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The role of cortisol in the association between perceived stress and pain: A short report on secondary adrenal insufficiency patients

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Abstract

Background: Given the pain-dampening effect of cortisol, low cortisol levels have often been proposed to mediate the association between perceived stress and pain. However, studying causal effects is difficult given the complex interplay between perceived stress, cortisol release and pain levels in people with an intact hypothalamic-pituitary-adrenal axis. In the current study, we approached this problem by examining the association between perceived stress and pain levels in patients with secondary adrenal insufficiency (SAI) who were successively supplemented by lower and higher doses of hydrocortisone in a double-blinded cross-over design.

Methods: Forty-seven patients with SAI (29 males, 18 females; mean [SD] age, 51 [14] years, range 19-73) participated in an RCT. Patients randomly received low doses of hydrocortisone (0.2-0.3 mg/kg body weight/day) during 10 weeks followed by high doses (0.4-0.6 mg/kg body weight/day) for another 10 weeks, or vice versa. Patients filled out a daily diary on perceived stress (GAD-7) and pain levels (PHQ-15) throughout the RCT. Non-seasonal autoregressive moving average (ARMA) modeling was performed to test associations between daily perceived stress levels and daily pain levels during low and high hydrocortisone dose.

Results: Out of 47 study patients, twelve patients showed high enough fluctuations in perceived stress and pain levels (MSSD>0.01) to study their associations during intake of two different hydrocortisone doses. Six patients showed associations between perceived stress and pain during both hydrocortisone doses, one showed this association only under the low dose, and two only under the high dose.

Conclusion: This study does not suggest a role for lower cortisol levels in the association between perceived stress and pain.

Keywords: perceived stress, pain, secondary adrenal insufficiency patients, diary study, randomized controlled trial

Introduction

A wide variety of stressors, such as sexual abuse, bullying, and daily hassles have been identified to predict pain levels (Gini and Pozzoli, 2009; Paras *et al.*, 2009; van Gils *et al.*, 2014). The exact physiological mechanisms behind this association are unknown. Stressors are known to increase perceived stress levels that in turn cause physiological effects, most importantly by increasing levels of the stress hormone cortisol (Hannibal and Bishop, 2014).

Increases in cortisol levels have been suggested to be in the short run beneficial for pain reduction, since cortisol release is known to suppress pain levels (Hannibal and Bishop, 2014). Long term stress-exposure has been suggested to result in down-regulation of the hypothalamic-pituitary-adrenal (HPA) axis and thus in low cortisol levels (Miller *et al.*, 2007). In turn, low cortisol levels have been found to be related to high pain levels (Tak *et al.*, 2011). However, it has recently been questioned whether these low cortisol levels are consequences rather than causes of high pain levels (Generaal *et al.*, 2015). Examining cause-effect relationships between perceived stress, cortisol levels and pain in healthy individuals is difficult, since perceived stress, cortisol levels, and pain are highly intertwined and several feedback loops play a role, particularly that of the HPA-axis.

Patients with secondary adrenal insufficiency (SAI) are characterized by loss of endogenous adrenocorticotrophic hormone (ACTH) and cortisol production and consequently lack the feedback loop of the HPA axis. These patients receive hydrocortisone substitution that mimics normal endogenous cortisol rhythms and compensates for low endogenous cortisol levels (Werumeus Buning *et al.*, 2015). Thus, cortisol levels can be externally controlled in these patients. Therefore, patients with SAI serve as a unique model to examine the association between perceived stress levels and pain under different cortisol conditions.

This study presents data from a double-blind cross-over RCT in patients with SAI who successively received a lower and higher hydrocortisone dose, in a random order, both administered for a substantial time period. Patients completed a daily diary about perceived stress and pain levels during the entire study. Given the pain suppressing effect of cortisol, we hypothesized that the association between perceived stress and pain would become particularly evident under low hydrocortisone doses.

Methods

Patients

This study is part of a double-blinded cross-over RCT (Werumeus Buning *et al.*, 2015). A total of 63 patients with SAI were included in the study, of whom 60 completed the

run-in phase and the baseline assessment (mean age 52 [SD 13] years, range 19–73 years, 35 males, 25 females). All patients fulfilled internationally recognized criteria for SAI, were 18–75 years old, had a body weight of 50–100 kg at screening, had a time interval between study entry and tumor treatment with surgery and/or radiotherapy of at least one year, and were on adequate and stable replacement of all other pituitary hormone deficiencies for at least six months prior to entry of the study.

Main exclusion criteria were inability of legal consent, documented major cognitive impairment, drug abuse or dependence, current psychiatric disorders, treatment for a malignancy, shift work, previous Cushing's disease, hospital admission during the study, diabetes mellitus with medication known to be able to induce hypoglycemia, and a history of frequent episodes of clinical hypocortisolism. The concomitant use of other corticosteroids and drugs known to interfere with hydrocortisone metabolism, e.g. anti-epileptics, was not allowed either.

Sixteen patients did not complete the study, since they violated the study protocol ($n=8$), withdrew consent ($n=6$), or were withdrawn by the investigator ($n=2$). A total of 47 patients remained for the analyses (29 men and 18 women, mean [SD] age 51 [14] years, minimum-maximum 19–73 years). Details about the patient group, the inclusion criteria, the exclusion criteria, and the study protocol can be found elsewhere (Werumeus Buning *et al.*, 2015).

Intervention

Patients were randomly divided into two groups. Group 1 first received a lower hydrocortisone dose during 10 weeks (i.e. a cumulative dose of 0.2-0.3 mg/kg body weight, in three divided doses: before breakfast, before lunch, before dinner) followed by a higher hydrocortisone dose during 10 weeks (i.e. a cumulative dose of 0.4-0.6 mg/kg body weight, in three divided doses). Group 2 first received the higher and then the lower hydrocortisone dose. Patients were allowed to double or triple their hydrocortisone intake in case of intercurrent illness or fever for a period of maximum 7 days during the research periods. A doubling of the dose was reported 150 times in patients on low dose and 146 times in patients on high dose.

Daily diaries

Patients filled out a daily paper-and-pencil diary at the end of each day during the study period in which they reported among other things about perceived stress and pain levels. Perceived stress levels were assessed with seven items of the GAD-7 (“Feeling nervous, anxious or on the edge”, “Not being able to stop or control worrying”, “Worrying too much about different things”, “Trouble relaxing”, “Being so restless that it is hard to sit still”, “Becoming easily annoyed or irritable”, and “Feeling afraid as if something awful might happen”); Spitzer, Kroenke, Williams, & Löwe, 2006).

Pain levels were assessed with five items of the Physical Health Questionnaire (PHQ-15; Kroenke, Spitzer, & Williams, 2002): “Stomach pain”, “Back pain”, “Pain in arms, legs or joints”, “Headaches” and “Chest pain”. Patients could endorse whether they experienced these perceived stress or pain symptoms during the past day on a seven-point scale ranging from 1 (‘not at all’) to 7 (‘extremely’). Daily mean item scores for perceived stress and pain were calculated for each patient. Patients completed these diaries during both study periods, for a period of 20 weeks in total, resulting in a maximum of 140 daily observations per patient. Cronbach’s alpha of the GAD-7 in our sample was 0.92; Cronbach’s alpha of the pain items was 0.72.

Statistical analysis

Since previous research indicated that the association between perceived stress and somatic symptoms differs for individuals, analyses were performed at the individual level (van Gils et al., 2014). Associations between perceived stress levels and pain levels could only be studied in patients showing high enough daily fluctuations (van Ockenburg et al., 2015). Insight in fluctuation level was obtained by calculating the mean squared successive differences (MSSD). Given the seven-point Likert scales used, the MSSD could range from 0 to 36. A score of 36 would be obtained if a participant alternately scored 1 and 7 during the entire diary period. Patients that showed a time series with an MSSD of <0.01 , indicating minimal fluctuations for both pain and stress, were excluded. Time series of participants with an MSSD <0.05 were visually inspected.

After the selection of suitable participants, serial correlations, also called autocorrelations, within the time series of perceived stress and pain were identified for each individual using non-seasonal autoregressive moving average (ARMA) modeling. To adjust for an increasing or decreasing trend over time and for weekly rhythm, time (date) and day of the week were included in these models if these variables were significant. If time-series showed significant autocorrelation, as indicated by the plots of the autocorrelation function (ACF) and the partial autocorrelation function (PACF) and a significant Ljung-Box test, autoregressive effects as suggested by the ACF and PACF were included in the ARMA model. The best model without autocorrelation was chosen based on the ACF and PACF, a non-significant Ljung-Box test, and BIC values. After running the best identified model, the residuals of this time series, also called “white noise” were saved and this autocorrelation free time series was used for the second step of cross-correlation calculation. If the ACF, PACF and Ljung-Box test did not indicate any form of autocorrelation, the original time series were used. During the second step, the cross-correlation function (CCF) was used to examine cross-correlations between (autocorrelation free) time series of perceived stress and (autocorrelation free) time series of pain. With these analyses, the lag numbers of the

cross-correlation and the sign of the association (positive or negative) between perceived stress and pain could be identified for each individual. A lag number is the number of past time points that contains meaningful information on current time point, for example a lag number of 1 means that today’s perceived stress level predict tomorrow’s pain level. All analyses were performed using SPSS Version 22. Associations were considered statistically significant if the p-value was lower than 0.05.

Results

Descriptive statistics

Reported daily perceived stress levels and pain levels during the study period were generally low. They were generally higher during low hydrocortisone dose (range stress levels: 1.09 to 3.87, range pain levels: 1.14 to 3.64) than during high hydrocortisone dose (range stress levels: 1.06 to 2.91, range pain levels: 1.09 to 2.66).

Association between perceived stress and pain levels

Thirty-two participants were excluded, since at least one of their time series showed insufficient fluctuations, as indicated by a MSSD of <0.01 . Time series of six participants with a MSSD of <0.05 were visually inspected to determine their suitability. Three out of these six patients showed patterns that were not suitable for analyses (i.e., more than 20 of the same observations in a row). So, ultimately twelve subjects showed enough fluctuation in the time series to allow us to study the association between perceived stress and pain during both hydrocortisone conditions. Characteristics of these 12 patients included in the present analysis, and the 35 patients that were excluded based on insufficient fluctuation, are shown in Table 1. Patients with sufficient fluctuation in pain and stress level did not differ from persons without sufficient fluctuation with regard to age, sex, and hydrocortisone levels. However, patients with sufficient fluctuation levels showed higher pain and stress levels during both low and high hydrocortisone dose than patients without sufficient fluctuation, which probably contributed to their higher fluctuation patterns. Mean pain levels, perceived stress levels, MSSD, information about autocorrelation and cross-correlation is given in Table 2a for low hydrocortisone dose and in Table 2b for high hydrocortisone dose. Six patients showed associations between perceived stress and pain during both hydrocortisone doses, one showed this association only under low dose, and two only under high doses. Six positive contemporaneous associations (i.e. lag number is 0) were found, which means that higher perceived stress levels were associated with higher pain levels on the same day. In seven cases, higher pain

Table 1. Differences between patients who show sufficient ($n=12$) and insufficient ($n=35$) fluctuation in perceived stress and pain levels

	Patients showing fluctuation on pain and stress scores ($n=12$)	Patients showing hardly or no fluctuation ($n=35$) on pain and stress scores.	P-value ^a
Sex (male/female), n	7/5	22/13	1.0
Age, years	41 (14)	54 (13)	0.88
Plasma cortisol LD 1 hr after intake HC, nmol/L	519 [445; 645]	482 [359; 599]	0.34
Plasma cortisol HD 1 hr after intake HC, nmol/L	819 [676; 888]	735 [667; 872]	0.39
Free cortisol LD	184 [127; 298]	204 [146; 268]	0.75
CL (L/h/70 kg)			
Free cortisol HD CL (L/h/70 kg)	169 [156; 240]	206 [153; 265]	0.88
Free cortisol LD AUC 24hr (h*nmol/L)	223 [149; 325]	202 [144; 259]	0.58
Free cortisol HD AUC 24hr (h*nmol/L)	478 [340; 513]	382 [308; 518]	0.43
Total cortisol LD CL (L/h/70 kg)	11 [8; 16]	10 [7; 14]	0.53
Total cortisol HD CL (L/h/70 kg)	13 [10; 17]	12 [10; 15]	0.66
Total cortisol LD AUC 24hr (h*nmol/L)	3795 [2776; 5122]	3907 [2843; 5343]	0.86
Total cortisol HD AUC 24hr (h*nmol/L)	6235 [5260; 8095]	6559 [5299; 7553]	0.97
Pain levels LD	1.99 (0.79)	1.24 (0.24)	0.001
Pain levels HD	1.78 (0.59)	1.16 (0.18)	<0.001
Stress levels LD	1.76 (0.76)	1.11 (0.25)	<0.001
Stress levels HD	1.66 (0.53)	1.10 (0.21)	<0.001

CL= Clearance, AUC= area under the curve HC = hydrocortisone. LD = lower dose. HD = higher dose. Data are frequency, mean (SD) or median [interquartile range]. ^aP-values were based on χ^2 -tests for dichotomous variables and Mann-Whitney U tests for continuous variables

Table 2a. Association between perceived stress and pain during low hydrocortisone dose

Patient	Mean (SD) perceived stress	MSSD perceived stress	Autocorrelation perceived stress	Mean (SD) pain	MSSD pain	Autocorrelation pain	Cross-correlation perceived stress and pain
A	2.17 (0.47)	0.27	AR(1) ^a	3.05 (0.84)	0.65	AR(1) ^a	1: $r=0.30$ $sd=0.12$; 4: $r=0.27$ $sd=0.13$
B	1.35 (0.32)	0.11	AR(1)	1.37 (0.33)	0.14	AR(1,4)	0: $r=0.49$ $sd=0.12$
C	1.53 (0.19)	0.04	AR(1) ^a	2.09 (0.47)	0.25	AR(1,5)	0: $r=0.30$ $sd=0.12$; -2: $r=0.37$, $sd=0.12$
D	1.59 (0.36)	0.15	AR(1) ^{a,b}	2.36 (0.53)	0.22	AR(1,7) ^a	NS
E	1.15 (0.21)	0.06	-NS ^a	1.32 (0.31)	0.15	AR(2) ^b	NS
F	1.88 (0.28)	0.11	AR(1)	1.83 (0.35)	0.07	AR(1, 4, 6)	0: $r=0.43$, $sd=0.12$
G	3.87 (0.74)	0.31	MA(1) ^a	3.64 (0.58)	0.41	AR(1,2,3)	NS
H	1.74 (0.68)	0.69	AR(1)	2.64 (0.60)	0.49	AR(1)	2: $r=0.25$, $sd=0.12$
I	2.30 (0.31)	0.18	NS	2.02 (0.31)	0.13	AR(7) ^a	-NS
J	1.16 (0.20)	0.04	AR(1,5,9) ^a	1.19 (0.23)	0.06	AR(1)	-5: $r=0.30$, $sd=0.13$; 2: $r=0.25$, $sd=0.13$
K	1.09 (0.17)	0.06	NS ^{a,b}	1.14 (0.16)	0.05	-NS ^{a,b}	NS
L	1.25 (0.28)	0.08	AR(1)	1.25 (0.27)	0.13	NS ^a	-4: $r=0.26$, $sd=0.13$

MSSD= mean squared successive differences, AR= autoregressive effect, e.g. AR(1,4) means that today's perceived stress level predict tomorrow's perceived stress level and the perceived stress level 4 days later. MA=moving average, e.g. MA(1) means that the sd of today's stress level predict tomorrow's stress level; ^aARMA model adjusted for time (date); ^bARMA model adjusted for weekly rhythm (day of week); NS= non-significant ($p<0.05$)

Table 2b. Association between perceived stress and pain during high hydrocortisone dose

Patient	Mean (SD) perceived stress	MSSD Perceived stress	Autocorrelation perceived stress	Mean (SD) pain	MSSD Pain	Autocorrelation pain	Cross-correlation perceived stress and pain
A	2.18 (0.31)	0.14	NS ^a	2.53 (0.47)	0.17	AR(1)	-1: r=0.24, sd=0.12
B	1.44 (0.38)	0.16	AR(1,3)	1.37 (0.32)	0.13	AR(1) ^a	0: r=0.37, sd=0.12
C	1.37 (0.15)	0.03	AR(1,2)	1.75 (0.45)	0.29	AR(1)	0: r=0.56, sd=0.12 2: r=0.27, sd=0.12
D	1.64 (0.27)	0.10	AR(7) ^a	2.33 (0.43)	0.16	AR(1)	0: r=0.28, sd=0.12 -1: r=0.25, sd=0.12
E	1.32 (0.26)	0.12	AR(4)	1.24 (0.28)	0.10	NS	NS
F	1.57 (0.29)	0.11	AR(1)	1.72 (0.42)	0.12	AR(1)	0: r=0.33, sd=0.12; 3: r=0.27, sd=0.12
G	2.91 (0.61)	0.30	AR(1) ^a	2.66 (0.43)	0.22	AR(1) ^a	0: r=0.37, sd=0.12 2: r=0.28, sd=0.14
H	2.01 (0.43)	0.25	AR(1)	2.53 (0.41)	0.27	AR(1)	NS
I	2.12 (0.47)	0.24	AR(1)	1.68 (0.42)	0.29	AR(2) ^b	0: r=0.26, sd=0.13
J	1.06 (0.12)	0.03	NS	1.09 (0.21)	0.07	AR(2)	-1: r=0.32, sd=0.12 2: r=0.33, sd=0.13
K	1.07 (0.10)	0.02	NS ^b	1.11 (0.15)	0.04	NS ^b	NS
L	1.38 (0.41)	0.30	NS ^{a,b}	1.26 (0.37)	0.26	NS	-7: r=0.26, sd=0.13

MSSD= mean squared successive differences, AR= autoregressive effect, e.g. AR(1,4) means that today's perceived stress level predicts tomorrow's perceived stress level and perceived stress level 4 days later. MA=moving average, e.g. MA(1) means that the sd of today's stress level predict tomorrow's stress level; ^aARMA model adjusted for time

levels predicted higher perceived stress levels on subsequent days (negative lags), and in eight cases higher perceived stress predicted higher pain levels on subsequent days (positive lags).

Discussion

This double-blinded cross-over trial in patients with SAI found that the association between perceived stress levels and pain levels was comparable during supplementation with lower and higher hydrocortisone doses. Therefore, this study does not provide evidence for a prominent role of cortisol in the association between perceived stress and pain.

One strong point of this study is the unique patient group in which we were able to study the role of cortisol in the association between perceived stress and pain without influence of HPA-axis feedback loops. Moreover, the combined diary and RCT approach offered the unique opportunity to study these effects on an individual level during daily life.

A weakness of this study is that fluctuations in stress and pain levels were on average low during the study periods, which allowed us to study the association between perceived stress and pain only in a subset of patients. The small sample size might have impaired the generalizability

of our findings. It is good to note that SAI patients who showed enough fluctuation to be included were comparable with regard to age, sex and cortisol levels to SAI patients who did not show enough fluctuation. Further, the SAI patients of the RCT were believed to be a representative sample of the total population of patients with SAI (Werumeus Buning et al., 2015). Nevertheless, findings could have been different for other SAI samples. Moreover, inherently to the design, SAI patients were studied and one has to be careful with generalizing the result, that is, a lack of moderation effect of cortisol in the relation between stress and pain, to healthy persons. Further, the levels of perceived stress and pain experienced during the research period were in general also low.

Another limitation was that the GAD-7 was used as a proxy to assess perceived stress. The GAD-7 is not specifically validated for measurement of perceived stress, but has a high face validity for the assessment of stress given the content of the items, especially when administered daily.

A final potential limitation was that participants were allowed to incidentally double their hydrocortisone dose in case of acute stress or illness. Such a doubling was allowed during a maximum of 10 per cent of the study period and patients were strictly informed not to double their hydrocortisone intake the week prior to their hospital visit (so in the week before they switched to the other hydrocortisone dose) (Werumeus Buning et al., 2015). A hydrocortisone

dose was doubled seventy-six times during low hydrocortisone intake and fifteen times during high hydrocortisone intake. The two patients who were mainly responsible (65 %) for the doubling of hydrocortisone intake during low hydrocortisone dose, showed significant associations between perceived stress and pain during both the period in which they were on the lower dose and the period in which they were on the higher dose. Therefore, we do not expect that the incidental doubling of hydrocortisone (substantially) affected our findings.

This is to the best of our knowledge the first study that examined the effect of cortisol on the association between perceived stress and pain in a diary design during a longer treatment period. We did not find a moderation effect of hydrocortisone in the association between perceived stress and pain. Although a negative finding can have the trivial explanation that the power to detect differences is too low, we do not believe that this is the case in our study. In idiographic research the power to detect an association is mainly determined by the number of data points for each individual and not by the number of participants (van Ockenburg *et al.*, 2015). The number of data points in this study was sufficient to show significant associations between stress and cortisol, as significant associations were found in 10 out of 12 participants. Therefore, this study was sufficiently powered to show differences in the association between perceived stress and pain during low and high hydrocortisone dose in individual patients. Our findings are in line with a recent general population cohort study that did also not found that a dysregulated HPA-axis could predict widespread pain onset in relation to stressful life events (Generaal *et al.*, 2015).

It should be kept in mind that our study tested the effect of hydrocortisone dose on the association between perceived stress and pain during normal daily life, and not during a stressful period, while the effect of hydrocortisone dose on the association between perceived stress and pain is likely to be particularly evident during stressful life periods. Therefore, repetition of the current study design with introduction of a mild stress experiment during both hydrocortisone doses is suggested.

Author contributions

KAMJ wrote the initial drafts of the manuscript and performed the ARIMA analyses, read and revised the manuscript, and approved the final manuscript for submission. JWB performed the descriptive statistics and analyses presented in Table 1, contributed to the data collection, wrote part of the method section, critically read and revised the manuscript, and approved the final manuscript for submission. AvB designed and conceptualized the RCT, was responsible for the data collection, critically read and revised the manuscript and approved the final manuscript for submission. JGMR designed the diary part of the study, conceptualized the current idea for the manuscript, read and

revised the manuscript critically, and approved the final manuscript for submission.

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