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Endogenous glucocorticoids may serve as biomarkers for migraine chronification

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Abstract

Aims: The aims of this study were to: (a) identify differences in serum and cerebrospinal fluid (CSF) glucocorticoids among episodic migraine (EM) and chronic migraine (CM) patients compared with controls; (b) determine longitudinal changes in serum glucocorticoids in CM patients; and (c) determine migraine-related clinical features contributing to glucocorticoid levels.

Methods: Serum and CSF levels of cortisol and corticosterone were measured using liquid chromatography-mass spectrometry among adult patients with EM, CM, and controls. Serum and CSF samples were collected from 26 and four participants in each group, respectively. Serum glucocorticoids were measured at a second timepoint after 2 years among 10 of the CM patients, six of whom reverted to EM while four persisted as CM. Receiver operating characteristic (ROC) analysis was made to assess the migraine diagnostic performance of glucocorticoids. Regression analysis was conducted to determine the link between glucocorticoid levels and migraine-related clinical variables.

Results: CM patients exhibited significantly elevated serum and CSF levels of cortisol and corticosterone compared with controls and EM patients (age, sex, body mass index adjusted; Kruskal–Wallis $p < 0.05$). ROC showed area-under-curve of 0.89 to differentiate CM from EM. CM patients with remission had their serum glucocorticoids return to control or near EM levels ($p < 0.05$). Persistent CM showed unremitting serum glucocorticoids. Migraine frequency and disability contributed to increased cortisol, while pain self-efficacy predicted lower cortisol levels ($p < 0.005$).

Conclusion: Endogenous glucocorticoids may be biomarkers for migraine progression and for monitoring treatment response. Improving pain self-efficacy skills may help optimize endogenous glucocorticoid levels, which in turn may prevent migraine attacks.

Keywords: migraine, chronic migraine, biomarker, glucocorticoids, cortisol, CSF, serum, self-efficacy, diagnostic accuracy, receiver operating characterisitc (ROC)

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Introduction

Migraine is commonly considered as a model disease of allostatic load in which repetitive headache attacks lead to a maladaptive neuronal response.[1,2] In this model, increased central and peripheral sensitivity coupled with various triggers can result in clinical progression of episodic migraine (EM) to chronic migraine (CM).[1,2] The distinction between EM and CM is currently based on frequency of headache days, which is arbitrary.[3] The third edition of the *International Classification of Headache Disorders* (ICHD-3) defines CM as headache occurring on 15 or more days/month for more than 3 months, which, on at least 8 days/month has the features of migraine headache.[3] Recurrent migraine attacks are thought to cause increased stress response.[1,2] Compared with EM patients, CM patients are believed to be unable to habituate to repetitive stimuli, thus failing to suppress stress response.[1,2,4] Moreover, CM patients are known to have impaired circadian regulation of corticotropic and somatotropic functions.[5]

Cortisol is the most important endogenous glucocorticoid responsible for regulation of stress

response.[6] By virtue of their lipophilic property and their significance in neuroendocrine cross-talk, glucocorticoids can reach the central nervous system (CNS) and thereby modulate several neuronal and glial functions.[7] In addition to lowering neuroplasticity and neurogenesis, persistently elevated cortisol level can impair glutamate activity and cause dendritic atrophy.[8,9] Cross-sectional studies have shown increased cortisol levels in CM patients compared with healthy controls.[10,11] Another observational study has found higher cortisol levels in migraine patients with increasing headache intensity compared with healthy controls.[12] Corticosterone administration was shown to increase cortical spreading depression,[13] a neurophysiological phenomenon that is thought to be the underlying mechanism of migraine with aura.[4]

To further understand the role of glucocorticoids in migraine, we conducted this study that compared group difference in endogenous cortisol and corticosterone among healthy controls, EM, and CM. In addition, we sought to determine clinical variables that contributed to group differences of endogenous glucocorticoids. Furthermore, we followed CM patients for a period of 2 years and repeated glucocorticoids measurement to compare longitudinal intra-individual changes of glucocorticoids between CM patients who reverted to EM and those who continued to have CM.

Methods

Study design and patients recruitment

This was a combined cross-sectional and longitudinal clinical study with the following inclusion criteria: migraine patients who were 18 years and older, migraine diagnosis made by headache specialist according to ICHD 3-beta[14] criteria, minimum migraine duration of 1 year, and ability to speak and write in English. Patients were allowed to be on their usual care and medications. Exclusion criteria were children under age 18, secondary headaches other than comorbid medication-overuse headache (MOH), chronic pain conditions, history of corticosteroid exposure, severe medical or neurological comorbidities (such as seizure disorder, diabetes, hypertension, alcoholism, cardiac disease, psychiatric problems, Cushing syndrome, drug or alcohol addiction, respiratory problems, liver disease, etc.). There were 26 EM and 26 CM patients included in the cross-sectional study. For the longitudinal study, the CM patients were re-contacted 2 years after initial participation for second timepoint repeat study, 10 of whom enrolled. All patients were recruited from the Stanford Headache Clinic between January 2015 and May 2019.

Healthy controls recruitment

Individuals who responded to our study announcement posted at notice boards around the university and surrounding community were screened *via* telephone interview using the ICHD 3-beta criteria. Controls met the same inclusion and exclusion criteria abovementioned except for the presence of migraine or another headache diagnosis. There were 26 healthy controls included in the study.

Phenotyping and assessing comorbidities

Migraine-related questionnaires. All migraine patients completed online self-administered questionnaires about their demographic information, headache features during the previous 3 months involving monthly frequency of headache days, headache severity on numeric rating scale of 0–10, headache medication use, and headache-related disability measured using Migraine Disability Assessment.[15] The CM patients retook these questionnaires at the second timepoint, that is, 2 years after initial participation.

Psychometric questionnaires. In order to assess for comorbid psychological and behavioral conditions, all migraine patients and healthy controls completed the following standardized questionnaires: Patient Health Questionnaire-9[16] for depression, Generalized Anxiety Disorder-7[17] for anxiety, Pain Catastrophizing Scale[18] to assess pain catastrophizing, Pittsburgh Sleep Quality Index[19] for sleep quality, Primary Care Post-Traumatic Stress Disorder[20] to assess for post-traumatic stress disorder (PTSD), Patient Health Questionnaire-15[21] for somatic symptoms, and Pain Self-Efficacy Questionnaire[22] to examine patients' confidence in performing daily activities despite head pain.

Blood collection

Whole blood (50 ml) was collected by median cubital venipuncture from EM ($n=26$), CM ($n=26$),

and healthy controls ($n=26$). Venipuncture was done during day time between 9 am and 4 pm. Whole blood was collected in vacutainer tubes containing no anticoagulant. Tubes were kept in upright position for 30–45 min to allow clotting. Tubes were centrifuged for 15 min at 1500 relative centrifugal force (RCF). Carefully, serum was aliquoted into 0.5 ml aliquots and stored at −80°C.

In 10 of the CM patients, serum samples were similarly collected at a second timepoint, that is, 2 years after initial serum collection.

Cerebrospinal fluid collection

Cerebrospinal fluid (CSF) (28 ml) was collected by performing lumbar puncture from EM ($n=4$), CM ($n=4$), and healthy controls ($n=4$), all of whom provided serum sample. CSF was collected during day time between 9 am and 4 pm. CSF samples were centrifuged at 1000 RCF for 10 min, aliquoted into 0.5 ml aliquots, and immediately stored at −80°C. Patients did not fast for serum and CSF collections. Except for six patients, all CM patients (20) were having headache during time of blood and CSF draws. There were four EM patients with headache, while the remaining EM patients (22) did not have headache at time of blood and CSF draws.

Liquid chromatography-mass spectrometry analysis

A Thermo DIONEX Ultimate 3000 – Q EXACTIVE high-performance liquid chromatography tandem mass spectrometry (HPLC-MS/MS) was applied for measuring free cortisol and free corticosterone levels. Samples were analyzed as follows: 100 µl of sample was applied to extraction procedure, and extracted with 300 µl of methanol and 10 µl of internal standard (2.8 mg/ml, DL-o-chlorophenylalanine), vortex mixing for 30 s. Samples were incubated for 1 h at −20°C. After 1 h, samples were centrifuged at 12,000 rpm and 4°C for 15 min and 200 µl of supernatant was transferred to vial for liquid chromatography-mass spectrometry (LC-MS) analysis. Hyper gold C18 column (10 cm × 4.6 mm × 3 µm) was used with flow rate of 0.35 ml/min.

Statistical analysis

The sample size was based on the available data. No statistical power calculation was conducted prior to the study. This is the primary analysis of these data. Group differences were analyzed using analysis of variance for parametric and Kruskal–Wallis test for non-parametric data followed by post-hoc tests. A one-way analysis of covariance (ANCOVA) was performed to determine statistically significant difference between groups (control, EM, CM) on serum cortisol and corticosterone levels after controlling for age, sex, and body mass index (BMI). A two-way ANCOVA was run to discover whether a statistically significant interaction effect exists between migraine and depression in terms of glucocorticoids, while controlling for covariates of age, sex, and BMI. The two-way ANCOVA analysis allowed us to examine whether depression (which may induce high cortisol secretion[23]) was not confounding our migraine-related cortisol assessments. Prediction analysis was conducted using linear regression to determine link between glucocorticoid levels and clinical variables (i.e. headache frequency, headache intensity, MOH, depression, anxiety, pain catastrophizing, sleep quality, somatic symptoms, PTSD, pain self-efficacy, migraine-related disability). Receiver operating characteristic (ROC) analysis was made to test the migraine diagnostic performance of glucocorticoids. Optimal cutoff was selected using Youden's index with equally maximum sensitivity and specificity measures. A significance level of $p<0.05$ was used.

Patient consents

All participants signed informed consent prior to study procedures. The study was approved by the Stanford University Institutional Review Board (IRB-30785).

Data availability and reporting guidelines

The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request. This study was in accordance with the Standards for Reporting of Diagnostic Accuracy Studies guidelines[24] (Supplemental Material I online).

Results

Patient characteristics (Table 1)

Demographics showed similar values for all participants who were middle-aged and mildly

overweight with comparable female-to-male sex ratio. EM patients had median frequency of 5 monthly migraine days with moderate severity and moderate migraine-related disability. CM patients had high frequency of 30 monthly migraine days with moderate severity, severe migraine-related disability, and median CM duration of 7.5 years. Half of the CM patients had MOH (54%). Compared with controls, CM patients were significantly more depressed with higher pain catastrophizing and somatic symptom severity ($p < 0.005$; Table 1). Of the 10 CM patients who participated in the longitudinal study, six reverted to EM while four persisted as CM.

Serum and CSF glucocorticoids

Results from the one-way ANCOVA analysis showed that there was a significant difference in cortisol [F (2, 73) = 4.15, $p = 0.02$] and corticosterone [F (2, 73) = 3.21, $p = 0.04$] among the groups (control, EM, CM), whilst adjusting for age, sex, and BMI. CM patients exhibited significantly elevated serum cortisol compared with controls and EM patients [Kruskal–Wallis $p < 0.001$; Figure 1(A)]. The two-way ANCOVA results showed that there was no statistically significant interaction between migraine and depression on serum cortisol [F (2, 69) = 0.71, $p = 0.50$] and on serum corticosterone [F (2, 69) = 0.22, $p = 0.81$] whilst controlling for age, sex, BMI. The main effect of migraine on serum cortisol [F (2, 69) = 2.92, $p = 0.04$] and on serum corticosterone [F (2, 69) = 3.94, $p = 0.02$] did not depend on depression, after controlling for age, sex, BMI. Similarly, CM patients had significantly higher levels of serum corticosterone levels compared with controls and EM patients [Kruskal–Wallis $p < 0.05$; Figure 1(B)]. There was no statistically significant difference in serum cortisol and corticosterone levels between controls and EM patients. CM patients with remission had their cortisol and corticosterone return to control or EM levels (Kruskal–Wallis $p < 0.05$), contrary to patients with persistent CM, who showed continued elevated cortisol and corticosterone levels [Figure 1(A) and (B)]; adjustment for age, sex, and BMI was not done with the longitudinal cases considering the low number of participants ($n = 10$). CSF cortisol level was observably highest in CM, followed by EM, and control [Figure 1(C)], while CSF corticosterone was only slightly increased in the CM group. CSF corticosterone-to-cortisol ratio was higher in controls and EM patients compared with CM patients [Figure 1(D)]. In contrast, serum corticosterone-to-cortisol ratio was increased in CM patients compared with controls and EM patients [Figure 1(D)]. Statistical difference was not computed considering $n = 4$ for CSF samples for Figure 1(C) and (D). There was no significant difference in serum and CSF glucocorticoid levels between males and females.

Association of glucocorticoids to clinical variables

The linear regressions revealed that higher headache frequency and migraine-related disability directly contributed to increased cortisol levels, while higher levels of pain self-efficacy predicted lower cortisol levels ($p < 0.005$; Figure 2). There was no difference in serum or CSF cortisone and corticosterone levels between CM patients with and without MOH.

ROC analysis

ROC analysis showed diagnostic accuracy performance of 0.89 and 0.86 area-under-curve for serum cortisol-based diagnosis of CM from EM, and CM from controls, respectively [Figure 3(A)]. For diagnosing CM from EM, optimum cutoff was selected at cortisol level of 55 ng/ml, indicating 72.4% sensitivity and specificity with Youden's index of 0.45 [Figure 3(B)]. Gold standard diagnosis was chosen to be ICHD-3 criteria.[3]

Discussion

Our study showed that elevation in endogenous glucocorticoids in migraine patients is associated with migraine; increased glucocorticoid level was robust to variations in age, sex, or BMI. Furthermore, we have shown that the elevated glucocorticoids were specific to migraine and its progression, not generally due to stress-induced activation of the hypothalamic–pituitary–adrenal axis as can be found in depression.[23] Our longitudinal results showing intra-individual glucocorticoids normalization in CM patients who had remission to EM implies that cortisol levels get elevated in response to CM, with the caveat of low sample size in our longitudinal study. In addition, strong association of high cortisol levels with both migraine frequency and migraine-related disability suggests a dose–response relationship. Moreover, inverse relationship between cortisol

Table 1. Patient characteristics and group differences of comorbidities and disabilities among controls, episodic migraine), and chronic migraine patients. Compared with controls, chronic migraine patients were significantly more depressed with higher pain catastrophizing and somatic symptom severity ($p < 0.005$).

Clinical variables	Control	Episodic migraine	Chronic migraine	Kruskal–Wallis, Dunn's post-test
Age: median (IQR), years				
• Serum, $n = 26$	40 (26, 49)	40 (29, 56)	41 (32, 53)	NS
• CSF, $n = 4$	48 (38, 67)	47 (38, 60)	43 (32, 53)	NS
Female:male ratio				
• Serum, $n = 26$	10:16	15:11	15:11	NS
• CSF, $n = 4$	3:1	3:1	3:1	NS
BMI				
• Serum, $n = 26$	24 (22, 27)	25 (22, 29)	26 (24, 30)	NS
• CSF, $n = 4$	24 (23, 26)	22 (22, 24)	22 (21, 23)	NS
Monthly frequency of migraine in last 3 months: median (IQR)				
• Serum, $n = 26$	NA	5 (3, 8)	30 (25, 30)	$p < 0.0001$
• CSF, $n = 4$	NA	4 (2, 5)	30 (29, 30)	$p < 0.001$
Migraine severity: median (IQR), 0–10 NRS				
• Serum, $n = 26$	NA	6 (5, 7)	6 (4, 7)	NS
• CSF, $n = 4$	NA	6 (5, 8)	5 (4, 5)	NS
MIDAS (migraine disability): median (IQR)				
• Serum, $n = 26$	NA	19 (9, 28)	90 (50, 184)	$p < 0.0001$
• CSF, $n = 4$	NA	20 (16, 21)	133 (73, 182)	$p < 0.001$
Medication-overuse headache: *n* (%)				
• Serum, $n = 26$	NA	NA	14 (54%)	NA
• CSF, $n = 4$	NA	NA	2 (50%)	NA
PHQ-9 (depression): median (IQR)				
• Serum, $n = 26$	1 (0, 2)	4 (2, 7)	9 (6, 11)	C *versus* CM, $p = 0.005$
• CSF, $n = 4$	0 (0, 1)	6 (4, 7)	10 (8, 13)	C *versus* CM, $p = 0.001$
GAD-7 (anxiety): median (IQR)				
• Serum, $n = 26$	1 (0, 1)	3 (1, 6)	4 (2, 8)	NS
• CSF, $n = 4$	0 (0, 1)	5 (2, 6)	2 (0, 7)	NS
PCS (pain catastrophizing): median (IQR)				
• Serum, $n = 26$	0 (0, 6)	16 (11, 22)	19 (9, 29)	C *versus* EM, $p = 0.0005$ C *versus* CM, $p = 0.001$
• CSF, $n = 4$	0 (0, 4)	15 (9, 20)	11 (5, 21)	C *versus* EM, $p = 0.005$ C *versus* CM, $p = 0.01$

(Continued)

Table 1. (Continued)

Clinical variables	Control	Episodic migraine	Chronic migraine	Kruskal–Wallis, Dunn's post-test
PC-PTSD: median (IQR)				
• Serum, $n=26$	0 (0, 0)	0 (0, 1)	0 (0, 0)	NS
• CSF, $n=4$	0 (0, 1)	2 (1, 3)	0 (0, 0)	NS
PSQI (sleep quality): median (IQR)				
• Serum, $n=26$	4 (2, 6)	7 (5, 9)	9 (6, 10)	NS
• CSF, $n=4$	5 (3, 6)	10 (9, 13)	7 (5, 10)	NS
PHQ-15 (somatic symptoms): median (IQR)				
• Serum, $n=26$	2 (0, 5)	7 (4, 9)	12 (9, 13)	C *versus* CM, $p=0.003$
• CSF, $n=4$	4 (3, 5)	9 (7, 10)	11 (8, 12)	NS
PSEQ (self-efficacy): median (IQR)				
• Serum, $n=26$	NA	32 (23, 46)	26 (18, 33)	NS
• CSF, $n=4$	NA	42 (36, 44)	24 (18, 30)	NS

Kruskal–Wallis with Dunn's post-test was utilized to test inter-median statistical differences.
BMI, body mass index; C, control; CSF, cerebrospinal fluid; GAD7, General Anxiety Disorder-7 questionnaire for anxiety assessment; IQR, interquartile range; MIDAS, Migraine Disability Assessment; NA, not available; NRS, numeric rating scale; NS, non-significant; PC-PTSD, Primary Care Post-Traumatic Stress Disorder; PCS, Pain Catastrophizing Scale; PHQ-9, Patient Health Questionnaire-9 for depression assessment; PHQ-15, Patient Health Questionnaire-15 for somatic symptoms assessment; PSEQ, Pain Self-Efficacy Questionnaire; PSQI, Pittsburgh Sleep Quality Index

level and pain self-efficacy, and that pain self-efficacy was linked to reduced migraine frequency and migraine-related disability, make these results clinically as well as biologically plausible. Based on our results, serum cortisol level may be considered as a biomarker for adequate CM management. Cortisol may play a role in modulating allostasis in migraine where persistently increased cortisol levels indicate maladaptive responses leading to migraine chronification. On the other hand, normalizing cortisol levels may signify adaptive responses heralding return to pre-CM state.

Cortisol is known to be released in a diurnal cycle as a "fight–fright–flight" response during times of anxiety, fatigue, stress, and pain.[6,25] Among its many physiological functions, cortisol is important in anti-inflammatory response.[6,25] There is some evidence for the role of neurogenic inflammation in CM.[26–29] Short-term administration of exogenous corticosteroids has a place in management of CM, particularly as a bridge therapy to non-steroidal medications and in treating resistant, severe, recurrent, and prolonged migraine attacks.[30]

Compared with serum glucocorticoids measurements, CSF levels reflect more consistent and direct measure of glucocorticoids in the CNS. Our CSF findings of observable progressive increment in CSF cortisol levels from healthy controls, EM, and CM similarly suggest CNS cortisol involvement in migraine chronification. A previous study of healthy individuals has demonstrated CSF corticosterone-to-cortisol ratio to be six times higher than in serum, indicating differential glucocorticoid expression in CSF compared with serum.[31] Our data of higher corticosterone-to-cortisol ratio in CSF of healthy controls than in serum corroborate previous findings showing corticosterone to be the more expressed CNS glucocorticoid. Interestingly, we found corticosterone-to-cortisol ratio to be inversely higher in serum than in CSF of CM patients, signifying cortisol to be the dominant CNS glucocorticoid in CM. We speculate this to

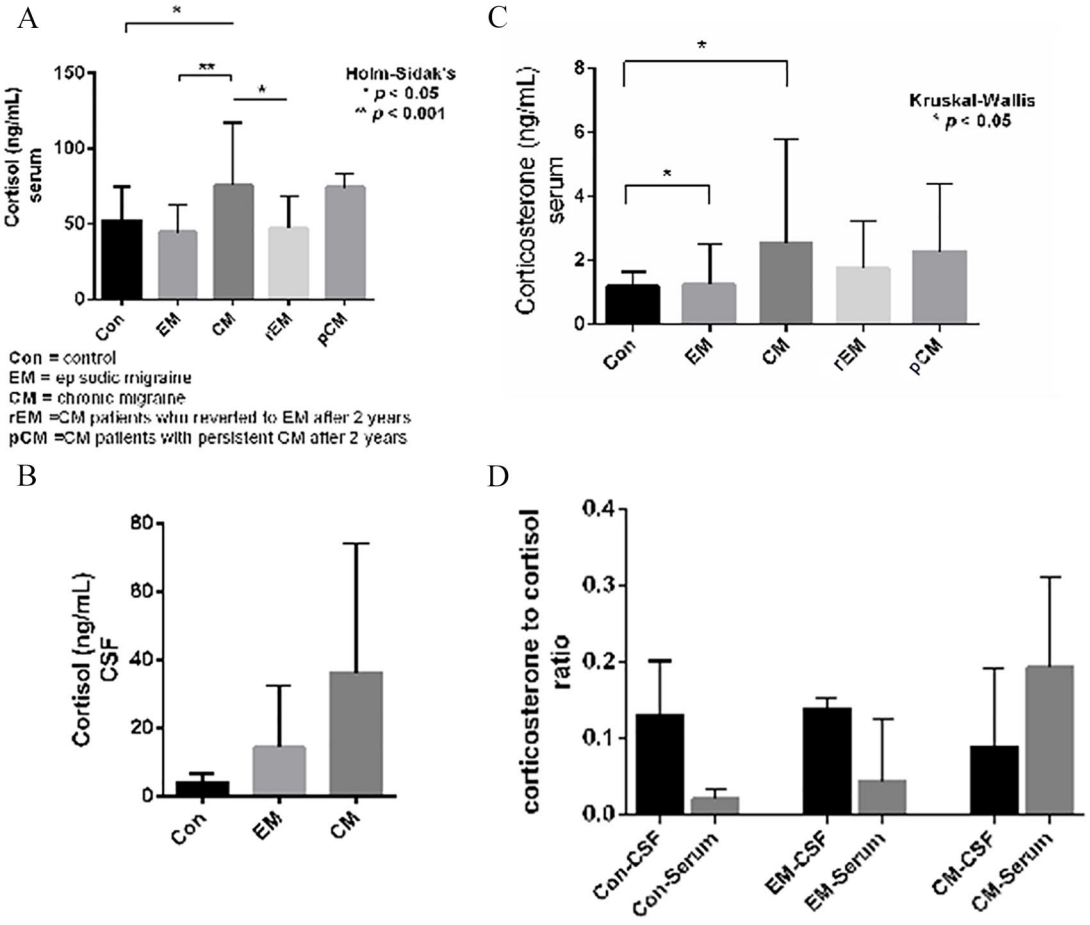

Figure 1. Comparison of serum and CSF glucocorticoids. CM patients exhibited significantly elevated serum cortisol and corticosterone compared with controls and EM patients [Kruskal–Wallis $p < 0.001$; (A) and (B)]. CM patients who reverted to having EM had their cortisol and corticosterone reduce to control or EM levels [$p < 0.05$; Kruskal–Wallis $p < 0.05$; (A) and (B)], contrary to patients with persistent CM who showed sustained elevated cortisol and corticosterone levels (A and B). C shows that CSF cortisol was observably highest in CM, followed by EM, and control. CSF corticosterone-to-cortisol ratio was higher in controls and EM patients compared with CM patients (D). Serum corticosterone-to-cortisol ratio was increased in CM patients compared with controls and EM patients (D).

CM, chronic migraine; Con, control; CSF, cerebrospinal fluid; EM, episodic migraine; pCM, CM patients with persistent CM after 2 years; rEM, CM patients who reverted to EM after 2 years;

be due to blood brain barrier (BBB) and blood-CSF barrier (BCB) changes in CM favoring cortisol access compared with corticosterone. Both the BBB and BCB express an active efflux membrane transporter called multidrug resistance 1a permeability-glycoprotein (MDR1/P-gp) membrane pump, which hinders cortisol access to the brain.[31,32] Our results suggest that the activity of MDR1/P-gp may get perturbed in CM, allowing increased CNS cortisol access. A previous human experiment has also shown that cortisol is more predominant than corticosterone in stress-type feedback.[31] Under normal conditions, cortisol levels follow a well-regulated chronobiology involving both circadian and ultradian rhythmicities that are important for neuronal and glial physiology.[33,34] As such, persistently elevated cortisol levels are related to recurrent pain attacks, maladaptive pain responses, and neuroinflammation, and can negatively impact neurocognitive and emotional behaviors.[25,33,34]

The cortisol cutoff level of 55 ng/ml (152 nmol/l) which we identified for differentiating CM from EM is less than what is generally found in overactive adrenal gland conditions such as Cushing's

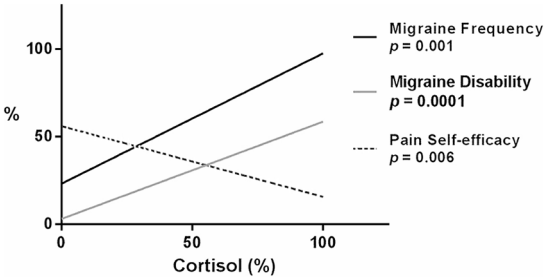

Figure 2. Clinical variables contributing to cortisol changes. Headache frequency and migraine-related disability directly contributed to increased cortisol levels. Pain self-efficacy was inversely related to cortisol levels. Increased pain self-efficacy levels contributed to reduced migraine frequency and lower migraine-related disability. All values were minimum–maximum scaled and shown as percentage.

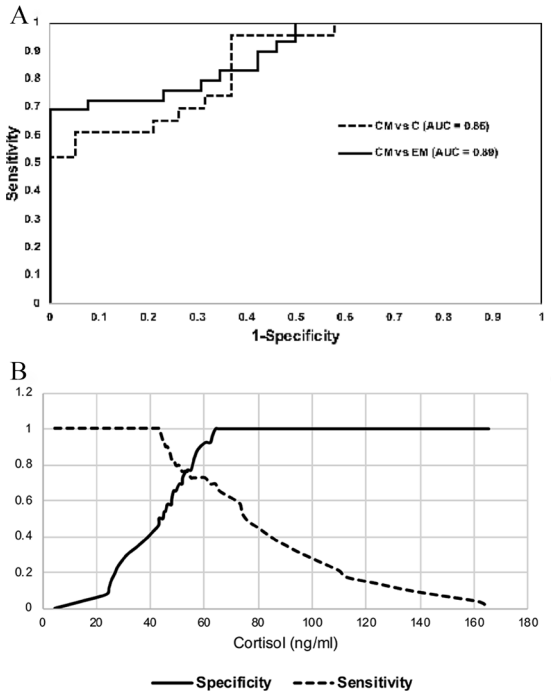

Figure 3. Receiver operating characteristic analysis assessing accuracy performance of serum cortisol in diagnosing CM. The AUC for cortisol-based diagnosis of CM from EM and CM from controls was 0.89 and 0.86, respectively (A). Optimum threshold for cutoff (55 ng/ml) was selected using the cortisol level with equally highest sensitivity and specificity of 72% (B).
AUC, area-under-curve; C, control; CM, chronic migraine; EM, episodic migraine

syndrome.[35] Our ROC results of over 0.80 signify excellent diagnostic performance of discriminating CM from EM as well as CM from controls.[36] Future glucocorticoid assessment studies may benefit from non-invasive sample collection such as saliva or hair. Segmental hair analysis can have the added benefit of providing a longitudinal study design where repeated glucocorticoid measurement can be conducted on the same participants.[37]

Persistent hypercortisolemia can trigger multiple complications such as hypertension, obesity, and depression. which are all known CM comorbidities.[6,38] In addition, hypercortisolemia can cause a secondary headache on its own classified under 10.7 Headache attributed to other disorder of homoeostasis within the ICHD-3.[3] Hence, CM patients may be suffering not only from primary CM itself but also from secondary cortisol-induced headache. Heterogeneity in glucocorticoid receptor sensitivity is known to modulate cortisol activity.[6,39] Some individuals may have cortisol resistance leading to perpetual inflammatory state while others may have increased cortisol sensitivity.[6,39] We speculate that sensitivity pattern and down-/up-regulation of glucocorticoid receptors might modulate burden of migraine attacks in CM. As well, the relationship between cortisol and migraine brings us to the Thompson Cortisol Hypothesis, which proposes yawning (a known premonitory migraine feature) and increased cortisol to be early indicators of neurological condition.[40–42]

Our study shows that optimum CM management may lead to normalization of endogenous glucocorticoids level. Our findings demonstrate that emphasis on improving socio-cognitive skills of pain self-efficacy may be a key area of focus in CM management. To this end, it will be useful to develop and validate protocols which enhance self-efficacy such as regular sleep and regular exercise behaviors. As such, self-management tools and improving coping skills that help to better handle migraine triggers may be effective strategies in CM management. By virtue of being patient-centric, self-management practices can enable migraine sufferers to become more proactive in their migraine management.[43,44] Of note, self-management programs have been shown to be effective in improving pain and depression outcomes as well as lowering disability in chronic pain.[45,46]

Our study has limitations. The following factors could possibly confound our results: migraine medications such as sumatriptan, phase of migraine at time of sample collection, timing of

serum and CSF collection. Cortisol has a diurnal circadian rhythm superimposed by an ultradian pulsatile secretion[47]: this oscillation is modulated by several internal and external stress factors.[48] The diurnal circadian rhythm reaches a peak level just after awakening and falls to its nadir late at night. The ultradian pulsatile secretion happens roughly every 90 min.[49,50] That our serum and CSF were collected between 9 am and 4 pm may influence our results due to circadian rhythmicity and ultradian pulsatility of cortisol secretion. We did not find sex-associated glucocorticoid level differences. Our low sample size is a limitation in our CSF and longitudinal studies; larger sample sized longitudinal studies are needed to validate our results. When designing CSF studies of cortisol, it is worthy to consider confounding factors that impact CSF cortisol level, that is, MDR1/P-gp, steroid metabolizing enzymes, for example, 11β-hydroxysteroid dehydrogenase type 1,[51] and BBB/BCB permeability. In addition, cortisol is known to vary along with diurnal pattern and perceived stress; we did not assess these potential confounders among our patient participants.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Supplemental material

Supplemental material for this article is available online.

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