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Research Article

Factors for Progression and Chronification of Episodic Migraine: One-year Face-to-face Follow-up Study

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Summary

Objectives: To investigate the factors influencing progression and chronification of episodic migraine, we conducted a 12-month face to face follow-up study of episodic migraine patients.
Methods: One hundred eighty patients with episodic migraine were enrolled. 120 parameters were analyzed including demographic factors, social and life-style features, comorbid medical illnesses and headache characteristics. After the first evaluation, all patients was scheduled to a structured face to face interview at 3-months interval for one-year.
Results: Thirty-two (17,7%) patients developed chronic daily headache. Four out of 32 (2,2%) had definite chronic migraine. Low education level, obesity, greater tea consumption (≥4 cups/daily), predominantly hot and spicy diet, high headache frequency, long duration of headache and presence of allodynia at baseline, and more days with symptomatic drug intake were significant risk factors for progression and chronification of migraine. Cox regression analysis revealed triptan and NSAID intake, hot and spicy eating habit and allodynia as risk factors for chronification.
Conclusion: Higher amount of tea consumption, hot and spicy diet appeared to be new risk factors for chronification of migraine. Weight gain is one of the most important risk factors. Patients should be warned about the risk factors to prevent chronification.

Key words: Chronic daily headache, Chronic migraine, Migraine, Risk factors, Transformation

Epizodik Migrenin Kronikleşmesinde ve Progresyonunda Etkili Faktörler: 1 Yıllık Yüz Yüze Takip Çalışması

Özet

Amaç: Epizodik migrenin kronikleşmesinde ve progresyonunda rolü olabilecek faktörleri araştırmak amacı ile epizodik migrenli hastaların 12 aylık yüz yüze takip çalışmasını gerçekleştirdik.
Gereç ve yöntem: 180 epizodik migren hastası çalışmaya alındı. Demografik verileri, sosyal yaşam ve yaşam tarzı özellikleri, eşlik eden hastalıklar ve başağrısı özellikleri olmak üzere 120 parametre analiz edildi. İlk değerlendirmeyi takiben tüm hastalar bir yıl boyunca 3 ayda bir yüz yüze yapılandırılmış görüşmeye alındı.
Bulgular: Otuz iki (17,7%) hastada kronik migren gelişti. Otuz iki hastanın dördüne (%2.2) kesin kronik migren tanısı kondu. Düşük eğitim seviyesi, obezite, yüksek miktarda çay tüketimi (≥4 bardak/gün), acılı ve baharatlı beslenme tarzı, yüksek başağrısı frekansı, uzun süreli başağrısı hikayesi, ilk değerlendirmede allodini varlığı ve fazla miktarda semptomatik ilaç alınması migrenin kronikleşmesi ve progresyonu için anlamlı risk faktörleri olarak

saptandı. Cox-regresyon analizinde fazla miktarda triptan ve NSAID alımı, acılı ve baharatlı beslenme tarzı ve allodini varlığı anlamlı risk faktörleri olarak bulundu.
Sonuç: Fazla miktarda çay tüketimi, acılı ve baharatlı beslenme migrenin kronikleşmesi ve progresyonunda yeni risk faktörleri olarak ortaya kondu. Kilo alımı en önemli risk faktörlerinden biridir. Hastalar migrenin kronikleşmesinin ve progresyonunun önlenmesi için risk faktörleri konusunda uyarılmalıdırlar.

Anahtar Kelimeler: Kronik günlük başağrısı, Kronik migren, Migren, Risk faktörleri, Transformasyon

INTRODUCTION

Migraine is a common disorder affecting more than 10% of adult population[26]. Its lifetime prevalence in women and men has been reported to be 15 to 25%, and 6 to 9% respectively[19,30]. Ertaş et al. reported that one-year migraine prevalence was 16.4% in Turkey[14]. World Health Organisation reported migraine as one of the world's top 20 most disabling diseases[35].

Migraine which used to be seen as a purely episodic disorder is now tended to be accepted as a chronic disorder with episodic manifestations. Some migraine sufferers may have attacks of increasing frequency over time leading to chronic migraine (CM) which, is termed as clinical progression of migraine[22]. CM was introduced in 2004 within the second edition of the International Classification of Headache Disorders (ICHD-II) under the title “migraine complications”[16]. The First Revision (ICHD-IIR) provides diagnostic criteria for both CM and medication overuse headache (MOH)[25].

CM forms an important part of the chronic daily headache (CDH). CDH is characterized by a high frequency of headaches with ≥15 headache days per month. Worldwide prevalence of CDH is approximately 4%. Chronic headache patients with medication overuse should be diagnosed as both probable MOH and probable CM. MOH diagnosis is not established until medication is withdrawn for 2 months and the headache resolves or reverts to its episodic pattern[27]. As criticized by many authors the diagnostic criteria of MOH is not practical and detain its use in studies. In most studies the required criterion for diagnosis of MOH, waiting period of two months without any acute medication, make it difficult to differentiate MOH from CM. The prevalence of CM in the population based studies has been reported as 2,4%. Medication overuse has accompanied to CM in 30-80% of the cases[13,18,21,22].

Recent studies have focused on the risk factors that might influence incidence, prevalence, and prognosis of CDH. Recognizing risk factors might help to prevent the transformation of headache, particularly migraine, into CDH and to improve better management strategies for each individual patient. Risk factors for CDH are classified into two groups as modifiable and non-modifiable (age, gender, socioeconomic status, obesity, snoring, smoking, caffeine intake etc.)[2-5,27]. Most of the reported studies about the risk factors conducted by telephone or email and evaluated the subjects only twice, at the beginning and at the end of the follow-up period[6].

In this face to face prospective, 12-month follow-up study, we aimed to identify the risk factors and predictors leading to progression and chronification of migraine.

MATERIAL AND METHODS

This study was conducted at the headache outpatient clinics of University of Uludag, School of Medicine, Department of Neurology and approved by the Ethics Committee of the Uludag University and written informed consent was obtained from all patients.

One-hundred eighty consecutive episodic migraine patients (<15 headache days/month) were included in the study between September 2008 and September 2009. The study consisted of a baseline and five follow-up visits over twelve months.

The questionnaire included questions about sociodemographic variables, headache characteristics, current depression and anxiety, physician-diagnosed comorbid conditions and life-style.

Baseline visit: All subjects were assessed by a fifth-year neurology resident (M.S.), who completed one year headache out-patient clinic rotation. During the structured interview age, gender, BMI, education, income level, marital status, family status, physical activity, social features, religious practices, exercise, questioned. Participants were also questioned about their medical history, duration of history of migraine, headache characteristics; localization, duration (in hours), headache intensity (0–10 scale), headache character (throbbing, aching, pressure, stabbing), accompanying signs and autonomic symptoms, aggravation of headache by physical activity, medication responsiveness, disability, headache frequency ("low" 0 to 4, "intermediate" 5 to 9, and "critical" 10 to 14 days/month), acute headache medication (none, analgesics (simple, NSAIDs), ergots, triptans, opioid), and regular intake (vs no intake) of preventive migraine medication, allodynia, triggers of migraine attacks.

Eating habits was evaluated based on subjects' answers by asking "What kind of food do you mostly eat?"; Mediterranean (vegetables, fish and fruit), Non-mediterrranean (meat, fast-food and pastry).

For allodynia evaluation during a migraine attack one question with multiple modalities was answered by the subjects; "Do you experience pain or any unpleasant sensation on your skin-scalp during a migraine attack with any of the following?" "combing your hair," "shaving," "showering," "exposure to cold or heat", "touching".

The patients were put on appropriate drug regimens (acute migraine attack treatment and/or preventive treatment for migraine). Preventive treatment was prescribed to the subjects who have 3 or more headache days in a month. Propranolol, topiramate, valproic acid and amitriptiline was prescribed for preventive treatment. For acute attack treatment NSAIDs and triptans were given to the subjects. During the baseline visit and follow-up visits only medical treatment arrangements were made and the subjects were told to avoid triggers. Treatment was changed whenever, unacceptable side effects by the subjects or the physicians were reported. No arrangements were made about their diet or weight gain. Subjects continued to take their previously prescribed medications for concomitant diseases.

Patients were asked to keep headache diaries on daily basis for each month until their next scheduled follow-up visit (3, 6, 9 and 12 months after the initial assessment). Headache diaries included data on headache frequency, headache duration (hours-days), headache intensity (VAS), menstrual period, accompanying symptoms (nausea, vomiting, photophobia and phonophobia), and acute medication intake. Patients with a current headache frequency of ≥15 days/month, history of chronic headache, accompanying serious systemic diseases and incapable of keeping diaries were excluded.

Follow-up visits: The same resident (M.S.) evaluated the patients at every visit and checked the pattern and characteristics of the headache reported by the patients against the information reported in the diary. Headache diaries were collected at every follow-up visit and the new ones given to the subjects. Changes in the management of headache were made when necessary. The patients whose headaches fulfilled CDH criteria during the follow-up

visits were excluded from the study. During the last visit, BMI were calculated again.

CDH was defined as headache frequency of ≥15 days/month for at least 3 months. The diagnosis of CM and MOH were made according to the ICHD-IIR[25]. At the end of the follow-up period, subjects were grouped into two groups; Group 1 – EM patients, Group 2 – CDH patients.

Psychiatric evaluation was made by psychiatrists or psychiatric comorbidities were recorded when the subjects reported a psychiatrist diagnosed disorder.

A total of 120 parameters were compared between Groups 1 and 2. Parameters measured only at baseline visit defined as predictors, where parameters continuously monitored during the year defined as risk factors. Descriptive statistics were obtained using SPSS version 13.0 Windows (SPSS Inc., Chicago, IL, USA). Pearson chi-square and Fisher's exact chi-square tests were used for categorical variables. Multivariate analysis was conducted by the Cox regression analysis. In all instances, p-value ≤0.05 were considered significant.

RESULTS

One-hundred eighty episodic migraine patients were recruited in the study and followed for 12 months.

The mean age (18-65) was 39.6 (±10.4) years. The majority of patients were females (91%) and 83% of the study subjects were married. More than half (56.7%) of the subjects were housewives and almost 50% of the patients were high school or college graduates.

No subject was lost during to follow-up. All patients complied with the protocol and the acute attack or preventive treatment regimens. Thirty-two (17.7%) subjects' migraine headache transformed to CDH. Only four of them were CM. Rest of them were classified as MOH/CM. Predictors and risk factors were analyzed separately.

In univariate analysis high educational level and cigarette smokers were significantly high in EM group ($p \leq 0.05$). About 69% of CDH patients reported allodynia during migraine attack ($p \leq 0.05$). There was no difference between the groups in terms of income. Group 2 patients had significantly more psychiatric comorbidity ($p<0.001$) and depression was the most common psychiatric diagnosis (63%) ($p \leq 0.05$) (Table 1).

Hot and spicy eating habit and greater tea consumption (≥4 cups/daily) was significantly more common where smoking was significantly less common in Group 2 (Table 1).

BMI of patients was calculated at initial and last visits. There was no significant difference between the groups in terms of BMI at baseline. At the last visit, significantly more subjects had higher BMI values in Group 2 ($p \leq 0,05$) (Table 1). BMI of Group 2 patients were significantly increased at the last visit when compared to baseline values ($P= 0,019$).

Both ergotamine using subjects and the amount of ergotamine consumption were significantly higher in group 2 than group 1 ($p \leq 0,05$). There was no difference between the groups according to headache characteristics other than allodynia which was reported to be more common in Group 2. None of the subjects reported medication overuse in Group 1. However, analgesic (78%) and triptan (9%) overuse was present in Group 2 subjects ($p \leq 0,05$).

Subjects who developed CDH had a history of migraine more than 4 years. Moreover, headache frequency was >4 days/month in 72% of the subjects in Group 2 during the last three months prior to the initial evaluation (Table 1).

Significantly more patients were on preventive treatment for migraine attacks at baseline in Group 2 ($p=0,05$). No difference between groups in terms of prophylactic treatment regimens was found.

Table 1: Predictors and risk factors for chronification of migraine headache (n=180)

	Group 1 n=148 (%)	**Group 2 n=32(%)**	**P**
Predictors			
Illiterate	2(1,4)	1(3,1)	
Literate	0	3(9,4)*	0,005
≤ 8 years of education	68(45,9)	18(56,3)	
> 8 years of education	78(52,7)	10(31,3)*	0,027
Headache history (>4 years)	128(86,5)	32(100) *	0,026
Baseline headache days/month (5-14 days/month)	59(39,9)	23(71,8) *	0,001
Allodynia	73(49,3)	22(68,8) *	0.046
Anxiety	12(8)	2(6)	
Depression	51(35)	20(63)*	0.003
Alcohol	8(5,4)	1(3,1)	
Coffee (≥4 cups/day)	85(57,4)	16(50)	
Tea (≥4 cups/day)	60(40)	22(69)*	0.003
Cigarette	38(26)	3(9)*	0.046
Exercise	17(11,6)	9(28,1)	
Regular praying	92(62,2)	19(59,4)	
Fasting	115(77,7)	26(81,3)	
Non-Mediterranean diet	75(50,7)	15(46,9)	
Mediterranean diet	131(88,5)	29(90,6)	
Hot-spicy diet	47(32)	17(53)*	0.022
Olive-oil use	88(59,9)	17(53,1)	
Other oil types	110(74,3)	23(71,9)	
Margarine	20(13,5)	5(15,6)	
Basal BMI <25	81 (54,7)	16(50,0)	
Basal BMI 25-30	39(26,9)	10(31,2)	
Basal BMI >30	28(18,9)	6(18,8)	
Risk factors			
Patients on preventive treatment	99(66,9)	27(84,4) *	0,050
BMI at last visit <25	83 (56,1)*	9 (28,1)	0,009
BMI at last visit 25-30	41(27,7)	12(37,5) *	0,010
BMI at last visit >30	24(16,2)	11(34,4) *	0,002
Analgesic overuse	7(4,7)	25(78,1) *	<0,0001
Triptan overuse	0	3(9,4) *	<0,0001

*p≤0,05

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In CDH group headache characteristics showed significant differences as expected. Both headache duration and monthly headache days were significantly increased at the last visit (p‹0.001). On the other hand, headache severity decreased compared to the first visit (p‹0.001).

For multivariate analysis Cox Regression analysis was made. Acute medication (both NSAIDs and triptans), allodynia and hot and spicy food eating habit appeared to be significant in the progression of EM in to CDH (Table 2).

Subjects with episodic migraine in Group 1 were divided in to two groups according to their headache days for further analysis; 0-4 days/month, ≥5 days/month. Those two groups were compared in terms of presence of MOH and BMI as given in Table 3.

Preventive medication data was given in Table 4.

Table 2: Cox regression analyses of predictors and risk factors for chronification of migraine headache (n=180) (only significant ones shown in the table)

Variable	p	HR	%95 CI for HR
Analgesic overuse	<0,001	64,55	18,60-224,24
Triptan overuse	<0,001	73,55	11,16-484,60
Allodynia	0,037	3,19	1,07-9,50
Hot and spicy diet	0,048	2,40	1,00-5,66

Table 3: Comparison of subgroups (according to headache days) of Group 1 patients in terms of presence of MOH and BMIs.

headache days	MOH absent	MOH present	BMI<25	BMI 25-30	BMI>30
0-4 days/m (n=112)	112 (100%)	0 (0%)	70 (62,5%)	25 (22,3%)	17 (15,2%)
≥5 days/m (n=36)	29 (80,6%)	7 (19,4%)*	13 (36,1%)	16 (44,4%)*	7 (19,4%)

*MOH:p<0.001 and BMI p=0.014

Table 4: Use of preventive medications according to groups

Medication	Group 1 n=148 (%)	Group 2 n=32 (%)	Total
Beta blockers	36(24,3)	6(18,8)	42(23,3)
VPA	21(14,2)	7(21,9)	28(15,6)
TPM	16(10,9)	4(12,5)	20(11,2)
Amitriptilin	20(13,5)	6(18,8)	26(14,4)
SSRI	22(14,9)	9(28,1)	31(17,2)
SNRI	20(13,5)	7(21,9)	27(15,0)

VPA: Valproic acid; TPM: Topiramate; SSRI: Selective serotonine selective re-uptake inhibitors; SNRI: Serotonine-Noradrenaline re-uptake inhibitor

DISCUSSION

A total of 180 (91% female, 9% male) episodic migraine patients were enrolled in the study. Thirty-two (17,7%) patients developed CDH. Four out of 32 (2,2%) CDH patients had definite chronic migraine headache. Twenty-eight subjects received the diagnosis of CDH (possible CM or possible MOH) according to the ICHD-2R. In line with the literature univariate analysis revealed low educational level, high number of headache days at baseline, medication overuse, allodynia, comorbid psychiatric disease, increased body mass index was significantly more common in Group 2 than Group 1. Other than known risk factors for chronification and progression hot and spicy diet, consumption of ≥4 cups of tea/day were also determined as risk factors. On the other hand, Cox Regression analysis showed acute medication (triptan and NSAID intake), allodynia and hot and spicy food eating habit as significant predictors and risk factors.

The CM prevalence in our study is 2,2%, in line with the literature and the data of the last headache epidemiological study in Turkey[14,21,30]. Nearly 18% of patients with EM developed CDH (CM and possible MOH/possible CM) during follow-up period, similar to the rates reported by Scher et al[27]. Our study population was based on tertiary headache outpatient clinic. Therefore, our results can not be generalized.

Like many other studies female subjects were predominant in our study. However, there was no significant difference between genders in terms of chronification. In most of the studies, female gender has been accepted as a risk factor for migraine chronification[3]. On the other hand, Wiendels et al. identified female sex as a risk factor for headache, but not for the chronification of headache[34].

High education level was significantly less common in Group 2 when compared to Group 1 ($p<0,027$). Low education level reported to be a risk factor both for

migraine and CDH[1,15,34]. Low income level is also a risk factor both for migraine and CDH[1]. However, in our study there was no difference in income levels between two groups. As our university hospital is a state run hospital, most of our headache outpatient clinic subjects belong to middle economy class. This might have resulted in a selection bias.

Sixty-nine percent of Group 2 patients had psychiatric comorbidity ($p<0,001$), mostly depression 63(%) ($p\leq0,05$). Our findings show similarity with a number of studies reporting high rates of comorbid psychiatric disorders in CDH[17,20,31].

The role of dietary or medicinal caffeine in the development of CDH has been investigated in many studies and has been shown to be a risk factor in migraine progression[27,28]. On the contrary, tea consumption alone has not been evaluated. Subjects in Group 2 were found to consume significantly more tea ($\geq$4 cups/day). The reason, we could not find any association between coffee and chronification may be tea consumption being a cultural habit and more common than coffee consumption in Turkey.

In our study, hot and spicy food eating habit was significantly high in Group 2. To the best of our knowledge, there is no data in the existing literature about the impact of eating habits on migraine chronification. Hot and spicy foods include capsaicine and it is known that capsaicine selectively and potently increases the spontaneous release of Substance-P, calcitonin gene-related peptide, neuropeptide Y and neurokinin A as well as glutamate both in vitro and in vivo[24]. Most of these neuromediators play an important role in migraine pathophysiology. Recent publications suggest a role for transient receptor potential vanilloid type 1 (TRPV1) receptors, which capsaicine bind to, in migraine pathophysiology[23]. We can speculate that paroxysmal capsaicine intake may trigger migraine attacks by stimulating TRPV1 and secreting neuromediators that play an important role in migraine pathophysiology and might cause peripheral and central sensitization which might lead increased attack frequency and chronification of migraine. Or simply, hot and spicy food might increase the appetite and result in more food in take and higher BMI, which might result in chronification of migraine. Further studies should be done to clarify this issue.

The BMI of Group 2 patients were significantly higher than Group 1 ($p<0,05$). At the end of one-year follow-up, Group 2 patients gained significantly more weight than Group 1. Primary headaches have previously been reported more frequent in obese cases. Additionaly, risk of CDH development has been found to be higher in patients with BMI$\geq$30[7-10,29]. Obesity has been related with the severity and frequency of headache attacks of migraineurs in some studies[18]. Frequent headache attacks in obese will lead to central sensitization which will eventually end up with both decrease in treatment response and increased risk of attack relapses[7]. Increased headache frequency was correlated with increased BMI.

Similar to the previous studies, duration of headache history, allodynia, number of days with headache at the baseline visit, medication overuse, symptomatic ergotamine use without overuse were found to be risk factors for chronification. All 32 patients who developed CDH had a history of headache more than 4 years ($p=0,026$). Frequency of attacks and number of days with headache has been reported among the most important risk factors of migraine chronification. The risk of CM development increased in subjects with three or more headaches per month at baseline[5,29]. In our study, 71,8 % of patients in Group 2 were experiencing 5 - 14 headache days per month at the baseline visit ($p=0,001$). As a result of increased headache frequency, the use of preventive treatment was higher in Group 2 ($p=0,05$).

At the end of one year 88% of Group 2 subjects developed medication overuse ($p<0,0001$). The relation of medication overuse and CDH development is still under debate[11].

One of the critical points in chronification of migraine is the importance of frequency of headache at baseline. The high frequency of headache at baseline is suspected to carry risk of progression even in the absence of medication overuse[11,12]. In our study, medication overuse at the end of one year follow-up developed only in Group 1 patients with a baseline headache frequency of ≥5 days/month. But these patients, in line with the above mentioned literature, did not show progression.

Two (6%) of Group 2 patients in our study reported to use ergotamine as a baseline symptomatic treatment. Their ergotamine use was significantly higher than Group 1 patients ($p\leq0,05$). However, as the numbers of subjects with ergotamine use was very small one must be cautious about the results.

Central sensitization, the manifestation of physiological progression, shows itself frequently as cutaneous allodynia during migraine attacks[6,32]. Cutaneous allodynia was significantly more frequent in Group 2 than Group 1 patients.

Cox Regression analysis revealed four significant items in the chronification of EM; triptan and NSAID intake, hot and spicy eating habit and allodynia ($p\leq0.05$).

In our study, all subjects (100%) completed the study protocol and complied with the given treatment. Face-to-face interview, short follow-up intervals and headache diaries all might have increased the compliance rate. Most of the studies about chronification of migraine are retrospective. To best of our knowledge, a great proportion of prospective studies on this subject have used either e-mail questionnaires or phone interviews to obtain follow-up data. We believe that face-to-face interviews might have increased the reliability of the study. On the other hand, relatively low number of the subjects and hospital based (tertiary care) study sample, which may introduce a bias, are the limitations of our study.

As a conclusion, CDH is an important problem for the society and EM sufferers should be informed about the prognosis of the headache and risk factors for chronificaiton. Together with the patients, better management of migraine would decrease the burden of CDH to the individual and to the society.

Conflict of Interest Statement: The authors declare that there is no conflict of interest and have the full Access to the data presented in this study and take full responsibility.

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