Hypothalamic involvement in chronic migraine

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Abstract

Objectives—**Chronic migraine (CM), previously called transformed migraine, is a frequent headache disorder that affects 2%-3% of the general population. Analgesic overuse, insomnia, depression, and anxiety are disorders that are often co-morbid with CM. Hypothalamic dysfunction has been implicated in its pathogenesis, but it has never been studied in patients with CM. The aim was to analyze hypothalamic involvement in CM by measurement of melatonin, prolactin, growth hormone, and cortisol nocturnal secretion.**

Methods—**A total of 338 blood samples (13/patient) from 17 patients with CM and nine age and sex matched healthy volunteers were taken. Melatonin, prolactin, growth hormone, and cortisol concentrations were determined every hour for 12 hours. The presence of comorbid disorders was also evaluated.**

Results—**An abnormal pattern of hypothalamic hormonal secretion was found in CM. This included: (1) a decreased nocturnal prolactin peak, (2) increased cortisol concentrations, (3) a delayed nocturnal melatonin peak in patients with CM, and (4) lower melatonin concentrations in patients with CM with insomnia. Growth hormone secretion did not differ from controls.**

Conclusion—**These results support hypothalamic involvement in CM, shown by a chronobiologic dysregulation, and a possible hyperdopaminergic state in patients with CM. Insomnia might be an important variable in the study findings.**

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Chronic migraine (CM) is a debilitating disorder that affects 2.4% of the general population[1] and accounts for most consultations in headache clinics—40%[2] to 65%.[3] Because CM affects people during their peak productive years, it imposes a significant decrease in their quality of life and considerable economical burden to society.[4]

Patients with CM often have a history of episodic migraine beginning in their teenage years. The headache frequency increases over months or years, and the associated symptoms of nausea, vomiting, photophobia, and phonophobia become less prominent.[5] Chronic migraine is a complex syndrome with many associated conditions including acute medication overuse,[6] generalised anxiety disorder (70%),[7] major depression (80%),[7] and insomnia (71%).[8]

Little is known about the causes and mechanisms of CM. The transformation of episodic migraine to CM (>15 days/month) remains an enigma. Several mechanisms have been alleged to be the cause of the change in frequency and symptoms, including chronic neurogenic inflammation, central sensitisation, defective central pain modulation, hypothalamic dysfunction, or a combination of these.

Hypothalamic involvement in the pathogenesis of cluster headache is well known,[9] whereas the role of the hypothalamus in the pathophysiology of chronic migraine has never been studied. For this reason we chose to explore the hypothalamic-tuberoinfundibular system (prolactin, growth hormone), the hypothalamic-hypophyseal-adrenal axis (cortisol), and pineal gland function (melatonin) in CM.

Material and methods

A study was performed from February to April 1999, at Sao Paulo Federal University Headache Clinic. A total of 26 subjects were enrolled in the study. All subjects provided written consent for the experimental procedure approved by the Sao Paulo federal university ethics committee. Seventeen patients, 14 women and three men, aged 31 (SD 9) met the criteria of Silberstein and Lipton[6] for CM. Nine healthy volunteers, seven women and two men, aged 29 (SD 6), also participated in the study as controls.

Eleven of the patients were overusing analgesic drugs (nine were overusing dipyrone, three caffeine, two isometeptene, two acetyl-salicilic acid, two acetaminophen, and two ergotamine. Four were diagnosed with fibromyalgia and eight with insomnia (table 1).

All patients with CM were instructed not to take acute medication more than 2 or 3 days a week during the week before the blood determination. None had taken any preventive medication for at least 3 months before the study. None had hypertension, alcoholism, or history of any relevant medical disease, and none smoked. Hormone concentrations were determined within 1 week after enrollment. Subjects were admitted to hospital and kept under controlled environmental luminosity conditions not exceeding 50 Lux. A venous line was placed at 1800 and blood samples were taken every hour from 1900 to 0700. A total of 13 samples/subject were collected. Women's samples were obtained during the follicular phase of the menstrual cycle.

Concentrations of hormones were determined in each blood sample by radioimmunoassay The intra-assay and interassay coefficients of variation (CVs) for the assays were as follows: prolactin 4% and 7%; cortisol 4% and 6%; growth hormone 5% and 8%; and melatonin 6% and 10% respectively. Four patients did not have growth hormone measured, two because their body mass index was greater than 30, and two because they were 21 years of age or younger (table 1).

Depression was assessed by the Beck depression inventory II,[10] and anxiety by the trait and state anxiety inventory.[11] The American College of Rheumatology diagnostic criteria were used for the diagnosis of fibromyalgia.[12] Patients were diagnosed with insomnia according to the criteria shown:

- Difficulty of sleep onset or maintenance
- Insomnia at least three times a week for at least 1 month
- Insomnia interfering with daily personal functioning
- Patient fulfills the proposed diagnostic criteria of Silberstein and Lipton[6] for CM.

ANALYSIS

The time of peak, peak concentration, area under the curve (AUC), and the average of 13 samples in patients versus controls for each hormone were analyzed. We also accounted for other variables such as depression, anxiety, analgesic overuse, insomnia, and fibromyalgia. A phase delay in the melatonin nocturnal peak was considered if the time of the peak occurred after 0300.[13]

The Mann-Whitney rank sum test and student's *t* test were used to compare the means, peak concentrations, and AUCs between subgroups (depression, anxiety, analgesic overuse, insomnia, and fibromyalgia). Fisher's exact test was used for the time of peak analysis. Analysis of variance (ANOVA) with repeated measures was used to compare
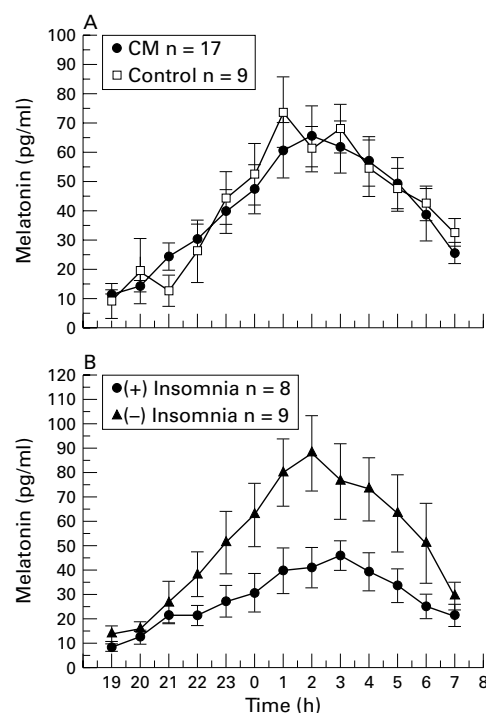

Figure 1   Melatonin nocturnal profile in patients with CM v controls and patients with CM with insomnia v without insomnia.

patients and controls. Pearson's test was used for the correlation analysis. Values are expressed as means (SD). The level of significance was taken as p<0.05.

Results

MELATONIN

Eight patients with CM (47%) had a phase delay in the melatonin peak whereas none of the controls had (p<0.05, fig 1). There was no significant difference in nocturnal melatonin secretion between patients and controls (40.3 (19.1) *v* 43.2 (16.0) pg/ml, respectively).

Patients who had CM plus insomnia (n=8) had melatonin concentrations (28.0 (19.9) pg/ml), AUC (347.5 (128.6) pg.h/ml), and peak concentration (50.3 (19.6) pg/ml) that were significantly lower than those in patients with CM without insomnia (51.9 (10.3) pg/ml; 643.3 (238.0) pg.h/ml, and 111.9 (45.7) pg/ml, respectively, all p<0.05) and that were also significantly lower than those in controls. There was no difference in time of peak or in the prolactin, cortisol, or growth hormone concentrations and between patients with and without nocturnal melatonin phase delay.

PROLACTIN

Fifty three per cent of patients had peak concentrations of prolactin lower than 25 ng/ml (18 (3) ng/ml), but only two of the nine controls did (15.6 ng/ml) (p<0.05; fig 2)). The mean concentration of prolactin in patients with CM was not significantly different from controls (26 (11) ng/ml *v* 37 (17) ng/ml respectively, p=0.06). There was no significant difference in the mean prolactin peak in patients with CM with or without analgesic overuse (23 (8) v 31 (13) ng/ml). There was no

Table 1   Clinical characteristics of the patients

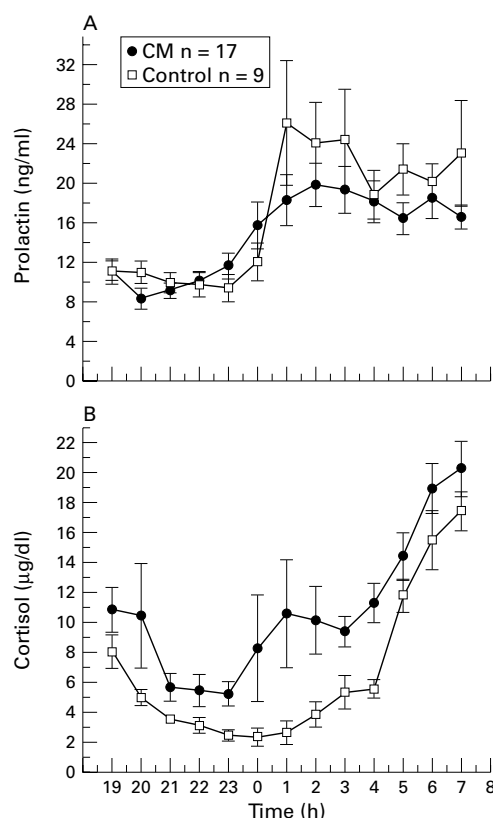| CM patient	Age	Sex	Years of CM	Fibromyalgia	Insomnia	Analgesic overuse
1	27	F	0.25			−
2	21	M	0.86			−
3	25	F	2		+	
4	28	F	2			Aspirin, caffeine
5	47	F	16	+		Ergotamine, dipirone
6	16	F	4			−
7	34	M	20		+	−
8	25	F	3	+	+	Dipirone
9	35	F	10		+	Dipirone, aspirin, acetaminophen
10	23	F	5			Dipirone
11	37	F	6	+	+	Dipirone, caffeine
12	28	F	3		+	Ergotamine, acetaminophen
13	38	M	20	+	+	−
14	46	F	20			Dipirone
15	26	F	1			Dipirone, isomepthene
16	44	F	30		+	Dipirone, caffeine, aspirin
17	27	F	10			Dipirone, isomepthene
Controls						
18	28	F	−	−	−	−
19	31	F	−	−	−	−
20	22	M	−	−	−	−
21	44	F	−	−	−	−
22	24	F	−	−	−	−
23	29	F	−	−	−	−
24	27	F	−	−	−	−
25	30	F	−	−	−	−
26	27	M	−	−	−	−

Figure 2 Prolactin and cortisol nocturnal profile in patients with CM v controls.

significant difference in the mean or AUC between patients and controls or between patients with or without analgesic overuse and with or without insomnia.

CORTISOL

Patients had higher cortisol concentrations than controls (10.3 (4.3) v 6.7 (1.2) µg/dl; higher AUC (101.7 (49.0) v 76.6 (14.3) µg.h/dl); and higher peak (22.5 (14.2) v 18.6 (4.1) µg/dl); all p<0.05, fig 2)). There were no significant differences between patients with or without insomnia, drug overuse, or fibromyalgia.

There was an increase in cortisol concentration between 2300 and 0100 that deviated from the expected pattern with respect to controls, although this increase did not reach significance.

GROWTH HORMONE

There was no difference between patients and controls in growth hormone secretion (mean 2.0 (1.2) v 2.9 (1.9) ng/dl, respectively). Repetitive measure analysis failed to show any significant difference. Analysis of the subgroups did not show any difference in concentrations or time of peak.

Discussion

Prolactin, growth hormone, cortisol, and melatonin concentrations were determined every hour for 12 hours to investigate the role of the hypothalamus in chronic migraine. The hormones were measured during the night as the highest concentrations are usually at this time.

We found decreased prolactin peak secretion, increased cortisol concentrations, a phase delay in the melatonin peak, and lower melatonin concentrations in patients with CM with insomnia.

MELATONIN

Lower melatonin concentrations have been reported in episodic migraine, menstrual migraine, and cluster headache. This is the first study of melatonin in patients with CM.

Forty seven per cent of patients with CM had a significant phase delay in the melatonin peak, and half had insomnia. Melatonin concentrations, peak secretion, and AUCs were significantly lower in patients with CM who had insomnia than in controls and patients with CM without insomnia.

Lower melatonin concentrations, but not a phase shift in the nocturnal peak, have been reported in patients with insomnia.[14] A phase delay in the nocturnal melatonin peak has been reported in patients with delayed sleep phase syndrome (DSPS),[15] and these patients treated with 5 mg melatonin had a great improvement of both sleep and its associated headaches.[16]

The circadian rhythm of melatonin secretion is regulated by the suprachiasmatic nucleus in the hypothalamus.[17] The phase delay in the melatonin peak found in patients with CM supports the theory that hypothalamic involvement in CM leads to a chronobiological dysfunction; however, it is not known whether it is a cause or a consequence of the disease. It could also be due to an underlying delayed sleep phase syndrome and other sleep disorder comorbidity.

Melatonin is a potent endogenous scavenger of reactive oxygen species acting as a neuroprotective agent in processes involving free radical formation and excitatory amino acid release.[18] Evidence in laboratory animals shows that this neuroprotective action is probably mediated through inhibition of NF-kappaB, a peptide upstream of tumour necrosis factor (TNFα), which is known to be involved in inflammatory processes and sensitisation[19] It is hypothesised that dysfunction in melatonin secretion can favour sensitisation and persistence of inflammatory products. Melatonin receptors have also been found in cerebral arteries and in the hypothalamus.[20]

Melatonin may have a role in the treatment of CM, particularly in those patients with insomnia, but further studies are necessary to confirm this. Its other favourable qualities for CM treatment include its analgesic properties,[21] and the fact that it potentiates a GABA inhibitory effect[22] and inhibits prostaglandin E synthesis.[23] Melatonin is a sensitive marker of endogenous rhythms[24] and is thought to play an important part in the adaptative mechanisms to changing enviromental and endogenous stimuli.[25]

PROLACTIN

Patients with chronic migraine show a decreased nocturnal prolactin peak. Studies have reported normal prolactin values in episodic migraine,[26–29] but none of them analyzed the

nocturnal prolactin profile. This is the first study on prolactin concentrations in CM. Based on the hypersensitivity of dopamine receptors that some migraineurs manifest, modulating dopaminergic neurotransmission has been a therapeutic target. This is demonstrated by the induction of yawning, nausea, vomiting, and hypotension by dopaminergic agonists.[30 31] In addition, some migraineurs show allelic variations within the DRD2 gene that has been hypothesised to predispose to a hypersensitive state to dopamine.[32] Prolactin secretion is one measure of dopaminergic function, as dopamine is its main inhibitory factor. The measurement of prolactin can indirectly provide information on the dopaminergic system in CM.

We hypothesise that there is a sustained nocturnal inhibition of prolactin by dopamine and, therefore, an indirect increase in dopamine secretion. Many antidopaminergic agents have been successfully used in acute (droperidol,[33 34] chlorpromazine,[35] prochlorperazine,[36] metoclopramide, domperidone,[37] haloperidol[38]), and preventive (flunarizine,[39] olanzapine (personal communication)) headache treatment. Our findings support the use of these drugs in CM, but clinical trials are needed to confirm their efficacy.

Tumour necrosis factor-α, a potent proinflammatory cytokine involved in pain and inflammatory disorders such as multiple sclerosis,[40] psoriasis,[41] meningitis,[42] and migraine,[43] has been shown to inhibit prolactin release. Its algesic effects are due to sensitising actions on nociceptive afferents, upregulation of other proinflammatory and algesic proteins, and a triggering of cyclooxygenase dependent pathways to synthesise prostaglandins. If we consider neurogenic inflammation as part of the pathogenesis of migraine, it is possible that the suppressed peak of prolactin could also be due to an increase in TNFα.

CORTISOL

Cortisol concentrations are raised in many conditions related to CM, such as depression,[44] anxiety,[45] insomnia,[46] fibromyalgia,[47] and chronic pain.[48] This is the first study of cortisol concentrations in patients with CM. We found higher concentrations of cortisol, suggesting that the hypophyseal-adrenal axis is activated in patients with CM compared with controls. Glucocorticoids exert numerous effects on metabolism, inflammation, and immunity,[49] and play an important part in pain inhibitory mechanisms.[50]

It is also important to consider the long term effect of a hypercortisol state in patients with CM. Arterial hypertension was found by Mathew[8] in the transformation of episodic to chronic daily headache. The increase in cortisol concentrations could be the biological basis for this finding, although patients with hypertension were excluded from our study. Cortisol concentrations should be studied in patients with CM and arterial hypertension in the future.

GROWTH HORMONE

Growth hormone regulation is complex; neuropeptides, neurotransmitters, and opioids are involved. Dopamine also inhibits growth hormone secretion in the hypophysis,[51] and the study of this hormone is another indirect way to address the dopaminergic system. Our data did not show any significant difference in the analysis of growth hormone. However, any differences may not have been great enough to be detected with the small sample studied. The role of growth hormone in headaches remains unknown.

Conclusion

We found an abnormal pattern of hypothalamic hormonal secretion in CM. This comprised: (1) a decreased nocturnal prolactin peak, (2) increased cortisol concentrations, (3) a delayed nocturnal melatonin peak in patients with CM, and (4) lower melatonin concentrations in patients with CM with insomnia. Secretion of growth hormone did not differ from controls. Overall, these results support the involvement of the hypothalamus in the pathophysiology of CM as shown by a chronobiological dysregulation, and a possible hyperdopaminergic state in patients with CM.

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