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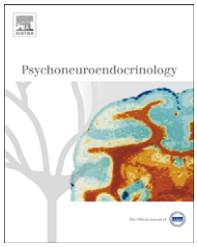

Is stress a trigger factor for migraine?

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Summary
Background: Although mental stress is commonly considered to be an important trigger factor for migraine, experimental evidence for this belief is yet lacking.
Objective: To study the temporal relationship between changes in stress-related parameters (both subjective and objective) and the onset of a migraine attack.
Methods: This was a prospective, ambulatory study in 17 migraine patients. We assessed changes in perceived stress and objective biological measures for stress (saliva cortisol, heart rate average [HRA], and heart rate variability [low-frequency power and high-frequency power]) over 4 days prior to the onset of spontaneous migraine attacks. Analyses were repeated for subgroups of patients according to whether or not they felt their migraine to be triggered by stress.
Results: There were no significant temporal changes over time for the whole group in perceived stress ($p = 0.50$), morning cortisol ($p = 0.73$), evening cortisol ($p = 0.55$), HRA ($p = 0.83$), low-frequency power ($p = 0.99$) and high-frequency power ($p = 0.97$) prior to or during an attack. Post hoc analysis of the subgroup of nine stress-sensitive patients who felt that $>2/3$ of their migraine attacks were triggered by psychosocial stress, revealed an increase for perceived stress ($p = 0.04$) but no changes in objective stress response measures. At baseline, this group also showed higher scores on the Penn State Worry Questionnaire ($p = 0.003$) and the Cohen Perceived Stress Scale ($p = 0.001$) compared to non-stress-sensitive patients.
Conclusions: Although stress-sensitive patients, in contrast to non-stress-sensitive patients, may perceive more stress in the days before an impending migraine attack, we failed to detect any objective evidence for a biological stress response before or during migraine attacks.

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1. Introduction

Migraine is a multifactorial brain disorder characterised by recurrent, disabling attacks of headache, associated autonomic features, and in one-third of patients, neurological aura symptoms (Goadsby et al., 2002). Although the pathogenesis of the migraine features is reasonably well understood, it is not clear how migraine attacks are actually triggered. Mental stressors are psychological events that in potential threaten homeostasis of a living organism (de Kloet et al., 2005) and they are commonly perceived as important trigger factors by both patients and physicians (Fanciullacci et al., 1998), although direct evidence for this claim is lacking. In retrospective questionnaire studies, up to 62% of migraine patients reported that psychosocial stress was an important trigger factor for their attacks (Van den Berg et al., 1987; Robbins, 1994; Zivadinov et al., 2003), but patients have a tendency to overestimate stress on retrospective measures (Wittrock and Foraker, 2001). In cross-sectional studies, migraine patients were found to have elevated plasma levels of cortisol, an indicator for stress, both outside a migraine attack compared to healthy volunteers (Ziegler et al., 1979) and during attacks compared to the inter-ictal phase (van Hilten et al., 1991). Stress-provocation studies, involving mental and physical stressors, have suggested sympathetic and parasympathetic changes in migraine patients outside attacks compared to healthy volunteers (Takeshima et al., 1987; Hassinger et al., 1999; Shechter et al., 2002; Avnon et al., 2004). However, experimental prospective studies examining whether stress-related biological changes are actually temporally related to the onset of migraine attacks, are conspicuously lacking.

We therefore performed a prospective, longitudinal ambulatory study, assessing perceived stress and objective stress-related biological changes in the 4 days prior to an impending migraine attack. We included both patients who claimed that stress would trigger the majority of their attacks (stress-sensitive) and patients who denied such a relationship (non-stress-sensitive).

2. Methods

2.1. Subjects

A total of 69 migraine patients were recruited from our headache outpatient clinic and 27 patients were included in the study. Inclusion criteria were (1) diagnosis of migraine with or without aura according to the criteria of the IHS (codes 1.1. and 1.2.1; Headache Classification Committee of the International Headache Society, 2004) and at least one migraine attack per month in the previous 6 months. Exclusion criteria were (1) pure menstrual migraine, (2) more than 15 days of headache per month, (3) use of beta-blockers and (4) inability to differentiate between migraine and other types of primary headache syndromes. We asked the patients whether they felt that their attacks were triggered by stress and if so, in what proportion. Patients who claimed that $>2/3$ of their attacks were triggered by stress were considered "stress sensitive" and those who reported that $<2/3$ of their attacks was triggered by stress were considered "stress non-sensitive". The study was approved by the local Medical Ethical Committee and the subjects gave informed consent prior to the start of the study. The study was conducted in the period January to August 2004.

2.2. Procedure

Patients filled out two stress questionnaires at the start of the observation period. The first was the Cohen Perceived Stress Scale (Cohen PSS) (Cohen et al., 1983) which is a measure for perceived stress in the past month. It is a 14-item questionnaire and the score ranges from 0 (no stress) to 56 (maximum stress). The second questionnaire was the Penn State Worry Questionnaire (PSWQ) (Meyer et al., 1990), a 16-item questionnaire to assess the trait of worrying (ranging from 16 (minimal worries) to 80 (maximum)). Both questionnaires are used to characterise the study population.

The observation period started at least 3 days after an attack and lasted up to the first day of the next attack. Migraine symptoms and stress events were scored daily around 22:00 h using an electronic diary (described below). Saliva samples were taken three times per day (30 and 45 min after waking up and around 22:00 h, before filling out the stress and migraine questionnaire); heart rate was measured daily between 18:00 and 22:00 h using an ambulatory monitoring system. The timings were chosen in such a way that the recordings would be influenced as little as possible by physical activity during the day.

2.3. Perceived daily stress and migraine symptoms

'Personal digital assistants' devices (Palm Tungsten E) were used as electronic diaries. Data were entered daily around 22:00 h using a database application (Pendragon Forms 3.2, Pendragon Software Corporation, Libertyville, USA) (Laskin and Davis, 2004). Perceived daily stress was measured with the validated Daily Stress Inventory (DSI). In short, this is a 58-item inventory of events experienced in the last 24 h (Brantley et al., 1987). The amount of stress felt in response to each event is rated on a Likert-type scale ($0 =$ event did not happen, $1 =$ event occurred but was not stressful to $7 =$ event caused panic). The perceived daily stress is the sum total of all ratings (DSI-sum). Migraine symptoms were assessed using the criteria of the IHS. The diaries were easy to use and retrospective data entry or alterations were disallowed by the PDA program. An alarm sounded daily at 22:00 h to remind patients to fill out the questionnaires.

2.4. Salivary cortisol

Saliva samples for cortisol assessment were obtained with 'Salivette' saliva collection tubes (Sarstedt, Germany). Each day patients collected three saliva samples, 30 and 45 min after waking up and around 22:00 h. Patients were instructed not to eat, exercise, smoke or brush their teeth 30 min prior to sampling. Patients stored the samples at 7 °C until the end of the observation period. At the end of the observation period, patients were asked to report sampling problems. After centrifugation, samples were stored

at −80 °C until analysis. Cortisol concentrations were determined using Elecsys 2010 (Roche Diagnostics, Mannheim, Germany). The functional sensitivity of this assay is 2 nmol/l (van Aken et al., 2003).

2.5. Heart rate and heart rate variability

Heart rate was measured by using the Vrije Universiteit Ambulatory Monitoring System (VU-AMS, version 4.6, Vrije Universiteit, Amsterdam) (de Geus et al., 1995) between 18:00 and 22:00 h during periods of 10 min every half hour. R–R wave intervals were recorded on line from a 3-lead ECG. Fast Fourier transformation was used to calculate spectral power of the RR interval (Bilchick and Berger, 2006); a trend was removed from the data to reduce the influence of very low frequencies. A cubic spline function corrected for missing values in the time series to result in regularly sampled time series. The data were multiplied by a Tukey window and transformed from the time domain to the frequency domain with the discrete Fourier transform. The spectra were smoothed by a triangular window (width ~0.01 cycles per RR interval). After integration of the area under the curve, the low-frequency (0.05–0.15 Hz) power (LF), reflecting a mix of sympathetic and parasympathetic activity, and the high-frequency (0.15–0.30 Hz) power (HF), largely reflecting parasympathetic activity were calculated.

2.6. Statistical analysis

Temporal changes and differences between the two stress-sensitive subgroups in perceived stress, cortisol (morning and evening), heart rate average (HRA), LF and HF power were analysed using a linear mixed model, with observation day and subgroup as fixed factors. A maximum of four premigraine days were included in the analysis since the premonitory phase may start up to 48 h prior to the onset of the headache phase (Silberstein and Young, 1995; Kelman, 2004). Cohen PSS and PWSQ differences between stress-sensitive subgroups were tested using an unpaired *t*-test. The Bonferroni correction was applied for multiple testing and $p<0.025$ was considered significant.

3. Results

3.1. Study population and observation periods

Of the 27 patients included in the study, 17 patients had a migraine attack during the observation period (Table 1). In 10 patients, we did not measure an attack: 6 patients dropped out because the ambulatory cardiovascular measurements interfered too much with daily activities and 4 patients did not have a migraine attack within the observation period. The duration of the pre-ictal observation period in the 17 patients who had a migraine attack was 4 days in 12 patients, 3 days in 2 patients, 2 days in 2 and only 1 day in 1 patient. Some patients developed an attack within a few days after starting the observation period which is the reason for the variability in observation duration. In 12 patients, the migraine attack began in the morning and in five patients in the afternoon.

3.2. Baseline characteristics

The demographics of the total study population and the various subgroups are given in Table 1. There were nine stress-sensitive and eight non-stress-sensitive patients. The baseline mean PSWQ and Cohen PSS scores were higher in the stress-sensitive patients.

3.3. Temporal changes in stress-related variables

The temporal profiles of the mean scores for perceived stress, morning cortisol, evening cortisol, heart rate, LF and HF power are shown in Figs. 1a–e for the whole study population and in Figs. 2a–e for the subgroup of nine stress-sensitive patients compared to eight non-stress-sensitive patients. In the total study population, the mean score for perceived stress was 17.8±16.2 on the migraine day, the mean morning cortisol 15.6± 9.7 nmol/l, the mean evening cortisol 5.3±2.7 nmol/l and the mean heart rate 79.7±12.1 bpm. Differences between observation days were not significant. The comparison between the stress-sensitive patients with non-stress-sensitive patients revealed an increase in perceived stress in the days prior to an attack in the nine stress-sensitive patients (Fig. 2a), but no other differences between the two groups.

Table 1 Demographic information of study participants.

	All patients ($n=27$)	Patients without an attack ($n=10$)	Patients with an attack ($n=17$)	Stress-sensitive patients ($n=9$)	Stress-insensitive patients ($n=8$)
Mean age (SD)	40.8 (9.9)	39.1 (10.1)	41.8 (9.9)	41.3 (8.5)	42.3 (11.9)
Ratio of men to women	7:20	3:7	4:13	1:8	3:8
Ratio of MO to MA	20:7	7:3	13:4	8:1	5:3
Attack frequency per month (SD)	4.4 (2.7)	3.9 (2.1)	4.7 (3.0)	3.7 (2.1)	5.8 (3.6)
PWSQ				58.3±12.5	39.0±9.8*
Cohen PSS				29.4±7.9	16.4±4.2**

MO: migraine without aura, MA: migraine with aura, PWSQ: Penn State Worry Questionnaire, Cohen PSS: Cohen Perceived Stress Scale (*$p=0.003$ and **$p=0.001$).

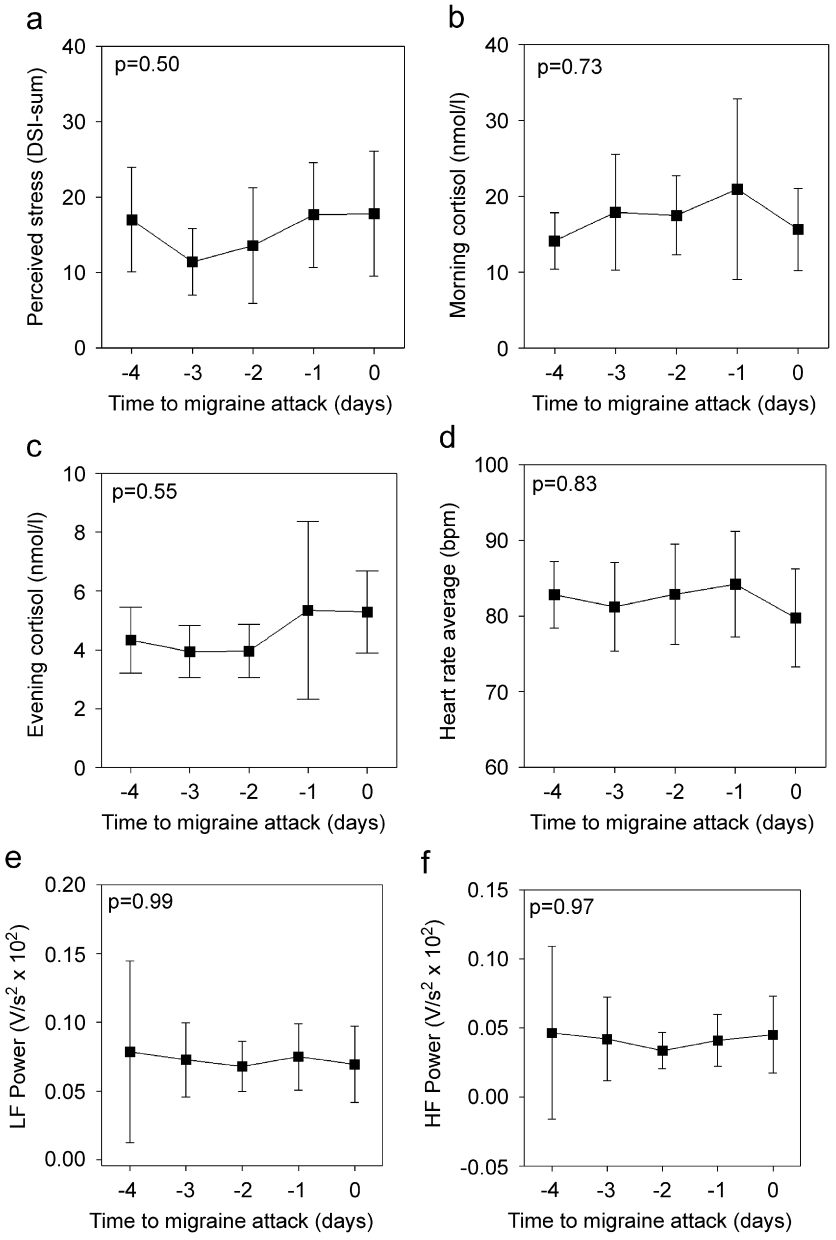

Figure 1 (a–f) Results for all 17 patients who were followed during an attack and for 1–4 days prior to the attack: mean perceived stress (a), mean morning cortisol concentration (b), mean evening cortisol concentration (c), mean heart rate average (d), mean LF power (e) and mean HF power (f) during observation days. Error bars represent 95% confidence intervals.

4. Discussion

In this prospective longitudinal study, we failed to find any objective evidence for a temporal relationship between perceived stress, biological indicators for a stress–response, and the onset of migraine attacks. Although stress-sensitive patients reported an increase in perceived stress in the days before an attack, this was not accompanied by objective signs indicating a biological stress response. The present results extend earlier negative findings on the putative relationship between stress and migraine. Autonomic function tests during migraine attacks failed to show changes in heart rate variability, blood pressure reaction (Havanka-Kanniainen, 1986) or transcranial Doppler response in the middle cerebral artery (Thomsen et al., 1995). In contrast, in the inter-ictal phase changes in both sympathetic and parasympatic autonomic function have been described (Hassinger et al., 1999; Shechter et al., 2002; Avnon et al., 2003). The increase in perceived stress in stress-sensitive patients is in accordance with previous prospective studies in which, however, no biological stress markers were included (Sorbi et al., 1996; Holm et al., 1997).

Stressors can be described as physical and psychological events that, in potential, threaten homeostasis of a living organism (de Kloet et al., 2005). Both acute stressors and stressful daily events have shown to increase cortisol (Brantley et al., 1988; Smyth et al., 1998) and heart rate (Vrijkotte et al., 2000). Although a profound effect of daily stressful events on migraine seems unlikely, we cannot fully exclude an association between mental stress and migraine.

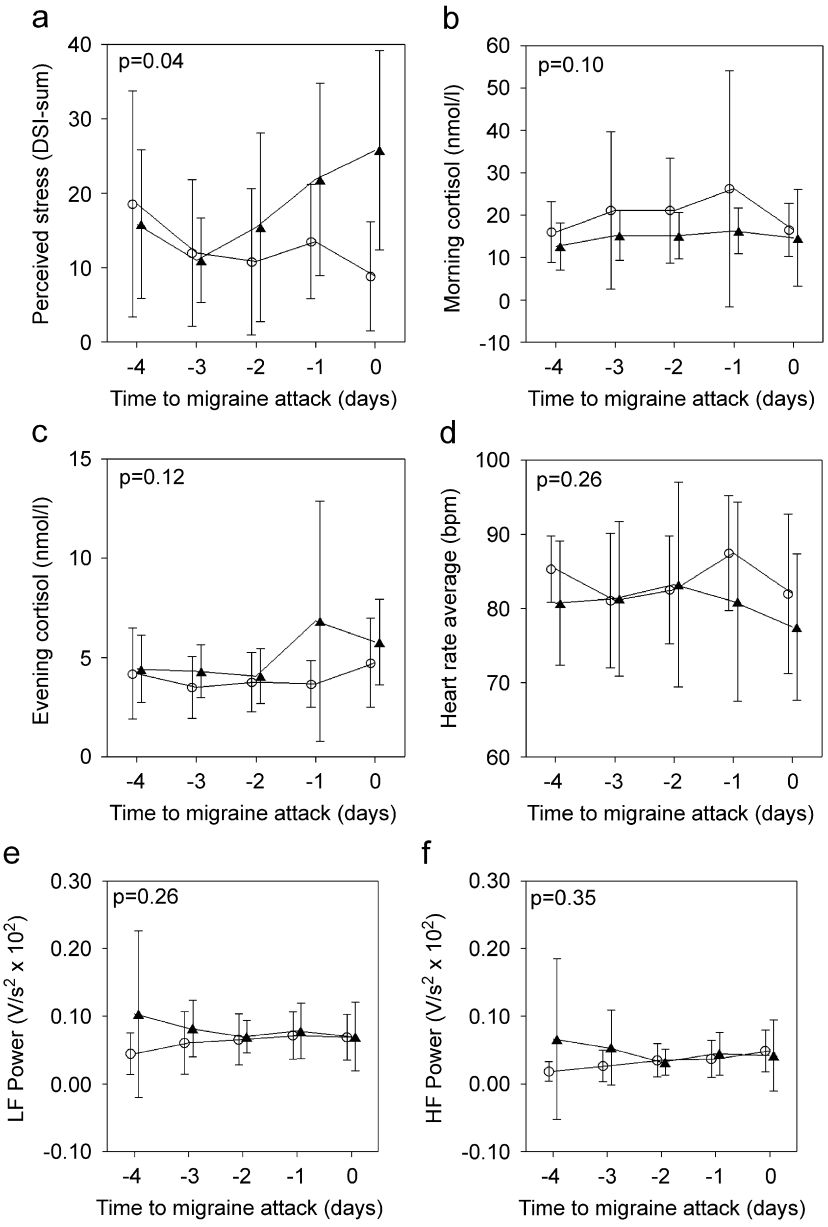

Figure 2 (a–f) Results presented separately for the nine stress-sensitive (filled triangles) and eight non-stress-sensitive (open circles) patients, who were followed during an attack and for 1–4 days prior to the attack: mean perceived stress (a), mean morning cortisol concentration (b), mean evening cortisol concentration (c), mean heart rate average (d), mean LF power (e) and mean HF power (f) during observation days. Error bars represent 95% confidence intervals.

We could only measure 17 migraine patients because of the rather demanding design of the study (daily observations for, in some instances, several weeks because of the unpredictable timing of attacks). Due to the prospective nature of our study, the pre-ictal interval varied between study subjects. Twelve out of 17 migraine patients were studied for the full length of 4 days, 5 patients for a shorter period of time because these 5 patients experienced their attack within a few days after starting the observation period. Because we did not observe differences for our parameters between day−4 and day−2, we believe that this shorter observation period will not influence our findings. Furthermore, the temporal resolution of our measurements was relatively low. Cortisol was measured only in the morning and evening, and heart rate only in the evening to reduce the effect of physical activity. Theoretically, a reduction in physical activity during evening hours because of the prodromal phase of a migraine attack (Bruni et al., 2004) may have masked an association between changes in heart rate and migraine. Also theoretically, due to the low resolution of measurements this could have resulted in missing changes occurring immediately before the onset of an attack. We feel however that, based on the time course of premonitory symptoms, changes are to be expected to occur 12–24 h prior to the onset of attacks (Kelman, 2004).

For our study, we excluded pure menstrual migraine. Free salivary cortisol is decreased during the follicular phase of the menstruation period and in oral contraceptive users

(Kirschbaum et al., 1999). We did not correct for the temporal relation between menstrual cycle or oral contraceptive use and the occurrence of the migraine attack in the 13 women who were included in this study. Therefore, oral oestrogens or the menstrual cycle might have influenced cortisol measurements.

Future studies could include continuous measurements including the full 24 h prior to the onset of attacks, although this will be logistically quite challenging. Although salivary morning cortisol is related to workstress (Lundberg and Hellstrom, 2002), short-lasting daily stressors are probably better assessed using high frequent daily measurements (Smyth et al., 1998). The cortisol response after acute stressors has shown to normalise after 1–2 h (Deinzer et al., 1997). Future longitudinal stress studies in migraine could also include epinephrine and norepinephrine as indicators for sympathetic–adrenal–medullary system-related changes after mental and physical stressors (Lundberg, 2005). Both catecholamines can be measured in urine enabling environmental measurements (James et al., 2004).

In conclusion, we were unable to show objective evidence for a biological stress response before and during migraine attacks. This could reflect a true negative finding or be the result of the discussed study limitations. The reported association between perceived stress and migraine in a subpopulation of stress-sensitive patients might suggest that these attacks were triggered by mental stress. It could be that in these patients migraine attacks are triggered by mental stress or that events are perceived as stressful due to functional brain changes occurring in the very early phase of a migraine attack.

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Conflict of interest

The authors declare no financial conflicts of interest.

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