Journal of Psychosomatic Research 77 (2014) 409–414

Contents lists available at ScienceDirect

Journal of Psychosomatic Research

Cortisol output in adolescents with chronic fatigue syndrome: Pilot study on the comparison with healthy adolescents and change after cognitive behavioural guided self-help treatment

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ARTICLE INFO

Article history:
Received 29 April 2014
Received in revised form 23 August 2014
Accepted 31 August 2014

Keywords:
Fatigue
Youth
Paediatric
Hypothalamic–pituitary–adrenal axis
Neuroendocrine
Perfectionism

ABSTRACT

Objective: This study examined cortisol in adolescents with chronic fatigue syndrome (CFS) compared to healthy adolescents and changes in cortisol after cognitive behavioural guided self-help treatment. Exploratory analyses investigated the association between cortisol output and psychological variables.
Methods: Salivary cortisol was measured upon awakening, at 15, 30, 45 and 60 min afterwards and at 12 noon, 4:00 p.m. and 8:00 p.m., in adolescents with CFS and healthy controls (HC). Groups were matched for age, gender, menarche status, menstrual cycle and awakening time. Twenty-four adolescents with CFS provided saliva samples six months after treatment. The main outcome measure was total salivary output over the day, calculated by area under the curve (AUC). The salivary awakening response was also assessed.
Results: Cortisol output over the day was significantly lower in the CFS group ($n = 46$) than in healthy controls ($n = 33$). Within the CFS group, lower daily cortisol output was associated with higher self-reported perfectionist striving and prosocial behaviour. There were no significant group differences in the awakening response ($n = 47$ CFS versus $n = 34$ HC). After treatment, adolescents with CFS ($n = 21$) showed a significant increase in daily cortisol output, up to normal levels.
Conclusion: The reduced daily cortisol output in adolescents with CFS is in line with adult findings. Associations between reduced cortisol output and two psychological variables—perfectionism and prosocial behaviour—are consistent with cognitive behavioural models of chronic fatigue syndrome. The mild hypocortisolism is reversible; cortisol output had returned to healthy adolescent levels by six months after cognitive behavioural guided self-help treatment.

Introduction

Chronic fatigue syndrome (CFS) is likely to be a multifactorial condition in which biological, psychological and social factors contribute and interact. Few biological changes have been reliably demonstrated in this condition, one of the exceptions being disturbed hypothalamic–pituitary–adrenal (HPA) axis dysfunction [28]. In adults with CFS, reduced cortisol output over the day has been demonstrated in salivary and urinary cortisol studies [16,17,41]. In adults, there is also evidence of an attenuation of the usual rapid increase in salivary cortisol levels after awakening [33]. The cortisol awakening response is not well understood but appears to be influenced by a number of factors in addition to HPA activation, such as sensitivity to light mediated by an extra-pituitary pathway (e.g., [7]). Therefore, it is important not to rely only on measures of the cortisol awakening response to assess HPA axis activation.

Reduced cortisol may be a primary etiological factor in CFS and/or secondary to sleep disturbance, reduced activity or other factors commonly associated with CFS such as increased stress or distress. Stress is reported by some young people with CFS as a contributory factor to their condition [14], and there are elevated rates of mood and anxiety problems in adolescents with CFS compared to young people with other chronic illness (e.g., [3,30]). Chronic stress is associated with hypocortisolism [23], and a study in adults with CFS found that blunted cortisol awakening responses were only present in those with a history of childhood trauma [15]. It has been suggested that hypocortisolism can reflect a protective response following a history of repeated high cortisol responses [11]. Hypocortisolism is associated with symptoms such as fatigue and pain, so once it has developed it could act as a maintaining factor for CFS.

Three previous studies have reported serum cortisol levels in adolescents with CFS, with inconsistent findings [19,35,44]. Each of these studies used a potentially stressful invasive testing procedure in a hospital environment. Given that cortisol is a hormone that shows diurnal

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http://dx.doi.org/10.1016/j.jpsychores.2014.08.018
0022-3999/

variation and is secreted in a pulsatile manner, another limitation is the use of a single blood cortisol measurement to assess basal HPA axis function. Studies are needed using repeated salivary measures of cortisol over the day, taken in a naturalistic home environment that eliminates the confounding stress associated with both intravenous cannulation and hospital attendance. Katz et al. [18] found little evidence of reduced salivary cortisol levels in adolescents with CFS but this had a number of limitations including a very small sample size (nine adolescents with CFS), just two measurement points (morning and evening) and the inclusion of adolescents who developed CFS after infectious mononucleosis only. Nijhof et al. [25] found lower cortisol awakening response in adolescents with CFS compared to healthy controls but they did not investigate cortisol output over the course of the day. This is the first salivary cortisol study to report both total daily cortisol output and the cortisol awakening response (CAR) in adolescents with CFS.

Nijhof et al. [25] compared characteristics of adolescents with CFS dichotomised by below and above average AUCg levels and found that only sleep duration before CAR was significantly different. They did not find differences in terms of depression but did not compare the groups on other psychological characteristics that relate to stress vulnerability such as anxiety or high standards for performance or personal conduct. The present study undertook exploratory analyses investigating associations between cortisol output and questionnaire measures of perfectionism and prosocial behaviour (as indications of high standards for performance and personal conduct) as well as other characteristics such as anxiety, depression, emotional and behavioural difficulties and fatigue severity.

Cognitive behavioural treatments are evidence-based interventions for CFS [5,39]. These interventions are based on a multifactorial approach to CFS in adolescents (e.g., [20,40]), in which it is hypothesised that certain premorbid characteristics, including high standards for performance or personal conduct, conscientiousness and stress vulnerability (e.g., [31]), increase the risk for developing fatigue in the context of challenges such as physical illness or extra environmental demands. For example, perfectionist or conscientious individuals may strenuously attempt to keep up with their usual standards despite the extra challenges, and end up more stressed and fatigued as a result (e.g., [9]). It is suggested that acute fatigue can become chronic via a number of mechanisms including level of physical activity (e.g., too high or too low; [42]), fearful beliefs about fatigue or the effects of fatigue (e.g., [38]) or emotional difficulties such as anxiety or depression [30,32]. Cognitive behavioural interventions typically aim to improve symptoms and functioning by (a) encouraging patients to achieve a balance between activity and rest, (b) gradually increasing activities, (c) establishing a sleep routine, (d) addressing unhelpful beliefs (e.g., about fatigue or high standards) and (e) paying attention to relapse prevention. Although initial studies focused on face-to-face treatment, travelling to the clinic can cause extra fatigue, and more recent studies have found evidence to support the use of Internet-based CBT [26] and telephone-based guided self-help [21].

Cognitive behavioural interventions address a number of variables that influence cortisol levels including activity patterns and deconditioning, stress, sleep and personality characteristics associated with stress vulnerability. A previous study in adults with CFS found that daily cortisol output normalized after cognitive behavioural treatment [34]. Nijhof et al. [25] reported that adolescents who recovered in their trial after either CBT or "treatment-as-usual" (which might have been CBT or graded exercise therapy or a rehabilitation programme) had a significant rise in their cortisol awakening response. That paper did not report change in the cortisol awakening response after a single type of treatment such as CBT. There have been no previous studies reporting the cortisol awakening response after a single type of treatment such as CBT, or changes in cortisol output *over the day* before and after treatment. In the present study, we investigated both cortisol output over the day and the cortisol awakening response before and after a telephone-based guided self-help cognitive behavioural intervention, which was the standard treatment on offer in our clinic at that time. We hypothesized that cortisol output would be significantly higher at six months after the end of cognitive behavioural guided self-help than at pre-treatment.

Methods

Participants

Participants were 49 adolescents with CFS, and 36 healthy adolescents who were selected to match for age and gender. The CFS group was composed of patients attending a specialist CFS Unit in London who met CDC [12] and Oxford [36] criteria for CFS. Assessment at the CFS clinic included the exclusion of depression or other psychiatric problems as the primary diagnosis. They had all been assessed by paediatricians who had conducted appropriate tests to exclude other possible diagnoses causing their fatigue. Self-reported mean duration of CFS was 25.3 months (SD = 16.1). Saliva samples were taken prior to treatment. The healthy adolescents were recruited via local schools and were required to have no history of CFS and no current medical condition likely to cause excessive fatigue. Of the CFS sample, 24 returned post-treatment questionnaires and cortisol samples; of the remainder, three did not complete treatment and the others did not return usable post-treatment cortisol samples or questionnaires or both. Independent *t*-tests indicated that there were no significant differences between participants for whom post-treatment questionnaire and cortisol data were or were not available, in terms of age, duration of CFS, baseline fatigue (Chalder fatigue scale; [4]) or any of the pre-treatment main cortisol measures ($ts < 1.9$).

Procedure

The study was approved by the Institute of Psychiatry (King's College London) Ethics Committee, reference 011/00. Written informed consent was obtained from the young people and their parents. Questionnaire completion and saliva collection was undertaken at home. Participants were asked to collect the samples on a Saturday when they were able to wake up between 6:00 a.m. and 09:00 a.m. Samples were taken using untreated Salivettes. Participants were instructed to provide a sample of saliva immediately after waking, 15, 30, 45 and 60 min after awakening, then at 12:00, 16:00 and 20:00 hours. Standard collection instructions were given, e.g., not to eat or brush teeth in the hour prior to collection. Participants were asked to note the time they took the samples and what they had been doing the previous hour before each sample, including anything eaten or drunk. Participants not complying with the collection instructions were not included. Samples were kept in the refrigerator overnight before being returned to the hospital. Cortisol was measured for a second time at six months after the end of treatment, to allow time for consolidation of the treatment response and for any effects on the HPA axis to occur. The same saliva collection procedure was used at Time 2.

Treatment

Treatment consisted of telephone-based guided self-help (described in the Introduction). After face-to-face assessment, patients received a self-help manual and up to 6 fortnightly telephone sessions of 30 min. The primary clinical outcome was school attendance.

Clinical measures

School attendance, the primary clinical outcome, was calculated as a percentage of the time that they should be attending; hours at school and hours they should have attended were self-reported by the young person. Questionnaires completed were the Chalder Fatigue Scale [4], the Birleson Depression Inventory [1], the Spence Children's Anxiety