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Article *in* Journal of Affective Disorders · April 2020

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Research paper

Cortisol levels in chronic fatigue syndrome and atypical depression measured using hair and saliva specimens

Andres Herane-Vives[a,b,*], Andrew Papadopoulos[a], Valeria de Angel[a], Kia-Chong Chua[a], Lilian Soto[c], Trudie Chalder[a], Allan H Young[a], Anthony J Cleare[a]

[a] Centre for Affective Disorders, Department of Psychological Medicine, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, United Kingdom
[b] Institute of Cognitive Neuroscience. University College of London (UCL), London, United Kingdom
[c] Facultad de Medicina, Universidad de Chile, Chile

A B S T R A C T

Background: Several diagnostic criteria for major depressive disorder (MDE) overlap with those of Chronic Fatigue Syndrome (CFS). Furthermore, atypical MDE (A-MDE), a subtype of MDE characterised by profound fatigue and which has frequently been linked with CFS, exhibits similar low cortisol levels to CFS. However, this result has been only found in specimens designed for measuring acute cortisol levels. In this study, we measure cortisol levels in subjects with CFS and in subjects with A-MDE, without psychiatric comorbidity, using both hair and saliva specimens, to gain a measure of both short and long-term cortisol levels in these two conditions.

Methods: Hair cortisol concentration, representing the cortisol concentration of the previous three months, and salivary cortisol, measured at six time-points across one day and including the cortisol awakening response (CAR), post-awakening delta cortisol and the total daily output, were assessed in an age and gender matched group of 34 controls, 15 subjects with A-MDE and 17 with CFS.

Results: CFS (mean 92.2 nmol/l.h, s.d. 33.2 nmol/l.h) and A-MDE (mean 89.1 nmol/l.h, s.d. 22.6 nmol/l.h) subjects both showed lower cortisol total daily output in saliva (AUCg) in comparison to healthy controls (mean 125.5 nmol/l.h, s.d. 40.6 nmol/l.h). However, hair cortisol concentration was not lower than that of controls in either patient group. CFS and A-MDE did not differ from one another on any cortisol measures. CFS subjects reported fewer daily hassles and less severe psychic anxiety symptoms in comparison to A-MDE subjects (all $p < 0.05$). However, they did not differ in the severity of somatic anxiety symptoms. There was also no difference in the presence of overlapping symptoms such as fatigability and concentration/memory problems between A-MDE and CFS subjects.

Conclusion: Low levels of cortisol found using short-term measures of daily output may be transient, since cortisol levels were normal when a long-term measure (hair) was studied. This might be explained by a potential cortisol rhythm alteration. Although these disorders have their distinctive depressive and somatic features, they may from part of a wider group of Somatic Symptom Disorders (SSD), given the findings of the same pattern of cortisol secretion in both disorders and increased frequency of overlapping clinical features.

1. Introduction

Fatigue is a frequent symptom (20%) amongst patients seeking medical help. However, this tends to be transient, moderate and self-limiting (Afari and Buchwald, 2014). In Chronic Fatigue Syndrome (CFS) fatigue is long-lasting and disabling, with no readily demonstrable alternative organic explanation (Papadopoulos and Cleare, 2012).

The scientific debate in relation to the definition of CFS is continuous and at times controversial. CFS is not included within the most recent edition of the Diagnostic and Statistical Manual (DSM-5; American Psychiatric Association 2013), although might fit within the new category of Somatic Symptoms Disorder (SSD), which explicitly includes patients with "medically unexplained symptoms" (Dimsdale and Creed, 2010). For some authors, CFS has also been understood as part of a wider group of stress-related bodily disorders, which include fibromyalgia, lower back pain, irritable bowel syndrome, burn-out syndrome and atypical major depression (A-MDE) (Fries et al., 2005). This is supported by the observation of a number of shared characteristics between these conditions, including decreased cortisol (Heim et al., 2000).

A previous study compared acute (saliva) and chronic (hair) cortisol levels between A-MDE and non-atypical depression (NA-MDE). Results suggested that A-MDE may have more in common with SSD as defined by DSM-5 than with NA-MDE (Herane-Vives, 2018). This conclusion was in part based on the results showing a higher association between A-MDE and common environmental disturbances ("daily hassles"). According to the authors of the Hassles Scale, subjects experiencing a higher frequency of these common environmental disturbances are under increased risk of developing stress-related bodily disorders or

* Corresponding author at: Centre for Affective Disorders, Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, King's College London, 103, Denmark Hill, London, United Kingdom, SE5 8AF.
E-mail address: andres.herane@kcl.ac.uk (A. Herane-Vives).

https://doi.org/10.1016/j.jad.2020.01.146
Received 31 May 2019; Received in revised form 9 December 2019; Accepted 25 January 2020
Available online 29 January 2020
0165-0327/

SSD (Kanner et al., 1981). Moreover, Herane-Vives, 2018 also found that the prevalence of fatigability and concentration impairment symptoms – key features of SSDs and two of the diagnostic criteria for CFS (Fukuda et al., 1994) – was higher in A-MDE than NA-MDE. The final important finding of Herane-Vives, 2018 was the absence of hypercortisolaemia – a very consistent biological biomarker in major depression (Moica et al., 2016) – in both hair and saliva cortisol measures in A-MDE, but the presence of hypocortisolism in saliva measures, as has been found previously (Lamers et al., 2013).

Decreased cortisol has been a common finding in SSDs, although not all studies have found this. One possible explanation for this inconsistency is because of differing methodologies for assessing cortisol levels, and in particular the absence of studies using measures designed to measure longer-term accumulated cortisol levels. The use of hair sampling has the potential to overcome this issue.

There is some preliminary evidence to show that CFS shares several clinical and neurobiological features with A-MDE (Juruena and Cleare, 2007). However, it is unclear the extent to which these common features are related to CFS itself or might be confounded by the high comorbidity with depression. Rates of diagnosable psychiatric disorder, and depression in particular, are high in CFS: Skapinakis et al., 2003 and Field et al., 1997 for instance, found similar figures, showing that over 74% of the patients with CFS also had mainly depression or anxiety disorders, although other studies find lower rates (Matsuda and Matsui, 2009). Whilst mild hypocortisolism has been a relatively consistent finding in CFS, meta-analysis suggests that this finding is in fact most apparent in those with, rather than without, comorbid depression (Tak et al., 2011).

This study was designed to investigate cortisol levels using both short-term (saliva) and long term (hair) measures in a matched group of subjects with CFS, A-MDE, and healthy controls. The aim was to characterise these two disorders in terms of their acute and chronic cortisol secretion patterns. A detailed clinical comparison of these disorders was also planned. We hypothesised, based on recent results from Herane-Vives, 2018, that A-MDE and CFS subjects would share the same pattern of cortisol secretion: normal cortisol level in hair and decreased cortisol in saliva. In addition, with regards to clinical characteristics, we hypothesised that CFS and MDE-A would show similarities both in symptom patterns, focussing on those symptoms common to the definitions of MDE and CFS, and in the presence of common environmental disturbances.

2. Methods

2.1. Participants

Participants were recruited in the UK and Chile. CFS participants were recruited in the UK from general practitioner referrals to the Chronic Fatigue Syndrome Research Unit at King's College Hospital in Camberwell, South London. Patients included both local catchment area and tertiary referrals from the South of England. In Chile, CFS patients were referred from a group of qualified psychiatrists and rheumatologists. CFS participants were assessed by a psychiatrist in UK and a trained researcher in Chile according to a standardised assessment protocol for CFS (Sharpe et al., 1997). Depressed participants were recruited in the UK from public advertisements (Wise et al., 2016) and local psychological therapy services. Depressed participants in Chile originated from referrals by a group of qualified psychiatrists at the Clínica Psiquíatrica Universitaria of University of Chile and from public advertisements. All depressed participants were assessed by a psychiatrist in the UK and a trained researcher in Chile using the Mini International Neuropsychiatric Interview (Sheehan et al., 1998). Depressive and fatigue symptom ratings, evaluated on an independent set of patients, showed high inter-rater reliability [Intraclass Correlation Coefficient (ICC) = 0.96, $p < 0.05$].

Depressed patients were required to meet axis I DSM-IV criteria for a major depressive episode as part of either unipolar major depression or bipolar disorder, and to have ongoing depressive symptoms assessed using the 17-item Hamilton Depression Rating Scale (HAMD-17; Hamilton, 1960) with a score of ≥11. CFS patients were required to meet the most recent Centers for Disease Control (CDC) consensus criteria for CFS (Fukuda et al., 1994); all also satisfied alternative consensus criteria for CFS (Sharpe et al., 1991) and were assessed by a physician not to be experiencing fatigue secondary to another medical illness. All patients were medication free for ≥2 weeks (≥4 weeks for fluoxetine) and not receiving any psychological intervention at the time of the assessment. Patients were excluded if they reported any illicit substance use in the previous three months, had any unstable medical condition or were unable or unwilling to give hair, with a minimum hair length of 3 cm required. We also measured depression symptoms using the clinician-rated version of the Quick Inventory of Depressive Symptomatology, the QIDS-C (Rush et al., 2003) which, unlike the HAMD-17, can assess reversed neurovegetative features (increased sleep and appetite/weight). Healthy controls were recruited in the UK and Chile. Controls were required to have no current or past psychiatric diagnoses and no history of psychiatric illness in first-degree relatives.

The research was approved by the relevant local ethics committees in the UK and Chile and written, informed consent was obtained from each participant in both countries. All participants were compensated for their time in taking part in the research.

To investigate the relative frequency of those MDE symptoms (fatigability and impaired concentration) that are shared between SSDs such as CFS (Fukuda et al., 1994) and fibromyalgia (Leavitt et al., 2002), we created a “Concentration and Fatigue Factor” from the QIDS-C. We decided to use that scale, instead of the HAMD-17, because it has two items that specifically enquire for these symptoms. It also gives more weight to these items allowing greater distinction between levels of the symptoms that are present (Cusin et al., 2010). We also investigated anxiety symptoms through an “Anxiety Factor” that was constructed using the anxiety items of the HAMD-17 (Levitt et al., 1993), whilst specific psychic and somatic anxiety symptoms (Rassaby and Paykel, 1979) were studied using “Psychic Anxiety” and “Somatic Anxiety” factors, respectively, from their corresponding HAMD-17 items.

The frequency and severity of the most common day-to-day environmental disturbances during the month prior to study enrolment was measured using the Hassles Scale (Kanner et al., 1981) and the severity of more unusual environmental factors, such as major life events during the three months prior to the study, were assessed using the Recent Life Changes Questionnaire (RLCQ; Miller and Rahe, 1997). Early life trauma was assessed using the Childhood Trauma Questionnaire (CTQ; Bernstein et al., 1994). All psychometric scales had been previously validated in Spanish. The presence of an identifiable neurobiological response to environmental disturbances or life events was also measured. Due to the lack of an objective and agreed definition for stress, a recent proposed definition for this term was used, in which stress may be understood as the reaction to an event – biological or psychological – that causes a significant cortisol variation in hair (Herane Vives et al., 2015).

2.2. Biological specimens

2.2.1. Hair specimens

A trained practitioner collected hair samples of suitable participants. The presence and frequency of any biological confounders and procedures potentially affecting hair cortisol levels were measured, including cosmetic treatments (dyeing, bleaching, permanent straightening or waving) and frequency of hair washing. Collection procedure and analyses for each participant were standardised according to a strict protocol to collect approximately 3 months of hair growth equivalent to 3-month retrospective assessment of endogenous cortisol production. Cortisol levels were determined using a commercially

available competitive ELISA (Salimetrics LLC, USA) and the results expressed in picograms of cortisol per milligram of hair (pg/mg). All hair samples were analysed at Salimetrics Laboratory, Cambridge, UK (www.salimetrics.com) (Albermann et al., 2012) (See supplementary material for procedural details).

2.2.2. Saliva specimens

Saliva samples collection was taken at the time of the baseline assessment on a weekday Tuesday to Friday following hair sampling. Subjects were asked to provide six saliva samples using plain salivettes (Sarstedt, Leicester, UK) as per the protocol of Roberts et al., 2004, with instructions given in writing at the time of the assessment. Samples were provided at awakening, 30 min and 60 min after awakening, and at 12:00, 16:00 and 20:00. Analyses of saliva cortisol concentrations were carried out in the Affective Disorders Laboratory at the Bethlem Royal Hospital, London UK. The area under the curve with respect to ground (AUCg) was used for calculating the total daily cortisol output using all six samples. Two measures of cortisol reactivity in saliva were analysed in this study: the cortisol awakening response (CAR) and the delta post-awakening cortisol. The CAR was calculated as the area under the curve with respect to increase (AUCi) using the first three morning saliva samples collected over a one-hour period. The delta post-awakening cortisol was calculated as the difference between cortisol measured at awakening and the sample taken at 30-minutes. All measures were calculated in nanomoles per litre (nmol/l.h) (see Supplementary material for procedural details).

2.3. Subjects

15 A-MDE subjects (4 males, 11 female) and 17 CFS subjects (4 males, 13 female) were matched with a control group of 34 subjects (9 males, 25 female). Mean ages ± standard deviation (s.d.) were 41.1 ± 12.6 years in the CFS group, 35.5 ± 8.2 years in the A-MDE group and 35.2 ± 8.1 years in the control group ($p = 0.11$) (see Table 1 for demographic features). A-MDE subjects had been included in a previous report comparing atypical and non-atypical subtypes of depression (Herane-Vives, 2018). This sudy had assessed cortisol levels, using hair and saliva specimens, in a larger A-MDE sample (27) who were compared with 44 patients with non-atypical MDE and 40 controls (Herane-Vives, 2018). However, as part of the present study, we had to reduce the number of A-MDE and controls in order to match CFS participants as closely as possible for age, sex and body mass index. Since the group of A-MDE and control participants of that previous study were significantly thinner and younger than the CFS group, a number of them with those physical and demographic features were randomly selected and excluded from the present analysis.

2.4. Statistical analysis

Demographics, clinical features and questionnaire measurements were compared with one-way ANOVA or *t*-test for continuous variables and Chi-square or Fisher's exact test for categorical variables. Differences in cortisol levels in hair and saliva measures amongst CFS, A-MDE and healthy controls were tested using ANOVA with Bonferroni *post-hoc* test. The study groups were frequency matched in age, BMI and sex.

3. Results

3.1. Clinical characterisation

There were no differences across the three groups in terms of age, sex, BMI, waist circumference, frequency of hair washing, use of cosmetic treatment, phase of the menstrual cycle, proportion taking contraceptive pills, and alcohol and tobacco consumption (all *p*-values > 0.05) (Table 1)

3.2. Psychometric results

Whilst A-MDE subjects had a moderate depressive episode according to the HAMD-17 (mean: 16.1), this episode was severe according to the QIDS-C (mean: 19.3). A-MDE and CFS subjects did not differ between them in the severity of total anxiety symptoms ($p = 0.16$) on the HAMD-17 scale. However, they did differ when psychic and somatic anxiety symptoms were separately analysed. Indeed, while they did not again show a significant difference in the severity of somatic anxiety symptoms ($p = 0.16$), psychic anxiety symptoms were more severe in A-MDE in comparison to CFS ($p < 0.01$). A-MDE and CFS patients did not differ in the frequency of concentration & fatigue symptoms ($p > 0.05$) (Table 1).

A-MDE subjects had experienced more early life trauma measurable through the CTQ than controls ($p < 0.01$) but not than CFS subjects ($p = 0.16$); CFS and control subjects did not differ between themselves ($p = 0.21$). Control subjects had experienced fewer current life events than A-MDE ($p = 0.02$) but not than CFS subjects ($p = 0.07$). There were also no differences between CFS and A-MDE subjects in terms of

Table 1
Group characteristics of chronic fatigue syndrome (CFS), atypical major depression (A-MDE) and control subjects.

Demographic & Health Indicators	Control ($N = 34$)	A-MDE‡ ($N = 15$)	CFS ($N = 17$)	Overall p-value	*Post Hoc* test
Age (years); mean (s.d.)	35.2 (8.1)	35.5 (8.2)	41.1 (12.6)	0.11	∞
Female; n (%)	23 (71.9)	11 (73.3)	13 (76.5)	0.94	∞
Single; n (%)	13 (40,6)	5 (33.3)	7 (41.2)	0.87	∞
Unemployment (yes); n (%)	1 (3.1)	2 (13.3)	1 (5.9)	0.34	∞
Tobacco (yes); n (%)	5 (15.6)	4 (26.7)	1 (5.9)	0.27	∞
Alcohol (yes); n (%)	27 (84.4)	11 (73,3)	11 (68.8)	0.28	∞
BMI (Kg); mean (s.d)	24.9 (3.7)	27.4 (5.2)	26.9 (5.9)	0.15	∞
Waist circumference (cm); mean (s.d.)	83.1 (10.8)	90.4 (14.8)	92.9 (21.4)	0.09	∞
Follicular phase; n (%)	15 (60)	7 (70)	11 (91.7)	0.13	∞
Length of the episode (months); mean (s.d.)	0 (0)	7.3 (5.9)	62.7 (58.8)	<0.0001*	B,C
Medical comorbidities; n (%)	2 (6.3)	4 (26.7)	7 (41.9)	<0.01*	B
Number of subjects taking:					
Medications; n (%)	13 (40.6)	11 (73.3)	7 (41.2)	0.08	∞
Contraceptive pills; n (%)	7 (21.9)	0 (0)	3 (17.7)	0.16	∞
Hair variables:					
Frequency hair washing per week; mean (s.d)	4.6 (1.7)	3.8 (2.4)	3.4 (2.1)	0.15	∞
Cosmetic treatment (yes); n (%)∫	10 (31.3)	3 (23.1)	9 (52.9)	0.22	∞

‡: Subtypes based on ADDS scale.∫ : dyeing, bleaching, permanent straightening or waving. *A*:Controls different from A-MDE. *B*:Controls different from CFS. *C*: A-MDE different from CFS. ∞:no differences.*: P-value significant at $p < 0.05$. s.d.: standard deviation.

Table 2
Psychometric results in chronic fatigue syndrome (CFS), atypical major depression (A-MDE) and control subjects.

Depressive symptoms	Control	A-MDE‡	CFS	Overall p-value	*Post Hoc* test
HAMD-17; mean (s.d.)	0.3 (1.0)	16.1 (3.6)	5.9 (5.6)	<0.0001*	A, B, C
HAMD-21; mean (s.d.)	0.3 (1.1)	18.1 (4.9)	6.8 (7.8)	<0.0001*	A, B, C
QIDS-C; mean (s.d.)	0.5 (1.5)	19.2 (4.5)	6 (5.7)	<0.0001*	A, B, C
Concentration & fatigue factor; mean (s.d.)	0.09 (0.4)	4 (0.8)	3.7 (1.7)	<0.0001*	A, B
Anxiety factor, total; mean (s.d.)Φ	0 (0)	4.4 (2.8)	2.9 (2.8)	<0.0001*	A, B
Anxiety factor, psychic; mean (s.d.)Φ	0.1 (0.3)	1.5 (0.9)	0.5 (0.7)	<0.0001*	A, B, C
Anxiety factor, somatic; mean, (s.d.)Φ	0 (0)	2.2 (1.4)	1.5 (1.4)	<0.0001*	A, B
Environmental factors:					
Childhood trauma (yes); n (%)	6 (18.8)	9 (60.0)	6 (35.3)	0.01*	A
Life events score (LCU); mean (s.d.)§	90.1 (170.0)	318.6 (332.3)	266.8 (345.0)	0.01*	A
Subjects with severe life events; n (%)§	2 (6.3)	9 (60.0)	7 (41.2)	<0.0001**	A, B
Hassles score; mean (s.d.)¥	18.0 (20.4)	123.7 (112.0)	66.4 (53.9)	<0.0001*	A, B, C
Subjects with severe hassles; n (%)¥	1 (3.1)	8 (53.3)	6 (35.3)	<0.0001**	A, B

‡: Subtypes based on ADDS scale. Φ: Anxiety factors were calculated using anxiety items of HAMD-17 scale. ¥: Hassles during the last month. §: Life events over prior 3 months calculated as Life Change Units (LCU); severe life events burden defined as a score >200 LCU. *: P-value significant at 0.05 level. *A*: Controls different from A-MDE. *B*: Controls different from CFS. *C*: A-MDE different from CFS. s.d.: standard deviation

the number of current life events ($p = 1$). Environmental disturbances in the form of daily hassles were less common and less severe in controls compared both to A-MDE (both $p < 0.01$) and to CFS subjects ($p = 0.04$ and $p < 0.01$, respectively). These daily hassles were more common in A-MDE than in CFS subjects ($p = 0.03$) but not more severe ($p = 0.37$). See Table 2 for full psychometric results.

3.3. Hair cortisol results

Hair cortisol measurements were obtained for 98.4% of the participants; one participant's hair sample was not able to be used. There were no significant differences in hair cortisol concentration across the three groups ($p = 0.91$). Hair cortisol concentration (mean (s.d.)) were: 8.7 (4.0) pg/mg hair in the control group, 8.1 (5.8) pg/mg hair in A-MDE and 8.4 (4.7) pg/mg hair in CFS.

3.4. Saliva cortisol results

Saliva cortisol levels were available in 81.3% of the subjects because of a failure to return all samples and/or a significant violation of the saliva sampling protocol. A graph with the means of daily salivary cortisol levels over six time points by groups is shown in Fig. 1. There was significantly lower daily cortisol output in both A-MDE and CFS groups in comparison to controls ($p < 0.01$) (Fig. 2). AUCg values (mean (s.d.)) were: 125.5 (40.6) nmol/l.h in the control group, 89.1 (22.6) nmol/l.h in A-MDE and 92.2 (33.2) nmol/l.h in CFS. This is illustrated in Fig. 2. There were no significant differences in other saliva measures (CAR or delta) across the three groups. CAR values (mean (s.d.)) were: 1.6 (8.2) nmol/l.h in the control group, 0.3 (4.7) nmol/l.h in A-MDE and 0.9 (5.7) nmol/l.h in CFS ($p = 0.83$). Delta cortisol values (mean (s.d.)) were: 2.2 (7.2) nmol/l.h in the control group, 1.8 (6.1) nmol/l.h in A-MDE and 2.7 (9.2) nmol/l.h in CFS ($p = 0.94$).

4. Discussion

These results showed a low total daily cortisol output but normal hair cortisol concentration in both A-MDE and CFS subjects in comparison to healthy participants, but no differences in either measure between CFS and A-MDE. CFS and A-MDE subjects did not differ in the frequency of fatigue and memory/concentration symptoms that are common to both MDE and CFS standard case definitions. However, CFS subjects had a significantly lower number of daily environmental disturbances and less severe psychic anxiety symptoms in comparison to A-MDE subjects.

Our findings suggest neurobiological overlap between A-MDE and CFS when cortisol levels are considered since they showed the same

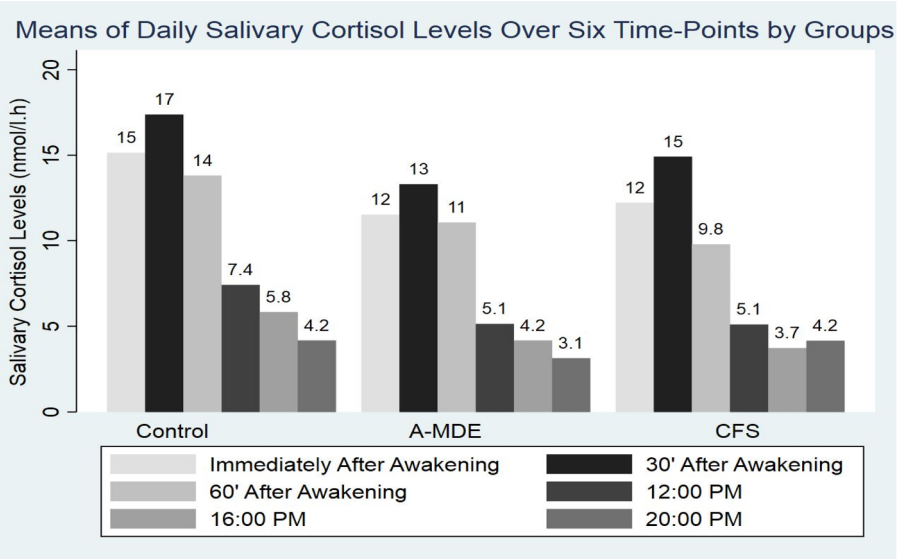

Fig. 1. Mean values of salivary cortisol over six time points in Control, A-MDE and CFS Groups.

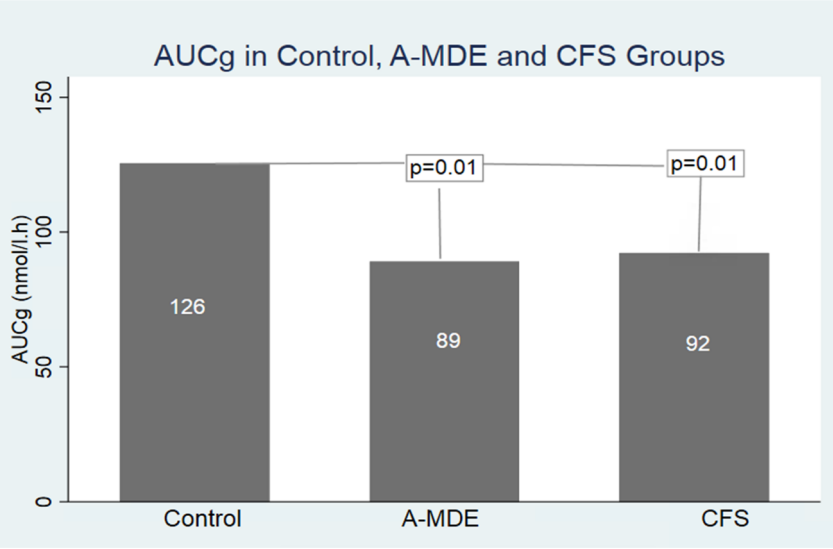

Fig. 2. Total daily salivary cortisol output measured as area under the curve with respect to ground (AUCg) in Control, A-MDE and CFS Groups.

patterns of cortisol secretion in both hair and saliva measures. Of note is that in both conditions there is a reduction in a short-term measure of cortisol output in saliva, but no change in a long-term measure in hair. We could speculate that these two findings could be reconciled if subjects with these disorders experience episodic periods of hypercortisolaemia – perhaps at night time, on some days, or in response to stressful triggers – which, coupled with a more general decreased cortisol as we found in saliva, would then average out to normal levels of cortisol accumulation in hair. This might suggest that both disorders have a cortisol rhythm alteration. However, the measure of acute cortisol reactivity that we did measure – the CAR and post-awakening delta cortisol – did not differentiate these two conditions from each other or controls. Thus, it may be that other more sustained measures of hyperreactivity are involved, which would require confirmation in future studies.

Erratic patterns of cortisol secretion have previously been described in other conditions. For example, in a condition called as transient generalized glucocorticoid hypersensitivity (Nicolaides et al., 2015; Krysiak and Okopien, 2012) subjects can present with clinical manifestations of Cushing's syndrome, such as high blood pressure and diabetes, but show low cortisol levels when using acute measures such as saliva and blood (Nicolaides et al., 2015; Iida et al., 1990; Krysiak and Okopien, 2012). Such a pattern could be explained by increased tissue sensitivity to glucocorticoids and compensatory hypoactivation of the hypothalamic pituitary adrenal axis (Nicolaides et al., 2015).

Furthermore, heightened cortisol reactivity to stressors has been previously found in both A-MDE and CFS. For instance, O'Keane et al. (2005) found that after a corticotropin releasing hormone challenge, a situation that emulates stressful situations, subjects with atypical depression had higher levels of corticotropin (ACTH) than controls. Similarly, subjects with CFS showed a heightened salivary cortisol response to the insulin tolerance test, although not to the Trier Social Test or a standardized exercise test (Gaab et al., 2002). Against this, other studies using measures of reactivity such as the CAR or the corticotropin releasing hormone test have not shown increases in CFS (Papadopoulos and Cleare, 2012). Direct observation of periods of heightened cortisol release would be needed to confirm such a pattern is present.

The exploratory comparison of concentration impairment and fatigability symptoms showed no differences between CFS and A-MDE subjects. This result is in line with our preliminary study comparing A-MDE and NA-MDE, which showed that these symptoms were more frequent in A-MDE. This result adds an overlapping pattern of clinical symptoms to the neurobiological findings, further strengthening the link between A-MDE, stress related disorders and CFS. There were, however, significant symptom differences, including not only the expected difference in depression severity, but also higher levels of psychic anxiety in A-MDE. On the other hand, the somatic component of CFS was also reinforced, after observing that CFS patients did not differ in the severity of somatic anxiety symptoms in comparison to A-MDE, conversely to those psychic anxiety symptoms that were more severe amongst A-MDE subjects.

Contrary to the idea that stress plays a central role in A-MDE and CFS (Heim et al., 2000), our data suggests that their shared clinical and neurobiological features may not be explained by environmental factors. First of all, although there was an association with several environmental factors, none of them qualified as stressors, according to our proposed definition (Herane Vives et al., 2015). Furthermore, CFS subjects had significantly fewer numbers of daily hassles than A-MDE subjects, which was the specific type of environmental factor that we found was significantly more associated with A-MDE than with other forms of depression. In addition to this, other environmental factors, such as early life trauma, were significantly less frequent (35.3%) in this sample of CFS than previous studies have shown (for example 63% in Heim et al., 2006). In this context, Georgiades et al., 2003 (2003) have provided evidence for a possible role of central nervous system mechanisms in fatigue disorders.

Finally, it is possible to speculate that childhood trauma and daily environmental disturbances may be risk factors for developing comorbid depression in patients with CFS. Moreover, not only might environmental factors have a role in the association between CFS and comorbid depression, but also in the degree of decreased cortisol that these subjects may present. Tak et al., 2011, for instance, showed that subjects with CFS and comorbid depression had a deeper degree of decreased cortisol than those with CFS alone. Gracely and Schweinhardt (2015) described how childhood trauma is associated with both hypercortisolism and SSD, such as fibromyalgia, and comorbidities such as depression can also contribute to different HPA-axis dysfunctions. Moreover, some authors have found that low cortisol in CFS is associated with a poorer response to Cognitive Behavioural Therapy (CBT) (Roberts et al., 2010).

Other than the lower rates of daily stressors in CFS, CFS and A-MDE present similarities in three key characteristics. First, they show no difference in the occurrence of fatigue and memory/concentration symptoms, both of which are defined features of somatic symptom

disorders, CFS and A-MDE (Fukuda et al., 1994; Leavitt et al., 2002; American Psychiatric Association 2013). Second, both disorders show lowered daily salivary cortisol output; this is especially relevant since it has been suggested that decreased cortisol is a common neurobiological feature across the spectrum of SSDs (Griep et al., 1998; Roberts et al., 2004; Pruessner et al., 1999). Finally, hair cortisol and cortisol awakening responses were similar and did not differ from controls. These results may provide additional support for the view that A-MDE may be a subtype of SSD with a mood component rather than primarily an affective disorder.

4.1. Limitations and future directions

4.1.1. Limitations

Apart from the modest sample size, there are still some uncertainties in relation to the reliability of hair specimens for measuring accumulated cortisol levels. The role of the wash-out effect and sweat contamination is not entirely clear. Future well-designed hair studies may corroborate the role of these possible covariates. The methodology for assessing hair cortisol may be important. All hair cortisol studies, regardless of the hair cortisol extraction protocol used, have found significantly lower hair cortisol concentration in comparison to salivary cortisol levels. However, there are some differences. Thus, Balagova and Jezova (2018) used an increased volume of methanol for extracting cortisol and decreased the speed and duration of hair pulverization; they found a lower variability and higher cortisol concentrations compared to the method used by Xiang et al. (2016). We used a different protocol (Albermann et al., 2012), but our protocol's parameters were more similar to those of Xiang et al. (2016) than the Balagova and Jezova (2018) (see supplementary material). Therefore, future studies should pay more attention to these points with the aim for obtaining more accurate and comparable hair cortisol results.

Although the 1994 Fukuda et al. CDC criteria that we used for the diagnosis of our CFS patients remain the most widely used and validated in the literature, they are consensus case definitions for clinical and research purposes. There is no diagnostic test for CFS and other proposed but less widely used or validated case definitions exist (Brurberg et al., 2014). The discrepancy in depressive episode severity between the two depression scales (QIDS-C and HAMD-17) may be explained by the fact that one of the main limitations of the HAMD-17 is that it fails to recognise all depressive domains, in particular reversed neurovegetative symptoms (Cusin et al., 2010), a key feature in A-MDE. The RCLQ scale was adapted to cover the 3 months corresponding to the period of hair cortisol accumulation; however, the Hassles Scale did not cover the same period. It was also not possible to differentiate the effect of severe stressors on hair cortisol concentration from that of the disorder itself, another potential confounding factor.

Fatigue and memory symptoms were not measured with a specific scale designed for these symptoms. Instead, an exploratory analysis was used which incorporated a specific factor for measuring these symptoms. This is a potential limitation to our assessment of fatigue symptoms.

Finally, the sample size was modest, and although sufficient to detect changes in total cortisol output, may not have been as sensitive to smaller changes in the cortisol awakening response. We note that both CFS and A-MDE groups had numerically lower CAR values, and that a previous study which did find a lowered CAR in CFS had significantly higher number of patients (Roberts et al., 2004).

4.1.2. Future directions

The use of antidepressants has not shown favourable outcomes in CFS (Afari and Buchwald, 2014) and subjects with atypical depression show a worse response to the use of standard antidepressants in comparison to subjects with classic subtypes of depression (Thase, 2009). If future studies confirm the presence of a cortisol rhythm alteration in these disorders, and that cortisol has a pathophysiological role rather than only being epiphenomenological, the development of a drug with cortisol stabilization properties may become a valuable alternative to explore.

Certain kinds of specific physical and multidimensional treatments (e.g. cognitive and behavioural interventions), have shown positive results in CFS patients (Castell et al., 2011; White et al., 2011; Chalder et al., 2012; Afari and Buchwald 2014; Whiting et al., 2001) and are recommended by the National Institute for Health and Care Exellence (NICE 2007). However, they have not been specifically studied in subjects with A-MDE. Finally, the combination of acute and chronic cortisol measures may provide additional information in the development of a future stratified medical practice specifically designed for providing individual solutions for each patient rather than a standardised treatment for all.

5. Conclusion

These results suggest that A-MDE and CFS subjects have very similar neurobiological features in terms of cortisol, with reduced daily salivary cortisol output but normal accumulated cortisol levels in hair. This pattern might be accounted for by a mid- to long-term cortisol rhythm alteration. Although these two disorders have their own distinctive features, they also share important clinical features, such as fatigue and concentration/memory symptoms. Given also the differences between A-MDE and more classical subtypes of depression (Herane-Vives, 2018), A-MDE may be better characterised as a subtype of SSD with a mood component rather than primarily an affective disorder.

Author statement contributors

Andres Herane Vives designed and conducted the research. He collected, managed, analysed and interpreted the data. He wrote, prepared and reviewed the manuscript.

Andrew Papadopoulos also designed the research. He supervised the cortisol analyses. He proof-read and reviewed the manuscript.

Valeria De Angel conducted the research in Chile. She collected and managed the data. She proof-read and reviewed the manuscript.

Kia-Chong Chua provided statistical analysis of the data. He proof-read and reviewed the manuscript.

Lilian Soto also conducted the research in Chile. She proof-read and reviewed the manuscript.

Trudie Chalder also designed the research. She interpreted the data. She proof-read and reviewed the manuscript.

Allan Hunter Young interpreted the data. He proof-read and reviewed the manuscript.

Anthony Cleare also designed the research. He interpreted the data, and proof-read and reviewed the manuscript.

All authors approved the final manuscript and the decision to submit for publication.

The funders had no role in the conducting of the research; collection, management, and analysis of the data; preparation, review and approval of the manuscript; and in the decision to submit the manuscript for publication.

Funding and disclosures

This research was funded by departmental funds generated by AJC and AHY, by charity and departmental funds obtained by AHV and start up funds from the Academy of Medical Sciences to DA (Ref. AMS-SGCL8). AHV was supported by a Chilean Bicentennial Fund Scholarship from the Bicentennial Fund for Human Capital Development (Becas Chile). AJC and AHY are supported by the NIHR Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. This study represents independent research part funded by the NIHR/Wellcome Trust, King's Clinical Research Facility and the NIHR Biomedical Research Centre at

South London and Maudsley NHS Foundation Trust and King's College London (UK). The views expressed are those of the author(s) and not necessarily those of the NHS.

Declaration of Competing Interest

AJC has in the last three years received honoraria for speaking from Lundbeck, honoraria for consulting from Allergan, Janssen, Lundbeck and Livanova. conference attendance support from Janssen, and research grant support from the Medical Research Council (UK), Wellcome Trust (UK), the National Institute for Health Research (UK) and Protexin Probiotics International Ltd. AHY has given paid lectures and sits on advisory boards for all major pharmaceutical companies with drugs used in affective and related disorders. DA has received travel grants from Janssen-Cilag and Servier. No other disclosures were reported.

Acknowledgements

We are grateful to Mrs Irene Papadopoulos for performing the saliva cortisol immunoassays. The authors would like to thank the staff of the NIHR/Wellcome Trust Clinical Research Facility at King's College Hospital and the Clínica Psiquíatrica Universitaria and OAIC of University of Chile for their support in the conduct of the study.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2020.01.146.

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