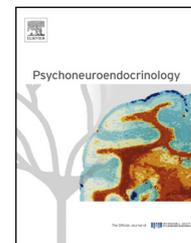




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# The role of hypocortisolism in chronic fatigue syndrome



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## KEYWORDS

Chronic fatigue;  
Adolescents;  
Cortisol;  
Awakening response;  
Recovery

## Summary

**Background:** There is accumulating evidence of hypothalamic–pituitary–adrenal (HPA) axis hypofunction in chronic fatigue syndrome (CFS). However, knowledge of this hypofunction has so far come exclusively from research in adulthood, and its clinical significance remains unclear. The objective of the current study was to assess the role of the HPA-axis in adolescent CFS and recovery from adolescent CFS.

**Method:** Before treatment, we compared the salivary cortisol awakening response of 108 diagnosed adolescent CFS patients with that of a reference group of 38 healthy peers. Salivary cortisol awakening response was measured again after 6 months of treatment in CFS patients.

**Results:** Pre-treatment salivary cortisol levels were significantly lower in CFS-patients than in healthy controls. After treatment recovered patients had a significant rise in salivary cortisol output attaining normalization, whereas non-recovered patients improved slightly, but not significantly. The hypocortisolism found in CFS-patients was significantly correlated to the amount

**Abbreviations:** AUC<sub>G</sub>, integrated area under the curve; CBT, cognitive behavioural therapy; CDC, Centre for Disease Control and Prevention; CFS, chronic fatigue syndrome; CIS-20, Checklist Individual Strength; CHQ-CF87, Health Questionnaire-Child Form; CSI, Children's Somatisation Inventory; CDI, Children's Depression Inventory; HPA-axis, hypothalamic–pituitary–adrenal axis; RCT, Randomized Clinical Trial; STAIC, State-Trait Anxiety Inventory for Children; UC, usual care; UMC Utrecht, University Medical Center Utrecht.

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of sleep. Logistic regression analysis showed that an increase of one standard deviation in the difference between pre- and post-treatment salivary cortisol awakening response was associated with a 93% higher odds of recovery (adjusted OR 1.93 (1.18 to 3.17),  $p = 0.009$ ). Pre-treatment salivary cortisol did not predict recovery.

**Conclusions:** Hypocortisolism is associated with adolescent CFS. It is not pre-treatment cortisol but its change to normalization that is associated with treatment success. We suggest that this finding may have clinical implications regarding the adaptation of future treatment strategies.

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## 1. Background

Chronic fatigue syndrome (CFS) is characterized by unexplained persistent or relapsing disabling fatigue that lasts for at least 6 months and is accompanied by at least four out of eight possible symptoms (memory or concentration problems, sore throat, tender lymph nodes, muscle pain, multiple joint pain, headache, unrefreshing sleep, postexertional malaise) (Fukuda et al., 1994). CFS is found in adolescents as well as in adults. Its primary adverse impact in adolescents is extreme disability, associated with considerable school absence (Nijhof et al., 2011a,b).

Despite substantial research, a biological substrate for this syndrome has not yet been established. It is considered to be a multifactorial condition in which biological, psychological and social factors play a predisposing, precipitating or perpetuating role.

Hypofunction of the hypothalamic–pituitary–adrenal (HPA)-axis as manifested by a low salivary cortisol awakening response (CAR) (Tak et al., 2011) is the most replicated biological finding in CFS, but only through studies in adulthood (Cleare, 2003; Demitrack et al., 1991; Heim et al., 2000; Roberts et al., 2004; Tak et al., 2011). The exact role of this hypofunction remains unclear. It is not known whether this is a relevant biological factor in the aetiology of CFS. It has been hypothesized that lowered cortisol occurs, in part, secondarily to aspects of CFS such as disturbed sleep, inactivity or stress (Roberts et al., 2004; Tak et al., 2011).

In adolescents, CFS has to be identified and treated as soon as possible, to lower the risk of developmental and educational disturbances (Bell et al., 2001; Nijhof et al., 2011a,b). Cognitive behavioural therapy (CBT) is one of the most successful treatments for adolescents with CFS (Chalder et al., 2010; Nijhof et al., 2012; Stulemeijer et al., 2005). Perpetuating factors such as fatigue-related cognitions and behaviour, are addressed by CBT. However, not all patients suffering from CFS respond to CBT. It is of paramount importance to differentiate between responders and non-responders as early as possible in order to change content, duration, or choice of treatment.

The factors that influence treatment outcomes in adolescent CFS are largely unknown. A number of factors in young patient and parents have been revealed to be associated with an unfavourable outcome after treatment (van de Putte et al., 2006; van Geelen et al., 2010; Knoop et al., 2008; Nijhof et al., 2013). Most consistent factors are an older age at inclusion (van Geelen et al., 2010), longer disease duration before start of treatment (Nijhof et al., 2013), and maternal focus on fatigue or bodily symptoms (Knoop et al., 2008; Nijhof et al., 2013; van de Putte et al., 2006). However, none

of these factors provide direct clues for pathophysiological treatment targeting and monitoring during treatment, while continued HPA-axis hypofunction monitoring might serve that purpose. Only in adults, was an association found between HPA-axis hypofunction and a poor response to CBT (Roberts et al., 2010), suggesting that hypocortisolism could be a factor in the persistence of CFS.

It has not been studied whether the change in HPA-axis after treatment is related to recovery from CFS in adolescents. We hypothesized that HPA-axis hypofunction is a relevant biological factor in adolescent CFS, and that an association exists between recovery from CFS and a change in cortisol levels after treatment.

The aims of our study were: to examine the association between salivary cortisol response to awakening and CFS, through (1) comparison between healthy adolescents and CFS adolescents, and (2) investigation of the change in salivary cortisol response to awakening in relation to recovery of CFS.

## 2. Methods

### 2.1. Subjects

One hundred and twenty-three adolescents (12–18 years) diagnosed with CFS participating in the FITNET (Fatigue In Teenagers on the interNET) trial (Nijhof et al., 2011a,b, 2012) were invited to participate in this cohort study on cortisol between March, 2008 and February, 2010. 118 (96%) patients agreed to participate. They all complied with CDC-criteria for CFS diagnosis (Fukuda et al., 1994). FITNET, an internet-based CBT program for adolescents with CFS, was developed as an alternative to face-to-face CBT (Nijhof et al., 2011a,b, 2012). A detailed description of the FITNET study protocol, methodology, and program has been reported elsewhere (Nijhof et al., 2011a,b, 2012). In the original trial, all patients were randomly assigned to either FITNET or usual care (pre-treatment). Participants were reassessed after 6 months of treatment (post-treatment).

As a reference group, healthy participants to a previous CFS research were re-invited between March 2009 and February 2010 (Nijhof et al., 2011a,b). Of these, adolescents with neurological abnormalities, chronic illnesses, or under treatment by a psychiatrist or psychologist were excluded from participation. Thirty-nine of 58 eligible healthy adolescents (67%) completed the saliva-sampling protocol. In view of the demographic characteristics and fatigue levels, both the CFS-patients and healthy peers were unselected samples of former studies (Nijhof et al., 2011a,b, 2012).

The medical ethics committee of the University Medical Centre Utrecht (UMCU) approved this study. Written

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