lose their brain function due to total depletion of intracerebral blood flow. Therefore, hormones of these glands and their end products are supposed to be decreased further in BD patients. TSH, fT3, LH, FSH, cortisol, and testosterone were demonstrated to be low in BD patients [5–8]. On the other hand, prolactin and thyroxine (T4) were mainly found within the normal limits [5, 7, 9]. The prolactin levels remain normal probably due to the loss of the inhibitory control of hypothalamic dopamine, except in patients who have dopamine infusion [5, 9]. T4 remains normal probably due to the long half-life compared to T3 and TSH, which are 6–7 days, 24-30 hours, and 35 minutes, respectively [6]. Reverse T3 (rT3) levels were found to be elevated and in no case were both TSH and T4 demonstrated to be subnormal, compatible with the euthyroid-sick syndrome [5, 6, 10]. The aim of this study was to determine changes in thyroid hormones in patients with BD on sequential measures from the moment of ICU admission until the diagnosis of BD.

Material and methods

All consecutive BD patients diagnosed in a medical intensive care unit (ICU) of a university hospital between May 2015 and April 2017 were included into the study. The study group comprised 11 patients (women/men: 6/5), ranging in age from 24 to 78 years. BD decision was given in eight patients by the absence of both cerebral and brain stem function and positive apnoea testing, and in three patients by computed tomography angiography as a confirmatory test to neurological examination because of the inability to conduct the apnoea testing in two patients and not waiting for the drug half-life in one patient. The legal observation time was 12 hours after the first neurological examination. The second neurological examination did not differ in all cases. All patients were admitted to the ICU from the emergency service, except for one patient from the ward after cardiopulmonary resuscitation. The ICU admission diagnoses were ischaemic cerebrovascular stroke (n: 2), intracranial bleeding (n: 6), hypoxic encephalopathy (n: 2), and pneumonia (n: 1). The patient with pneumonia had left middle cerebral arter stroke while in the ICU on his third day. Admission Glasgow coma scores (GCS) were ≤ 5 except in one patient with GCS 7. Exclusion criteria were pre-existing endocrine diseases except diabetes mellitus.

First blood samples (referred to as "BD before") were drawn when the clinician encountered the clinical signs of BD such as the absence of spontaneous breath, polyuria, brain-stem areflexia, and drop of GCS to 3. Second blood samples (reffered to as "BD day") were taken just after the legal documentation of BD, signed by a neurologist and an intensivist. All patients had GCS 3 when the BD-before blood samples were drawn. The time interval between two blood samples was 18–24 hours. After centrifugation, serums were stored at –80°C and all samples were studied in the same run. Since thyroid hormones were routinely measured among all patients admitted to our ICU in the first six hours, we had admission thyroid hormones of the patients. The following parameters were also included in the study: vasopressor and corticosteroid use, lactate level, liver and kidney function tests, admission GCS, and APACHE II score. An age-matched healthy control group (n: 11) was used to compare hormone levels (patients, 57 [47–65] vs. control, 66 [50–69] years, p = 0.452). The study protocol was approved by the Ethics Review Board of Düzce University.

Standard treatments included mechanic ventilation, fluid resuscitation, therapeutic heating in hypothermic patients, desmopressin therapy if diabetes insipidus developed, vasopressor treatment if hypotensive after volume expansion, in order to keep mean arterial blood pressure above 65 mmHg, and insulin infusion if two blood glucose measures were > 180 gr/dl. Serum electrolytes were normalised with appropriate amounts of electrolytes and free water. Diabetes insipidus was diagnosed by the criteria of urine output > 3 ml/kg, urine gravity < 1.005, and serum osmolality > 300 mosmol/L in 10 patients. Vasopressor treatments were started for all patients during BD diagnosis, norepinephrine for 10 patients with 0.45 (0.3–1) mcg/kg/minute, and dopamine for one patient with 5 mcg/kg/minute. Six patients were treated with dexamethasone as first-line therapy after ICU admission, and two patients had methylprednisolone therapy during the BD diagnosis period.

Six patients were treated with dexamethasone as first-line therapy after ICU admission. Two more patients had 300 mg hydrocortisone equivalent methylprednisolone because of hypotension during the BD diagnosis period.

The serum concentration of TSH, free triiodothyronine (fT3), and free thyroxine (fT4) were measured by the chemiluminescence method (Advia Centaur, Siemens, New York, America) Normal limits: TSH: 0.35––5.5 μIU/mL; fT3: 2.3–4.20 pg/mL; fT4: 0.88–1.76 ng/dL.

All values were expressed as the median with interquartile ranges. Study and control groups were compared using the Mann-Whitney U test. The Wilcoxon test was used to compare consecutive hormone values with each other. The Spearman test was used to show the correlation between variables. $P < 0.05$ was accepted as significant.

Results

BD diagnosis was done 2.9 (1.5–4.1) and 2.7 (1.5–3.7) days after hospital and ICU admissions. APACHE II

Table I. *Thyroid hormone levels on admission, BD before, and BD day and their comparisons with the control group*

Tabela I. *Stężenia hormonów tarczycy przy przyjęciu na OIOM, przed stwierdzeniem śmierci mózgu i w dniu zdiagnozowania śmierci mózgu w porównaniu z wartościami zmierzonymi w grupie kontrolnej*

Parameters	Control	Admission†	BD Before	BD Day¶
TSH, μIU/mL	1.56 (0.75–2.63)	0.39 (0.24–0.79)[a]	0.40 (0.04–1.52)[a, b]	0.61 (0.19–1.12)[b, c]
fT3, pg/mL	3.12 (2.92–3.85)	2.45 (1.51–2.65)[a]	1.81 (1.21–2.73)[b, d]	1.79 (1.38–2.79)[b, d]
fT4, ng/dL	1.19 (1.14–1.35)	1.12 (0.98–1.47)[e]	1.20 (1.01–1.80)[b, e]	1.18 (1.00–1.56)[b, e]

BD — brain death; †blood samples were drawn in the first six hours of ICU admission; BD Before — blood samples were drawn when the clinical signs of BD were first noticed; ¶BD Day — blood samples were drawn after the documentation of BD

[a]p < 0.01 vs. control; [b]p = not significant vs. admission; [c]p < 0.05 vs. control; [d]p < 0.001 vs. control; [e]p = not significant vs. control

and GCS were calculated as 26 (24–28) and 4 (3–4). All patients had normal kidney and liver function tests when they were admitted to the ICU.

When thyroid hormones of the patients were compared to thyroid hormones of the control group, the patients had significantly lower TSH and fT3 levels on admission (p_{TSH} = 0.002, p_{fT3} = 0.004), BD before (p_{TSH} = 0.007, p_{fT3} < 0.001), and BD day (p_{TSH} = 0.024, p_{fT3} < 0.001) than the control group (Table I). Then, admission thyroid hormones were compared to both the BD-before and BD-day thyroid hormones, and no significant differences were found. After the hormones were analysed separately, it was disclosed that fT3 levels were subnormal in 36.3%, 54.5%, and 60% of the patients on admission, BD before, and BD day, respectively. TSH levels were below the normal limits in 45.5%, 45.5%, and 30% of the patients on admission, BD before, and BD day, respectively. TSH values were found to be increasing in six patients on BD day compared to BD-before values. One patient had a low FT4 level both on BD before and BD day with normal TSH levels. Sequential changes in thyroid hormones are shown in Figure 1.

None of the patients was on steroid therapy when admission blood samples were taken. Six patients were on steroid treatment while BD-before blood samples were drawn, and no significant difference was encountered in thyroid hormone levels measured on BD before between steroid users and nonusers (p_{TSH}: 0.935, p_{fT3}: 0.143, p_{fT4}: 0.570). Because eight patients were on steroid therapy on BD day, a comparison could not be made between steroid users and non-users due to the limited number of nonusers. Lactate levels were 3.1 (1.2–4.2), 2.0 (1.4–2.9), and 2.2 (1.0–2.8) mg/dL on admission, BD before, and BD day, respectively, and no statistical difference was encountered between lactate levels.

Correlation analysis showed a positive association between $TSH_{admission}$ and GCS (r: 0.743, p = 0.014) and a weak negative association between $fT3_{admission}$ and APACHE II (r: –0.617, p = 0.077). In addition,

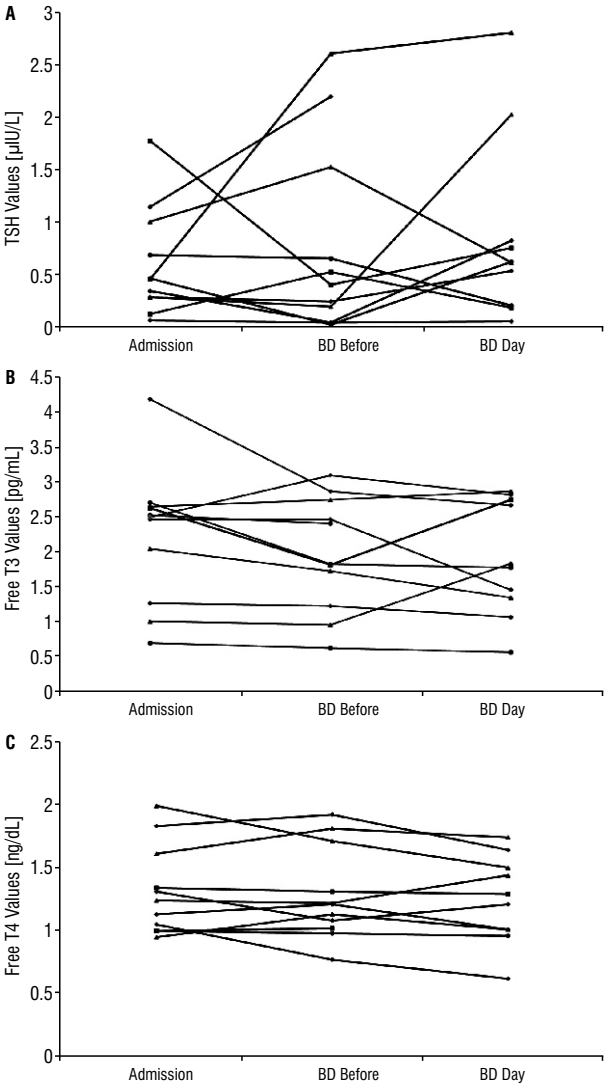

Figure 1. *Serum TSH, fT3, and fT4 concentrations in BD patients from admission until BD diagnosis. Lines connect hormone determinations of the same subject. Thyroid hormones were not studied in one patient on BD day*

Ryciny 1. *Stężenia TSH, fT3 i fT4 w surowicy chorych z rozpoznaniem śmierci mózgu w okresie od przyjęcia na oddział OIOM do postawienia diagnozy śmierci mózgu. Linie łączą pomiary stężeń hormonów u tych samych chorych. U jednego chorego ze stwierdzoną śmiercią mózgu nie zbadano stężeń hormonów tarczycy*

negative correlations were found between $fT3_{BDbefore}$ and APCAHE II (r: –0.706, p = 0.015), between $fT4_{BDday}$ and GCS (r: –0.708, p = 0.033) and between TSH_{BDday} and $fT4_{admission}$ (r: –0.720, p = 0.029). There was not any relationship between lactate levels and thyroid hormone levels.

Discussion

In the present study, patients with severe cerebrovascular accidents had low TSH and fT3 levels on admission to the ICU. The decrease in fT3 was continued as the neurological condition of the patients deteriorated. On the other hand, TSH levels were seen to be increased in six patients after brain-dead diagnosis. FT3 levels were disclosed to be negatively correlated with APACHE II, but TSH levels were positively correlated with GCS.

Severe head injuries are known to be associated with low thyroid hormones, especially TSH and fT3. Olivecroen et al. showed that patients with severe brain injury who died at three months had lower acute TSH levels on day 1 and day 4 than did those who survived [3]. Additionally, TSH levels were noticed to be increasing in survivors and in patients with good neurologic outcomes from day 1 to day 4, whereas they remained low in non-survivors. TSH was discovered to be negatively correlated with neurological disease severity indexes, as shown in our study. Similar results were also shown for fT3, where fT3 level was shown to be significantly low at day 4 in patients who died within three months. A study done by Cernak et al. reported that patients with GCS 4–6 due to traumatic brain injury had a significant decline in TSH and T3 concentrations compared to patients with GCS 13–15 in a seven-day observation period [11]. Brain injured patients with complicated clinical course were demonstrated to have low mean seven-day TSH and T3 concentrations than patients with uncomplicated clinical course in another study [12]. The decreases in thyroid hormones were shown in cranial haemorrhage, traumatic brain injury, and ischaemic events [4, 11–13]. The critical point here is the severity of brain injury; the worse the neurological disease severity indexes are, the greater the decrease in TSH and T3 [3, 11, 12]. Low thyroid hormone concentrations at the early phase of neurological diseases were demonstrated to be correlated with unfavourable six-month and one-year neurological outcomes [12, 13]. Similar to those studies, our patients with severe brain injuries had low median TSH and fT3 levels on admission and also on follow-up. The decrease in TSH is probably due to cytokine-related hypothalamic TRH suppression, as documented in the studies [4, 14].

The decline in T3 occurs in acute disease states, including those patients admitted to the ICU due to any critical illness, or those patients having major surgery [1]. The drop in T3 level is thought to be an adaptive response to reduce energy expenditure, as happens in fasting healthy subjects [1]. Cytokines released during acute disease states are considered to be responsible for the decreased conversion of T4 to T3 in the peripheral tissues by altering the activity and expression of deiodinase enzymes of D1, D3, and D3 [1, 15]. Additionally, thyroid hormone synthesis is down regulated by the cytokines, leading to deceased secretion of T4 and T3 from the thyroid gland [15]. Considering our patient, they had severe acute diseases requiring ICU admission. Their condition was getting worse and ended up with BD in a short time. Therefore, the percentage of patients with low fT3 increased as time passed. In contrast to T3, T4 generally remains normal or sometimes decreases in acute disease states. Low T4 level is mostly encountered in the chronic phase of acute illness (from seven days onwards) [1]. This could be due to its long half-life, which is 6–7 days. The median time from hospital admission to BD was three days in our study, which was not enough time to meet declined T4 levels.

There are several studies showing drops in TSH and T3 concentrations, and to some extent in T4 concentration in patients with BD [5–7, 9, 10]. The main point of these studies is to have the serum measurement of the hormones after the diagnosis of BD and no early hormonal measurements exist to compare them with each other, except in two studies. A study done by Masson et al. showed low fT3, fT4, and TSH levels in 80%, 65%, and 50% of BD patients on sequential measurements, respectively [16]. Luckily, thyroid hormone levels were measured before BD in seven out of 20 patients. They did not show any difference between hormonal levels measured before and after BD, similarly to our results. Pownear et al. also did not show any statistically significant changes between thyroid hormone levels measured before and after BD diagnosis, and showed that 88% of the subjects had low fT3 levels before BD diagnosis [6]. Another hallmark of the euthyroid-sick syndrome is the increased reverse T3 (rT3) [1, 15]. rT3 was measured as high in BD subjects in a number of studies [5, 6, 17]. Increments in TSH levels on sequential measurements after BD were also demonstrated in studies, as we have shown [7, 9, 10]. This increase could be due to complete necrosis of the pituitary gland, thus releasing the preformed TSH into the circulation [7]. There are some limitations of this study. First, it included a limited number of patients, although the statistical results were meaningful. Second, we did not measure rT3, which would strengthen our hypothesis of the euthyroid-sick syndrome.

Conclusions

We have shown that patients with severe cerebrovascular accident had decreased TSH levels both on admission to the ICU and after BD diagnosis. The median level of fT3 was also measured to be subnormal from ICU admission until the BD diagnosis. The decrement in fT3 level was negatively correlated with APACHE II. FT4 levels were similar to their healthy controls. The results were compatible with the euthyroid-sick syndrome, which are seen in many acute disease states in the ICU. Therefore, thyroid hormonal changes encountered in BD patients can be considered as part of non-thyroidal illness syndrome.

Acknowledgement

Part of this study was presented in the 14th Congress of the International Society for Organ Donation and Procurement, September 6–9, Geneva, 2017.

Authorship

T. Akbaş designed the study, followed the patients, gathered the raw data of the study, and contributed to writing the paper. İE Şahin did the laboratory work and contributed to writing the assay part of the manuscript. A. Öztürk designed and followed the study and contributed to writing the manuscript. All authors read, edited, and ultimately approved the final manuscript.

Conflict of interest

The authors declared that there are no conflicts of interest.

Funding

The authors declared that this study received no financial support. The authors have charged the study.

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