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The pituitary–gonadal–thyroid and lactotroph axes in critically ill patients

Oś przysadka–gonady–tarczyca i oś laktotropowa u chorych w stanie krytycznym

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Abstract

Introduction: The normal circadian rhythm of hormones in critical patients becomes chaotic causing some hormones to increase and others to decrease abnormally. The goal of this study is to evaluate hormonal changes in severely ill patients and to investigate the relationship between hormonal changes and mortality and morbidity.

Material and methods: We enrolled 20 patients (10 F/10 M). Blood samples were collected on day 0, day 5, and day 10. If a patient was discharged before these defined days, a sample was drawn on that day. Twenty healthy controls were included.

Results: Female patients had lower LH, FSH, and fT_3 and higher PRL and cortisol levels than controls on admission to the intensive care unit (ICU) ($p_{LH} = 0.021$, p_{FSH}:0.001, $p_{fT3} = 0.021$, $p_{PRL} = 0.042$, $p_{Cortisol} < 0.001$, respectively). Men had significantly low testosterone and fT_3, and high PRL and cortisol levels on ICU admission ($p_T = 0.01$, $p_{fT3} = 0.043$, $p_{PRL} = 0.005$, $p_{Cortisol} < 0.001$, respectively). The lowest levels of gonadotropins in both genders and testosterone in men were measured on day 5. Cortisol levels decreased in the patients discharged from the ICU ($p = 0.01$). FSH levels increased in recovered women ($p_{FSH} = 0.043$). The mortality rate was 30%. There were correlations between admission TSH and NIMV duration ($p = 0.006$), fT_3 and APACHE II ($p = 0.001$), and PRL and mortality ($p = 0.044$). Positive correlations between E_2 and APACHE II ($p = 0.003$) in females, and PRL and APACHE II ($p = 0.022$) in males were also displayed.

Conclusions: Critically ill patients develop significant changes in neuroendocrine axes. Alterations in hormones correlate with the disease severity and mortality. **(Endokrynol Pol 2016; 67 (3): 305–312)**

Key words: *mortality; neuroendocrine changes; prolactin; severe illness*

Streszczenie

Wstęp: Prawidłowy rytm dobowy wydzielania hormonów u chorych w stanie krytycznym staje się chaotyczny — wydzielanie jednych hormonów nadmiernie się zwiększa, natomiast innych maleje. Badanie przeprowadzono w celu oceny zmian stężeń hormonów u osób ciężko chorych oraz zbadanie zależności między zmianami stężeń hormonów a śmiertelnością I chorobowością.

Materiał i metody: Do badania włączono 20 chorych (10 K/10 M). Próbki krwi pobierano w dniach 0, 5 i 10. Jeśli pacjent został wypisany przed tymi dniami, próbkę pobierano w dniu wypisu. Utworzono również grupę kontrolną złożoną z 20 zdrowych osób.

Wyniki: U kobiet stwierdzono niższe stężenia LH, FSH i fT_3 oraz wyższe stężenia PRL i kortyzolu przy przyjęciu na oddział intensywnej opieki medycznej (OIOM) niż u osób z grupy kontrolnej (odpowiednio $p_{LH} = 0{,}021$; $p_{FSH} = 0{,}001$; $p_{fT3} = 0{,}021$; $p_{PRL} = 0{,}042$; $p_{Cortisol} < 0{,}001$). U mężczyzn w chwili przyjęcia na OIOM stężenia testosteron i fT_3 były istotnie niższe, a stężenia PRL i kortyzolu wyższe niż w grupie kontrolnej (odpowiednio $p_T = 0{,}01$; $p_{fT3} = 0{,}043$; $p_{PRL} = 0{,}005$; $p_{Cortisol} < 0{,}001$). Najniższe stężenie gonadotropin u obu płci, a testosteron u mężczyzn zmierzono w dniu 5. Stężenia kortyzolu zmniejszyły się u chorych wypisanych z OIOM-u ($p = 0{,}01$). Stężenia FSH zwiększyły się u kobiet, których stan się poprawił ($p_{FSH} = 0{,}043$). Odsetek zgonów wynosił 30%. Występowały korelacje między stężeniem TSH przy przyjęciu na OIOM a czasem stosowania nieinwazyjnej wentylacji mechanicznej ($p = 0{,}006$), fT_3 i oceną w skali APACHE II ($p = 0{,}001$) oraz między stężeniem PRL a śmiertelnością ($p = 0{,}044$). Stwierdzono także dodatnie korelacje między stężeniem E_2 a oceną w skali APACHE II ($p = 0{,}003$) u kobiet oraz między stężeniem PRL a ocean w skali APACHE II ($p = 0{,}022$) u mężczyzn.

Wnioski: U chorych w stanie krytycznym występują istotne zaburzenia osi neuroendokrynnych. Zmiany stężeń hormonów korelują z ciężkością choroby I śmiertelnością. **(Endokrynol Pol 2016; 67 (3): 305–312)**

Słowa kluczowe: *śmiertelność; zmiany czynności neuroendokrynnej; prolaktyna; ciężka choroba*

Introduction

Critical illness is associated with various neuroendocrine changes that have been linked to increased morbidity and mortality [1, 2]. Critical illness has two stages: acute (first few hours to days) and chronic stages (from seven days onwards). Each stage has unique neuroendocrine alterations. Cytokines are considered to be responsible for early changes, and increased endogenous dopamine, hypercortisolism, and medications ordered in the ICU are thought to be responsible for chronic alterations [1, 3].

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Testosterone (T) levels decrease during the early phase and the secretions of luteinising hormone (LH) and follicle stimulating hormone (FSH) are generally increased to attenuate T concentration [4, 5]. However, normal or low LH and FSH levels can sometimes be observed even though the simultaneous T level is low [5, 6]. In the chronic phase, T decreases further and gonadotropins are measured low, supporting hypothalamic-pituitary dysfunction [7, 8]. Similar alterations in LH and FSH values are encountered in women [4, 6, 9, 10].

Serum thyroid stimulating hormone (TSH) and free thyroxine (fT_4) levels increase and free triiodothyronine (fT_3) decreases shortly after an acute insult [11]. The low fT_3 level is due to decreased peripheral conversion of fT_4 to fT_3. The secretions of TSH and T_4 increase to improve peripheral resistance [12]. After a few hours, TSH and fT_4 levels return to normal [11]. In protracted patients, the fT_3 concentration remains low, with low/normal TSH and fT_4 levels [12, 13]. The prolactin (PRL) level increases during acute illness but decreases to a low/ /normal level in the chronic phase [13]. Hypothalamic-pituitary dysfunction is also considered to be responsible for alterations in thyroid and lactotrophic axes in protracted patients [3, 12, 13].

The aim of our study was first to determine serial changes in sex, thyroid, PRL, and cortisol hormones in severely ill patients. The second goal was to investigate the relationship between hormonal changes and morbidity and mortality.

Material and methods

Twenty critically ill patients (10 M/10 F) who were admitted to the ICU of Marmara University Hospital were included in the study. Admission diagnoses were pneumonia and heart failure (n: 4), gastrointestinal bleeding (n: 1), acute coronary syndrome (n: 1), diabetic ketoacidosis (n: 1), and sepsis due to pneumonia (n: 11), pyelonephritis (n: 2), and cholecystitis (n: 1).

Exclusion criteria were age < 18 years; pre-existing neurological, psychiatric, metabolic, or endocrine diseases (except diabetes mellitus); intracranial lesions, haemorrhage or infarction (except lacunar infarct); malignancy (except basal cell cancer); body mass index (BMI) < 18.5; renal failure requiring renal replacement therapy; chronic and acute liver disease; autoimmune diseases; HIV-positive patients; electrolyte disturbances; resuscitation; heavy alcohol intake (≥ 80 gr/ /day); premenopausal women; ICU admission for simple observation/monitoring; and concomitant treatment with calcium channel blockers, amiodarone, dopamine agonists/antagonists, benzodiazepines, opioids, immunosuppressants, antipsychotics, antidepressants, antiepileptics, thyroid hormones, oestrogens, and glucocorticoids.

Table I. *Demographics of the study groups*
Tabela I. *Dane demograficzne badanej grupy*

Sex	Control*	Patients*	p
Female (n)	13	10	
Age (year)	72.0 (63.0–83.5)	79.0 (67.5–81.7)	0.780
BMI [kg/m²]	27.4 (24.7–29.8)	26.3 (21.4–27.4)	0.186
Male (n)	7	10	
Age (year)	74.0 (52.0–85.0)	74.0 (4.25–79.2)	0.758
BMI [kg/m²]	26.2 (20.3–27.5)	22.65 (22.2–27.3)	0.470
Total	20	20	

*Values are expressed as median and interquartile ranges

Severity of illness was rated by Acute Physiologic and Chronic Health Evaluation II scoring (APACHE II). Administration of drugs suspected of affecting the neuroendocrine axis and types of mechanical ventilation [invasive and noninvasive MV (IMV and NIMV)] were recorded. Blood samples were collected within the first four hours of ICU admission and on days 5 and 10. If a patient was discharged before these defined days, a sample was taken before leaving the ICU. After centrifugation, samples were kept frozen at –80°C until assayed. All patients were followed until they died or until they were discharged from the hospital. Twenty age- and BMI-matched healthy controls were included (Table I). Informed consent was obtained from the controls and patients. The study protocol was approved by the ethics review board of Marmara University (MARYC-2005-0092).

Assays

All samples from each patient were processed in the same run. LH, FSH, T, TSH, fT_3, and fT_4 were measured by the electrochemiluminescence immunoassay "ECLIA" method (Modular Analytics E170, Roche, America), PRL by the ECLIA method (Elecsys 2010, Roche, America), C-Reactive protein (CRP) by particle-enhanced immunoturbidimetric assay (Hitachi 917, Roche, America), and estradiol (E_2) and cortisol by chemiluminescent enzyme immunoassay (Immulite 2000, Roche, America), as described elsewhere [6]. The intra-assay coefficient of variation for cortisol was 5.2% at 8.5 μg/dL and 6.2% at 26 μg/dL.

Normal levels of LH, FSH, E_2, and PRL for adult men are 1.7–8.6 mIU/mL, 1.42–15.4 mIU/mL, 0–30 pg/m, and 4.04–15.2 ng/mL; for postmenopausal women 7.7–58.5 mIU/mL, 19.3–100.6 mIU/mL, 0–56 pg/mL, and 4.79–23.3 ng/mL, respectively. Normal levels of T for adult men are between 2.8 and 8.0 ng/mL. Normal limits of TSH,

Table II. *Hormone levels of female patients*
Tabela II. *Stężenia hormonów u kobiet*

Parameters	Controls (n:13)	Female patients Day 0 (n:10)	p†	Female patients Day 5 (n:8)	p‡
LH [mIU/mL]	26.5 (20.6–33.1)	3.1 (0.4–30.2)	**0.021**	1.9 (0.4–25.8)	0.401
FSH [mIU/mL]	70.2 (62.3–88.1)	9.9 (3.8–60.0)	**0.001**	6.1 (1.7–49.9)	**0.025**
E_2 [pg/mL]	27.0 (20.2–31.0)	65.8 (36.1–124.2)	**< 0.001**	42.2 (27.6–102.5)	0.327
PRL [ng/mL]	12.4 (9.1–19.9)	22.1 (11.1–39.0)	**0.042**	20.1 (11.8–38.3)	0.329
Cortisol [μg/dL]	16.4 (14.3–20.9)	27.3 (22.2–41.7)	**< 0.001**	16.5 (13.9–32.5)	0.050
TSH [μIU/mL]	1.8 (1.2–2.9)	1.9 (0.3–4.8)	0.784	1.8 (0.2–3.6)	0.779
fT_3 [pg/mL]	2.8 (2.5–3.2)	1.9 (1.7–3.1)	**0.021**	1.6 (1.2–2.3)	0.575
fT_4 [ng/mL]	1.2 (1.1–1.3)	1.3 (0.9–1.9)	0.410	1.2 (0.9–1.6)	0.889
APACHE II		23 (20–26)		15 (11–12)	**0.012**
CRP [mg/dL]	0.78 (0.78–0.78)	46.1 (18.4–52.2)	0.001	29.1 (10.3–48.9)	0.735

†Hormone levels of the patients on ICU admission were compared with the hormone levels of healthy controls. ‡represents the comparison between the hormone levels measured on days 0 and 5 in eight patients. Values are expressed as median and interquartile ranges; $p < 0.05$ denotes significant differences between groups

fT_3, fT_4, and cortisol are 0.27–4.2 μIU/mL, 2.6–4.4 pg/mL, 0.93–1.7 ng/dL, and 10–22.4 μg/dL, respectively.

Statistical analysis

Since data did not meet parametric test conditions, nonparametric tests were utilised. Study and control groups were compared using the Mann-Whitney U test for continuous variables. The Wilcoxon test was used to compare consecutive hormone values with one another. Correlations between variables were evaluated using the Spearman test. Results were expressed as median with interquartile ranges unless indicated otherwise. $P < 0.05$ was considered significant.

Results

The median APACHE II score was 25 (22–28) and admission CRP was 48.0 (30.2–52.8) mg/dL. Male and female patients had comparable APACHE II scores ($p = 0.14$) and CRP levels ($p = 0.22$). Energy intake was 940 (940–1850) kcal/day. NIMV and IMV were applied to 9 and 10 patients, respectively. The duration of NIMV was 46 (22–92) hours, IMV 75 (7–870) hours, ICU stay 5 (2–10) days, and hospital stay 11 (3–26) days. Four patients (3M/1F) had tracheostomy. Multiorgan failures were recorded in 65% of patients and the mean number of affected organs was 4 ± 1.8.

Postmenopausal female patients had lower gonadotropins and fT_3, and higher PRL, E_2, and cortisol concentrations on admission to the ICU than control females (Table II). When women were reviewed individually, LH and FSH levels were low in seven patients and within normal limits in three patients. Abnormally low values for LH (≤ 5.0 mIU/mL) and FSH (≤ 10.0 mIU/mL) were measured in seven and five females, and severely depressed LH (≤1.0 mIU/mL) and FSH (≤ 5.0 mIU/mL) were measured in four and three women, respectively. Of the three patients with normal gonadotropins, two patients had normal LH and FSH levels during the ICU course and had non-infectious diagnoses (ketoacidosis and bleeding). The remaining patients had low gonadotropins during the ICU stay.

The median levels of gonadotropins were noticed to decrease more on day 5, and the decrease in FSH concentrations became significant (Table II). Since there were just two patients on day 10, the median hormone levels were recorded: FSH: 5.3 (0.9–6.9) mIU/mL, LH: 0.9 (0.3–1.1) mIU/mL, E_2: 76.4 (38.1–76.5) pg/mL, PRL: 58.0 (9.1–77.9) ng/mL, cortisol: 18.2 (10.9–16.4) μg/dL, TSH: 1.7(1.0–1.6) μIU/mL, fT_3: 1.2 (0.9–0.9) pg/m L, and fT_4: 1.07 (0.55–1.06) ng/mL. When hormones of seven discharged patients were compared with their admission values, a small but significant rise only in the FSH concentration was observed [$FSH_{admission}$:6.9 (4.4–60.1) *vs.* $FSH_{discharge}$: 7.3 (1.5–59.8) mIU/mL, $p = 0.043$].

Male patients had low T and fT_3, and high PRL and cortisol levels (Table III) on admission. T concentrations were below the normal limits in 80% of the subjects. Of the patients with low T, four patients had hypergonadotrophic hypogonadism (high LH and high/normal FSH), and the other half had hypogonadotrophic hypogonadism (normal/Low LH and FSH). Gonadotropins and T were reduced further on day 5, and the reduction of T and FSH reached statistical significance. All patients had low T levels during the ICU course. LH and FSH levels tended to increase on day 10 but did not reach statistical significance. Since blood samples of three men were studied on discharge, the statistics could not be

Table III. *Hormone levels of male patients*
Tabela III. *Stężenia hormonów u mężczyzn*

Parameters	Controls (n:7)	Male patients Day 0 (n:10)	p†	Male patients Day 5 (n:6)	p‡	Male patients Day 10 (n:5)	p‹
LH [mIU/mL]	5.2 (4.4–8.7)	9.4 (5.3–12.7)	0.368	4.7 (1.4–9.2)	0.463	8.9 (4.8–11.1)	0.080
FSH [mIU/mL]	4.9 (4.2–22.3)	3.5 (2.4–7.0)	0.220	2.1 (0.8–3.9)	**0.028**	3.5 (1.5–5.9)	0.080
E_2 [pg/mL]	36.4 (27.3–47.7)	54.8 (28.6–121.6)	0.492	54.0 (34.2–91.8)	0.345	43.1 (33.8–129.6)	0.686
T [ng/mL]	3.4 (2.3–5.3)	1.3 (0.9–2.4)	**0.010**	0.4 (0.2–0.8)	**0.046**	0.6 (0.2–0.8)	0.500
PRL [ng/mL]	9.7 (7.5–11.6)	21.2 (12.7–47.1)	**0.005**	18.4 (12.4–24.2)	0.116	24.0 (4.5–29.5)	0.686
Cortisol [μg/dL]	12.6 (10.1–14.1)	32.5 (29.0–41.3)	**< 0.001**	12.7 (9.6–37.6)§	0.109	18.4 (6.0–19.1)§	0.593
TSH [μIU/mL]	1.1 (0.9–1.5)	0.9 (0.4–2.0)	0.713	0.5 (0.06–2.3)¶	0.249	0.06 (0.03–2.0)¶	0.893
fT_3 [pg/mL]	3.1 (2.6–3.8)	2.3 (1.2–2.9)	**0.043**	2.1 (1.7–3.2)	0.917	1.8 (1.6–3.1)	0.345
fT_4 [ng/mL]	1.2 (1.1–1.3)	1.1 (0.9–1.5)	0.475	1.3 (0.9–1.5)	0.600	1.2 (1.0–1.4)	0.893
APACHE II	–	25 (24–32)		20 (13–28)	**0.042**	19 (9–30)	1.000
CRP [mg/dL]	2.7 (0.78–4.5)	48.0 (43.7–72.2)	**0.006**	34.7 (26.3–44.2)	0 0.173	38.2 (6.2–42.5)	0.345

†Hormone levels of the patients on ICU admission were compared with the hormone levels of healthy controls. ‡represents the comparison between the hormone levels measured on days 0 and 5 among six patients. ‹indicates the statistical differences between hormone levels measured on days 5 and 10 in five patients. ¶Five patients had methylprednisolone therapy on days 5 and 10. Four males among these patients had low TSH levels on days 5 and 10, ranging between 0.089 and 0.007 μIU/mL. These patients had normal TSH values on ICU admission. §Cortisol levels measured on days 5 and 10 in five patients were under methylprednisolone therapy. Values are expressed as median and interquartile ranges; $p < 0.05$ denotes significant differences between groups.

Table IV. *Thyroid hormone, cortisol, and PRL levels on admission to and prior to discharge from the ICU*
Tabela IV. *Stężenia hormonów tarczycy, kortyzolu i PRL przy przyjęciu na OIOM i przed wypisaniem z OIOM-u*

Parameters*	Controls (n:20)	Patients (n:20)	p†	Discharge (n:10)	p‡
TSH [μIU/mL]	1.4 (1.1–2.6)	1.07 (0.4–3.1)	0.355	1.9 (0.6–3.8)	0.722
fT_3 [pg/mL]	2.9 (2.6–3.3)	2.1 (1. 7–2.6)	**0.001**	1.8 (1.3–2.3)	0.657
fT_4 [ng/mL]	1.2 (1.1–1.3)	1.3 (0.9–1.7)	0.904	1.2 (1.1–1.4)	0.722
PRL [ng/mL]	11.4 (8.9–12.8)	21.3 (12.56–39.9)	**0.004**	17.5 (11.4–34.9)	0.790
Cortisol [μg/dL]	16.1 (12.1–20.1)	30.8 (25.4–39.4)	**< 0.001**	17.4 (1.4–21.7)	**0.010**
APACHE II		25 (22–28)		12 (7–16)	**0.005**
CRP	0.78 (0.78–2.6)	48.0 (30.2–52.8)	**< 0.001**	24.5 (9.5–41.0)	0.074

*None of the patients had methylprednisolone therapy. †The hormone levels of the patients on ICU admission were compared with the hormone levels of healthy controls. ‡denotes the statistical comparison between hormone levels measured on admission to and discharge from the ICU among 10 patients. Values are expressed as median and interquartile ranges; $p < 0.05$ denotes significant differences between groups

applied and the median hormone levels were noted: FSH: 4.2 (2.3–6.5) mIU/mL, LH: 12.6 (8.4–12.9) mIU/mL, E_2: 57.3 (43.3–216.0) pg/mL, PRL: 17.5 (6.7–26.4) ng/mL, T: 0.8 (0.6–0.9) ng/mL, TSH: 2.8 (0.3–3.79) μIU/mL, fT_3: 2.0 (1.4–2.3) pg/mL, and fT_4: 0.97 (0.90–1.46) ng/mL.

Medications given to the patients during the ICU stay included methylprednisolone (5 M), neuroleptic (3 M/3 F), dopamin (2 M), benzodiazepine (1 M), and morphine (1 F). A statistical evaluation could not be done for medications due to the small numbers. Methylprednisolone was given to vasopressor unresponsive septic shock patients. Four men under methylprednisolone therapy had TSH levels between 0.089–0.007 μIU/mL on days 5 and 10. They had normal TSH values on admission to the ICU.

When thyroid hormones and PRL of all 20 patients were compared with the hormones of healthy subjects, fT_3 was found to be significantly low, and PRL and cortisol were seen to be high (Table IV). Except for cortisol, no significant changes in thyroid hormone and PRL levels were documented compared to the admission values in 10 discharged patients, and none of these patients was on methylprednisolone therapy. Four patients had hormone levels measured on day 15 (3 M/1 F). The sex hormonal profiles of these three patients with different clinical courses were individually depicted in graphics (Fig. 1–3).

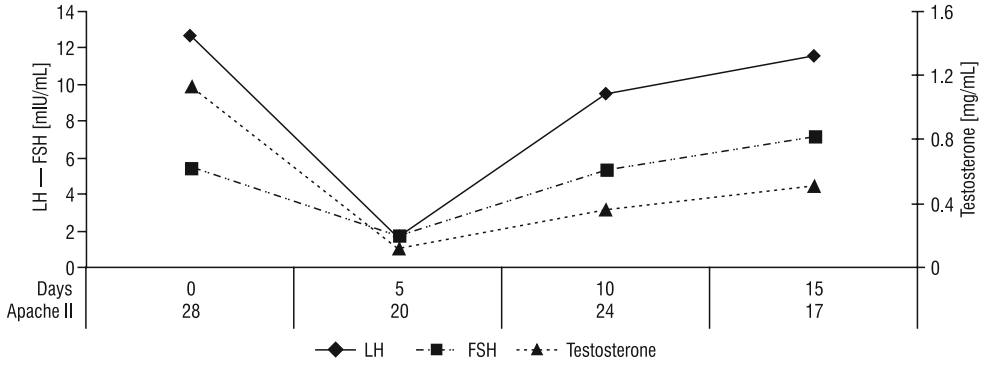

Figure 1. *An 83-year-old male patient was admitted to the ICU with severe pneumonia and acute coronary syndrome. The hormone levels increased as the patient got better*

Rycina 1. *Chory w wieku 83 lat został przyjęty na OIOM z ciężkim zapaleniem płuc i ostrym zespołem wieńcowym. Kiedy stan chorego się poprawił, stężenia hormonów wzrosły*

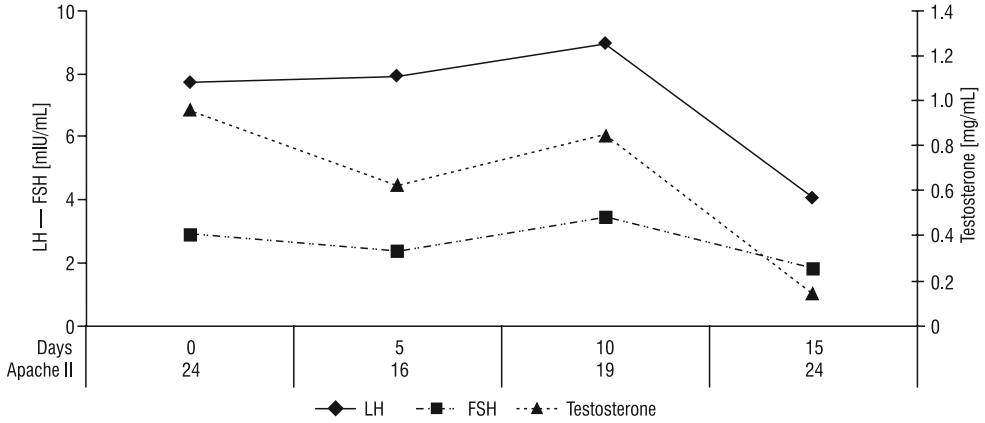

Figure 2. *A 50-year-old male patient was admitted with pneumonia and severe ARDS. As the patient got better, hormone levels increased. Then, the patient had severe sepsis due to ventilator-associated pneumonia and hormone levels started to fall again*

Rycina 2. *Chory w wieku 50 lat został przyjęty na OIOM z powodu zapalenia płuc i ciężkiego zespołu niewydolności oddechowej. Kiedy stan pacjenta się poprawił, nastąpiło zwiększenie stężeń hormonów. Następnie u chorego rozwinęła się ciężka posocznica spowodowana respiratorowym zapaleniem płuc i stężenia hormonów znów uległy obniżeniu*

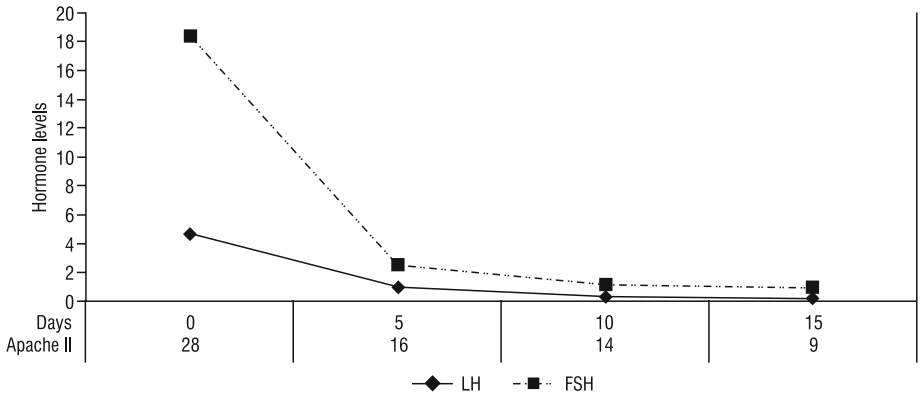

Figure 3. *An 80-year-old female patient was admitted with cholecystitis-related severe sepsis and developed multiorgan failure. The patient could not be weaned from MV and stayed in the ICU for more than one month. Hormone levels stayed low during the ICU course. The patient was sent to a nursing home with a home ventilator*

Rycina 3. *Chora w wieku 80 lat została przyjęta na OIOM z powodu ciężkiej posocznicy związanej z zapaleniem pęcherzyka żółciowego. Rozwinęła się niewydolność wielonarządowa. Pacjentka wymagała wentylacji mechanicznej i pozostała na OIOM-ie przez ponad miesiąc. W czasie pobytu na OIOM-ie stężenia hormonów pozostawały niskie. Chora została odesłana do placówki opiekuńczej z zaleceniem stosowania respiratora do użytku w warunkach domowych*

There were significant correlations between admission TSH and NIMV duration (r: 0.83, p = 0.006), fT_3 and APACHE II (r: 0.69, p = 0.001), and PRL and mortality (r: 0.45, p = 0.044) in 20 patients. Significant correlations between these variables were also illustrated when both genders were analysed separately. Positive correlations between E_2 and APACHE II (r: 0.83, p = 0.003) in females, and PRL and APACHE II (r: 0.71, p = 0.022) in males were displayed. The association between mortality and T (r = –0.61, p = 0.063) in males, and mortality and E_2 (r = 0.62, p = 0.054) in females was high but did not reach statistical significance. Six patients (6 M/2 F) died due to sepsis (n: 6) and cardiac reasons (n: 2). None died after ICU discharge. Admission hormonal values of deceased men were not different from surviving ones. The hormonal comparisons between deceased and surviving female patients could not be done due to limited numbers.

Discussion

In the current study, the male subjects had lower T concentrations than controls. T levels continued to decline further during the first week of critical illness, which is in line with the literature [4, 5, 14]. T concentration decreases in many systemic diseases and critical illness [4, 14, 15]. As the disease becomes serious, the decline becomes more severe [14, 16]. The reason for decreased T is the inhibition of testicular androgenesis or central LHRH secretion or both. Cytokines have been shown to take part in either situation [17, 18]. Our patients had high CRP concentrations and APACHE II scores that prove the presence of inflammation and disease severity. We observed a high correlation between mortality and admission T values, but it did not reach statistical significance, probably due to the small study group.

As demonstrated in our patients, LH and FSH levels decrease in severely ill women [4, 6, 9, 14]. The decrease was not dependent on disease type, patient's age, and medications used [5, 14]. A decline in gonadotropins occurred within 24 hours of an acute insult and continued until the nadir decline in 4-6 days, as in the present study [4, 14]. As the disease becomes more severe, so the hormonal suppression gets worse, with very low LH (≤ 0.5 mlU/mL) and FSH (≤ 1 mlU/mL) [9, 14]. We observed severely depressed values with LH ≤ 1.0 mIU/mL in four and FSH ≤ 5.0 mIU/mL in three women on admission, and even lower LH (≤ 0.5 mlU/ /mL) and FSH (≤ 1 mlU/mL) levels in three and one patient/s, respectively, during ICU stay. The presence of inflammation is considered to be responsible for hormonal alterations [19]. Our patients had high APPACHE II scores and CRP levels that exhibited disease severity and presence of inflammation, except for two females who had non-infectious diagnosis and normal gonadotropins.

Suppressed hormones rebound with disease improvement [9, 10, 20]. In our patients, discharged female patients had a significant increase in FSH levels. Since LH is more severely affected than FSH, the rise in FSH occurs first during recovery [6, 20]. Return of gonadotropins to normal limits was reported to take months, even years in some patients [6, 9, 10]. Since we did not have serial hormone measurements after ICU discharge, we could not say anything about the return of gonadotropins to normal limits. However, even small increases in FSH levels proved that the synthesis and secretion of hormones were enhanced in clinically improved patients. The same is true for T, and the normalisation of T was reported to take 2–12 months [4–6]. Our three male patients had low T levels when discharged from the ICU, in accordance with the literature.

In this study, the median fT_3 level was detected to be low and the result is similar to other studies that included seriously ill patients [2, 6, 21]. Severe physical stress, such as surgery, starvation, trauma, and infection, leads to alterations in the thyroid axis within hours [1, 11, 21]. The drop in fT_3 correlates with disease severity [2, 21]. We could not show this relation, probably due to inclusion of a small group of patients. We showed high E_2 levels in female patients and a correlation between E_2 and disease severity. E_2 level increases in critically ill patients [22, 23] and is reported to be associated with mortality [24]. Elevated aromatisation of adrenal androgens to E_2 mediated by cytokines is proven to result in increased serum E_2 levels [23, 25]. PRL also increases in response to acute illness [6, 22, 26]. We showed that male and female critically ill patients had high PRL levels compared to controls, and correlations between admission PRL and mortality and disease severity were observed that were new findings compared to the literature. Highly elevated PRL can show disease severity, as our patients had elevated CRP levels and APACHE II scores.

There are some limitations of this study. First, we studied a small number of patients. This could be an important reason for not demonstrating relationships between hormonal changes and mortality and morbidity, except for PRL, TSH, and E_2. Second, we did not make serial hormonal measurements after the patients left the hospital. Therefore, we can say nothing about the course of hormones. Third, we just included medical patients. The result could not be generalised to other groups of patients.

Conclusions

We have shown significant changes in the neuroendocrine system of seriously ill patients. Female patients

had low gonadotropins and fT_3, but high PRL, E2, and cortisol levels, while males had low T and high PRL and cortisol levels on the day of ICU admission. The concentrations of gonadotropins in females and T in males decreased further during ICU stay. Since the patients had severe disease with regard to high APACHE II scores and CRP levels, they presented with severe hormonal changes.

Conflict of Interest Statement

Dr. T. Akbaş has no conflicts of interest to disclose. Dr. G. Firuzel has no conflicts of interest to disclose. Dr. O. Deyneli has served on the advisory board of Sanofi Aventis, Novo Nordisk, MSD, Boehringer Ingelheim and has given lectures for Sanofi Aventis, Novo Nordisk, MSD, Boehringer Ingelheim, and Astra Zeneca. Dr. S. Akalın has no conflicts of interest regarding this study.

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