Original Article

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Frequency of Prodromal Symptoms in Patients Suffering from Migraines with Aura

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Abstract

Aim: Prodromal findings of migraine may be overlooked when patients are not questioned well. The International Classification of Headache Disorders classifies the prodromal phase as the symptomatic phase, which may last from 2 to 48 h and manifests before the onset of pain in migraine without aura and before the aura in migraine with aura. This study aimed to evaluate the frequency and duration of prodromal symptoms and their relationship with the presence of aura in migraine patients.

Methods: This observational study was designed as a survey where participants took an online questionnaire between July and November 2020. The questionnaire consisted of two parts; in the first part, the diagnostic criteria for migraine were questioned. After the participants completed the migraine diagnostic criteria, they moved on to the second part, in which headache characteristics, the presence and type of the aura, and prodromal symptoms were asked.

Results: This study included 521 participants with migraine according to the International Classification of Headache Disorders. Two hundred seventy-one participants responded that they had auras; 169 of these experienced visual auras. Considering the frequency of prodromes, the three most common symptoms in participants with migraine with or without aura were sensitivity to light, sensitivity to sound, and mood changes. When the two groups were compared, the percentages for the prodromal symptoms except for neck pain were found to be higher in patients with migraine with aura ($p<0.05$ for each).

Conclusion: Our study's findings suggest that migraine patients with or without aura do not recognize the symptoms in this phase well enough. Also, the most crucial finding was that prodromal symptoms were more common in migraine patients with aura. This could be evaluated as the patients with migraine aura might have interpreted prolonged prodromal symptoms as aura. To predict the onset of attacks in migraine patients and enhance their treatment compliance, knowing and recognizing prodromal symptoms is essential.

Keywords: Migraine, aura, prodromal symptoms, prodrome

Introduction

Migraine is an episodic headache that is the second cause of disability and first among women under 50 years of age, according to the Global Burden of Disease study (1). Considering the ictal disability alone, it has been ranked as the seventh most disabling disease globally (2).

Migraine's clinical presentation changes with age, and it presents in shorter durations with specific paroxysmal symptoms such as abdominal pain, vomiting, or vertigo in childhood as opposed to an absence of autonomic symptoms in the elderly (3).

Attacks often begin with prodromal and/or aura symptoms originating from the hypothalamus, brainstem, or cortex (4). Even though the headache resolves within 4 to 72 h, prodromal signs may begin up to 48 h before the headache, and the postdromal signs may persist for another 48 h after the headache passes, meaning an attack may long outlast a headache. The third edition of the International Classification of Headache Disorders (ICHD-3) classifies the prodromal phase as the symptomatic phase, which may last from 2 to 48 hours and manifests before the onset of pain in migraine without aura and before the aura in migraine with aura. As for the prodromal

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symptoms, ICHD-3 classifies them as the individual or combination of symptoms of loss of appetite, difficulty in concentrating, neck stiffness, increased sensitivity to light or sound, nausea, blurred vision, yawning, and pallor, all of which appear during the prodromal phase (5). Both the words "premonitory symptoms" and "prodromal symptoms" are frequently used in the literature. It seems that there is no consensus on this issue. This survey aimed to evaluate the frequency and duration of prodromal symptoms and their relationship with the presence of aura in migraine patients.

Materials and Methods

Study Design

This observational study was designed as a survey where participants took an online questionnaire due to the pandemic conditions between July and November 2020. Patients between the ages of 18 and 65 who were diagnosed with migraine and followed up on at the Haydarpasa Numune, Umraniye, and Fatih Sultan Mehmet Training and Research Hospitals neurology outpatient headache polyclinics and agreed to participate in the questionnaire study were included in the study. Patients under the age of 18 and over the age of 65 who were diagnosed with non-migraine primary headache or secondary headache and who did not agree to participate in the survey study were excluded from the study.

The questionnaire consisted of two parts, the first of which had five questions inquiring if the participants had frequent headaches, whether these headaches lasted longer than 4 h, limited their physical or mental activities, and whether they were accompanied by nausea, photophobia, or phonophobia. Having completed the diagnostic criteria for migraine, which means participants answered "yes" to at least 4 of the first 5 questions, they proceeded to the second part of the questionnaire. The second part of the survey asked 10 questions about their headache characteristics, such as frequency, duration, and severity of attacks; usage of analgesics; the presence and type of the aura; and type and duration of prodromal symptoms. Consistency among responses was evaluated by 3 neurology specialists.

Compliance with Ethical Standards

The Clinical Research Ethics Committee of the University of Health Sciences Turkey, Istanbul Haydarpasa Numune Training and Research Hospital approved the study (approval no: HNEAH-KAEK-2020/160, date: 27.07.2020). Informed consent was obtained from the patients.

Statistical Analysis

SPSS 20.0 package program was used for the statistical analysis. A chi-square test was used for evaluating the significance of categorical data and comparing the inter-group percentages. The p-value for statistical significance was $p<0.05$.

Results

This study included 1095 participants reporting headaches, and then proceeded with 521 who completed the diagnostic criteria for migraine according to questions in the first part of the survey. The mean age was 37.23±7.98 years and 91% of the 521 participants were women (Table 1).

The second part of the questionnaire investigated if they had ever been diagnosed with migraine. 444 of the participants stated that they had been diagnosed with migraine before, and the mean duration of diagnosis was 141 months. The remaining 77 participants reported no previous diagnosis of migraine. The presence and type of aura were evaluated (Table 1).

While 53 of the 250 participants with migraine without aura stated that they had no prodromes, this number was six times higher for the participants with migraine with aura, which was found to be statistically significant ($p=0.0001$). Considering the durations of prodromal symptoms, both groups had the highest activity in the 1 to 2-hour and >2 to 4-hour periods, and they had similar percentages. The ratio of prodromes persisting for more than 12 h was statistically significant in migraine with aura compared to migraine without aura ($p=0.001$) p (Figure 1).

Considering the frequency of prodromes, the most common symptom in participants with migraine with aura was sensitivity to light, followed by sensitivity to sound and mood changes, respectively, and the three most common symptoms in participants with migraine without aura were the same, with mood changes being the most common, followed by sensitivity to light and sensitivity to sound. When the two groups were compared, the percentages

Table 1. Clinical features of patients with migraine

	Patients with migraine (n=521)
Sex Female Male	 476 (91%) 45 (9%)
Age (years)	37.23±7.98
Diagnosed with migraine before study Yes No	 444 (91%) 77 (9%)
Presence of aura Yes No	 271 (52%) 250 (48%)
Visual aura Yes No	 169 (62.3%) 102 (37.7%)

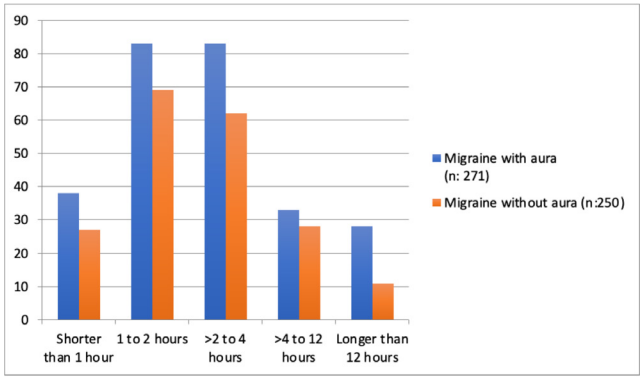

Figure 1. Distribution of the duration of prodromal symptoms among patients with migraine with and without aura

for the prodromal symptoms except for neck pain were found to be higher in patients with migraine with aura ($p<0.05$ for each) (Table 2).

Discussion

The properties and durations of prodromal symptoms in patients who were divided into two groups, namely, migraine with aura and migraine without aura, were evaluated. The number of participants who reported a previous diagnosis of migraine was 444, and 271 of them reported auras. Considering the durations of prodromal symptoms in the migraine with the aura group, only the category with a duration of prodromal symptoms longer than 12 h had significantly higher values compared with the migraine without the aura group. The durations of prodromal symptoms were similar in both groups for the other durations. It was found that only the neck pain among the prodromal symptoms was more common in the migraine without the aura group, while all other symptoms were significantly more common in the migraine with the aura group. Considering the frequency of prodromal symptoms, the most common one was sensitivity to light, followed by sensitivity to sound and mood changes in the migraine with the aura group, whereas the most common symptom was mood changes followed by sensitivity to light and sensitivity to sound in the migraine without the aura group.

In migraine, the headache phase characterized by nausea, vomiting, photophobia, and phonophobia accompanying a moderate-to-severe headache is the best-known phase (6). The fatigue and concentration problems that may develop after the headache are considered the accompanying symptoms (7,8). The phenotype and prevalence of prodromal symptoms have recently been better understood (9,10). Among the typical prodromal symptoms are extreme tiredness, increased yawning, changes in taste, craving for certain foods, attention deficit, and mood changes. The literature has an insufficient number of prospective studies and is often based on retrospective studies. The prevalence of prodromal symptoms in migraine patients ranges from 30 to 90% (11,12). In this study, 88.7% of the patients were reported to have had at least one prodromal symptom, and this ratio was higher in the migraine with aura group compared to the migraine without aura group.

Table 2. Distribution of the frequency of prodromal symptoms among patients with migraine with and without aura

Prodromal symptom	Migraine with aura (n=271)		Migraine without aura (n=250)		p-value
	Number	%	Number	%	
Loss of appetite	39	14.7	16	8.1	0.004
Nausea	144	54.3	85	43.1	0.0001
Sensitivity to light	194	73.2	113	57.3	0.0001
Difficulty in concentrating	165	62.2	78	39.5	0.0001
Anxiety	142	53.5	85	43.1	0.0001
Sleep disorder	102	38.4	55	27.9	0.0001
Yawning	50	18.8	33	16.7	0.073
Facial change	56	21.1	12	6	0.0001
Irritability	119	44.9	61	30.9	0.0001
Neck pain	138	52	105	53.2	0.043
Sensitivity to sound	192	72.4	113	57.3	0.0001
Mood changes	189	71.3	126	63.9	0.0001
Hyperactivity	16	6	1	0.5	0.0003
Osmophobia	36	13.5	10	5	0.0002
Craving for certain foods	56	21.1	26	13.1	0.0016

*Chi-square test was used

The greatest clinical significance of prodromes is that they allow an early diagnosis and thus an efficient treatment of migraine (13). Prodromal symptoms may not be thought to be associated with migraine attacks, so patients should know them quite well. The study by Atalar et al. (14) showed that, migraine affects daily life and causes limitations in all headache phases; prodromal (34%), headache (62%), and postdrome (31%). Patients may mistake these symptoms for migraine triggers, just like in the case of the idea that eating chocolate triggers migraine attacks, while in fact it results from the craving for sweets developing as a prodromal symptom (12). In the study by Karsan et al. (15), it has been shown that situations such as light exposure, sound, or consumption of certain foods, which can be considered triggers by patients, may be associated with prodromal findings.

The durations of prodromal symptoms vary as well. In both groups, symptoms most frequently lasted for 1-2 h, followed by more than 2-4 h. The durations were similar between the migraine with aura and migraine without aura groups, with only the symptoms persisting longer than 12 h being more frequent in the aura group than in the migraine without the aura group (Figure 1). This could be evaluated as the patients with migraine aura might have interpreted prolonged prodromal symptoms as aura.

The most reported prodromal symptoms in the literature are fatigue, mood changes, and yawning (16). In a prospective study where the attacks were triggered with nitroglycerin, the most common complaint was photophobia, with mood changes being less common (17). Consistently with those findings, our study reported sensitivity to light and sensitivity to sound as the most common symptoms in the migraine with aura group. In the migraine without the aura group, the most common complaint was the mood changes (Table 2). The fact that 32.4% of our patients described visual aura suggested that some patients might have evaluated the prodromal symptoms of photic hypersensitivity as aura.

A study by Laurell et al. (16) included 2,223 migraine patients and found prodromal symptoms in 77% of them, with yawning being the most common one, followed by mood changes. It was the first time a study showed that the number and frequency of prodromal symptoms were higher in patients with migraine with aura than in patients with migraine without aura (16). Consistent with this study, our study found that the prodromal symptoms except for neck pain were more common in the migraine with the aura group than in the migraine without the aura group (Table 2). Neck pain is a common finding in patients with migraine (18), and no clear interpretation has been made as to why neck pain is more common in patients with migraine without aura. Similar to our study's findings, sensory hypersensitivity-induced phonophobia and photophobia were the most frequently co-occurring symptoms (16).

Study Limitations

The most important limitation of this study is that it is a survey. As the patients were not examined by doctors, their migraine diagnoses could only be determined based solely on their responses to the questionnaire. The prevalence of migraine with aura was found to be higher than migraine without aura, suggesting that patients might have interpreted the prodromal symptoms as aura. It is assumed that the frequency of prodromal symptoms was found to be high because of memory illusions in patients. Electronic migraine diaries may ensure more reliable results (19).

The frequency and number of prodromal symptoms are higher in women. Furthermore, there is a positive correlation between the duration, number, and severity of migraine attacks and the number of early signs (16). Another important limitation is that this study does not evaluate the prevalence of prodromal symptoms according to sex and migraine attacks.

The strongest aspect of the study was the high number of patients. This allows for better identification of the type and frequency of prodromal symptoms. Additionally, the detailed evaluation of migraine patients with and without aura presents the most comprehensive approach in the literature in this regard.

Conclusion

The most important finding of our study was that prodromal symptoms were more common in migraine patients with aura than in the migraine without aura group. The high frequency and duration of prodromal symptoms in our large patient group suggests that migraine patients with or without aura do not recognize the symptoms in this phase well enough. Prodromal symptoms, which reduce the quality of life and precede the migraine attacks, may contribute to an increased loss of workforce and limitations in daily life. Thus, knowing and recognizing prodromal symptoms better may act as an important factor in predicting the onset of attacks in patients and enhancing their treatment compliance and adherence. Comprehensive studies where patients are interviewed in person are important in that they can provide more precise information on this matter.

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Ethics

Ethics Committee Approval: The Clinical Research Ethics Committee of the University of Health Sciences

Turkey, Istanbul Haydarpasa Numune Training and Research Hospital approved the study (approval no: HNEAH-KAEK-2020/160, date: 27.07.2020).

Informed Consent: Informed consent was obtained from the patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: B.R.H.B., Design: B.R.H.B., Data Collection or Processing: B.R.H.B., G.G., M.F.P., Analysis or Interpretation: B.R.H.B., G.G., M.F.P., Literature Search: B.R.H.B., G.G., M.F.P., Writing: B.R.H.B., G.G.

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