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Endocrine disorders in women with complex regional pain syndrome type I

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Abstract

Background: The question of hormonal dysregulation in patients with CRPS I in whole was investigated very scantily. There are only a few studies concerning catecholamines, oestrogens and endorphins independently. Other hormones were studied in patients with different other chronic pain conditions. Considering the accumulation of sufficient knowledge about the role of disadaptation processes in CRPS I pathogenesis and the role of the hypothalamic-pituitary-adrenal and hypothalamic-pituitary-ovarian systems in the process of adaptation it was logical and consistent to define the role of hormonal dysregulation of these systems in patients with CRPS I.
Objectives: Our objective was to determine the role of hypothalamic-pituitary-adrenal and hypothalamic-pituitary-ovarian systems in pathogenesis of complex regional pain syndrome type I (CRPS I) in women.
Methods: We investigated the pituitary gonadotropic function and the function of sex glands in women with CRPS I and healthy volunteers by measuring the plasma levels of estradiol (E_2), follicle-stimulating hormone, luteinizing hormone, prolactin, adrenocorticotropic hormone, and cortisol, and urinary excretion of 17-ketosteroids, 17-oxycocorticosteroids, epinephrine and norepinephrine.
Results: Women with CRPS I were characterized by the decreased content of oestrogens in the blood plasma and increased pituitary gonadotrophic function. The disturbed ratio of anabolic and catabolic steroids in women with CRPS I was detected due to lower adrenal cortex function.
Conclusions: In patients with CRPS I endocrine status is characterized by hormonal imbalances of the hypothalamic-pituitary-adrenal and hypothalamic-pituitary-gonadal systems. The changes in reproductive and adaptation homeostasis characterize CRPS I as a form of the disease of disadaptation.
Significance: This study determined the role of hypothalamic-pituitary-adrenal and hypothalamic-pituitary-ovarian systems in pathogenesis of CRPS I.

1. Introduction

The relationship between chronic pain syndromes and hormonal disorders have been described in many studies. However, till present, researchers have usually investigated only some hormones, which is not enough for the comprehensive review of the problem. Thus it is shown in many studies that patients with complex regional pain syndrome type I

(CRPS I) have low levels of endorphins (Hooshmand and Hashmi, 1999; Takahashi et al., 2000) and its increase during physical exercises is one of the possible explanation for the positive effect of physical activity on chronic pain symptoms.

CRPS I seems to have a tight connection to the endocrine status (particularly sex hormones) because of the well-known female predominance (female/male ratio is from 3:1 to 4:1) (Sandroni et al., 2003; de Mos et al., 2007; Schwenkreis et al., 2009). Even in childhood CRPS I is more frequent in girls (Kavanagh et al., 1995; Clinch and Eccleston, 2009) and characterized by a more favourable course then in adults, which can be the result of a higher somatotropin, some sex hormones and endorphins level. Better course of CRPS is also described during pregnancy (Hooshmand and Hashmi, 1999).

Another hormone, which may play an important role in chronic pain states, is testosterone. The decrease in serum testosterone level in chronic pain patients has been widely described in the scientific literature. Opioid use and inhibition of the hypophysis function caused by chronic pain are considered to be the possible causes of decreased serum testosterone in some patients (Tennant, 2010a). Little is known about testosterone level in CRPS patients, but the chronic pattern of pain and female predominance might indicate the testosterone participation in CRPS pathogenesis (Tennant, 2010b).

The results of studies on sex hormones in CRPS I patients are not consistent. de Mos et al. (2009) did not find any association between oestrogen level and CRPS I development, though the authors noticed the decrease in CRPS I incidence during pregnancy and its increase during the first 6 months after delivery (de Mos et al., 2009). There are only a few published reports about CRPS manifestation during pregnancy, but most scientists consider pregnancy as a protective factor (Poncelet et al., 1999; Zrigui et al., 2002; Sergent et al., 2003).

Tennant (2010a,b), McBeth et al. (2006) and Sergent et al., (2003) pointed at the role of the hypothalamic-pituitary-adrenal and pituitary-adrenal-gonadal axes hormones (particularly cortisol) in the pathogenic mechanisms of chronic pain syndromes development. Harden et al. (2004) suggested that disturbances of stress hormones – norepinephrine (NA) and epinephrine (E) – might be the consequence of or risk factors for CRPS I development (Harden et al., 2004).

The diagnosis of CRPS I is also a challenge, because there are no reliable diagnostic criteria and the majority of patients meet only some of them (McBride et al., 2006), thus for the correct diagnosis it is critical to perform complete evaluation of each patient and exclude other possible diagnoses.

Undoubtedly the hormonal dysregulation in CRPS I patients need detailed investigations.

1.1 Objectives

To determine the role of hypothalamic-pituitary-adrenal and hypothalamic-pituitary-ovarian systems in complex regional pain syndrome type I (CRPS I) pathogenesis in women.

2. Materials and methods

We studied the pituitary – gonadotropic and ovarian function in 47 women – 24 controls (group 1 and 2) and 23 women with established CRPS I (group 3).

Group 1 and 2 included controls without CRPS and any other serious medical conditions, known diseases or states. Group 1 consisted of nine women of reproductive age (27–31) with normal menstrual cycle without any trauma during previous 6 months. Group 2 consisted of 15 women of age comparable to that of group 3 (46–57, all menopause) with the same types of injury as women in group 3 during the six previous months before study. The division of controls into two groups was only with the purpose to separate the study of several sex hormones. Some data of the endocrine function in control groups 1 and 2 were calculated together in cases of absence of statistically significant difference and absence of theoretical presupposition of dissimilarity.

Group 3 consisted of 23 women aged 46–57 years (all in menopause) who were diagnosed with CRPS I after extremities injury (fracture or ligaments injuries of ankle or wrist) with duration of CRPS symptoms of 1, 5–6 months. Group 3 women were allowed to take prescribed non-steroidal anti-inflammatory drugs and/or gabapentin for pain relief in minimal effective dose before study beginning.

CRPS I was diagnosed in accordance to Bruehl's criteria for research purposes because of their greater sensitivity and specificity (Dijkstra et al., 2003; Harden et al., 2007, 2010). The other diagnoses were excluded during complete medical examination.

None of the women of groups 1–3 received hormonal preparations for treatment or contraception. Exclusion criteria for all the groups were any known hormonal disturbances in past medical history (except menopause in groups 2 and 3), pregnancy or breastfeeding 3 years before the investigation. Participants with any other significant clinical conditions were also excluded.

The level of estradiol (E_2), follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin, adrenocorticotropic hormone (ACTH) and cortisol was determined in plasma; urinary excretion of 17-ketosteroids (17-KS), 17-oxycocorticosteroids (17-OCS), epinephrine (E) and norepinephrine (NE) was measured in all participants, results were demonstrated as arithmetic mean ± SD (standard deviation). The level of significance was established at $p < 0.5$. The correlation analysis was performed with the correlation ratio (r) and its standard error (mr) calculation. Regression analysis was performed to evaluate the connections between estradiol and other hormone levels.

All the hormones demand special conditions and sampling time. This is of particular importance for women of reproductive age and often less important for menopausal women due to the lesser fluctuations of hormonal levels. To get more reliable measurements we strictly followed the following rules: the sport and sexual activity, alcohol, smoking, use of pharmacologic agents (other than NSAIDs and gabapentin in group 1) was forbidden for 48 h before blood sampling, any hormonal medications intake was excluded for at least 6 weeks before the investigation, patients slept from 10 p.m. till 6 a.m., blood samples were taken at 9 a.m. after a three-hour interval after the awakening and 30 min of complete rest.

The blood samples for estradiol (E_2), prolactin, follicle-stimulating hormone (FSH), luteinizing hormone (LH), adrenocorticotropic hormone (ACTH) and cortisol levels were taken at the period form the 5th–7th day of the menstrual cycle. The urine samples for the daily urinary excretion of 17-ketosteroids (17-KS), 17-oxycocorticosteroids (17-OCS), epinephrine (E) and norepinephrine (NE) were taken any day of the menstrual cycle in all the three groups after 2 weeks of avoidance of sport and sexual activity. Alcohol, smoking, some food which can influence serotonin level (e.g. chocolate, pineapple, walnuts), and caffeinated products were excluded for 48 h before sampling.

Urine was collected in a dark glass jar with 10 mL of 6 mol/L HCL as a preservative during 24 h. The urine was stored in a cool dark place during collection. The sample of daily volume (25 mL) was taken for testing into a dark single-use bottle, sealed and transported to the laboratory.

The study received local ethics committee approval. All subjects provided written informed consent in accordance with the Helsinki declaration.

3. Results

The mean levels of all hormones are shown in Table 1.

Women with CRPS I had the lowest level of estradiol compared to both control groups. Levels of gonadotropins (FSH, LH), to the contrary, were highest in the third group.

We found that prolactin level highly varied in women with CRPS (from 15 to 891 mcIU/mL) probably reflecting individual reactions to stress (chronic pain) in these women. Prolactin level did not differ in control groups.

Cortisol level was slightly decreased in the third group compared to controls probably due to insufficient regulation from pituitary gland (level of ACTH was highest in this group) or the impairment and exhaustion of hypothalamic-pituitary-adrenal axis as a result of chronic pain.

The functional activity of the adrenal cortex was evaluated by the level of 17-KS and 17-OCS urinary excretion. Women with CRPS (group 3) showed a significant decrease in urinary 17-KS excretion compared to controls (15.02 ± 5.59 mmol/day, $p < 0.01$). The mean ratio 17-KS/17-OCS in women with CRPS was 0.86, whereas in the control group it was 3.16, which can be the sign of hormone synthesis dysregulation.

The state of the sympathetic-adrenal system was evaluated by the daily urinary excretion of epinephrine (E) and norepinephrine (NE). According to our results, catecholamine excretion depends on the duration of the disease in group 3. Thus, there was a significant increase in NE excretion (195 ± 20.0 nmol/day, $p < 0.01$) with normal E excretion level in patients at early stages of CRPS (6–12 weeks) compared to the control group. Longer duration of the CRPS (13–24 weeks) was accompanied by a significant decrease in both NE and E excretion compared to controls.

As a next step, we performed the correlation analysis and found several significant correlations between different hormones in healthy women. Thus in group 2 the associations between gonadotropic hormones – FSH and LH ($r = 0.6865$, mr = 0.0137); 17-KS excretion and plasma prolactin ($r = 0.4813$; mr = 0.1131); plasma LH and cortisol ($r = 0.5548$; mr = 0.0612): LH and E_2 ($r = 0.8343$; mr = 0.0007), E_2 and cortisol ($r = 0.7615$; mr = 0.0040), E_2 and FSH ($r = 0.4710$; mr = 0.1222) were found.

To the contrary, the correlation analysis performed in the third group (women with CRPS) showed that

Table 1 Levels of hormones in studied groups.

Hormones	Group 1	Group 2	Group 3
Estradiol[a]	1.69 ± 0.34 nmol/L $P_1 < 0.001$ $P_2 < 0.001$	0.39 ± 0.1 nmol/L	0.23 ± 0.05 nmol/L $P_3 < 0.001$
Follicle-stimulating hormone[a]	4.23 ± 0.61 mIU/mL $P_1 < 0.001$ $P_2 < 0.001$	30.5 ± 6.1 mIU/mL	36.4 ± 3.73 mIU/mL $P_3 > 0.05$
Luteinizing hormone[a]	5.60 ± 0.80 mIU/mL $P_1 < 0.001$ $P_2 < 0.05$	20.1 ± 4.11 mIU/mL	42.1 ± 5.8 mIU/mL $P_3 < 0.01$
Prolactin[a]	212.2 ± 32.1 mcIU/mL $P_1 > 0.05$	200 ± 24.3 mcIU/mL	319 ± 317.24 mcIU/mL[e]
Adrenocorticotropic hormone[a]	87.9 ± 32.7 pg/mL $P_4 < 0.001$		216 ± 32.8 pg/mL
Cortisol[a]	334.6 ± 12.71 nmol/L $P_4 < 0.05$		277 ± 42.6 nmol/L
17-ketosteroids[b]	36.6 ± 1.49 mmol/day $P_4 < 0.001$		15.02 ± 5.59 mmol/day
17-oxycocorticosteroids[b]	11.57 ± 2.52 mmol/day $P_4 > 0.05$		17.86 ± 5.6 mmol
Epinephrine[b]	63.75 ± 5.1 nmol/day $P_5 > 0.05$ $P_6 < 0.001$		56 ± 13.8 nmol/day[c] $P_7 > 0.05$ 33.3 ± 4.0 nmol/day[d]
Norepinephrine[b]	139.4 ± 9.56 nmol/day $P_5 < 0.05$ $P_6 < 0.001$		195 ± 20.0 nmol/day[c] $P_7 < 0.001$ 61.6 ± 6.8 nmol/day[d]

P_1 – statistical significance of differences between groups 1 and 2.
P_2 – statistical significance of differences between groups 1 and 3.
P_3 – statistical significance of differences between groups 2 and 3.
P_4 – statistical significance of differences between control groups (1 and 2 together), and CRPS group (group III).
P_5 – statistical significance of differences between control groups (1 and 2 together), and early CRPS group.
P_6 – statistical significance of differences between control groups (1 and 2 together), and late CRPS group.
P_7 – statistical significance of differences between early and late CRPS groups.
[a]Plasma levels.
[b]Daily urinary excretion.
[c]Early stages of CRPS I (6–12 weeks).
[d]Advanced stages of CRPS I (13–24 weeks after the onset).
[e]Sharp fluctuations of prolactin from 15 to 891 mcIU/mL were noticed.

relations between hormones mainly were destroyed or attenuated. A significant connection was found only between pituitary gonadotropic hormones FSH and LH ($r = 0.6618$; mr = 0.0137); between pituitary hormones ACTH and FSH (mild negative correlation; $r = -0.3357$; mr = 0.0297), prolactin and LH ($r = 0.4449$; mr = 0.0294), prolactin and cortisol ($r = 0.4669$; mr = 0.0214).

Regression analysis had shown that in healthy menopause women estradiol level depended on gonadotropic hormones, cortisol, 17-KS, 17-OCS and catecholamines. The women with CRPS were characterized by a sharp decrease in the number of dependent relationships and only the dependence between prolactin and catecholamines changes was determined.

4. Discussion

Numerous studies devoted to the problem of chronic pain have focused on the hormonal status of the patients, trying to identify the role of ovarian hormones in several types of chronic pain. However, due to the lack of consistency in study designs and difficulties in interpreting test results in different phases of the menstrual cycle, a direct comparison of the results is not possible (Hassan et al., 2014). CRPS I has a female predominance, with a peak incidence at 45–55 years. We hypothesized that CRPS I, as a chronic pain condition, might be connected to low oestrogen synthesis. Oestrogens are known to exert an important influence on the bone system. Changes in serum E2 concentration are associated with

fluctuations in bone turnover and are one of the possible explanations for patchy osteoporosis development in CRPS I patients (Zittermann et al., 2000). The lack of oestrogen-mediated enkephalin transcription in the spinal cord might be one of the possible mechanisms of sensitization and pain centralization (Amandusson and Blomqvist, 2001).

Not surprisingly, we have found the lowest level of E2 in women with CRPS I, compared to healthy women of different ages. Decreased estradiol seems to be a reflection of ovarian exhaustion, developed at the background of highest levels of LH, FSH, prolactin and norepinephrine (in long-term CRPS). In their study de Mos et al. (2009) did not find any association between oestrogen level (endogenous oestrogens level, or oral contraceptive drug intake, or hormonal replacement therapy) and CRPS I development (de Mos et al., 2009). It does not mean that our results conflict with these data. The scientists found only non-significant protective effects of hormone replacement therapy in chronic pain but they did not measure oestrogen levels in CRPS I patients directly.

Prolactin is considered to be not only the milk production stimulus but also the stress hormone (Noel et al., 1972; Lennartsson and Jonsdottir, 2011; Ranabir and Reetu, 2011). Its increase seems to be not only due to the restructuring of subcortical autonomic centres but also due to other changes in homeostasis that act as a chronic stress factor.

A significant increase in ACTH plasma concentrations in combination with a clear tendency to decrease in cortisol might be the consequence of the exhaustion of the adrenal cortex functional reserves, which increases the release of its specific stimulator by the mechanism of negative feedback. In turn, the decrease in cortisol level, determined in 6–24 weeks after trauma, can be seen as the outcome of long-term stress-induced stimulation of the adrenal cortex. Our results have shown that, unfortunately, high ACTH secretion cannot help in coping with pain in CRPS I patients and the data conflict with the report of Bogdanov and Yarushkina (2004) about ACTH induced analgesia in rats.

Analysis of the clinical features of CRPS with impaired function of the hypothalamic-pituitary-gonadal axis and the hypothalamic-pituitary-adrenal axis leads to the conclusion that the most severe persistent forms are observed in patients with severe hyperprolactinaemia, inadequately increased levels of ACTH and cortisol decrease. In these patients, the disease develops with pronounced vegetovascular and neurotic states in the background, the severity of CRPS was positively correlated with the degree of neuroendocrine imbalance and it is a sign of adoptive mechanisms deterioration.

Cortisol is a well-known stress hormone. It is one of the most studied hormones in chronic pain patients. However, it was not investigated in CRPS along with other hormones. The majority of investigations evidenced the decrease in cortisol level in chronic pain states. Muhtz et al., (2013) suggested that chronic back pain is associated with low cortisol secretion. Riva et al. (2010) found significantly lower cortisol levels in fibromyalgia syndrome. However, several studies controversially showed that patients with chronic pain have higher levels of cortisol than control subjects (Vachon-Presseau et al., 2013). Such a variance can be the result of numerous factors and the impact of investigation methods (McEwen and Kalia, 2010), including pain duration (Sudhaus et al., 2009).

We noted above that there was a tendency towards the decrease in cortisol plasma level in women with CRPS. It is important to point that patients had the simultaneous increase in 17-OCS secretion, which might indicate an increase in glucocorticoid metabolic clearance (rapid elimination from the blood). Androgenic function of the adrenal cortex was significantly reduced in women with CRPS, as evidenced by the level of 17-KS.

The ratio 17-KS/17-OCS can be used to determine the degree of changes in balance of anabolic and catabolic hormones. Thus, according to our results the ratio of anabolic (17-KS) and catabolic steroids in patients with CRPS is altered due to lower adrenal cortex function. These changes are significant for women and can reflect 'chronic stress', accompanied by decrease in glucocorticoid adrenal function. It is reasonable to suggest that these changes develop as individual adaptive reactions.

Therefore, the changes detected in the early CRPS I indicate increased activity of sympathetic-adrenal system mediators without significant changes in the hormone level. In longstanding CRPS I activity of both components is significantly reduced.

Our results correspond to the modern ideas that levels of E and NE are appropriate to the nature of the pathological process. Synthesis of E ('hard hormone') mainly reflects the action of acute stress, NE secretion ('soft hormone') is intrinsic to the chronic stress and reflects the individual adaptive potential (Vassiliev and Chugunov, 1985; Mazzeo et al., 1991). The dynamic of E and NE secretion between 6 and 24 weeks after injury indicates the initial sympathetic-adrenal system exertion and its subsequent exhaustion.

Results of control group demonstrated the interdependence in functioning of the hormonal regulation in normal homeostasis. Along with this, endocrine status in CRPS is characterized by hormonal imbalance of the hypothalamic-pituitary-adrenal and hypothalamic-pituitary-gonadal systems. Women with CRPS were characterized by the decreased plasma oestrogens and increased pituitary gonadotrophic function. The changes in hormonal and adaptive homeostasis characterize CRPS as a form of the disease of disadaptation.

Pathogenesis of CRPS can be seen as a chain of interrelated processes. Age-related changes in the reproductive system lead to decreased oestrogen level and other hormone imbalance. Due to the cessation of the inhibitory effects of oestrogens the increased excitability of hypothalamic structures that control the activity of peripheral sympathetic nerves develops which leads to the higher levels of neuronal secretion of the mediators – NE in the vasomotor nerve endings and acetylcholine in sympathetic nerve endings.

Thus, the overactivation of the sympathetic-adrenal system leads to increase in intra- and extravascular concentrations of the catecholamines and other active substances. Reducing the ratio of precapillary and postcapillary resistance, i.e. capillary filtration coefficient, determines the preponderance of the filtering process in the capillary bed compared with absorption. This leads to the development of oedema. In the case of maintenance of high neurogenic tone of arterial and venous vessels pale skin is observed.

5. Conclusions

(1) The dysfunction of the autonomic centres and endocrine glands is the important part in CRPS pathogenesis. The system of regional circulation mediates the effect of these factors, and the ultimate goal is the cellular homeostasis.
(2) In patients with CRPS I endocrine status is characterized by hormonal imbalance of the hypothalamic-pituitary-adrenal and hypothalamic-pituitary-gonadal systems. Reduction in oestrogen levels is evident in women with CRPS particularly.
(3) The early stages of the CRPS I are characterized by increase, and then a sharp decline of neurogenic tonic vasomotor reactions at the background of persistent changes in the activity of the sympathetic-adrenal system.
(4) The changes in adaptation homeostasis characterize CRPS I as a form of the disease of disadaptation.

Author contributions

None.

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