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Low hair cortisol concentrations in obsessive compulsive disorder: A cross-sectional study

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ABSTRACT

Recent findings have highlighted the association between changes in the activity of the HPA axis, primarily its end-hormone, cortisol and OCD. However, to date, cortisol levels of OCD patients have been assessed mainly in body fluids, such as serum, saliva or urine, frequently leading to ambiguous results because of their inherent lack of stability. The aim of this study was to investigate time-integrated levels of stress exposure in 32 OCD patients and 32 sex and age-matched healthy controls by measuring endogenous cortisol in hair segments reflecting the last 3 months preceding hair collection. Psychometric parameters, including BDI, FQ, STAI, PSS and ECQ-R, were obtained in all participants; Y-BOCS was performed in the OCD patients. The OCD patients exhibited significantly higher scores in all psychometric instruments administered and lower hair cortisol concentrations than the healthy controls ($p = 0.001$, $r = 0.41$). No significant correlations were found between the HCC and the Y-BOCS total scores. After having sorted OCD patients into subtypes, according to the nature of their symptomatology, the "washers/cleaners" category showed the lowest HCC (compared to the "checking/harming", "ordering/symmetry" and "sexual/religious obsessions" categories). The novel finding of chronic low cortisol secretion in OCD patients could be attributed to a possible down-regulation of the HPA axis, as an adaptive response to chronic stress exposure. Given that the OCD subtypes reflect the great heterogeneity in the OCD spectrum, studies with larger samples should extend the investigation of HCC in patients with distinctive symptomatology, so as to develop a basis for better neuroendocrine profiling and understanding of the pathophysiology of OCD. Further work is needed in exploring HPA axis' activity over the natural course and treatments of the disorder.

1. Introduction

Obsessive compulsive disorder (OCD) is a chronic and debilitating psychiatric disorder with an estimated lifetime prevalence of 2.3%. It rarely presents alone, carrying a 90% comorbidity with other disorders, such as anxiety disorders (75.8%), mood disorders (63.3%), impulse-control disorders (55.9%), and substance use disorders (38.6%) (Ruscio et al., 2010). OCD is characterized by *obsessions*, which are recurrent, intrusive and persistent thoughts, images or impulses that cause anxiety or disgust, and *compulsions,* repetitive behaviors or mental acts performed in order to alleviate distress and/or avoid feared consequences (APA, 2013). It has a young mean age of onset at about 24 years, with an

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even earlier onset in countries with a higher Human Development Index (de Lijster et al., 2017). OCD is frequently under-diagnosed, thus, diagnosis may be severely delayed (Rintala et al., 2017).

In recent years, there has been a growing interest in the pathophysiology of OCD. Dysfunctions in orbitofrontal cortex and striatal circuits constitute the most common findings (Abramovitch et al., 2015). In both animal and human studies these circuits promote habitual behavior and are reportedly highly sensitive to prolonged stress, an effect mediated by stress hormones (Morgado et al., 2013). Stress may decrease prefrontal cortex control over goal-directed behavior, through decreased effects on the caudate and increased effects on the putamen, and thus, increasing habitual behavior (Adams et al., 2018; Gillan et al., 2016). Moreover, studies have indicated that stressful events or conditions, such as increased responsibility, major losses and exposure to traumatic events may antedate onset of OCD (Brander et al., 2016; Fontenelle et al., 2011). An increase in OCD symptoms under stressful situations may then itself cause considerable distress or impairment in social, occupational, or other significant areas of functioning (APA, 2013; Drubach, 2015). Indeed, patients with OCD have significant more stress than healthy controls, and this leads to a decreased quality of life for them, their caregivers and/or their families (Faravelli et al., 2012; Hollander et al., 2016).

Taken together, these findings point towards a role for the hypothalamic-pituitary-adrenal (HPA) axis in the pathophysiology of OCD. Dysregulation of the HPA axis has been associated with all forms of stress and psychopathologic symptomatology (Staufenbiel et al., 2013). Specifically, in OCD, elevated levels of cortisol have been observed (Furtado and Katzman, 2015). Fluitman and colleagues found that OCD patients showed significantly higher serum cortisol levels than controls ($p = 0.015$), both at baseline and at all other time points, when participants confront aversive situations (Fluitman et al., 2010). In another study, OCD symptoms correlated with basal serum cortisol and perceived stress levels, indicating that increased levels of perceived stress in OCD patients were associated with elevated serum cortisol (Morgado et al., 2013). However, no significant correlation ($r = 0.222$, $p = 0.376$) was observed between serum cortisol levels and severity of OCD, as assessed by the Yale-Brown Scale (Y-BOCS). In another study by Kluge et al. (2007), patients showed significantly higher nocturnal plasma cortisol levels than controls, confirming an elevated activity of the HPA axis in OCD patients (Kluge et al., 2007). Thus, these researchers suggested that the increased HPA axis activation plays an important role in the pathophysiology of OCD, contributing to sensitization of the neural circuits involved in this disorder. Finally, in a pilot study by Lord et al. women suffering from OCD symptoms during the postpartum period had significantly higher afternoon salivary cortisol levels than controls, while they reported increased levels of stress and anxiety in a physiological stress test (cold pressor test) (Lord et al., 2011). These results are in line with the aforementioned findings indicating a hyperactive HPA axis in OCD patients and may indicate a relation to hormonal sensitivity changes as found in the postpartum. Interestingly, Kawano et al. (2013) found no differences in salivary cortisol concentrations between patients with OCD and controls before or after electrical stimulation. Surprisingly, patients demonstrated no response to physiological stressors, despite their reports of high anxiety during the procedure (Kawano et al., 2013).

Until now, cortisol levels in OCD patients have been assessed in body fluids, such as serum, saliva or urine. Yet, these measures reflect circulating cortisol, providing data about the HPA axis activity or reactivity over periods of time no longer than 48 h (urine) (Andrade et al., 2016). Hence, such measurements by these methods lack longer-term stability, considering that salivary, serum/plasma and urinary cortisol levels can be affected by several minute-to-minute, hour-to-hour and day-to-day factors, for instance spontaneous secretory pulsatility, acute stress, circadian rhythmicity, day of the menstrual cycle etc. (Aas et al., 2019; Wester and van Rossum, 2015). The majority of studies evaluate HPA axis functioning by using saliva, serum/plasma or urine, have led to contradictory results. Also, the above measurements cannot detect extended changes in allostatic stress load. On the other hand, measuring cortisol concentrations in hair has attracted considerable interest thanks to its ability to evaluate long-term circulating cortisol levels, retrospectively. As hair grows approximately 1 cm per month, hair analysis allows assessing cumulative time-integrated cortisol exposure (Manenschijn et al., 2012; Staufenbiel et al., 2015). In other words, measuring cortisol in hair provides the advantage of having a thorough picture of the mean HPA axis activity levels during the chosen extended period, amounting to months. Additional advantages of this method are its non-invasive character, the easy storage of samples at room temperature, and the relatively small quantity of sample required (Russell et al., 2012; Stalder and Kirschbaum, 2012; Stavropoulos et al., 2017).

The principal aim of this study was to explore long-term endogenous cortisol exposure of tissues of OCD patients compared to that of healthy controls through hair segments reflecting the 3 months preceding the sample collection. To our knowledge, this has not been studied in OCD to date. Additionally, we investigated whether the baseline activity of the HPA axis of OCD patients is associated with symptom severity, as assessed by Y-BOCS, or other parameters of the disorder, such as depressive symptoms, anxiety, perceived stress, fear symptoms and attachment type.

2. Methods

2.1. Study sample

The study was approved by the Ethics Committee of Eginition Hospital in Athens, Greece, as consistent with the Declaration of Helsinki. The total sample of this cross-sectional study consisted of 32 adult outpatients with OCD and 32 healthy sex- and age-matched controls, described in detail below.

Participants with OCD were recruited from the Outpatient Specialty Clinic for Obsessive Compulsive Disorder and Behavioral Therapy in the Department of Psychiatry of the Medical School of the National and Kapodistrian University of Athens at Eginition Hospital between October 2017 and September 2019. The clinic serves a diverse patient population seeking help for a wide range of mental disorders, commonly referred to the clinic by other mental health professionals. Inclusion criteria were i) OCD diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders - 5th Edition (DSM-V) criteria and ii) no medication therapy or stable medication regimen for, at least, six months prior to sampling. Exclusion criteria included comorbidity with psychotic disorders, personality disorders, substance or alcohol abuse, suicidal intent or therapy with glucocorticoids. Healthy controls were recruited from the community, namely existing social networks and authors' personal contacts. Afterwards, they were screened and clinically evaluated by the head psychiatrist of the Specialty Clinic[a], using the Mini-International Neuropsychiatric Interview (M.I.N.I.), for exclusion of any current or past psychiatric disorder. In general, all participants were considered eligible if they had not taken psychoactive medications or glucocorticoids 6 months prior to their inclusion in the study and if they had had at least 3 cm of hair growth at the posterior vertex area.

2.2. Procedure

Written informed consent was obtained from all the participants after being provided precise and comprehensive information about the study aims and procedures. Patients were diagnosed by the head psychiatrist of the Clinic (I.M.), as having primary OCD, according to the M.I.N.I. criteria (Sheehan et al., 1998) and extensive clinical interview. The type and severity of the symptoms of OCD patients were assessed by the head psychologist of the Clinic (T.C.), using Y-BOCS (Koumantanou et al., 2012). Both groups completed a questionnaire concerning hair color, weekly frequency of hair wash, hair treatment

(dyeing/bleaching/permanent waving or straightening) and use of hair products (e.g. wax, gel or hair spray) (Davenport et al., 2006). Afterwards, hair samples were collected and psychometric measures were administered to the participants (for details, see below).

2.3. Collection and preparation of hair samples

According to the established methodology (Stalder and Kirschbaum, 2012; Wester and van Rossum, 2015), approximately 100–150 hair strands were obtained from the posterior vertex. Hair samples were cut off as near to the scalp as possible and the hair was taped on a piece of paper at the scalp side end. The date and the code of the participant were then marked. Samples were kept at room temperature until the day of the analysis.

The hair sample was weighed (minimum of 25 and maximum of 30 mg of hair/sample) and placed in homogenization tubes (Precellys Lysing tubes) along with beads (2 large and 7 small beads for each sample). The test tubes were then placed in a homogenizer Minilys (Bertin Instruments) to lyse the hair. Each sample was centrifuged at least 7 times (60 s in 5000 rpm). When powder-form was ready, 1 ml of methanol was added in each sample and the tubes were put in a shaker for 16 h. Later, the tubes were centrifuged in 13000 rpm for 10 min, the supernatant was then placed in glass tubes and methanol was allowed to evaporate. Finally, samples were diluted/reconstituted in 100 μL phosphate-buffered saline (pH 8.0, 1xPBS) and were vigorously vortexed for 1 ½ minute, until they were well mixed for the analysis.

Eventually, samples were measured by using automated electrochemiluminescence immunoassay "ECLIA" via an automated analyzer Cobas e411- Roche Diagnostics (limit of detection was 0,054 pg/dL).

2.4. Psychometry

Participants' depressive symptoms were scored by using the Greek Version of Beck Depression Inventory II (BDI II) (Giannakou et al., 2013), while the Greek Version of Spielberger's State-Trait Anxiety Inventory (STAI) was administered to assess state and trait anxiety (Fountoulakis et al., 2006). Fear, in terms of phobic anxiety and avoidance, was measured via the Fear Questionnaire (FQ) (Kasvikis et al., 2006), a commonly used instrument in our Specialty Clinic for both evaluation and treatment planning. The Greek Version of the Perceived Stress Scale (PSS-14) was used to measure the subjects' perception of stress (Andreou et al., 2011). Lastly, anxiety and avoidance in romantic relationships were evaluated using the revised questionnaire of Experiences in Close Relationships (ECR-R) (Tsagarakis et al., 2007). This was evaluated because OCD patients tend to show higher attachment insecurity than healthy controls (Myhr et al., 2004).

2.5. Statistical analyses

Data are presented as frequencies (%) for qualitative variables (i.e. marital or educational status). For quantitative variables (i.e. age, wellbeing-related characteristics etc.), the distribution was first checked. According to the Shapiro-Wilk normality test, the distribution of continuous data was skewed and, hence, apart from means and standard deviations (SD), median and interquartile ranges of continuous variables were obtained and presented, as well. Also, the non-parametric tests Mann-Whitney and Kruskall Wallis, were used to evaluate differences between patients and controls. Moreover, for quantitative variables Spearman's rho correlation coefficient was used. Consequently, effect sizes were estimated, as standardized for a Mann-Whitney test, following this formula $r = Z/\sqrt{N}$ (Rosenthal, 1994). Spearman's rank correlation method was used to test the relations between hair cortisol concentrations and psychometric values. The data collected were analyzed using the Statistical Package for the Social Sciences vol.25 (SPSS Inc., Chicago, IL). The level of significance p was 0.05.

3. Results

Demographic characteristics of the participants are summarized in Table 1. As mentioned above, the two groups of the study were well matched on sex and age (±3 years). The healthy controls, however, had a significant higher educational level ($p = 0.021$). No other significant differences were observed between the two groups. The median of the years passed since the onset of the disorder was 9.00. In relation to comorbidities, based on M.I.N.I. results, only two of the patients were screened positive for depression, two different patients presented social anxiety symptoms and three other patients reported anxiety regarding daily matters or health issues (without fulfilling the criteria for depression, social anxiety disorder, generalized anxiety disorder or illness anxiety disorder, respectively).

With regard to depression, despite the fact that only two patients were screened positive for depression by the M.I.N.I., the mean BDI scores of the patient sample indicated moderate depressive symptoms for the group. This apparent discrepancy may reflect more burnout symptoms rather than clinical depression for our group of OCD patients, and will be further elaborated below.

Concerning long-term cortisol, OCD patients showed significantly lower hair cortisol concentrations than healthy controls ($p = 0.001$, $r = 0.41$). The median of HC for OCD patients was 2.86, while for controls' it was 5.49. In contrast, the OCD patients demonstrated significantly higher scores than the control group, in all psychometric scales administered (Table 2). The effect sizes for the mentioned differences were medium to high ($r = 0.5–0.81$).

Table 3 demonstrates meaningful associations between hair cortisol concentrations and psychometric results. More specifically, hair cortisol was negatively and significantly correlated with total BDI score ($r = -0.329$, $p < 0.01$), FQ ($r = -0.294$, $p < 0.05$), agoraphobia and social

Table 1
Main demographic and clinical characteristics of patients with OCD and healthy controls (N = 64).

	Patients (OCD) N = 32	Controls N = 32	p-value
Sex N (%)			
- Females	16 (50%)	16 (50%)	1.000
- Males	16 (50%)	16 (50%)	
Age Mean (SD)	33.78 (8.96)	34.41 (8.97)	0.767
Median (IQR)	33.50 (31)	35.50 (34)	
Educational level N (%)			
- Primary/Secondary education	14 (43.75%)	4 (12.5%)	0.021
- Institute of vocational education/ Bachelor degree	12 (37.5%)	18 (56.3%)	
- MSc/PhD	5 (18.75%)	10 (31.3%)	
Marital status N (%)			
- Unmarried	25 (78.1%)	21 (65.6%)	0.181
- Married	7 (21.9%)	8 (25%)	
- Divorced	0 (0%)	3 (9.4%)	
Having children N (%)			
- Yes	5 (16.1%)	8 (25%)	0.577
- No	26 (83.9%)	24 (75%)	
Smoking N (%)			
- Yes	7 (21.9%)	12 (37.5%)	0.274
- No	25 (78.1%)	20 (62.5%)	
Frequency of hair wash N (%)			
- ≤ 2 times/week	11 (35.5%)		
- ≥ 3 times/week	20 (64.5%)	32 (100%)	
Duration of obsessive-compulsive disorder N (%)			
- ≤ 10 years	16 (51.5%)		
- ≥ 11 years	15 (46.9%)		
Psychiatric medication N (%)			
- Antipsychotics	10 (31.3%)		
- TCAs	5 (15.6%)		
- SSRIs/SNRIs	21 (65.6%)		
- BZDs	7 (21.9%)		

IQR= Interquartile Range, TCAs = Tricyclic Antidepressants, SSRIs = Selective Serotonin Reuptake Inhibitors, BZDs = Benzodiazepines.

Table 2
Hair cortisol concentrations and psychometric values of OCD patients and healthy controls.

Variables Mean (SD) Median (IQR)	Patients (OCD) N = 32	Controls N = 32	p-value	Effect Size r
Hair cortisol (pg/mg)	5.09 (5.77) 2.86 (25.61)	7.04 (4.28) 5.49 (14.41)	0.001*	0.41
BDI total	22.69 (10.54) 20.50 (29)	6.34 (6.26) 5 (29)	<0.0001*	0.73
FQ total	40.59 (24.35) 33 (103)	11.66 (9.18) 10.5 (40)	<0.0001*	0.66
FQ Agoraphobia subscale	8.84 (10.48) 5 (40)	0.88 (1.51) 0 (6)	<0.0001*	0.54
FQ Blood-injury phobia subscale	16.41 (10.9) 13.5 (39)	6.47 (7.54) 4 (32)	<0.0001*	0.48
FQ Social phobia subscale	15.34 (9.57) 15 (34)	4.31 (3.4) 4 (16)	<0.0001*	0.58
FQ Associated anxiety and depression	24.84 (9.04) 26 (36)	8.84 (8.69) 6 (31)	<0.0001*	0.67
STAI Y1	48.63 (13.81) 46.5 (51)	29.22 (7.25) 26.5 (29)	<0.0001*	0.7
STAI Y2	57.44 (11.91) 57 (43)	30.97 (7.25) 28 (29)	<0.0001*	0.81
PSS-14 total	32.53 (8.64) 31.5 (38)	17.31 (6.63) 36 (26)	<0.0001*	0.72
ECR-R anxiety	4.17 (0.66) 4 (2.5)	3.45 (0.52) 3.39 (2.67)	<0.0001*	0.56
ECR-R avoidance	4.24 (0.34) 4.30 (1.22)	4.63 (0.33) 4.67 (1.39)	<0.0001*	0.5
Y-BOCS/Obsessions	12.66 (2.91) 12 (14)			
Y-BOCS/Compulsion	12.97 (3.97) 13.50 (17)			
Y-BOCS Total	26.19 (5.41) 25.50 (29)			

IQR= Interquartile range, BDI= Beck Depression Inventory, FQ=Fear Questionnaire, STAI=State Trait Anxiety Inventory, Y1 = state anxiety subscale, Y2 = trait anxiety subscale, PSS-14 = Perceived Stress Scale, EC-R = Experiences in Close Relationships Scale-Revised, Y-BOCS=Yale-Brown Obsessive Compulsive Scale and × indicate significance at a level of 0.05.

phobia subscales of FQ ($r = -0.334$, $p < 0.01$ and $r = -0.263$, $p < 0.05$, respectively), both dimensions of STAI ($r = -0.295$, $p < 0.05$ and $r = -0.354$, $p < 0.01$) and total score of PSS-14 ($r = -0.291$, $p < 0.01$). The median for Y-BOCS total score of OCD patients was 25.50, which indicates severe symptomatology. It is noteworthy that no significant correlation was found between hair cortisol concentrations and OCD severity, as evaluated by Y-BOCS.

Afterwards, OCD patients were sorted into four subtypes (washing/cleaning, checking/harming, symmetry/ordering and religious/sexual obsessions), according to their primary type of obsessive and compulsive symptoms, as demonstrated on the Y-BOCS symptom checklist. The patient assignment to each category was based on their overt symptoms. Table 4 includes HCC for each OCD subtype. The Bonferroni correction for multiple tests was used and the results indicated that "washers/cleaners" had significantly lower hair cortisol concentrations, than the ones classified into the "checking/harming" and "ordering/symmetry" subtypes ($p = 0.035$, $\eta^2 = 0.262$). With respect to the psychometric results, the only difference detected was in the trait anxiety subscale. More specifically, patients with sexual or religious obsessions had significantly higher STAI-trait subscores ($p = 0.041$) than checkers (result not shown).

4. Discussion

It is fundamental to point out that this is the first study exploring

Table 3
Correlations between hair cortisol concentrations and psychometric values.

Variables	BDI total	FQ total	FQ Agoraphobia subscale	FQ Blood-injury phobia subscale	FQ Social phobia subscale	FQ Associated anxiety and depression	STAI YI	STAI Y2	PSS-14 total	EC-R anxiety	EC-R avoidance	Y-BOCS obsessions	Y-BOCS compulsions	Y-BOCS total
HCC (pg/mg)	−0.329**	−0.294*	−0.334**	−0.208	−0.263*	−0.190	−0.295*	−0.354**	−0.291*	−0.195	0.218	0.138	0.101	0.087

HCC=Hair cortisol concentrations, BDI= Beck Depression Inventory, FQ=Fear Questionnaire, STAI=State Trait Anxiety Inventory, Y1 = state anxiety subscale, Y2 = trait anxiety subscale, PSS=Perceived Stress Scale, EC-R = Experiences in Close Relationships Scale-Revised, Y-BOCS=Yale-Brown Obsessive Compulsive Scale, * indicate significance at a level of 0.05 and ** indicate significance at a level of 0.01.

Table 4
Hair cortisol concentrations per OCD type.

Variables (Mean ± SD) (Median, IQR)	Washing/cleaning	Harming/checking	Symmetry/ordering	Religious/sexual obsessions	p-value	Effect size Eta squared
Hair cortisol (pg/mg)	(2.86 ± 1.00) (2.56, 0.51)#^	(5.00 ± 3.12) (3.51, 3.78)#	(12.09 ± 13.5) (5.22, 19.75)^	(6.19 ± 7.81) (2.98, 5.95)	0.035[a]	0.262

[a] Indicate significance at a level of 0.05, Kruskal Wallis test, Bonferroni correction for multiple comparisons was used, #,^ show significant differences between OCD types.

long-term integrated baseline activity of the HPA axis in OCD patients using hair cortisol analyses. Because no other study has reported the same type of measurement, we have no basis to compare our findings to those of other investigations. In disagreement with earlier studies measuring cortisol in saliva, serum or urine (Sousa-Lima et al., 2019), we found that OCD patients had significantly lower HCC than healthy controls, even though our patients reported higher levels of stress, anxiety, depressive and avoidance symptoms in their daily life and in close relationships. This type of long-term "hypocortisolism" has been reported before in other mental disorders. For example, in a study of female participants with major depression, hair cortisol levels were significantly lower than in a healthy control group ($p = 0.007$), although the women with depression exhibited higher serum cortisol concentrations than the controls. As a result, a significant negative correlation between HCC and HAMD-17 scores ($\eta^2 = 0.03$) was shown (Wei et al., 2015).

In addition, a similar trend towards HCC-inferred hypocortisolism was earlier shown in generalized anxiety disorder and PTSD (Steudte et al., 2013, 2011; van Zuiden et al., 2019). In PTSD the authors found strong negative associations between hair cortisol concentrations and number of traumatic events ($r = -0.282$, $p = 0.010$), frequency of traumatic events ($r = -0.255$, $p = 0.022$), duration since traumatization ($r = -0.302$, $p = 0.033$) and severity of intrusion symptoms ($r = -0.348$, $p = 0.012$). As far as OCD is concerned, the hypothesis behind these novel findings could be a possible chronic down-regulation of the HPA axis, as a protective response to chronic stress conditions. Namely, under the persistent and cumulative stress that the OCD patients report, the prolonged cortisol release may cause chronic time-integrated hypocortisolism as an adjustive, counter-balancing process (Finitsis et al., 2013). The mechanisms supporting this phenomenon may be several: reduced release of CRH, ACTH and/or cortisol accompanied by decreased stimulation glucocorticoid receptors, down-regulation of these receptors, increased sensitivity to the HPA axis negative feedback loop at the level of the hippocampus, hypothalamus and/or pituitary gland, reduced chronic production and availability of free cortisol and morphological changes in the hippocampus and pituitary gland (Fries et al., 2005). Heim et al. have indicated that habituation of the HPA axis depends on specific characteristics of the stressors, such as their frequency, power and controllability; taking into consideration the definition of obsessions, a similar pattern of hypocortisolism could be justified by the nature of OCD itself (Heim et al., 2000).

OCD is recognized as a chronic, and often debilitating – if untreated – psychiatric disorder (Kühne et al., 2020). In this study, the majority of the patients had lived with the disorder for more than two years. The time since the onset of a disorder plays a crucial role in the interpretation of the results, given that findings revealed an inverse – although, not statistically significant – relation between the duration of the disorder and HPA axis activity. Namely, as more time since the disorder first appeared elapses, cortisol levels tend to decrease (Miller et al., 2007).

In spite of the cross-sectional design of our study, a hypothesis of chronic stress playing a role in the etiology of OCD could be proposed: thus, the mainly goal-directed nature of the compulsions at the onset of the disorder, may shift to habitual behavior later on, through hypersensitization of the neural circuits involved in this condition. Strong evidence from animal models support the notion that under prolonged release of glucocorticoids, because of chronic stress, a synaptic reorganization in the frontal cortex may lead to a shift towards habitual rather than goal-directed strategies (Dias-Ferreira et al., 2009). More specifically, the high stress that patients undergo during the early stages of the disorder, may disrupt orbito-fronto-striatal circuits and favor habitual performance, reducing the control of the prefrontal cortex – which demonstrates high density of GC receptors – over other neural domains (Schwabe and Wolf, 2009). In the long run, this initial increase of cortisol may become counterbalanced by activation of compensatory mechanisms, which progressively result in a decreased cortisol secretion (i.e. hypocortisolism) (Gold and Chrousos, 2002). However, an alternative hypothesis that hypocortisolism might not be a consequence of the OCD pathophysiology but instead a vulnerability factor for the disorder, is still a matter of dispute.

Associations of HCC with self-reported measures are inconclusive, on the grounds that the reliability of retrospective psychometric measures has been questioned. Wells et al. noted that in a diverse sample, correlations between HCC and chronic stress and perceived stress levels were non-significant (Wells et al., 2014). In this study, patients with OCD scored higher than controls, in all the aforementioned psychometric scales, as expected. However, in disagreement with earlier findings (Sousa-Lima et al., 2019), the results revealed a significant negative correlation between self-reported stress, anxiety/fear, depressive and symptoms and hair cortisol levels. This concurs well with previous findings regarding patients with depression (Jahangard et al., 2019; Pochigaeva et al., 2017).

Interestingly, in our group of OCD patients, only two patients were screened positive for clinical depression by the M.I.N.I., but assessment of depressive symptoms by the Beck Inventory showed a mean score in our group that reflected moderate depressive symptoms. As it should be kept in mind that the BDI in not a diagnostic instrument but merely a scoring instrument mainly for depressive cognitive ideation, this apparent discrepancy may reflect more the mental fatigue and despair experienced by chronic OCD patients, a sort of "burnout" syndrome, so to speak, which may be reflected in the downregulation of the HPA axis.

Regarding OCD subtypes, statistically significant differences were shown between "washers/cleaners" and two out of three other subgroups. The patients sorted as "washers/cleaners" exhibited the lowest HCC. This study constitutes the first attempt to compare cortisol levels between different types of symptoms, although obsessive and compulsive subtypes seem to contribute to the great heterogeneity in the OCD spectrum. It has been reasonably assumed, on the basis of cluster analysis, that different neurotransmitter systems (i.e. dopaminergic, serotonergic etc.) mediate different types of symptoms (Lochner et al., 2005). Naturally, different symptom-based subtypes of patients, demonstrate various neuropsychological deficits and distinct neuroimaging evidence (McKay et al., 2004). For instance, on the one hand, checkers tend to show difficulties in verbal memory and in memory confidence (Bragdon et al., 2018; Moritz and Jaeger, 2018), while fMRI showed increased activity in the motor cortices of these patients (Ravindran et al., 2019). On the other hand, "washers" seem to show impaired inhibitory control between the frontal cortex and insula. Consequently, anxiety related to washing may be associated with disgust and negative emotional salience (Ravindran et al., 2019). Following similar reasoning, studies with larger samples could explore HCC in different patient subtypes, in order to examine theories on the role of HPA axis in OCD psychopathology and develop a basis for neuroendocrine profiling, hopefully leading to subtype-specific therapeutic interventions.

It is plausible that a number of limitations might have influenced the final results, including the study design. Inevitably, this cross-sectional study makes it impossible to draw conclusions about whether the HPA axis dysregulation comprises an etiological factor in OCD psychopathology or an aftereffect of the disorder, or both. In addition, the study sample was relatively small and no BMI data were available in either group. Body mass index might be a possible confounder regarding cortisol, although all participants were of an average body size and weight. Likewise, it was not possible to include exclusively drug naïve patients or patients without other symptomatology (i.e., mild to moderate depressive symptoms), given the high rates of comorbidity between OCD and other mental disorders. However, our patient group was quite homogenous. Finally, it is worth noting that although HCC reflect the cumulative stress of the past three months, the PSS measures of the participants' perception of stress were obtained in the last month. Despite this inconsistency, participants were screened for major life events or changes during the clinical evaluation, in order to ensure that they had not experienced severe stress in the past three months. One of the strengths of this study is the fact that two important factors which contribute to disorder heterogeneity, age of onset and disease subtype, were taken into account in the analyses. Hair sampling ruled out a common confounding factor in cortisol protocols: the acute effect of anticipatory stress on cortisol levels.

It would be vital for diagnostic purposes, to conduct more cross-sectional or longitudinal studies with larger samples in order to define specific hair cortisol profiles for each major psychiatric disorder, including OCD. Further work is needed to clarify if altered HCC in the OCD patients are accompanied by differentiated reactivity of the HPA axis (e.g. CAR-cortisol awakening response) or by a general dysregulation of other neurogically active steroids, as well (e.g. DHEA) (Bigos et al., 2009; Wintermann et al., 2016). Regarding response to psychotherapy, it has been shown that the higher cortisol levels are during the first exposure session, the better the outcome of the treatment (Fischer et al., 2017). In future studies, it might be useful to add a SCID interview to establish comorbidities more accurately, as well as a burnout scale to assess quality of the depressive symptoms experienced by the patients.

5. Conclusions

There is evidence to support the hypothesis of HPA axis dysregulation in patients with OCD. Future findings, connecting HCC with possible risk for OCD or investigating HCC in different subtypes of the disorder may lead to greater insight into the pathophysiology of OCD and might have vital implications, not only for developing etiology models, but also, for the clinical management of the patients. On a broader level, research needs to explore how the HPA axis may adapt over the course of the disorder or during possible relapses or remission of symptoms. Generally, acquiring such information about HCC will encourage the use of hair cortisol measurement for treatment prognosis and assessment of therapeutic outcomes. Therefore, a dimensional way of conceiving OCD through a clinical staging model could be established and employed to the benefit of the patients.

Statement of ethics

The study was approved by the Ethics Committee of Eginition University Hospital in Athens, Greece, and was conducted in accordance with the Declaration of Helsinki.

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Author contributions

E.K.M., I.M. and I.Z. designed and performed the study. C.D., N.V., G. C. and C.P. supervised the project. E.K.M., I.M., T.C., M.M., N.N. and A. M. performed the measurements; E.K.M. and M.M. analyzed the data; E. K.M. wrote the article with the assistance of I.M., C.D., N.V., I.Z., G.C. and C.P.

Declaration of competing interest

None of the authors report any actual or potential conflict of interest.

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