Trigger factors and mechanisms in migraine

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CHAPTER 1

THE PREVALENCE OF PREMONITORY SYMPTOMS IN MIGRAINE: A QUESTIONNAIRE STUDY IN 461 PATIENTS

Cephalalgia 2006;26:1209-13

Abstract

Migraine attacks are often preceded by premonitory symptoms. Prevalence rates of migraine patients reporting one or more premonitory symptoms show considerable variability and rates range between 12% and 79%. Sources of variability might be differences in study population or research design. Using a questionnaire we retrospectively studied the prevalence of 12 predefined premonitory symptoms in a clinic based population. Of 461 migraine patients, 374 responded (81%). At least one premonitory symptom was reported by 86.9%, and 71.1% reported two or more. The most frequently reported premonitory symptoms were fatigue (46.5%), phonophobia (36.4%) and yawning (35.8%). The mean number of premonitory symptoms per person was 3.2 (± 2.5). Women reported 3.3 premonitory symptoms compared to 2.5 symptoms in men (p=0.01). Age, education, migraine subtype (with or without aura), and mean attack frequency had no effect on the mean number of symptoms per individual. In conclusion, premonitory symptoms are frequently reported by migraine patients. Sensitivity and specificity of premonitory symptoms for migraine need to be assessed using prospective methods.

Introduction

Migraine is a severe paroxysmal neurovascular disorder and considered a major cause of disability by the World Health Organization[1]. The primary cause of a migraine attack is unknown but probably lies within the central nervous system[12]. Prior to the start of the headache phase several non-headache symptoms (often called premonitory symptoms) are reported by migraine patients, such as changes in mood, behavior and sensory perception[4]. In a selected population migraine patients were able to predict an upcoming migraine attack well before the start of the headache phase[131]. Prevalence rates of patients reporting one or more premonitory symptoms ranges between 12%[132] and 79%[133]. One soure of variability in prevalence rate might be differences in study population. In population based studies rates range from 12% in migraine patients without aura to 18% in migraine patients with aura[132], whereas in clinic based studies prevalence rates range from 33%[134,135] to 79%[133]. Other sources of variability might be differences in study design such as preselection of patients or unclear definitions of premonitory symptoms. In this study we assessed the prevalence of 12 frequently reported premonitory symptoms using a questionnaire in a large unselected clinic based population and only symptoms preceding 2/3 of attacks or more were considered a premonitory symptom.

Methods

Migraine patients (diagnosed according to the criteria of the IHS[3]) from the Neurology outpatient clinic of the Leiden University Medical Centre received a questionnaire by mail. A reminder was send out to the patients who had not responded after 8 weeks. The questionnaire addressed migraine characteristics, sociodemographic factors and possible premonitory symptoms. Migraine related variables were: migraine subtype (migraine with or without aura according to the criteria of IHS[3]) and mean attack frequency per month in the last half year. The following sociodemographic variables were included: age, sex and education in 3 categories: primary school or low vocational training, middle academic/vocational training, and higher academic/vocational training. Twelve possible premonitory symptoms were included based on reports in the literature[4,131,135]: Concentration problems, depression, food craving, physical hyperactivity, irritability, nausea, phonophobia, fatigue, sleep problems, stressed feeling, stiff neck and yawning. For every possible premonitory symptom patients answered the question: "How often is a migraine attack preceded by this symptom?" Answers were categorized as never, less

than 1/3 of attacks, 1/3 to 2/3 of attacks or in more than 2/3 of attacks. Photophobia was not included in the questionnaire since co-occurrence of aura symptoms and visual hypersensitivity might introduce bias. The duration of the premonitory phase was not strictly defined. The local ethical committee had approved the study. Symptoms were considered a premonitory symptom when at least 2/3 of migraine attacks were preceded by this particular symptom.

Prevalence of every premonitory symptom was calculated and presented as percentage. The number of premonitory symptoms per individual was calculated and presented as mean (and SD). A difference in mean number of symptoms between subgroups was tested using the non-paired t-test (for sex and migraine subtype) or one-way ANOVA (for age, education and attack frequency). In case of non-normality the Mann-Whitney U test or Kruskal Wallis test were used. The Bonferroni correction was applied for multiple testing and a p value <0.01 was considered significant. The co-occurrence of PS within patients was tested using Spearman's rank correlation coefficient and presented as correlation matrix.

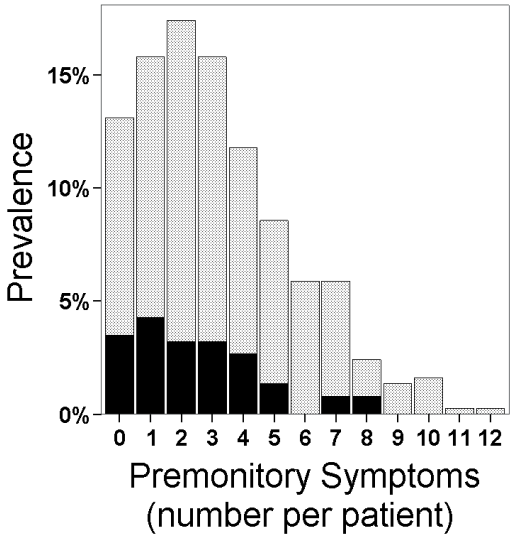

Figure 1 Number of premonitory symptoms per subject. Black bars represent males, gray bars females.

Results

The questionnaire was sent to 461 migraine patients; 374 (81%) responded. The characteristics of the study population are shown in Table 1. Forty-nine patients (13.1%)

reported no premonitory symptoms, 86.9% of patients reported at least one symptom and 71.1% reported two or more (Figure 1). The most frequently reported premonitory symptoms were fatigue (46.5%), phonophobia (36.4%) and yawning (35.8%) (Table 2). The mean number of premonitory symptoms reported per person was 3.2 (SD 2.5). Women reported a mean of 3.3 symptoms compared to a mean of 2.5 in men (p=0.01). The effects of age, education, migraine subtype, and mean attack frequency on the mean number of symptoms per individual were not statistically significant (Table 1). Of the migraine patients 52% had migraine with aura (Table 1). No significant difference in premonitory symptoms was found between migraine subtypes (with and without aura) (Table 2). The co-occurrence of symptoms is presented in Table 3. Depression and irritability showed the strongest correlation, followed by depression and concentration problems and depression and a stressed feeling.

Table 1 Migraine and sociodemographic properties of all interviewed patients.

	Subgroups	N (%)	Mean number of PS per individual (SD)	
Total population		**374**	**3.2 (2.5)**	
Sex				
	Male	74 (20%)	2.5 (2.1)	
	Female	300 (80%)	3.3 (2.5)	**p=0.01**
Age (years)				
	<30	29 (8%)	3.6 (2.5)	
	30-50	172 (46%)	3.0 (2.2)	
	50>	173 (46%)	3.2 (2.7)	p=0.59
Education				
	low	147 (39%)	3.5 (2.4)	
	middle	78 (21%)	2.9 (2.7)	
	high	148 (39%)	3.0 (2.5)	p=0.03
Migraine subtype				
	without aura	179 (48%)	2.9 (2.4)	
	with aura	195 (52%)	3.4 (2.6)	p=0.12
Attack frequency				
(per month)	<2	94 (25%)	2.9 (2.4)	
	2-4	139 (37%)	3.1 (2.4)	
	>4	140 (38%)	3.3 (2.6)	p=0.65

Table 2 Prevalence of premonitory symptoms

Premonitory symptom	Prevalence (%)						
	All patients (N=374)	Male (N=74)	Female (N=300)	P value	MO	MA	P value
Fatigue	**46.5**	39.1	48.3	0.16	47.5	45.6	0.72
Phonophobia	**36.4**	24.3	39.3	0.02	30.7	41.5	0.03
Yawning	**35.8**	31.1	37.0	0.34	34.6	36.9	0.65
Stiff neck	35.0	32.4	35.7	0.60	40.8	29.7	0.03
Nausea	28.6	16.2	31.7	**0.008**	22.9	33.8	0.02
Concentration problems	28.1	29.7	27.8	0.74	20.7	35.1	0.002
Irritability	28.1	25.6	28.6	0.59	24.0	32.0	0.09
Depression	17.6	13.5	18.6	0.29	18.4	16.9	0.70
Craving	17.4	6.7	20.0	**0.007**	14.0	20.5	0.10
Stressed feeling	15.2	14.8	15.3	0.92	14.0	16.4	0.51
Physical hyperactivity	15.0	6.7	17.0	0.03	12.8	16.9	0.27
Sleep problems	13.9	10.8	14.6	0.39	14.0	13.9	0.98

*Prevalence is the percentage of patients of the total population (or subgroup) reporting a certain symptoms. MO denotes migraine without aura, MA migraine with aura.

Table 3 Co-occurrence of premonitory symptoms: Spearman's rank correlation coefficient matrix. Field shading indicates correlation strength.

	SF	SN	PHH	IR	YA	DE	FA	CR	PH	CP	NA	SP
Stressed feeling (SF)												
Stiff neck (SN)	,234											
Physical hyperactivity	,197	,116										
Irritability (IR)	,198	,126	,171									
Yawning (YA)	-,038	,129	,171	,144								
Depression (DE)	,350	,160	,179	,397	,151							
Fatigue (FA)	,171	,203	,149	,290	,220	,313						
Craving (CR)	,120	,048	,262	,200	,113	,084	,053					
Phonophobia (PH)	,082	,144	,228	,306	,084	,190	,164	,211				
Concentration problems (CP)	,132	,101	,137	,324	,057	,350	,267	,137	,294			
Nausea (NA)	,044	,130	,049	,130	,206	,188	,181	,100	,186	,170		
Sleep problems (SP)	,109	,125	,004	,127	,024	,138	,153	,121	,194	,075	,104	

Discussion

The proportion of migraine patients reporting premonitory symptom was high: 86.9% of patients reported at least one symptom. This high prevalence rate is comparable to one previous clinic based study where the rate was 79%[133], but in contrast with two other studies where rates were about 33%[134,135]. Variability in rates might be explained by differences in study design such as preselection of patients[133] or differences in symptoms that are included in the questionnaire[135]. Furthermore, the study of Amery[133] was conducted before the introduction of the IHS migraine criteria. Another source of variability might be the studied population. For instance prevalence rates in population based studies have shown to be as low as 12%[132]. It may be that patients identified in a population based setting are not informed about premonitory symptoms in migraine and, therefore, are less aware of these symptoms. Fatigue was the most common premonitory symptom and the order of reported symptoms is comparable with a previous study in a selected population[131]. In our study the percentage of patients presenting with aura was high. Patients with aura are more likely to consult a neurologist than patients without aura and this differences might be increased due to the fact that all patients in the Netherlands see there General Practioner first in case of complaints. However, no significant difference in PS was seen between migraine subtypes.

Females reported more premonitory symptoms than males. An overlap between premonitory symptoms and premenstrual syndrome might explain this difference[136]. Furthermore more females reported craving and nausea as premonitory symptom compared to males. This is an interesting finding since chocolate and sweet cravings are more common in females than males[137]. Nausea is also more frequently reported in females than in males in acute myocardial infarction[138] and after anaesthesia[139]. The physiological basis for this gender difference is not clear. Besides gender differences co-occurrence of premonitory symptoms within one subject were studied. The strongest associations were found between depression and symptoms such as irritability, concentration problems and fatigue. Co-occurrence of these mood symptoms might not be a coincidence since they are all part of the DSM IV criteria for dysthymic disorder and major depression[140].

There might also be an overlap between premonitory symptoms and trigger factors in migraine. A migraine trigger is any factor that on exposure or withdrawal leads to the development of a migraine attack whereas PS are a consequence of an ongoing attack. For instance mental stress (either the acute episode or the relieve period after an acute episode) is often considered a trigger factor in retrospective questionnaires. However, it is unclear whether migraine attacks can be triggered in an experimental provocation

study[141]. So, It could be that mental stress trigger a migraine attack or that patients perceive more mental stress because they are in the premonitory phase of a migraine attack. Future prospective diary studies or experimental studies are needed to address this question.

This study, as well as other retrospective studies assessing premonitory symptoms in migraine, has some limitations. First, the list of possible premonitory symptoms is based on previous studies[4,131,135] and may seem somewhat arbitrary. To be complete one should do a full exploration of all possible symptoms associated with a migraine attack. Second, non-responders might have introduced some bias. However, the response rate was 81% and there was no difference in age, sex or migraine subtype between responders and non-responders (data not shown). Third, when should a symptom be classified as a premonitory symptom? We excluded photophobia as a premonitory symptom but it could be argued that phonophobia and nausea are actually part of the headache phase and therefore no PS. Furthermore, in this study we considered symptoms as premonitory symptom if 2/3 of attacks were preceded by this particular symptom. In order to assess sensitivity and specificity of individual premonitory symptoms for migraine attacks, possible premonitory symptoms and migraine attacks need to be studied prospectively preferably[131,142]. Also the temporal relation between possible premonitory symptoms, aura and the occurrence of headache needs to be assessed in a prospective design.

In conclusion, premonitory symptoms are frequently reported by migraine patients. Sensitivity and specificity of premonitory symptoms for migraine need to be assessed using prospective methods.