SHORT REPORT

Cluster headache in women: relation with menstruation, use of oral contraceptives, pregnancy, and menopause

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In contrast with migraine, little is known about the relation between cluster headache and menstrual cycle, oral contraceptives, pregnancy, and menopause. A population based questionnaire study was performed among 224 female cluster headache patients, and the possible effect of hormonal influences on cluster headache attacks studied. For control data, a similar but adjusted questionnaire was sent to healthy volunteers and migraine patients. It was found that menstruation, use of oral contraceptives, pregnancy, and menopause had a much smaller influence on cluster headache attacks than in migraine. Cluster headache can, however, have a large impact on individual women, for example to refrain from having children.

Cluster headache (CH) is a severe primary headache disorder accompanied with autonomic symptoms.[1] It has long been regarded as a ''male dominant'' disease, but male preponderance seems to decrease in recent years.[2 3] In contrast with migraine, which seems to be influenced by hormonal fluctuations in many women,[4] little is known about the influence of hormonal factors like menstruation, use of oral contraceptives, pregnancy, and menopause on CH. The aim of this study was to investigate whether these factors influenced CH episode characteristics.

METHODS

All neurologists (about 560) and general practitioners (about 5800) in the Netherlands were asked to invite CH or CH-like patients to join the study. Patients could also register on a Dutch CH web site. A screening questionnaire based on the International Headache Society (IHS) criteria for CH was used to verify the diagnosis in each patient.[5] Because the study started before 2004, patients were diagnosed according to the 1988 IHS criteria.[6]

Patients

All female patients above the age of 18 fulfilling IHS criteria for CH were asked to fill in a questionnaire, including items about onset of headache, age at first menstruation, duration of menstrual cycle, use of oral contraceptives (not specified whether it was oestrogen containing), pregnancies, menopause, and the influence of these events on frequency and severity of headache attacks. Patients were classified as episodic or chronic CH.

Controls

CH patients were asked to approach a friend, colleague, or neighbour without CH or migraine to serve as healthy control. A number of questions in the questionnaire for controls checked the presence of CH or other headache syndromes. The questionnaire was also sent to 384 women with migraine with or without aura, randomly recruited from a migraine database at our department (n>1200).

Definitions

Ovulatory menstrual cycle was defined as a regular cycle with a duration varying between 21 to 35 days between the first day of two succeeding menstruations.[7] Menopause was defined as at least one year amenorrhoea.

Menstruation related migraine was defined as attacks occurring more often, but not exclusively, during menstruation. Pure menstrual migraine was defined as attacks occurring exclusively during the two days preceding or following the first day of menstruation.[8]

Statistics

Data were stored in a database (MS Access) and analysed using SPSS software. We used relative risks (RR), χ^2 test, and *t* test for comparisons, and considered $p<0.05$ as significant. Data are expressed as RR (95% confidence interval (95% CI)), as mean (SD) or as n (%).

RESULTS

Of 224 women with CH, 196 (88%) responded, as did 211 of the 384 (55%) migraine patients and 189 healthy controls. Seven of the healthy controls seemed to have migraine according to the IHS criteria and were excluded. None had CH.

Demographics

Current age of migraine patients (43.9 years (SD 11.6)) tended to be lower than that of CH patients (47.3 years (SD 13.1), $p = 0.05$). Age at onset of CH was higher (32.3 years (SD 15.2)) compared with migraine (18.1 years (SD 9.2), $p<0.001$). The age at menarche did not differ between groups.

Menarche and menstrual cycle (table 1)

During menstruation mean CH episode frequency was not increased (3.0 (SD 1.9) attacks/day) compared with the non-bleeding period of the cycle (3.1 (SD 2.6) attacks/day). Severity of CH episodes was increased in 17 (9%) women during their menstruation.

Menstruation related migraine was reported by 141 (67%), and pure menstrual migraine was reported by four (2%) patients.

CH patients reported less frequently an increase of attack severity during their menstruation compared with migraine patients (RR 0.33 (95% CI 0.20 to 0.55)).

Use of oral contraceptives (table 1)

Oral contraceptives were ever used by 169 women with CH, of whom 20 (12%) reported an increase of headache after

Table 1 Influence of menstruation, use of oral contraceptives, pregnancy, and menopause on cluster headache attacks

	Cluster headache n = 196	Migraine n = 211	RR (95% CI)	Healthy controls n = 182	RR (95% CI)
Menstruation					
Headache before menarche	7 (4)	74 (35)			
Non-ovulatory menstrual cycle	12 (6)	26 (12)	0.50 (0.26 to 0.96)	11 (6)	1.01 (0.46 to 2.24)
Increased episode severity during menstruation	17 (9)	55 (26)	0.33 (0.20 to 0.55)	–	–
Oral contraceptives (OC)					
Number using OC	169	190	–	–	–
Increase of headache frequency and/or severity using OC	20 (12)	54 (28)	–	–	–
Decrease of headache frequency and/or severity using OC	7 (4)	21 (11)	–	–	–
Pregnancy					
Number ever pregnant	143 (73)	147 (70)	1.05 (0.93 to 1.18)	136 (75)	0.98 (0.87 to 1.10)
Increase of headache severity during pregnancy	3 (2)	7 (5)	0.44 (0.12 to 1.67)	–	–
Increase of headache frequency during pregnancy	2 (1)	10 (7)	0.21 (0.05 to 0.92)	–	–
⩾1 miscarriage	48 (34)	54 (37)	0.91 (0.67 to 1.25)	29 (21)	1.57 (1.06 to 2.34)
Menopause					
Number in menopause	64 (33)	47 (22)	1.47 (1.06 to 2.02)	35 (19)	1.70 (1.12 to 2.43)
Increase of headache severity during menopausal transition	7 (9)	16 (25)	0.32 (0.14 to 0.72)	–	–
Increase of headache frequency during menopausal transition	8 (10)	32 (51)	0.18 (0.09 to 0.36)	–	–
Hysterectomy and/or ovariectomy	22 (11)	11 (5)	2.15 (1.07 to 4.32)	7 (4)	2.92 (1.28 to 6.67)

Data are mean (SD) or n (%) and RR (95% CI). RR is relative risk of CH patients compared with migraine patients and CH patients compared with healthy volunteers.

starting. Seven patients (4%) reported an improvement. A total of 190 migraine patients had ever used oral contraceptives, 54 (28%) experienced increase of headache, 21 (11%) reported a decrease.

Pregnancy (table 1)

The mean number of children did not differ between groups. Fifty three of the 143 CH patients who had ever been pregnant had their first attacks before the first pregnancy, 89 had the first episodes after the first pregnancy. One patient had the first attacks during the first pregnancy. Twenty six of 111 (23%) episodic CH patients who had been pregnant reported that an ''expected'' cluster period did not occur during pregnancy. In eight of these a cluster period started within one month after delivery.

Nineteen patients had had CH attacks during a pregnancy. Of these, 11 reported no increase in severity or frequency compared with attacks outside pregnancy. Three patients reported improvement of the attacks, the remaining five patients reported increased attack frequency and/or severity during pregnancy.

Patients who did not have children at the onset of CH (n = 53) had significantly fewer children (mean 1.8 (SD 1.0) children) than those who had their first CH attack after their first pregnancy (n = 89, mean 2.3 (SD 0.9) children, $p<0.01$). Twenty three patients intentionally had no children: seven reported that having CH was the reason.

In 63 (43%) migraine patients, the attacks were absent during pregnancy, and returned within one month after delivery in 29 of them. Three patients had their first migraine attack during a pregnancy. There were no differences in the number of children between migraine patients who were nullipara during their first attack, and patients who had their first attack after the first pregnancy. Nine patients, of 22 who had no children intentionally, reported that the reason for not having children was migraine.

Menopause (table 1)

CH started during or after menopausal transition in 47 (24%) patients. Of the patients who were in menopause during the study (n = 64), 9% reported increased severity of attacks and 10% increased frequency of attacks.

In migraine patients, headaches started before menopausal transition in 209 (99%) patients.

Migraine patients more often reported increased severity (RR 0.32 (95% CI 0.14 to 0.72)) and frequency (RR 0.18 (95% CI 0.09 to 0.36)) of attacks than CH patients during menopausal transition. Five of the 47 migraine patients who were in menopause during the study reported that the headache had decreased in severity, five other reported a decrease in frequency and two patients reported that the attacks had completely stopped.

DISCUSSION

In this study we found that menstruation, use of oral contraceptives, pregnancy, and menopause had a limited influence on attack characteristics in CH patients in general, a finding that was also found by an earlier study.[3] There were, however, clear examples of the impact of CH on the particpants.

CH during pregnancy may be difficult to treat, as the only treatment that is permitted during pregnancy is inhalation of 100% oxygen, which is effective in about 70% of attacks.[9] We found that patients who had their first attack before their first pregnancy had fewer children than those who already had children at the time of their first CH attack. This was also found in an earlier study.[10] Apparently, the prospect of having to stop effective treatment can be a reason for some women to give up the idea of having (more) children. In contrast, 26 (23%) patients with episodic CH stated to have had no attack during pregnancy, although they had expected such a period. It is not sure if this is caused by the episodic nature of CH or by a possible hormonal influence that resulted in delay of that particular cluster period. To our knowledge, no prospective studies have been performed that would inform us about the intra-individual reliability of ''predicting'' a cluster period.

There are some limitations of this study. Firstly, the data were obtained retrospectively by questionnaire. This can be a particular problem studying features such as menstruation,

as 33% of CH women already were in menopause and may not have remembered menstruation related phenomena in detail. Another limitation concerns the fact that no information was gathered about the exact headache characteristics (frequency, severity) before and after menarche, before and during oral contraceptive use, before and during pregnancy, and before and after menopause. Although this is a limitation, this information would also be prone to be distorted by recall bias and can only be reliable obtained through prospective studies.

Furthermore, the number of responders to the questionnaires in the migraine group was rather low. The reason for this low response may have been that pregnancies or menstruation occurred too long ago. However, to our knowledge this is the first study concerning the influence of menstruation, oral contraceptives, pregnancy, and menopause in a large population based sample of CH women.

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