

# Impact of Trigger Factors on Clinical Profile of Migraine Patients

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## Abstract

**Introduction:** Migraine is a primary headache disorder. The study was designed to provide a better understanding of the potential role of triggers in the cause of migraine and their impact on its clinical profile and to emphasize strategy of avoiding or coping with dietary and other migraine triggers before initiating long-term drug therapy.

**Methods:** A prospective study was conducted between June 2018 - May 2020 in 323 patients suffering from migraine in outpatient department of Neurology. Patients were labelled as migraine on the basis of Simplified Diagnostic Criteria for Migraine. (Headache Classification committee of the International Headache Society 2013). A structured self designed questionnaire was used to interview patients about endogenous and exogenous migraine triggers. Triggers were correlated with various clinical variables.

**Results:** In 323 patients of migraine males were 30 (9.3%) and females were 293 (90.7%). All had migraine without aura and presented most commonly with phonophobia (88.2%), nausea (87%),

photophobia (76.8%), vomiting (56.9%), and light headedness (38.1%), relief after vomiting (21%), scalp tenderness (4.6%) and vertigo (2.8%). Episodic migraine found more frequently (62.2%) than chronic daily headache (37.8%). Trigger factors were present in 234 (72.4%) and absent in 89 (27.6%) patients. Common triggers were hot climate 118 (36.5%), emotional stress 118 (36.5%), lack of sleep 86 (26.6%) and fasting 78 (24.1%). Common food items to precipitate an attack are tomatoes 35 (10.8%), cheese 24 (7.4%), collard greens 21 (6.5%). Mean duration of headache in patients with history of trigger factors is  $5.67 \pm 4.99$  years with a significant p value ( $p < 0.02$ ). Mean frequency of headache in trigger positive patients is  $15.22 \pm 8.28$  (days/month) and the p value is 0.081. Clinical symptoms significant in trigger positive patients are nausea ( $p < 0.0001$ ) (OR=3.94;95% CI=2.02-7.68), vomiting ( $p = 0.0001$ ) (OR=2.62;95% CI=1.50-4.59), photophobia ( $p < 0.0001$ ) (OR=2.69;95% CI=1.56-4.64), phonophobia ( $p < 0.0001$ ) (OR=5.16; 95% CI=2.54-47), pulsating headache ( $p = 0.006$ ) (OR=2.09;95%CI=1.22-3.56), unilateral ( $p < 0.0001$ ) (OR=2.88; 95% CI=1.74-4.77).

**Conclusion:** Most of the triggers are not easily modifiable, and avoiding triggers may not be realistic. Healthy life style choices like exercise, adequate sleep, stress management and eating regularly may prevent triggers and transformation to chronification over time.

**Keywords:** Migraine; Trigger factors; Clinical symptoms

## INTRODUCTION

Migraine is a primary headache disorder. It is the second most common painful and incapacitating disorder in the world, afflicts approximately 15% of women and 6% of men over a one year period <sup>[1]</sup>. It has a global prevalence of around one in seven people <sup>[2]</sup>. According to Global burden of Disease Study, it ranks as the seventh most common cause of disability worldwide, rising to the most common cause in the age of under 50 <sup>[3]</sup>. Migraine is an important cause of reduced health related quality of life and has a significant and negative personal, societal and economic burden and is often underdiagnosed, misdiagnosed (e.g. in sinusitis) and undertreated in both primary and secondary care perhaps in part because there are no biological markers to confirm the diagnosis <sup>[4-8]</sup>. The latest version of the International Headache society's International Classification of Headache disorders ICHD – III (beta) (Headache Classification Committee of the International headache Society, 2013) <sup>[9]</sup> classifies migraine as: (i) Migraine without aura (ii) Migraine with aura (iii) Chronic migraine (iv) Complications of migraine (v) Probable migraine (vi) Episodic syndrome that may be associated with migraine. A simplified diagnostic criteria for migraine is quite reproducible which mentions as: Repeated attacks of headache lasting 4-17 h in patients with a normal physical examination, no other reasonable cause

for the headache and at least 2 of the these features as (i) Unilateral pain. (ii) Throbbing pain (iii) Aggravation by movement (iv) Moderate or severe intensity plus at least one of the features like Nausea/Vomiting, Photophobia and Phonophobia <sup>[1]</sup>.

Clinical understanding and the definition of Chronic Migraine (CM) have evolved over time. In ICDH- 3b, CM is broadly defined as migraine experienced greater than or equal to 15days/month for more than 3 months with migrainous features, whereas in Episodic Migraine (EM) headache frequency lasts less than 15 days/month <sup>[9]</sup>. Migraine attacks usually occur in response to identifiable triggers <sup>[10]</sup>. Headache triggers have been defined as “factors that, alone or in combination, induce headache attacks in susceptible individuals” <sup>[11]</sup>. Triggers (also called precipitating factors) usually precede the attack by less than 48 h. Headache can be initiated or amplified by various triggers, including stress and negative emotions; hormonal factors for females; flicker, glare and eyestrain; noise; odours; hunger and consumption of certain foods and alcohol; weather; fatigue; and lack of sleep. The knowledge about migraine triggers is important for proper management of the patients. Trigger avoidance is sometimes referred to as ‘headache hygiene’. There is paucity of studies in different ethnic populations of India to identify various triggering factors depending on diverse dietary habits <sup>[12]</sup>. The study was designed with an objective to provide a better understanding of the potential role of triggers in the cause of migraine and to emphasize strategy of avoiding or coping with dietary and other migraine triggers before initiating long term drug therapy. In addition migraine triggers were correlated with various clinical variables to understand the link between the trigger factors and headache in order to yield evidence based therapeutic approach in management protocol.

## **MATERIAL AND METHODS**

A prospective study was conducted between June 2018 – May 2020 in 323 patients suffering from migraine in outpatient department of neurology in a tertiary care teaching hospital. The study received an approval from Institutional Ethics Committee. Patients were labeled as migraines on the basis of Simplified Diagnostic Criteria for Migraine adapted from International Headache Society Classification (Headache Classification committee of the International Headache Society 2013) Patients were enrolled in the study after an informed written consent. A structured self designed questionnaire was used to interview the patients clinically diagnosed as migraine for evaluation of endogenous (stress, negative emotions; hormonal factors for females) and exogenous (flicker, glare, eyestrain, noise, odours, hunger and consumption of certain foods and alcohol, weather, fatigue, and lack of sleep) triggers. Detailed clinical history was taken in all patients and a clinical examination with specific reference to Central Nervous System (CNS)

examination like Romberg's sign, Tandem gait, Drift of outstretched hands, Finger–nose test, Finger dexterity, Binocular visual fields, to confrontation, Eye movements, Facial weakness, Pupillary responses and Horner's syndrome, Tendon reflexes and plantar responses and Fundoscopy was carried out. The location of headache, total duration of migraine, its frequency per month and associated clinical presentation were also noted. Investigations like CT Head and MRI Brain was advised in some patients who did not respond to the initial treatment. The data was analyzed by using Statistical Package for Social Sciences- 22 program (SPSS Inc, Chicago, IL, USA). Fisher's exact test is used to identify the significant clinical symptoms with respect to trigger. The odds ratios (OR) and 95% confidence intervals (CI) were calculated to evaluate the measure of association between clinical variables and trigger factors. Descriptive statistics of clinical symptoms, triggering factors and other numeric variables is reported for an overview description of parameters. Independent sample t-test is employed, to assess the significance of age of patients (years), duration (years) and frequency of headache (days/month) between trigger positive and trigger negative patients. The level of significance was set at less than 0.05 for all analyses. Results were given as mean  $\pm$  SD.

## RESULTS

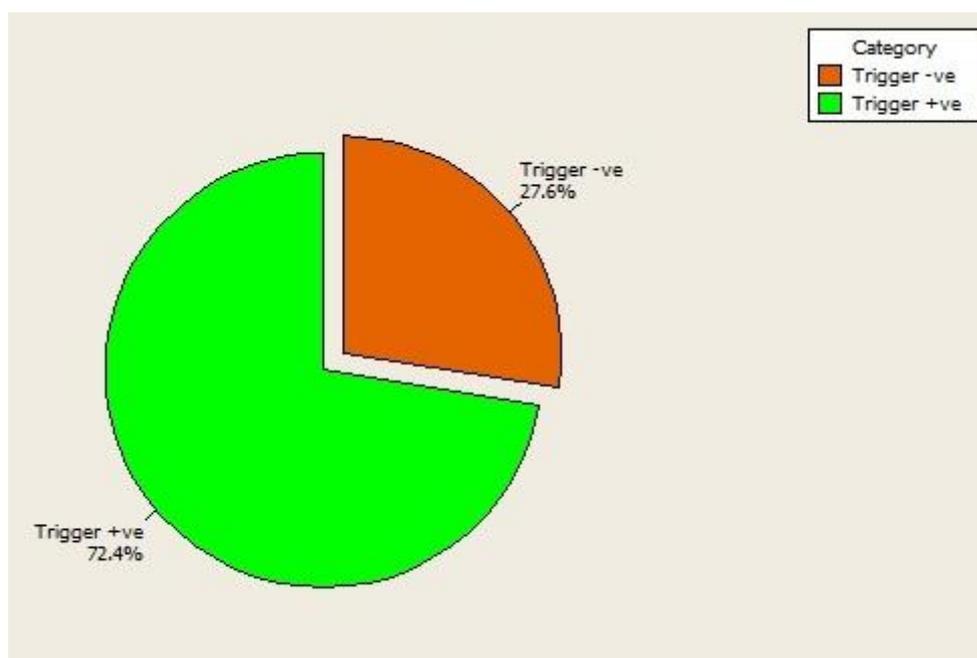
The study included 323 patients of migraine among which males were 30 (9.3%) and females were 293 (90.7%). The mean age of males is  $38.80 \pm 17.53$  years and of females  $35.38 \pm 13.29$  years, with a p value of 0.307. Most of them were in 21-30 years age group (26%), followed by 31-40 years (24.45%). Table 1 summarizes the clinical symptoms, location, frequency of attacks and quality of headache in migraine patients. All the patients had migraine without aura and presented most commonly with phonophobia (88.2%), nausea (87%), photophobia (76.8%), vomiting (56.9%), light headedness (38.1%), relief after vomiting (21%), scalp tenderness (4.6%) and vertigo (2.8%). Patients presented with episodic migraine more frequently (62.2%) than chronic daily headache (37.8%). Classical pulsating headache was found in 69.3% of patients while others presented with pain of mild to moderate severity with no pulsating quality. With regards to location of headache, unilateral was found in 59.1% of patients followed by holocranial (37.8%), occipital (9.9%), frontal (5.6%), bitemporal with supraorbital (5%) and bilateral (1.5%). The mean duration of headache was  $5.3 \pm 4.7$  years and the frequency of attacks was  $14.74 \pm 8.2$  (days /month).

<b>Clinical Symptoms</b>	<b>Present/Absent</b>	<b>Frequency</b>	<b>Percentage</b>
Nausea	No	42	13%
	Yes	281	87%
	Total	323	100%
Vomiting	No	119	43.1%
	Yes	157	56.9%
	Total	276	100%
Relief after Vomiting	No	252	79%
	Yes	67	21%
	Total	319	100%
Light-headedness	No	200	61.9%
	Yes	123	38.1%
	Total	323	100%
Scalp Tenderness	No	308	95.4%
	Yes	15	4.6%
	Total	323	100%
Photophobia	No	75	23.2%
	Yes	248	76.8%
	Total	323	100%
Phonophobia	No	38	11.8%
	Yes	284	88.2%
	Total	322	100%
Vertigo	No	314	97.2%
	Yes	9	2.8%
	Total	323	100%
Frequency of Headache (Days/month)	Episodic Migraine (EM)	201	62.2%
	Chronic Daily Headache (CDH)	122	37.8%
	Total	323	100%
Pulsating quality headache	No	95	30.7%
	Yes	214	69.3%
	Total	309	100%
Unilateral/Hemicranial	No	132	40.9%
	Yes	191	59.1%
	Total	323	100%
Global/Holocranial	No	201	62.2%
	Yes	122	37.8%
	Total	323	100%

Occipital/Nuchal	No	291	90.1%
	Yes	32	9.9%
	Total	323	100%
Bilateral	No	318	98.5%
	Yes	5	1.5%
	Total	323	100%
Bitemporal with Supraorbital	No	307	95%
	Yes	16	5%
	Total	323	100%
Frontal	No	305	94.4%
	Yes	18	5.6%
	Total	323	100%

**Table 1:** Clinical symptoms, location of pain, frequency of attacks and quality of headache in migraine patients.

Trigger factors were present in 234 (72.4%) and absent in 89 (27.6%) patients as shown in Figure 1.



**Figure 1:** Percentage of presence and absence of trigger factors in migraine patients. -ve = trigger absent, +ve = trigger present.

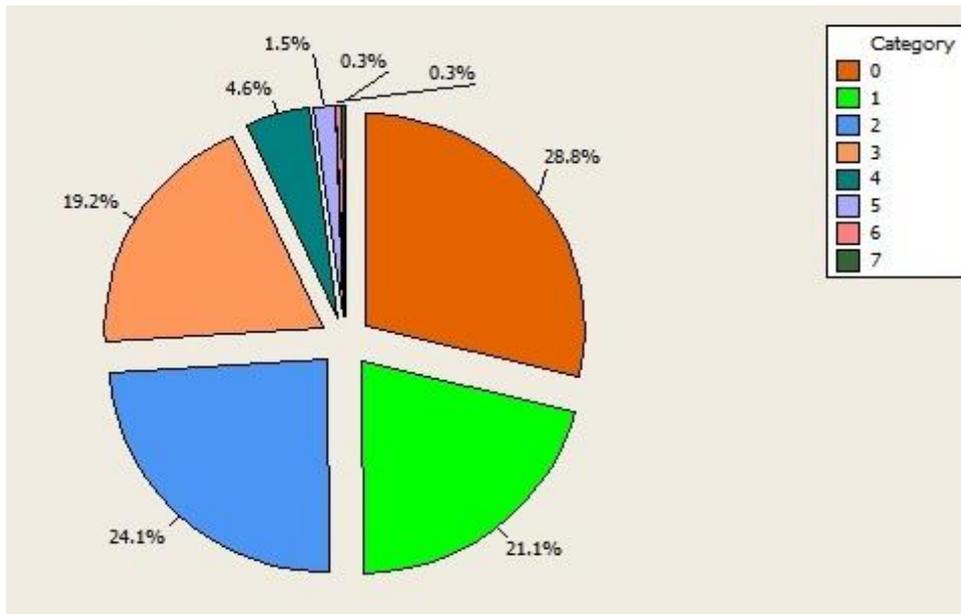
The trigger factors which were observed are depicted in Table 2. Most common among these are hot climate 118 (36.5%), emotional stress 118 (36.5%), lack of sleep/sleep deprivation 86 (26.6%) and fasting 78 (24.1%). The common food items which are seen to precipitate an attack

are tomatoes 35 (10.8%), cheese 24 (7.4%), collard greens /kale (Haakh) 21 (6.5%), (In Kashmir Valley collard greens popularly known as Haakh in local parlance are included in most of the meals and both the leaves and roots are consumed. It belongs to species *Brassica oleracea*) turnips and radish 5 (1.5%), pulses and beans 5 (1.5%), pickles 4 (1.2%) and onions 2 (0.6%).

<b>Trigger Factors</b>	<b>Number of Patients (N=323)</b>	<b>%Age</b>
Tomatoes	35	10.8%
Cheese	24	7.4%
Onions	2	0.6%
Collard greens/Kale (Haakh)	21	6.5%
Hot Climate	118	36.5%
Fasting	78	24.1%
Lack of Sleep/Sleep deprivation	86	26.6%
Emotional Stress/ Anxiety	118	36.5%
Spicy Junk Food	4	1.2%
Exposure to Cold	3	0.9%
Pickles	4	1.2%
Turnips and Radish	5	1.5%
Pulses and Beans	5	1.5%
Workload	2	0.6%
Menstrual Cycle	3	0.9%
Total	508	157.3%

**Table 2:** Trigger factors in migraine patients.

Majority of patients had multiple trigger factors varying from nil to maximum of seven. Figure 2 depicts the percentage of patients with none, one or more than one trigger factors responsible for precipitating an attack.



**Figure 2:** Percentage of zero to seven trigger factors in migraine patients.

Table 3 represents the relationship between mean age of patients, duration of headache and frequency of attack with patients presenting with or without trigger factor in the neurology clinic. The mean duration of headache in patients who present with a history of trigger factor or factors is  $5.67 \pm 4.99$  years with a significant p value ( $p < 0.02$ ). The mean frequency of headache in trigger positive patients is  $15.22 \pm 8.28$  (days/month) and the p value is 0.081.

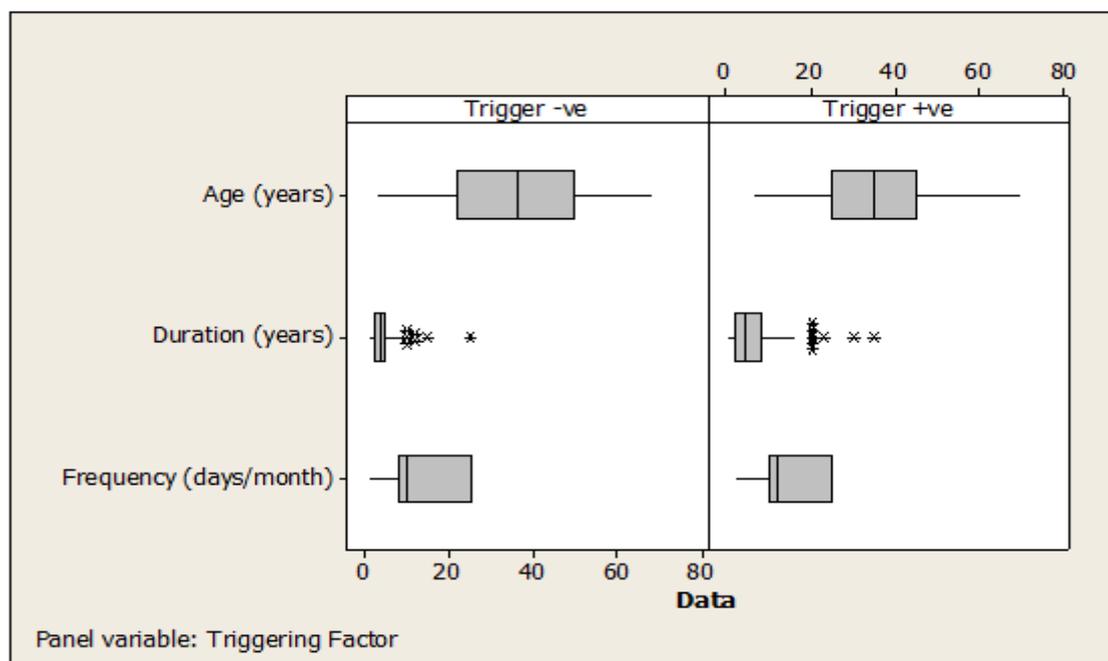
Trigger Factor		N	Mean $\pm$ SD	p-value
Age of subjects (years)	Trigger -ve	82	$35.659 \pm 15.736$	0.974
	Trigger +ve	233	$35.717 \pm 13.028$	
Duration of Headache (years)	Trigger -ve	78	$4.397 \pm 3.822$	0.020
	Trigger +ve	232	$5.672 \pm 4.998$	
Frequency of Headache (days/month)	Trigger -ve	79	$13.342 \pm 8.184$	0.081
	Trigger +ve	231	$15.225 \pm 8.288$	

\*Results are given as Mean  $\pm$  SD. Independent T-test was used to compare groups with significance of  $p < 0.05$ , -ve = Absent, +ve = Present, N frequency

**Table 3:** Relationship of age, duration of headache and frequency of attack in migraine patients with and without trigger.

Figure 3 is a Boxplot representing the results as mentioned above. Table 4 summarizes the

correlation between the clinical symptoms, location of pain, frequency of attacks and quality of headache with the trigger factors associated with migraine patients.



**Figure 3:** Boxplot of Age (years), Duration of Headache (years) and Frequency of Headache (days/month) in migraine patients with respect to trigger factors.

Clinical symptoms	Triggering Factor	Triggering Factor		Total	p-value	Odds Ratio (OR)	95% Confidence interval	
		Trigger -ve	Trigger +ve				Lower Limit	Upper Limit
Nausea	No	23 54.8%	19 45.2%	42 100.0%	<0.0001	3.943	2.023	7.685
	Yes	66 23.5%	215 76.5%	281 100.0%				
Total		89 27.6%	234 72.4%	323 100.0%				
Vomiting	No	42 35.3%	77 64.7%	119 100.0%	0.001	2.626	1.501	4.596
	Yes	27 17.2%	130 82.8%	157 100.0%				
Total		69 25.0%	207 75.0%	276 100.0%				
Relief after Vomiting	No	74 29.4%	178 70.6%	252 100.0%	0.218	1.574	0.823	3.010
	Yes	14 20.9%	53 79.1%	67 100.0%				

Total		88	231	319				
		27.6%	72.4%	100.0%				
Light headedness	No	57	143	200	0.628	1.134	0.683	1.881
		28.5%	71.5%	100.0%				
	Yes	32	91	123				
		26.0%	74.0%	100.0%				
Total		89	234	323				
		27.6%	72.4%	100.0%				
Scalp Tenderness	No	86	222	308	0.768	1.550	0.427	5.626
		27.9%	72.1%	100.0%				
	Yes	3	12	15				
		20.0%	80.0%	100.0%				
Total		89	234	323				
		27.6%	72.4%	100.0%				
Photophobia	No	33	42	75	<0.0001	2.694	1.563	4.644
		44.0%	56.0%	100.0%				
	Yes	56	192	248				
		22.6%	77.4%	100.0%				
Total		89	234	323				
		27.6%	72.4%	100.0%				
Phonophobia	No	23	15	38	<0.0001	5.166	2.548	10.476
		60.5%	39.5%	100.0%				
	Yes	65	219	284				
		22.9%	77.1%	100.0%				
Total		88	234	322				
		27.3%	72.7%	100.0%				
Frequency of Headache (Days/month )	EM	55	138	193	0.139	1.544	0.894	2.668
		28.5%	71.5%	100.0%				
	CDH	24	93	117				
		20.5%	79.5%	100.0%				
Total		79	231	310				
		25.5%	74.5%	100.0%				
Pulsating Headache	No	34	61	95	0.006	2.093	1.228	3.567
		35.8%	64.2%	100.0%				
	Yes	45	169	214				
		21.0%	79.0%	100.0%				
Total		79	230	309				
		25.6%	74.4%	100.0%				
Unilateral/Hemicranial	No	53	79	132	<0.0001	2.889	1.747	4.775
		40.2%	59.8%	100.0%				
	Yes	36	155	191				
		18.8%	81.2%	100.0%				
Total		89	234	323				
		27.6%	72.4%	100.0%				
Global/Holocranial	No	48	153	201	0.073	0.620	0.377	1.018
		23.9%	76.1%	100.0%				
	Yes	41	81	122				
		33.6%	66.4%	100.0%				
Total		89	234	323				
		27.6%	72.4%	100.0%				

Occipital/ Nuchal Headache	No	82 28.2%	209 71.8%	291 100.0%	0.536	1.401	0.583	3.365
	Yes	7 21.9%	25 78.1%	32 100.0%				
Total		89 27.6%	234 72.4%	323 100.0%				
Bilateral Headache	No	88 27.7%	230 72.3%	318 100.0%	0.703	1.530	0.169	13.882
	Yes	1 20.0%	4 80.0%	5 100.0%				
Total		89 27.6%	234 72.4%	323 100.0%				
Bitemporal with Supraorbital	No	85 27.7%	222 72.3%	307 100.0%	0.815	1.149	0.360	3.660
	Yes	4 25.0%	12 75.0%	16 100.0%				
Total		89 27.6%	234 72.4%	323 100.0%				
Frontal Headache	No	84 27.5%	221 72.5%	305 100.0%	0.983	0.988	0.342	2.857
	Yes	5 27.8%	13 72.2%	18 100.0%				
Total		89 27.6%	234 72.4%	323 100.0%				

-ve = Trigger absent, +ve = Trigger present, EM Episodic Migraine, CDH Chronic Daily Headache

**Table 4:** Correlation of clinical symptoms, location of pain, and frequency of attacks and nature of pain in patients with and without trigger.

Nausea was present in 281 patients out of which 215 (76.5%) presented with history of one or more trigger factors with a p value of ( $p < 0.0001$ ), (OR=3.94; 95% CI=2.02-7.68). Vomiting in 130(82.8%) patients with trigger factors with a p value of ( $p = 0.0001$ ), (OR=2.62; 95% CI=1.50-4.59). Photophobia was seen in 192 (77.4%) patients with trigger with a p value of ( $p < 0.0001$ ), (OR=2.69; 95% CI=1.56-4.64). Phonophobia in 219 (77.1%) patients with trigger with a p value of ( $p < 0.0001$ ), (OR=5.16; 95% CI=2.54-10.47). Pulsating nature of headache was seen in 169(79.0%) patients with history of one or more trigger factors, with a p value of ( $p = 0.006$ ), (OR=2.09; 95% CI=1.22-3.56). The pain was most commonly perceived as unilateral /hemicranial in 155(81.2%) patients with triggers and a p value ( $p < 0.0001$ ), (OR=2.88; 95% CI=1.74-4.77). Other clinical symptoms, frequency of headache (days/month) and other locations of headache did not show significant values with respect to presence or absence of different trigger factors.

## RESULTS AND DISCUSSION

The present study observed that in our ethnic population all the patients had migraine without aura and most frequently reported symptoms were phonophobia, nausea, photophobia, vomiting, light headedness, relief after vomiting, scalp tenderness and vertigo. Pulsatile pain was found in 69.3% and unilateral pain in 59.1% of migraineurs Table 1. Similar findings have been observed in a US population based survey conducted by Lipton et al.,<sup>[13]</sup> which shows photophobia (80% of migraineurs), phonophobia (76% of migraineurs), nausea (73%), vomiting (29%), pulsatile pain (85% of migraineurs) and unilateral pain in 59%. Our study shows trigger factors were present in 72.4% of patients. The commonest trigger factors which have been identified are hot climate, emotional stress/anxiety, lack of sleep/ sleep deprivation and fasting. Common food items identified as triggers were tomatoes, cheese and collard greens Table 2. Majority of patients had multiple trigger factors, with no trigger in 28.8% of migraineurs, one in 21.1%, two in 24.1%, three in 19.2%, four in 4.6%, five in 1.5%, six in 0.3% and seven in 0.3% of patients. According to study conducted by Martin et al.,<sup>[14]</sup> anxiety emerged as one of the most common triggering factor of migraine. Predominantly individuals react to the headache in the form of anxiousness, related to cause of headache, how to manage it and its impact on them. The anxiety reaction creates negative feedback loops, thereby increasing the perception of pain and exacerbates anxiety trigger factor. A clinical study by Kelman<sup>[15]</sup> found that 76% of migraineurs responded affirmatively when asked whether they had triggers for migraine attacks. Moreover, Van den Berg et al.,<sup>[16]</sup> indicated that migraineurs reported a median of 3 triggers with a range from 1 to 12. These studies are consistent with our study where triggers range from nil to 7. Fasting was one of the common trigger in our study (24.1%). In our ethnic population fasting is commonly observed as a religious obligation especially in the holy month of Ramdhan. Missing a meal due to occupational reasons is yet another reason for fasting. Similar findings have been reported in a study conducted by Yadav et al., in India<sup>[17]</sup>. Stress hormone release and hypoglycemia has been implicated to trigger a migraine attack due to fasting<sup>[18]</sup>. Water deprivation has also been attributed to trigger migraine attack<sup>[19]</sup>. Diet can play an important role in the precipitation of headaches in children and adolescents with migraine. The list of foods, beverages, and additives that trigger migraine includes cheese, chocolate, citrus fruits, hot dogs, monosodium glutamate, aspartame, fatty foods, ice cream, caffeine withdrawal, and alcoholic drinks, especially red wine and beer<sup>[20]</sup>. In our study the dietary triggers which have been implicated to trigger headaches are tomatoes, cheese, collard greens, pickles and junk food. A study carried by Spierings et al., reported the factors indicated most frequently as precipitating headache by the patients with migraine were stress/tension (84%), not eating on time/ fasting (82%), fatigue (79%), and lack of sleep (74%)<sup>[21]</sup>. These studies are consistent with our study except for certain dietary items which

are native to our ethnic population. In current study clinical symptoms have been correlated in patients with and without precipitating factors for migraine attacks. Very little studies have been so far conducted where the influence of trigger factors on clinical presentation has been studied. In our study clinical symptoms like nausea, vomiting, photophobia, phonophobia, pulsatile and unilateral location of headache show significant p-values in patients who have established precipitating factors. The study has paved way for further research with a robust data to establish a link between intensity and degree of occurrence of clinical symptoms and presence of trigger factors in patients of migraine.

## **CONCLUSION**

Both EM and CDH are significant health issues, because much suffering adversely affects an individual's functional capacity and has a high societal cost. Headaches are precipitated by triggers and advice to avoid triggers is a standard feature of clinical management. But currently the concept of "coping with triggers should replace the idea of avoiding triggers". A behavioural management involves graded exposure to desensitize the headache sufferers to some triggers, whilst reserving avoidance only for selected ones with an increased potential for eliciting headache with a secondary benefit of less restricted lifestyle, encouragement of a well balanced diet, avoidance of inadequate or excessive sleep and enhanced self efficacy for preventing headache. This may be preferable to long-term prophylactic drug treatment with attending adverse reaction.

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## **CONFLICT OF INTEREST**

There is no conflict of interest among the authors.

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