Dynamic neuroendocrine changes in critically ill patients with polytrauma

ORIGINAL ARTICLE

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Abstract

OBJECTIVE: Acute multiple-trauma induces activation of neuroendocrine system. Nonthyroidal illness syndrome (NTIS) is considered to be associated with adverse outcome in intensive care unit (ICU) patients. This study was aimed to assess dynamic changes of neuroendocrine hormones in patients with polytrauma and their association with the polytrauma score (PTS).

METHODS: Blood samples from 24 critically ill patients with polytrauma were obtained on 1st, 2nd, 3rd and 7th day after admission to ICU for analysis of thyroid-stimulating hormone (TSH), total triiodothyronine (T3); free triiodothyronine (fT3), total thyroxine (T4), free thyroxine (fT4), growth hormone (GH), prolactin (PRL) and procalcitonin levels.

RESULTS: Acute Physiology and Chronic Health Evaluation (APACHE) II score was 16±5 points on average at the admission to ICU. All patients had normal baseline TSH, T4, fT4, but low T3, and fT3 levels were found in 20% and 33% ICU patients, respectively. On the 7th day after admission to ICU TSH had tendency to increase (*p*=0.07) and fT4 significantly decreased (*p*=0.03). The PRL level significantly increased on the 3rd day after admission as compared to 1st day (*p*=0.04). PTS positively correlated with fT3 (r=0.582, *p*=0.004) and negatively with fT4 (r=−0.422, *p*=0.04) at the 1st day in ICU.

CONCLUSION: Critical illness in patients with polytrauma leaded to trauma severity-dependent alterations of the thyroid axis response early after injury. Our findings suggest that detection of dynamic hormonal response is more appropriate than single measurement. However supplemental therapy for NTIS should be used after more detailed studies are completed.

INTRODUCTION

Critical illness is a dynamic process during which a life-threatening condition induces an acute adaptive stress response with subsequent dysregulation of all hypothalamic-anterior-pituitary axes (Van den Berghe 2001). Polytrauma might involve also traumatic injury of the brain and it has been suggested that might lead to concomitant disturbances in hormones secretion. In the acute phase the most important is not to overlook an acute insufficiency in the hypothalamic-pituitary-adrenal and/or the hypothalamic-pituitary thyroidal axis with inadequate cortisol or thyroid hormone secretion. An alteration in HPT axis during critical illness is well known. The constellation of low T3 levels, increased reverse T3 levels, and/or low total T4 levels with normal fT4 levels in the absence of an obvious thyroid disease is commonly called the "euthyroid sick syndrome" or "nonthyroidal illness syndrome" (NTIS; (McIver & Gorman 1997; Farwell 2013). Thyroid dysfunction is associated with the mortality of patients admitted to the ICU (Slag *et al.* 1981; Rothwell *et al.* 1993) and is a predictor of long-term outcome in general ICU patients (Meyer *et al.* 2011; Van den Berghe 2014). Some studies suggested that low levels of thyroid hormones are predictors of poor outcome in sepsis and critical illness (Joosten *et al.* 2000; Rothwell *et al.* 1993; Wang *et al.* 2012). However, other studies found no, or even opposite, associations of thyroid hormone concentrations with outcome (Lodha *et al.* 2007; Ray *et al.* 1995). Majority of the studies done in critically ill patients measured hormones only at the day of admission to ICU mainly to predict outcome. However these endocrine responses to severe polytrauma can rapidly change and over few days it might lead to endocrine failure. We therefore undertook a prospective observational study of selected ICU patients with polytrauma to investigate dynamic changes in plasma levels of thyroid hormone levels (fT3, T3, fT4, T4, TSH), procalcitonin (PCT), prolactin (PRL), cortisol, and growth hormone (GH). We also investigate the association of measured hormone levels with Acute Physiology and Chronic Health Evaluation II (APACHE II) score and with polytrauma score (PTS).

MATERIALS AND METHODS

This prospective, observational study involved adult patients admitted to the ICU of Department of Anesthesiology and Intensive Medicine of University Hospital Bratislava, which is affiliated with Faculty of Medicine, Slovak Medical University in Bratislava. The patients were recruited between January 2012 and July 2014. The inclusion criteria were: polytrauma, age 18–70 years and admission to ICU within 24 h after the polytrauma. We excluded patients who met the following criteria: (1) history of any thyroid diseases, such as hyperthyroidism, hypothyroidism and thyroid tumors; (2) pregnancy within the previous 6 months; (3) undergoing any hormonal therapy except insulin use (4); and patients who died or were discharged from the ICU within 4 hours of admission. All subjects or subject´s legally authorized representative gave informed written consent and the study was approved by Ethics Committee of Derer´s Hospital, part of University Hospital Bratislava and was carried out in accordance with the Declaration of Helsinki.

Patients anthropometric data, admission diagnosis, and co-morbidities were recorded; the severity of critical illness was determined using the Acute Physiology and Chronic Health Evaluation Score II (APACHE II) (Knaus *et al.* 1985), polytrauma score (PTS; (Baker *et al.* 1974)) and Glasgow Coma Scale. Venous blood samples were obtained from each patient on the 1st, 2nd, 3rd and 7th day of hospitalization. All samples were immediately centrifuged; plasma and serum were stored at –70 °C until analysis.

Assays

Plasma TSH, fT3, fT4, T3, T4, PRL, and GH were analyzed by enzyme Immunoassay kits (ELISA; Demeditec Diagnostics Gmbh, Kiel, Germany). The normal ranges of serum hormone concentrations in our laboratory are as follows: TSH, 0.40 to 4.00 mIU/l, fT3, 1.4 to 4.2 ng/dl; T3, 0.8 to 1.9 ng/ml; fT4, 0.8 to 2.0 ng/dl; T4, 5.0 to 13.0 µg/dl). Serum C-reactive protein (CRP) concentrations were assayed by immunoturbidimetric assay (Siemens Healthcare Diagnostics Inc., Tarrytown, NY, USA). Serum lactate concentrations were measured by enzymatic assay (Siemens Healthcare Diagnostics Inc., Tarrytown, NY, USA). The PCT level was determined using the immunoassay ADVIA Centaur XP (Siemens Healthcare Diagnostics, Inc., Tarrytown, NY, USA).

Statistical analysis

All variables are presented as mean values ± SD. To determine changes of measured parameters during ICU stay analysis of variance (ANOVA) was used. General Linear Model repeated measures (GLM-RM) procedure was used to determine main effects of time on measured

parameters, individual differences within parameters were determined by pos-hoc analysis. Pearson's correlation analysis was computed to determine relationship between the parameters measured. All analyses were performed using SPSS software (SPSS Inc, Chicago, IL, USA).

RESULTS

Twenty four patients (4 women and 20 men) fulfilled the inclusion criteria. Basic characteristics and severity scores are shown in Table 1. Mean Glasgow Coma Score (GCS) at intubation and sedation was 3.2±1.1. The APACHE II score significantly decreased during 7 days of hospitalization at ICU ($p<0.001$; Figure 1). Patients were hospitalized at the ICU for a mean of 12.5±0.6 days. A total of 3 patients (12%) died during their ICU stay. The baseline laboratory characteristics of the patients are listed in Table 1 and Figure 1. The CRP level significantly increased on the 2nd day (142.5±93.0 mg/l, $p=0.005$) and remained higher on the 7th day (113±80 mg/l). The mean PCT at 1st day was 4.74±6.21 µg/l and decreased on the 7th day (2.97±3. 5 µg/l; $p=0.001$). Lactate level as a marker of hypoxia was higher in 67% of all patients at the 1st day (Table 1) and significantly decreased on the 7th day (1.70±0.54 mmol/l; $p=0.007$). The baseline PRL level was 16.2±10.0 pmol/l and significantly increased on 3rd day (22.7±15.5 pmol/l, $p=0.04$). The baseline GH levels were 2.66±3.68 µIU/ml and significantly increased

on 7th day (5.05±5.04 µIU/ml, $p=0.01$). The morning cortisol concentrations in those who did not received glucocorticoid treatment (n=18) at admission day were 488±466 nmol/l and did not increased significantly after 7 days. Thirty-nine percent of patients had insuffi-

Tab. 1. Demographic and clinical data of critically ill patients with polytrauma on the 1st day of ICU stay.

Demographic data	All (n=24)
Age (yrs.)	38.9±13.8
BMI (kg/m²)	26.5±3.5
Male/Female (No)	20/4
Clinical findings of critical illness	
APACHE II	16.2±5.0
PTS score	30.4±9.8
Length of stay (days)	12.5±0.6
Routine laboratory screening	
C- reactive protein (mg/l)	69.2±74.2
Plasma lactate (mmol/l)	4.03±2.75
Procalcitonin (µg/l)	4.74±6.21
T3 (ng/ml)	1.75±0.57
T4 (ng/ml)	11.1±1.5

Data are expressed as means ± SDs.
BMI, body mass index; APACHE II, Acute Physiology and chronic health Evaluation II; PTS, Polytrauma score
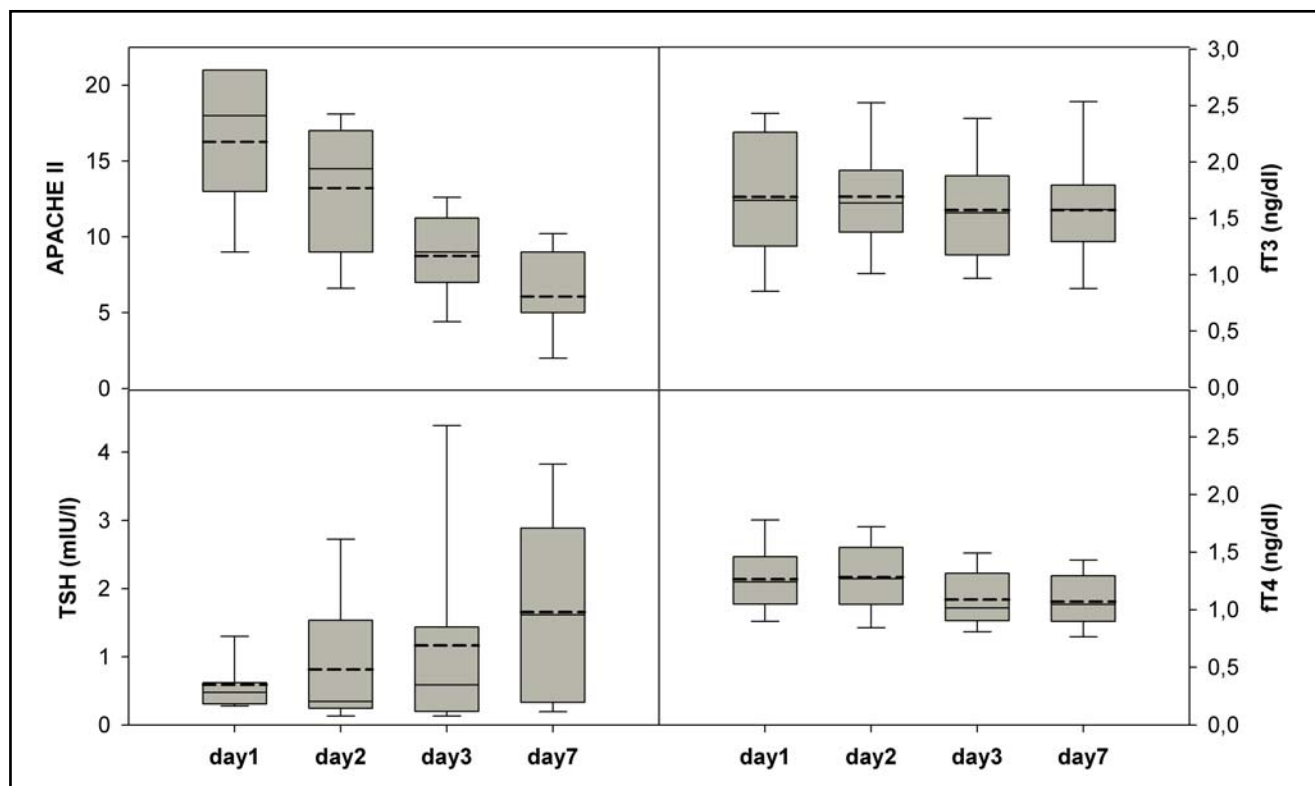
Fig. 1. Time course of APACHE II score, thyroid stimulating hormone (TSH), free triiodothyronine (fT3) and free thyroxine (fT4) in patients with polytrauma. Data are shown as box for 25th–75th percentile, median solid line, mean dashed line, whiskers for 5th–95th percentile.

cient levels of cortisol using the proposed limit for critical illness related corticosteroid insufficiency (Annane 2010) for total serum cortisol <276 nmol/l at the day 1. The very low serum cortisol (<100 nmol/l) on day 1 had 11% of polytrauma patients. On the basis of the normal ranges given above, all patients had normal baseline TSH, T4, and fT4. Day one T3 levels were lower in 20%, and fT3 levels were lower in 33% of ICU patients. On the 7th day TSH had tendency to increase, however it did not reach statistical significance ($p=0.07$) and fT4 significantly decreased ($p=0.03$; Figure 2). The level of fT4 was negatively correlated with PTS score ($r=-0.422$, $p=0.04$), on the other hand PTS was positively associated with fT3 ($r=0.582$, $p=0.004$). There was no correlation between any of the measured hormones and APACHE II score.
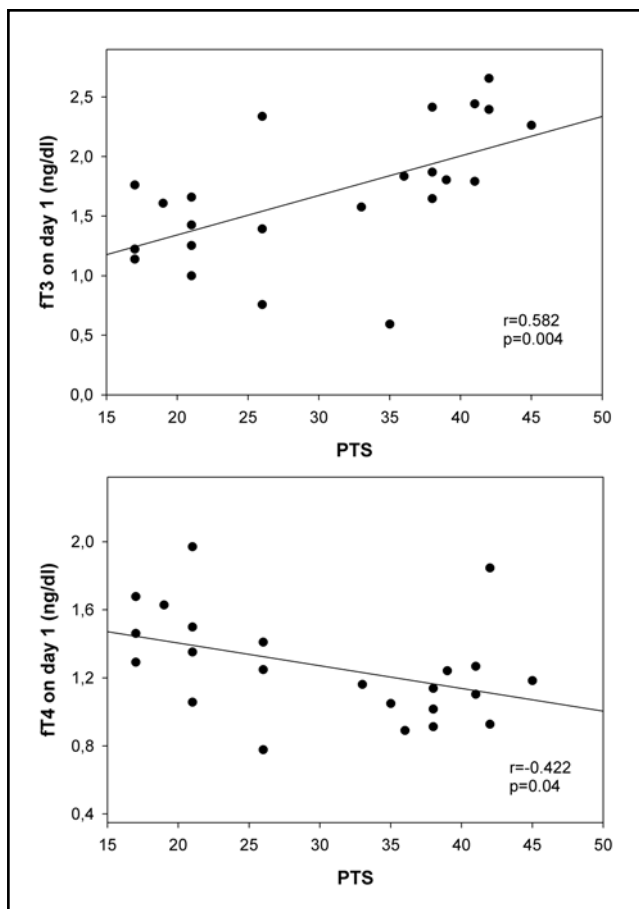
DISCUSSION

Results of our study in patients with polytrauma showed dynamic changes of thyroid hormones during first 7 days of ICU stay in well defined group of patients with polytrauma. We found tendency to decreased fT4 levels and higher levels of TSH after 7 days, suggesting "euthyroid sick syndrome" development during ICU

Fig. 2. Correlation of the polytrauma score (PTS) and free triiodothyronine (fT3) and free thyroxine (fT4) in patients with polytrauma.

stay. As expected the severity of polytrauma expressed as PTS positively correlated with day one fT3 and negatively with day one fT4 levels. Moreover PRL significantly increased during first 7 days at ICU. Our results are in good agreement with previous studies (Agha *et al.* 2004; Olivecrona *et al.* 2013). However these studies were focused on patients with severe head trauma injury.

Regarding the pituitary-thyroid axis, conflicting results have been presented in patients in critical condition (Van den Berghe 1999b; Van den Berghe 2014; Sesmilo *et al.* 2007). Kleindienst *et al.* (2009) found similar decreased TSH, T3 and T4 levels on the third day after trauma brain injury. In some studies, low or high TSH and low T3 or low T4 have been associated with higher mortality (Wang *et al.* 2012; Rothwell *et al.* 1993; Jarek *et al.* 1993; Maldonado *et al.* 1992), while other studies have not found any such association (Ray *et al.* 1995; Gottardis *et al.* 1993). Moreover, in a study of multiple trauma patients, low T4 was associated with higher mortality (Kaptein *et al.* 1982; Langouche & Van den Berghe 2014). In our study overall thyroid function was within normal limits; however, the hormones levels significantly dropped after few days and correlated with the polytrauma score. This may possibly indicate that the condition of these patients is improving, since it is known that in critically ill patients a high TSH is an indication of recovery from "non-thyroidal illness" ("euthyroid sick syndrome") (Utiger 2001).

The mechanisms of endocrine changes in patients with trauma are not well known. For those with head trauma, anatomical abnormalities (vascular or mechanical insult in the hypothalamic-pituitary area or skull fractures (Bondanelli *et al.* 2005) or functional alterations related to elevated intracranial pressure, brain edema (Feibel *et al.* 1983; Kelly *et al.* 2000), hypotension and/or hypoxia and cytokines, in particular interleukin-6 (Dimopoulou *et al.* 2004) have all been implicated. Several studies suggest a possible central origin of changes in the hypothalamic-pituitary-thyroid gland axis during the acute phase of the disease. During the acute phase of a critical illness, there is a drop in concentrations of acute phase proteins (thyroid binding globulin – TBG, transthyretin and albumin), which in turn causes the level of thyroid hormones to fall (Warner & Beckett 2010). The decline in transport protein levels in critically ill patients results from reduced synthesis of the proteins and their rapid breakdown (Bello *et al.* 2010), moreover activity of hormone activation or deactivation enzymes (deiodinases) are changed (Van den Berghe 2014). Catabolism in critically ill patients also causes central changes in the hypothalamic-pituitary-thyroid gland axis. In summary, it can be remarked that NTIS, as a result of catabolism during the acute phase of a critical illness, is a possible sign of an adaptive response to energy depletion. Obviously, this is not an unequivocal fact due to the complex causes behind activation of an endogenous stress response and con-

sequent metabolic dysbalances, including symptoms of catabolism in critically ill patients changed (Van den Berghe 2014).

Prolactin rises in the acute phase of critical illness (Olivecrona *et al.* 2013; Van den Berghe 1999a, b). Higher PRL has been noted in trauma patients compared to other ICU patients (Sharshar *et al.* 2011; Olivecrona *et al.* 2013). In our study we found higher PRL levels on the 3rd day compared to 1st day after polytrauma. The possible association between PRL and survival and the mechanism involved warrants further investigation (Van den Berghe *et al.* 1999; Langouche & Van den Berghe 2014).

Our results are in good agreement with results of other studies of initial stress response with activated growth hormone release (Ross *et al.* 1991; Elijah *et al.* 2011; Olivecrona *et al.* 2013). Treatment with some medication (e.g. clonidine or metoprolol) has been shown to increase GH secretion (Leckman *et al.* 1984; Clausen-Sjobom *et al.* 1987). Therefore analyses of GH sampled only once or twice daily under multiple pharmacological treatments should be interpreted with caution. Similarly to previous studies we found increased levels of PCT in critically ill patients with polytrauma. Procalcitonin, specifically increase in response to systemic bacterial infection and is significantly higher in ICU patients with trauma and sepsis (Uzzan *et al.* 2006; Sakran *et al.* 2012), moreover an elevated PCT level is associated with increased mortality (Poddar *et al.* 2015).

It has to be noted that majority of clinical studies evaluated only single measurement of hormonal levels immediately after admission to ICU. However to analyze the dynamic changes of hormonal parameters during first 7 days of critical illness might reveal more comprehensive picture and improve therapeutic approach decision.

Among those who study the condition, the question of whether NTIS is a protective adaptation of the organism to illness or a maladaptive response to a stressful insult remains unanswered. In either case, thyroid hormone abnormalities are likely to play a role in the critically ill patient. However, there is currently no convincing evidence to suggest that restoring physiological thyroid hormone concentrations in unselected patients with NTIS would be beneficial. It is still under debate whether these patients with NTIS should be treated with direct administration of T3 and/or T4 to raise circulating T3 levels (Langouche & Van den Berghe 2014). Treatment with T4 has yet failed to demonstrate a clinical benefit (Brent & Hershman 1986; Van den Berghe *et al.* 1999), however Bettendorf *et al.* (2000) reported improved cardiac function after substitution with T3 in pediatric patients after cardiac surgery.

The limitations of the present study include the small number of patients is counterbalanced by the careful diagnosis and selection of the patients which allows us to perform repeated measurements. This study is observational in nature. The biological effects of hormones depends not only on their circulating levels but also on hormone-binding proteins and their expression and regulation of hormone receptors, on activity of hormone activating/deactivating enzymes e.g. deiodinases. Furthermore, medication and acute systemic inflammation can alter thyroid hormones levels. It has been shown that short-term infusion of IL-6 to human volunteers causes a suppression of TSH but daily injections over 42 days caused a modest decrease in T3 (Stouthard *et al.* 1994).

CONCLUSION

Results of our study suggest that level of trauma injury result in hormonal disturbances of hypopituitary-adenohypophyseal axes early after injury, suggesting trauma severity-dependent alterations of the thyroid, adrenal, pituitary hormone responses. Our findings suggest that detection of dynamic hormonal response is more appropriate than single measurement. However supplemental therapy for NTIS should be used after more detailed studies are completed.

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Conflict of interest statement
The authors declare no conflict of interests.

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