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CHRONIC FATIGUE SYNDROME – BEING IN GOOD OR BAD HEALTH OR SOMETHING IN BETWEEN?

Abstract: Chronic fatigue syndrome is complex disturbance with so far unknown etiology which is characterized with marked fatigue that lasts more than six months. Fatigue of this origin is different than usual – it isn't reduced after rest and is followed by decrease of previous psychophysiological activity and some number of symptoms that are of undefined origin. Due to its still unclear etiology, scientists are still debating on whether this disturbance can be characterized as illness or not. Most of them recognize the syndrome as illness provided there are several symptoms in concomitance present. In searching for etiology scientists have examined the hypothalamic-pituitary-adrenal axis as one of the most important axis in stress response. In 19th century neurologist George Miller Beard was the first to describe people who felt fatigued, anxious, depressed with impotence and neuralgia with term 'neurasthenia'. Following this some other terms were in use, depending on part of the world, like myalgic encephalomyelitis, chronic Epstein-Barr virus syndrome, chronic mononucleosis syndrome, atypical poliomyelitis, epidemic vasculitis, post-viral fatigue syndrome, syndrome of chronic neuroendocrineimmune dysfunction so this disturbance is called 'disease with thousand names'. Early information on disruption of hypothalamic-pituitary-adrenal axis appeared for the very first time in the 1980s. The interest in disturbance of the hypothalamic-pituitary-adrenal (HPA) axis rose when Potheliakhoff reported cases of hypocortisolemia in such patients in 1981. Although, at the time, the criteria for chronic fatigue syndrome (CFS) were not clearly defined, this report was fundamental in further research regarding HPA axis in this syndrome.

Keywords: chronic fatigue syndrome, HPA axis, hypocortisolemia, ACTH test, ITT

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What is, actually, chronic fatigue syndrome?

Until nowadays much effort has been made in defining chronic fatigue syndrome. Finally in 1994. this was made by a group of scientists and this definition is somehow equally useful both to researchers studying the illness and to clinicians diagnosing it. In order to receive a diagnosis of chronic fatigue syndrome, a patient must satisfy two criteria:

1. existence of chronic fatigue lasting for six months or longer with other medical conditions excluded by clinical diagnosis
2. concurrent existence of four or more of the following symptoms: substantial impairment in short-term memory or concentration; sore throat; tender lymph nodes; muscle pain; multi-joint pain without swelling or redness; headaches of a new type, pattern or severity; unrefreshing sleep; and post-exertional malaise lasting more than 24 hours.

It should be pointed out that besides a minimum time interval of six months these symptoms must not precede chronic fatigue (1). Centers for Disease Control and Prevention (CDCP) Report informed that 18 percent of patients previously showed indicative signs of medical conditions that probably resulted in chronic fatigue (1).

CFS is diagnosed by means of exclusion since there are no patognomonic signs or tests that would determine this diagnosis as such. Unfortunately there is also no specific treatment of the same. There are no evident signs showing that viral infection causes CFS. On the other hand, these patients show high degree of depressiveness (about 60%), emotional symptoms and lack of self-confidence, although many experts claim that CFS is not simply a subtle form of depression or somatoform disorder. The acute post-viral fatigue syndrome often occurs in the period of adolescence, but it is not clear enough what triggers the chronic condition with some patients (2). Longitudinal studies have showed that with certain number of patients suffering from CFS, the symptoms disappear over time, but the majority remains functionally disrupted for several years.

Assessment of fatigue? That's the easy one! I am really tired... but...

...we must accept that exhaustion or fatigue is a usually a perfectly normal condition. As Giovannoni says 'fatigue is a subjective feeling of tiredness and exhaustion that can reflect both physical process (mobility) and psychic process (cognitive and emotional)' (3). The definition remains questionable, provisional but very important. Fatigue itself and susceptibility to fatigue are not pathological per se. The notion of fatigue refers to tiredness or disability to maintain strength. Susceptibility to fatigue refers to one's tolerance to fatigue. The scope of fatigue ranges from utter exhaustion after running a marathon to light sleepiness followed by prolonged awakening. What

is most important is the fact that complaints about psychic and physical fatigue are often not in correlation with either cognitive function or muscular fatigue. Some authors say that ″true fatigue... and exhaustion are absolutely different notions″, or they say that ″fatigue is much more than mere tiredness″ and that it refers to 'pathological exhaustion' (4). However, such claims are questionable. Persistent refusal of being exhausted or insistence on being too exhausted defines the way and the mode this notion is to be used by both the doctors and the patients in a questionnaire thereof. Does the notion 'exhaustion' imply that the physiological exhaustion of athletes is in fact pathological? Some authors point out that fatigue is pathological only if it is disabling, that is if it affects social, physical and professional abilities. Yet, this criterion also assumes a strong subjective moment in which a patient defines his/her own critical point of whether fatigue is disabling or not.

Hypothalamic-pituitary-adrenal axis and chronic fatigue syndrome

The research methodology of HPA axis participation in CFS faces numerous dilemmas. Considering so many methods of testing basal and stimulated endocrine activity, psychiatric comorbidity and fatigue as a common symptom of many diseases, it is very difficult to choose adequate group of patients for endocrinology testing. Higher concentration of cortisol, seen in major depression, often affects the results of studies (5). Also, in cases of atypical major depression, in which fatigue is one of the main symptoms, the existence of hypocortisolemia and disturbance in HPA axis have been shown (6). On the other hand, some studies have showed that somatoform disorders or panic disorders are connected to changes in HPA axis (7). Joint factors may affect neuroendocrine function (previously or currently used medicines, sleeping disturbance, loss of energy during the testing and present psychosocial stress).

Sudden interest in HPA changes in this syndrome has been aroused in 1981 when Poteliakhoff for the first time detected hypocortisolemia with patients (8). At that time 25 patients with ongoing symptoms of chronic fatigue that lasted at least one month were examined and hypocortisolemia was reported. Although criteria for CFS were not clear at the time, this finding was fundamental in further investigation of HPA axis in this syndrome. Most studies on HPA axis point out to hypocortisolemia with certain number of patients with fairly good likelihood that this is in correlation with the symptoms and their persistence thereof. There is evidence of strong negative feedback and alteration in glucocorticoid receptors, whereas some studies have pointed out to reduced response of adrenocorticotropic hormone (ACTH) and cortisol in some tests. Still, there is no uniform dysfunction of HPA axis.

Central or peripheral dysfunction of hormone secretion in hypothalamic-pituitary-adrenal axis?

Scientists that are doing researches in CFS are permanently asking themselves one question: is the main problem in central nervous system i.e. in hypophysis or is it a peripheral disturbance of adrenal gland? The goal of one research was to see secretion of pituitary and adrenal hormones during the 24h period of time. The specificity of this study was to see how these hormones secrete in short intervals during one day. On one side, secretion of ACTH, growth hormone (GH) and prolactin (PRL) as hormones that are produced in anterior lobe of pituitary gland was taken into consideration and on the other side they monitored the secretion of cortisol produced in adrenal gland. The profiles of secretion were followed in the period between 10 AM - 10 PM at one-hour regular intervals and between 10 PM - 10 AM at 15-minute regular intervals (9). The result of this study was insignificant change in HPA axis reflecting a lower secretion of ACTH during the whole period of circadian rhythm and a lower peak of ACTH secretion between 8 AM – 10 AM. There were no changes in secretion of GH, PRL and cortisol. This was to some extent in accordance with some authors' opinion, who consider pituitary as a problem in terms of inadequate secretion of pituitary under various types of stress and that they can secrete enough cortisol under the same conditions. However, this study was not in accordance with previous studies pointing out to hypocortisolemia, though there was one more study that observed cortisol secretion in short intervals during 24h period which also did not find changes in cortisol concentration (except for numerically lower concentration of cortisol in the morning) (10). So, circadian rhythm of cortisol, as the main index of circadian rhythm generally, was very similar with both CFS patients and healthy controls, but there was a significant difference in earlier acrophase of the modeled cosinor curve in secretion of ACTH (9). Still, these data cannot prove whether this is a primary characteristic of the illness or its side effect, being a consequence of CFS persistence.

In contrast to aforementioned studies, another study has shown significantly lower concentration of cortisol with CFS patients in contrast to control group as Cleare and associates reported (11). The study of Hamilos and associates was especially interesting as it showed lower peak of cortisol secretion during circadian rhythm (12). On the other hand, Demitrack and associates have used corticotropin-releasing hormone (CRH) test in their study and reported weaker ACTH response and normal cortisol response, which they explained as possible disruption in CRH secretion or lower central response of HPA axis in CFS (13). Yet, so far there is no clear explanation about differences in concentration of cortisol in these studies, since the results mostly depend on the way cortisol is measured (14). The study done by Cleare and associates has shown normal response of ACTH in insulin tolerance test (ITT) and CRH test and lower cortisol response in CRH test in the group of patients with CFS (15). These results were not

in accordance with earlier findings or with a hypothesis about dysfunction in secretion of CRH and lower central response of HPA axis in CFS, yet they pointed out to weaker response of adrenal gland to stimulation. The reasons for such different results the scientists find in different methodologies used, psychiatric comorbidity, use of drugs, testing time, differences between men and women.

Žarković and associates used low-dose (1 μg) ACTH test and ITT to detect a cause of CFS. They compared responses of CFS patients and those of healthy control group and of a group of patients with secondary adrenal insufficiency (suppressed HPA axis because of chronic corticosteroid therapy given for Graves' opthalmopathy) (16). All groups of patients had been thoroughly examined for previous exclusionary diagnosis as cause of their fatigue. CFS was diagnosed in accordance with CDC criteria. The examined patients did not consume any medications at least one month before the actual testing. ACTH test indicated a significantly higher concentration of cortisol in the 15th and 30th minute in control group as compared to the group of patients with chronic corticosteroid therapy. The concentration of cortisol in CFS group was not statistically much different from other groups. In ITT just a few patients had cortisol concentration beyond 500mmol/l and only two of them below 550mmol/l. From these results one can conclude several things. First, the response of cortisol with CFS patients to ACTH stimulation is similar to that of patients with secondary adrenal insufficiency. Second, CFS patients show heterogeneous response to different stimuli. Third, there is a disparity between cortisol response during ACTH test and ITT (16).

Negative feedback in hypothalamic-pituitary-adrenal axis with patients with chronic fatigue syndrome

The goal of the study done by Gaab and associates was to test the negative feedback in HPA axis with CFS patients (17). Since one of the assumed mechanisms regarding the etiology of CFS is stronger negative feedback, these scientists decided to use low-dose dexamethasone test which is sensitive enough in diagnosis of this disturbance. This test implies giving a low dose of dexamethasone (0.5mg) at 11 PM and the measurement of cortisol at 8 AM the next day. The scientists used low-dose instead of standard dexamethasone test (1mg of dexamethasone under the same conditions) as healthy patients have shown higher sensitivity to the differences between suppressors and non-suppressors than those suffering from depression (18). Still, the information obtained from low-dose dexamethasone test seems to refer to negative feedback in HPA axis (19). In this research CFS patients did not use any medications (antidepressives, anxiolytics, antibiotics, antihypertensives, steroids), whereas laboratory analyses showed no reasons for chronic fatigue. A psychiatrist has excluded any accompanying illnesses. During the examination, which lasted three consecutive

days, the scientists took samples of cortisol right after awakening, then 15, 30, 45 and 60 minutes after and again at 8 AM, 11 AM, 3 PM and 8 PM to monitor circadian rhythm of cortisol in saliva. The patients did not wake up at the same time because it seems that the time of awakening is not related to early morning concentration level of free cortisol (20). The first two days saw a significant rise in free salivary cortisol immediately upon awakening in case of both groups. After using 0.5mg dexamethasone, the concentration of free cortisol was not statistically different over time in both groups as compared to the first two days. Nevertheless, the patients with CFS had significantly lower concentration of saliva cortisol on the 3rd consecutive day, in contrast to similar concentrations showed in the first two days, when compared to control group. The area under curve was also statistically lower on the 3rd day in case of CFS patients in contrast to the first two days. As far as circadian rhythm is concerned, a significant change in cortisol was noted during the first two days, but not during the 3rd day. Patients with CFS had significantly lower total concentration of salivary cortisol upon awakening on the third day, with no differences among groups. This was the first study that reported stronger suppression of HPA axis in response to low-dose dexamethasone test in case of patients with CFS under both basal and reactive conditions (17). The daily rhythm of cortisol secretion was very similar in case of both healthy and CFS patients under basal conditions; however, upon receiving a low-dose of dexamethasone, the concentration of cortisol in case of CFS patients was statistically speaking significantly lower during the whole day. Yet, the scientists did not take into consideration the menstrual cycle of women (there were 13 women out of 23 examined) because it has been shown that women in luteal phase show higher concentration of saliva cortisol in response to psychosocial stressors in contrast to women in follicular phase of the menstrual cycle (21). Thus, the only negative aspect of this research would be the unknown phase of menstrual cycle and its potential influence on cortisol concentration.

Demitrack and associates supposed that the lower suprahypothalamic drive and weaker hypothalamic response of CRH lie in the genesis of this syndrome (13). Still, in this case one would expect positive regulation of pituitary CRH receptors and consequent enhanced response of ACTH to CRH stimulation, but the research did not show such results. Scott and associates pointed out to the fact that CFS is in correlation with stress (22). They noted that initial stress increases the concentration of CRH and leads to negative regulation of CRH receptors. This negative regulation of receptors cannot recover spontaneously once the stress is alleviated. This explanation is similar to major depression, so it remains unclear how to differentiate between these two conditions. Cleare and associates thought that primary problem lies in adrenal gland (15). Cleare and Wessely had a hypothesis that chronic stress leads to such symptoms, no matter whether it is caused under the influence of external or internal factors (23). Heim and associates thought that one can make a parallel between endocrine findings in CFS and in other illnesses

such as posttraumatic stress disturbances, seasonal affective disorders and atypical depression (24). These findings could be non-specific markers of vulnerability to such conditions. Since there is no research that can determine a specific cause of disturbance, these authors also suggested that there is no universal explanation for the changes in HPA axis in CFS.

Arginine vasopressin (antidiuretic hormone) and chronic fatigue syndrome

Scientists also used arginine vasopresin (AVP) test in order to explain HPA axis changes. AVP acts synergistically with CRH in order to release ACTH (25). The response of ACTH to AVP depends on central concentrations of CRH, because it is enabled by coadministration in dose-depend way and varies in circadian rhythm like changes in CRH (26). They hypothesised the disturbance of AVP secretion or disturbance of their receptors. Scott and associates thought that the deficit in AVP may contribute to a weaker ACTH response which can be seen in exogenous stimulation of CRH (25). The same authors used desmopressin (DDAVP), which is AVP analogue, in two ways: alone and in coadministration with CRH (27). They pointed out to a weaker ACTH and cortisol response in case of CFS patients. DDAVP did not show any visible effects in either group. But, the use of 10μg DDAVP in bolus enabled normalization of the effect, so that both CFS patients and healthy controls showed the same ACTH response. They considered this to be a result of positive regulation of AVP receptors in pituitary of CFS patients.

Dehydroepiandrostenedione and its sulphate in chronic fatigue syndrome

Dehydroepiandrostenedione (DHEA) and its sulphate (DHEA-S) are known as precursors of sex steroids but besides that these hormones have other functions associated with memory, depression and sleep. It has been suggested that CFS may be associated with a state of relative DHEA(-S) deficiency. That is why scientists came to idea of investigating basal levels of DHEA(-S), the cortisol/DHEA ratio and the responsiveness of DHEA to stimulation by CRH. Recent studies have suggested that low dose hydrocortisone may be effective at reducing fatigue in CFS. Therefore scientists assessed these parameters before and after treatment with low dose oral hydrocortisone (28). For that purpose basal levels of serum DHEA, DHEAS and cortisol were measured in 16 patients with CFS without depression and in group of 16 persons as controls. After CRH tests (1 g/kg i.v.), DHEA was measured at 0, +30 and +90 min. In the patient group, CRH tests were repeated twice on different occasions after treatment with 5-10mg of hydrocortisone per os. Basal levels of DHEA were higher in the patient than in control group, while levels of DHEAS in patients

were not different from controls. Higher DHEA levels were i correlation with higher disability scores. Basal cortisol levels were higher in patients so the cortisol/DHEA ratio did not differ between patients and control group. Levels of DHEA and DHEA-S were lower in patients after hydrocortisone treatment. There was a rise in DHEA responsiveness to CRH in the patients after treatment but that was without statistical significance. Still, patients who's fatigue reduces after hydrocortisone treatment have shown significantly increased DHEA responsiveness to CRH. Scientists concluded that DHEA levels are raised in CFS and correlate with the degree of self-reported disability. Hydrocortisone therapy leads to a reduction in these levels towards normal, and an increased DHEA response to CRH, most marked in those who show a clinical response to this therapy (28).

In one study that has been conducted in Japan on CFS patients, scientists pointed on lower concentration of DHEA-S, which is shown to have psychophysiological phenomena (29). Therefore, these scientists thought that the deficiency of DHEA-S might be related to the neuropsychiatric symptoms in patients with CFS.

Growth hormone axis

The idea of testing the GH axis in CFS comes from several resources. First, there is a similarity with fibromyalgia, in which low concentration of GH is related to sleeping disturbance and muscular pains (30). It has been determined that there is a correlation between lower concentrations of GH with adults and appearance of certain symptoms such as fatigue and myalgia (31). Some studies pointed out to a lower concentrations of GH, insulin-like growth factor 1 (IGF-1) and IGF-2 in case of CFS patients (32), whereas other studies did not prove the same (33). Namely, the study done by Allain and associates has showed a lower GH response in ITT (34) while this was not the case with the study undertaken by Berwartes and associates (35). Furthermore, the data gathered from a large-scale study done on 37 CFS patients and on the same number of controls have showed no changes in either GH or during dynamic tests (36). Another study was conducted on even larger group of patients and a little bit smaller control group with an aim to test basal concentrations and concentrations in dynamic tests, also including clonidine test in its scope (37). In contrast to the previous study, it showed a lower concentration of GH during the night and weaker response of GH in ITT in case of CFS patients. Yet, there were no significant changes in concentrations in IGF and GH response in other tests was normal. The drawback of these studies is the fact that they do not clearly define the subgroup of patients with fibromyalgia who often show symptoms of CFS and disturbance of GH secretion. Moreover, it is necessary to exclude the possibility of depression with such patients (37). Overall, there is not enough evidence that would prove GH to be a main cause of symptomatology in CFS.

Necessity of multidisciplinary approach to the problem of hypothalamic-pituitary-adrenal axis

Chronic fatigue syndrome is still enigmatic disease for modern medicine. Since the etiology of disease is unknown, the most important questions for further investigation in future are:

1. When do changes in HPA axis take place?
2. Are the changes in HPA axis in connection with the genesis of CFS with regard to some other precipitating factors?
3. Is there a subgroup of patients with CFS that have some changes in HPA axis that have not been discovered in cohort studies so far?

It is highly unlikely that there is a specific or uniform change in HPA axis in CFS. Therefore it has been suggested that the etiology of HPA axis changes is characterized by multifactorial fluctuations. With that regard, it is of utmost importance that HPA axis research takes into consideration potential occurrence of confounding factors which might in many ways influence changes in HPA axis (14). This is why scientists recommend that future researches should take into consideration patients' structural nature of sleep, their physical activity, neuroendocrine parameters, as well as to make sure the patients have undergone a detailed psychiatric examination, and that they have been tested in specific phases of illness (acute, subacute and chronic phase of fatigue), to perform a prospective cohort studies, to determine all previous events in the life of a patient that could have affected HPA axis (for example child abuse), to have certain information on use of any medications including those from over-the-counter group, to have information on the patient's diet and degree of exposition to stress which can affect HPA axis. It is this heterogeneity of confounding factors that may have influenced different results in researches so far. Therefore the author of one study recommends that the examination should be undertaken in different phases of illness: acute, subacute and chronic phase of fatigue (38). In this manner one could discover factors that predispose, precipitate and maintain pathogenesis of CFS during b*iopsychosocial continuum.*

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