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Neurological comorbidities in migraine and associated white matter hyperintensities in patients undergoing MRI.

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Abstract

Background: Migraine is the most common disability causing headache. Migraine patients have frequently associated white matter Hyperintensities on Brain MRI. In this study we aimed to establish a relationship between clinical profile of Migraine and white matter Hyper intensities.

Methods: Cross sectional analytical study of Migraine patients was conducted in GMC Srinagar, Department of Medicine for two years. Detailed history, Examination and MRI Brain of patients was done.

Results:0ut of 90 patients,75.6% were females and 24.4% were males, mean age of patients was 34 years, 46.7 % had white matter Hyper intensities, while 53.3 % of patients didn't had any presence of white matter Hyper intensities. We tried to establish a relation between clinical profile of Migraine and White matter Hyper intensities.

Among the patients with vomiting, 80% had white matter hyperintensities. 58.8% of the patients with severe headache had white matter hyper intensities while as it was absent in 41.2% of the patients. 69.2% of the patients with more than one attack per week had white matter hyperintensities while as 30.8% of the patients had no white matter hyperintensities.

Conclusions: Our study concludes that age, duration of migraine, intensity of pain, nausea/vomiting, frequency of attacks, duration of attacks, intensity of migraine as

per MIGSEV scale have a role in the presence and absence white matter hyper intensities. Our study found that the presence of white matter hyper intensities has more chances in patients who are aged, have frequent attacks of migraine, have intense pain, feel highly nauseated, have longer duration of attacks and have Grade III migraine on MIGSEV scale.

Keywords: Migraine, white matter Hyper intensities, MRI Brain, MiGSEV scale

Introduction

Migraine is a ubiquitous neurologic disorder that is estimated to affect approx. imately 1 billion people worldwide, predo minantly females[1]. Migraine is the second most prevalent neurologic disorder (after tension-type headache), with a female-to-male ratio of 3:1 and an estimated 1-year prevalence of approximately 15% in the general population[1].

The prevalence peaks between the ages of 35 and 39 years, and about 75% of affected persons report the onset of migraine before the age of 35 years[1,2]. The diagnosis is based on clinical criteria provided by the International Classification of Headache Disorders, 3rd edition (ICHD-3)[3]. Broad clinical features suggestive of migraine are recurrent headache attacks of moderate-to-severe pain intensity, with a duration of 4 to 72 hours[3].

A diagnosis of migraine should be considered if a typical attack of head pain is unilateral, pulsating, and aggravated by physical activity[3]. Common accom panying symptoms are nausea, vomiting, photo phobia, and phonophobia[3]. Some persons report that the migraine is preceded by an aura, which is characterized by reversible focal neuro logic symptoms, typically compri sing visual or hemisensory disturbances[3].

The trigemino vascular system is considered to be the anatomical and physio logical substrate from which nociceptive trans mission originates and yields the perception of migraine pain[4]. In 1984, Moskowitz proposed that migraine initiation depends on activation and sensitization of first-order trigemino vascular neurons. The afferent fibers of these neurons innervate the meninges and its vessels and also project to structures in the central nervous system5. Activation of these neurons releases vasoactive peptides and induces local inflammatory reactions[5].

This process, in turn, sensitizes and discharges second-order neurons in the brain stem and then third-order neurons in the thalamus[4], until ultimately nociceptive impulses reach the somatosensory and other cortical areas that are involved in pain perception[4]. Pharmacologic therapy, the mainstay of treatment, includes initial and preventive medications, with nonpharmacologic therapies used as adjuncts to medication[6].

Migraine sometimes is associated with White Matter Hyperintensities (WMHs)[7], which are hyperintense brain lesions in T2-weighted and Fluid-Attenuated Inversion Recovery (FLAIR) images[8].

The relation between WMHs and the clinical features of migraine is still unclear. Some studies suggested that WMHs are more frequent in migraine patients with more headache attacks[7]. Other studies demo nstrated that disease duration was associated with WMHs in migraine patients[9]. One study found an association between WMHs and the older age of patients[10].

Other studies have reported that WMHs are not associated with disease duration or attack frequency[11]. Understanding the relation between WMHs and migraine may help patient management[12]. Previous population-based studies have indicated that WMHs in migraine are not associated with stroke or the decline in cognitive function[13, 14]. Eggers proposed that WMHs might be caused by multiple micro emboli, which are induced by

platelet aggregation abnormalities usually observed in migraine patients[15]. This supports that WMHs may reflect an abnormal internal environment in patients. A previous study has shown that hyper homo cysteine Mia is associated with migraine, especially migraine with aura[16].

A high level of homocysteine is associated with vascular insults such as thrombosis, atherosclerosis, and ischemic diseases, such as myocardial infarction and ischemic stroke[17, 18, 19].

Hyper homo cysteine Mia may stimulate the initiation of migraine attacks through changes in pain threshold[20]. A previous study revealed that higher levels of homo cysteine are related to higher severity and frequency of migraine attacks[21], whereas others showed no relationship between homo cysteine levels and frequency of these attacks[22]. Association between elevated serum homo cysteine level and WMHs have been documented in several studies[23, 24, 25]. This study was aimed to assess the frequency of migraine attacks and duration of migraine in years and WMHs.

Material and methods

This cross-sectional study was conducted in post graduate department of medicine Government Medical College Srinagar after obtaining ethical clearance from the institutional ethical committee.

patents fulfilling the inclusion and exclusion criteria were included atter obtaining proper informed consent in local language. This study was completed within the span of 2 years

Inclusion criteria

All patients fulling the ICHD-3 criteria for migraine were included.

1. At least five attacks fulling 2-4
2. headache attacks lasting 4-72 hours
3. Headache has two of following four characteristics.
   a) Unilateral
   b) Pulsating
   c) Moderate or severe in intensity
   d) Aggravated by physical activity
4. During headache at least one of the following.
   a) Nausea and or vomiting
   b) Photo phobia and phonophobia

We also included patients with history suggestive of vascular, demyelinating, infection or other disorders with CNS pathology and patients with focal neurologic deficits, all having underlying migraine.

Exclusion criteria

Patients with hyper tension, dyslipidemia, diabetes mellitus, cardiac disease, history suggestive of any malignancy.

Study method

Participants were defined as having migraine if they advocated a lifetime history of headaches that;

1. Lasted 4 or more hours in duration.
2. Were characterized as throbbing, pounding or pulsating in nature or that were unilateral in locations.
3. Were accompanied by nausea. vomiting or sensitivity to light or sound and
4. Constituted one or more years with history of such headaches. Headaches lasting at least 4 hours but not meeting all of the other criteria were defined as non-migraine headaches. Relation between white matter hyper intensities and clinical profile of migraine patients was established.

Results and observation

Table 1: Gender Break-up of Patients.

Gender	Frequency	Percentage
Males	22	24.44%
Female	68	75.55%

Graph 1:

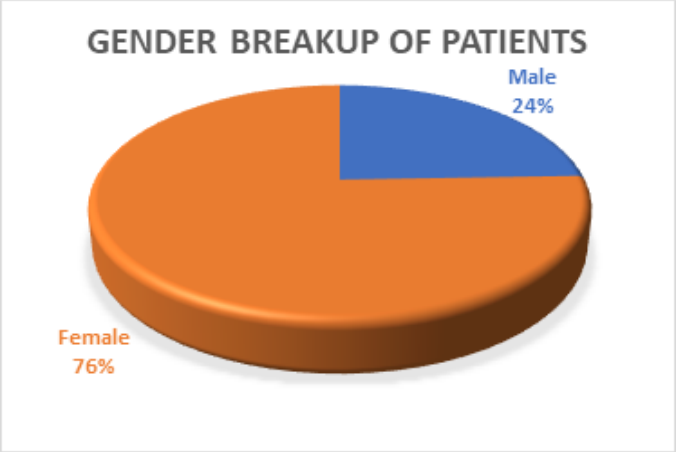


Table 2: Migraine and Aura.

Aura in Patients	
Absent	50
Present	40
Total	90

Graph 2:

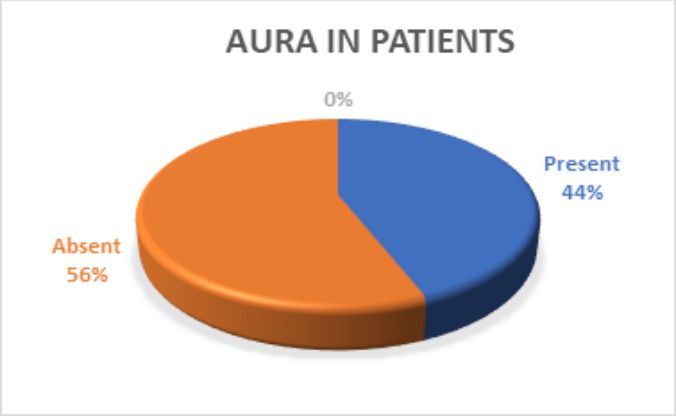


Table 3: Age wise break-up of patients.

Age wise breakup of patients	
Age Group in Years	Frequency
10-20	2
21-30	36
31-40	34
41-50	18
Total	90

Graph 3:

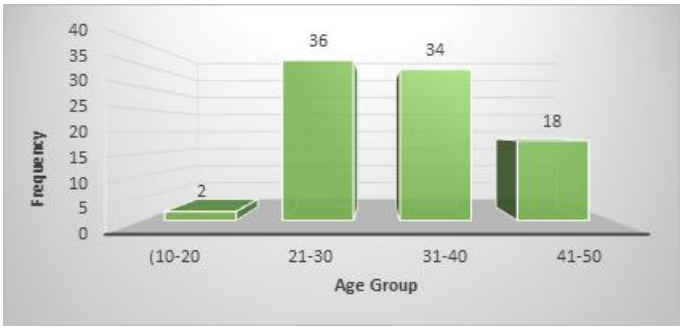


Table 4: Duration of migraine (in Years)

Duration of Migraine (years)	Frequency
2	6
3	8
4	12
5	6
6	8
7	8
8	10
9	12
10	12
12	8
Total	90

Graph 4:

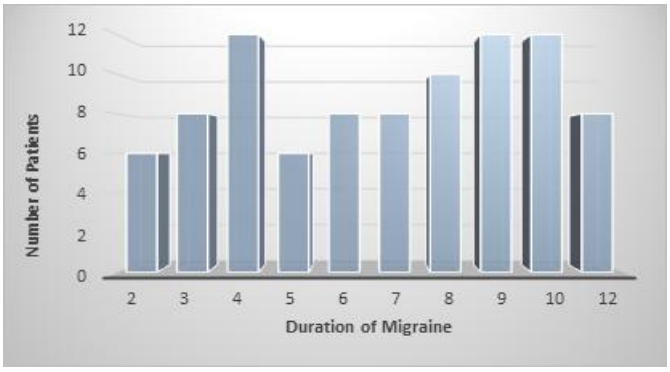


Table 5: Migraine and Nausea/Vomiting.

Nausea	
Types of Nausea	Frequency
Mild	30
Intense	40
None	10

Vomiting	10
Total	90

Graph 5:

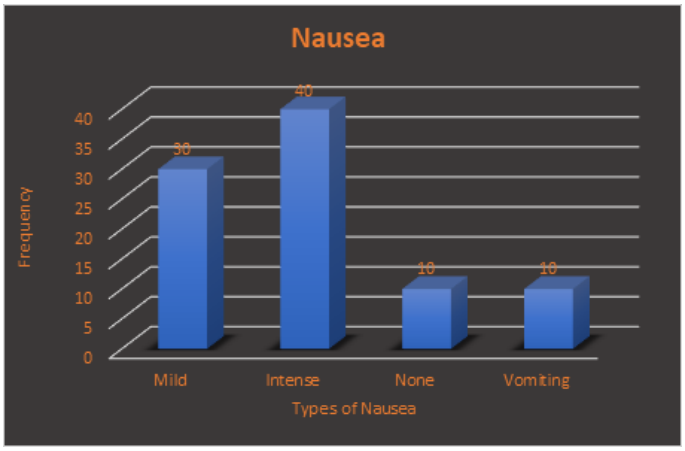


Table 6: Migraine and Intensity of pain

Pain	
Intensity of pain	Frequency
Intense	24
Very intense	24
Moderate	22
Mild	20
Total	90

Graph 6:

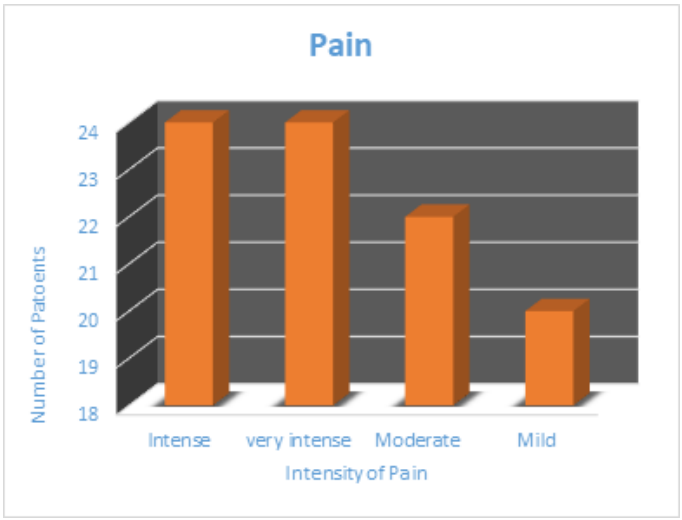


Table 7: migraine and Duration of Attack (in hours)

Duration Of Attack (in hours)	No. of Patients
> 24 hours	34
04-12 hours	20
12 - 24 hours	36
Total	90

Graph 7:

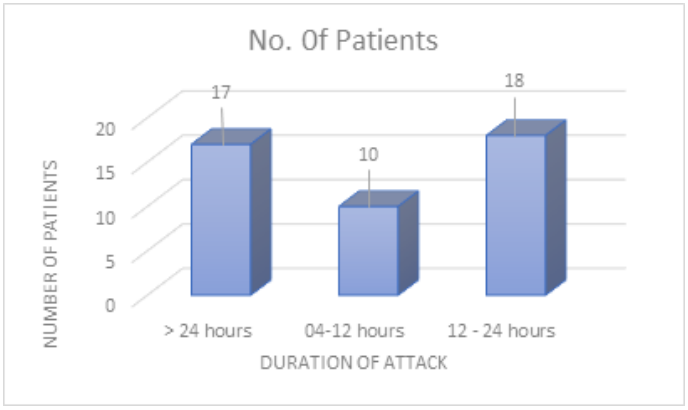


Table 8: Migraine and Frequency of Attacks

Frequency of Attacks	Frequency
<1/ year	0
<04/ year	12
>1 / week	26
1/ week	20
1-2 / month	16
5 - 10 / year	16
Total	90

Graph 8:

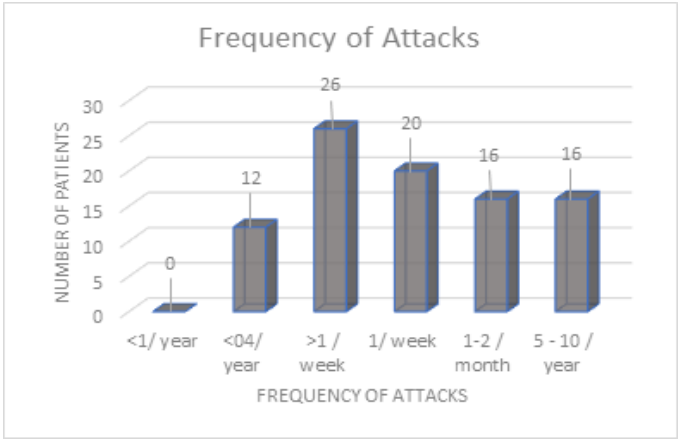


Table 9: Migraine and WMH in patients of Nausea/ Vomiting.

Nausea	Discrete T2/FLAIR hyperintensities		
	Total	Present	Absent
Mild	48	14	34

Intense	28	20	08
None	04	0	04
Vomiting	10	08	02
Total	90	42	48

Graph 9:

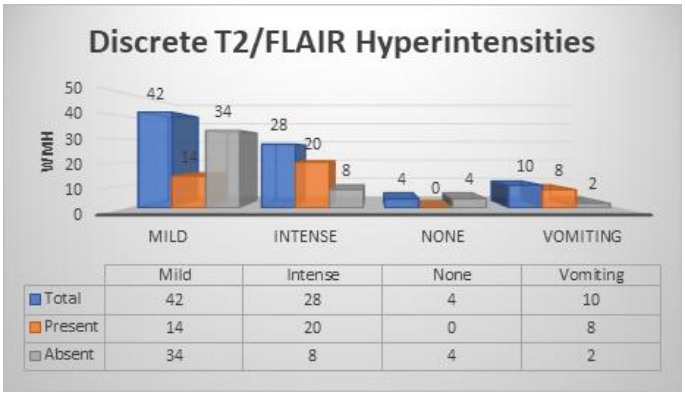


Table 10: Duration of Migraine and WMH

Duration of migraine (years)	Discrete T2/ FLAIR hyper intensities		
	Total	Present	Absent
2-5 years	32	12	20
6-12 years	58	30	28

Graph 10:

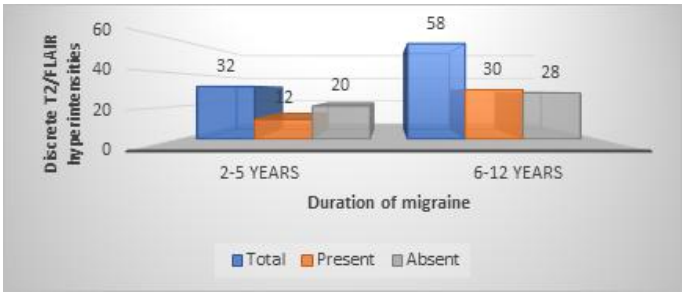


Table 11: Duration of Attack (in hours) and WMH in Migraine

Duration Of Attack (in hours)	Discrete T2/FLAIR hyper intensities		
	Total	Present	Absent
In 24 hours	34	20	14
In 12-24 hours	36	16	20
In 4-12 hours	20	06	14

Graph 11:

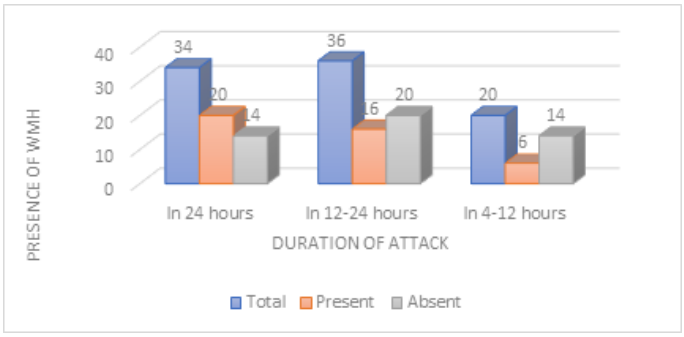


Table 12: Frequency of Attacks in migraine and WMH

Frequency of Attacks	Discrete T2/FLAIR hyper intensities		
	Total	Present	Absent
>1/ week	26	18	08
1/ week	20	12	08
1-2/ month	16	06	10
</ year	0	O	0
<04/ year	12	02	10
5 - 10 / year	16	04	12

Graph 12:

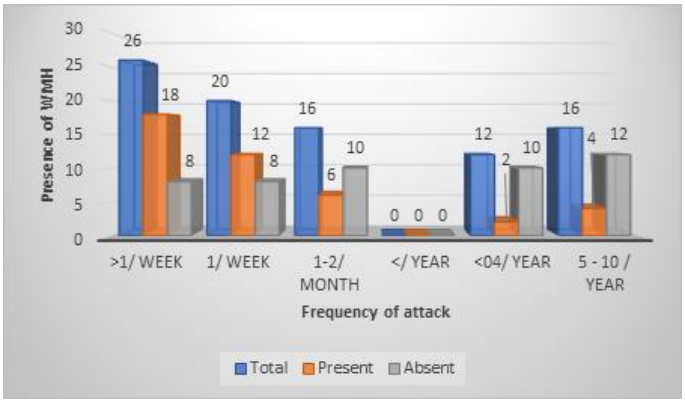


Table 13: Intensity of Pain and WMH

Intensity of Pain	Discrete T2/FLAIR hyperintensities		
	Total	Present	Absent
Intense	24	14	10
Very intense	24	18	06
Moderate	22	08	14
Mild	20	02	18

Graph 13:

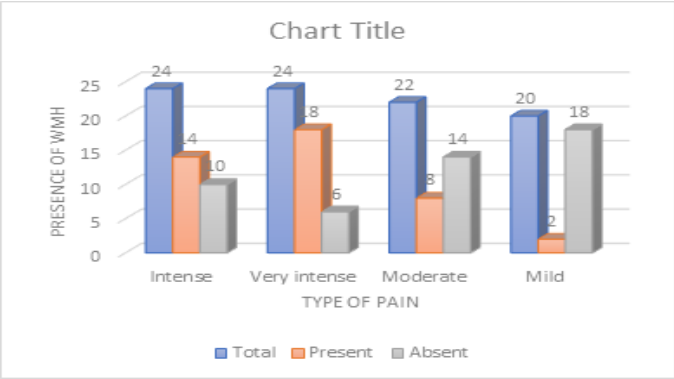


Table 14: WHM and Severity as per MIGSEV scale in Migraine

Severity as per MIGSEV scale	Discrete T2/ FLAIR hyper intensities		
	Total	Present	Absent
Grade 1	30	4	26
Grade 2	18	8	10
Grade 3	42	30	12

Graph 14:

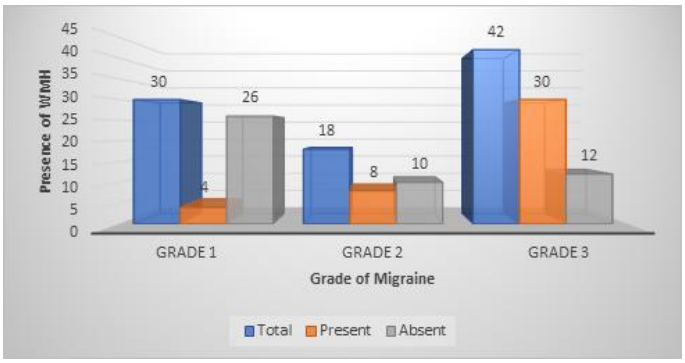


Table 15: Discrete T2/ FLAIR hyper intensities in MRI Brain of Migraine Patients.

Discrete T2/ FLAIR hyper intensities	No. of Patients	Discrete T2/ FLAIR hyper intensities		Discrete T2/ FLAIR hyper intensities		
b/l frontal lobes	2	Present	42	Age group	Present	Absent
left frontal lobe and r pariatal	2	Absent	48	15-35	28	30
B/L frontal lobe and temporal lobe	2	Total	90	36-55	14	18
b/lpariato occipital lobe	2			Total	42	48
b/l frontal, b/lpariatal lobe,	2					
b/lfrontoparital lobes	2					
b/lparaito occipital lobes	2					
b/lpariatal and occipital	2					
b/lpariato occipital lobes	4					
left occipital lobe and pariatal lobe	2					
left basal ganglia	2					
left centrum semi ovale and periventricular	2					
left frontal lobe and r occipital	2					
Lt fronto pariatal lobes	4					
periventricular	8					
rt frontal and pariatal lobe	2					
Total	42					

Discussion

This study was conducted on 90 patients. Participants of this were evaluated in OPD and the data was collected there. No follow ups were required as all the necessary data was available in the first meet. Out of these 90 patients 24.4% were males and 75.6% patients were female. This coincides with Messoud Ashina[4,5] study that the gender ratio of migraine patients is 3:1, female male. Other studies have also confirmed that females suffer more from migraine than males. Chaibi et al[26] also conclude in their study that there is significant pre ponderance in females of all the sub types of migraine.

Migraine can be found in patients of all ages. The youngest patient in our study was 17-year-old female and the oldest was 50-year-old male. 34 is the mean age of the patients of this study. We divided our patients into two age groups, 15-35 years and 36-55 years. 53.4% people belonged to the lower age group while as 46.6% belonged to the higher age category. Most of the patients of our study had a long history of migraine. There were no children in our study although Ashina et al have confirmed that migraine effects a good proportion of children too. This may be because children are usually referred to the Pediatric Hospital of our college.

While recording the duration of migraine we found mixed results. 6.6% of the patients had migraine from last two years while as 8.88%, 13.3% and 6.66% patients had reported migraine since 3, 4 and 5 years respectively. 8.88% patients had migraine for 6-7 years. 46.6% patients had migraine complaints since more than 9 years. in our study 53.4% of patients are of the age group of 15-35 years. This indicates that most of the patients report the onset of migraine before the age of 35. Ashina et al are also of the same opinion.

Migraine is actually the acute pain in head. While recording the pain of the patients of the study we used MIGSEV Pain scale to categorize the severity of pain. 22.2% of the patients suffered from mild pain while as 24.4% suffered from moderate pain. 22.2% patients came under the category of intense pain while as 31.22% came under the category of very intense pain. The inference we could draw from this data is that a good number of patients suffer from intense pain in migraine. Most of these patients with intense pain were young. In young people migraine is the most common disability causing headache.

Patients with migraine often get Nausea. Around 80% of the migraine patients suffer from nausea. Migraine is a very strong trigger of nausea. There are many proposed mechanisms of how migraine triggers nausea but none of them has been established scientifically. We used MIGSEV scale to grade nausea in the patients of our study. 33.3% patients had mild nausea while as 44.4% patients had intense nausea. From participants 11.1% vomited during migraine attack. 11.1% patients from our study had neither nausea nor vomiting. Farooq et al[27]. conclude that occurrence of nausea in the premonitory phase of migraine is associated with activation of the NTS, dorsal motor nucleus of vague, nucleus ambiguous and the PAG, in the absence of pain, and hence likely represents a primary event.

Migraine patients feel pain attacks which last from 4-72 hours ranging from patient to patient. 22.2 % patients from our study had headache lasting from 4-12 hours. 40% of the patients had acute attack lasting from 12-24 hours. 37.7% patients had an acute headache lasting for more than 24 hours. Most common duration of attack in our patients was 12-24 hours.

In our study, we found that 13.3% patients had less than 4 attacks per year. 17.7% of patients had 5-10 attacks per year. 17.7% patients had 1-2 attacks per months. 22.2%

patients had 1 attack per week. 28.8% of patients had more than one attack per week.

In this study we studied the correlation between nausea/ vomiting and white matter hyper intensities. Out of total 90 patients 86 patients suffered from vomiting/ nausea. As discussed above we categorized the nausea into mild, intense and vomiting. 48 patients had suffered from mild nausea and out of these patients, 29.1% patients showed the presence of white matter hyper intensities and in 70.9% patients' white matter hyper intensities were absent. 28 patients in the study had intense nausea and out of these patients 71.4% patients showed white matter hyper intensities on MRI while as 28.6% had no white matter hyper intensities. Among the patients with vomiting 80% patients had white matter hyper intensities while as rest of the 20% had no white matter hyper intensities. From the above statistical analysis, we can infer that the intensity of nausea had a direct relation on the severity of WMH. Patients with white matter hyper intensities have severe nausea/ vomiting. The results of our study coincide with the study carried out by Hasnaoui at el[28]. This study has also confirmed that migraine related nausea/ vomiting have an association with white matter hyper intensities.

People frequently experience a wave of sensory problems, ranging from nausea and hallucinations to feelings of numbness, before having a seizure or getting a migraine. A warning sign that can persist from a few seconds to an hour before an event, such as a seizure or migraine, occurs, this collection of symptoms is referred to as aura. In our study 44.4% patients with migraine had preceding history of aura while as 55.6% patients did not have such history. The results of our study coincide with the study of Fraser et al[29]and Negmet al[30].

We divided the patients on the basis of duration of migraine into two groups, patients with migraine from last 2-5 years and 6-12 years. This division was done to segregate the patients with long history of migraine from those who had recent onset of migraine. 37.5% patients with 2–5-year history of migraine had white matter hyperintensities while as 62.5% patients had no white matter hyperintensities.

On the other hand, in later group, we found that 51.7% patients had white matter hyper intensities while as 48.3% patients had no white matter hyperintensities. This statistical analysis gives the inference that patients with longer history of migraine have more common presence of white matter hyper intensities and coincide with the study conducted by Xie et al[31].

As already discussed above we divided the patient according to the duration of attack of migraine. Patients were divided into three groups, 1st group with 4-12 hours attack duration, 2nd group with 12-24 hours and 3rd greater than 24 hours duration of attack. Then we analyzed the MRI scans of these patients to check for the white matter hyperintensities. It was found that 30% patients from group one had white matter hyperintensities white as 70% patients from that group showed no white matter hyperintensities.

from group 2nd 44.4% patients had white matter hyperintensities present while as 55.6% patients had no white matter hyperintensities. In the third group 58.8% patients had white matter hyperintensities while as it was absent in remaining 41.2% patients.

From this we can analyze that the occurrence of white matter hyperintensities increases as we go from patients with lower duration of attack to those with longer duration of attack. It was found lowest in the group of patients with lower duration and highest in the group of patients with the longer duration of attack. white matter hyper intensities seem to have an impact on the duration of attack of migraine.

The findings of our study are in agreement with those of the research done by Jasem et al[32] and Hasnaoui at el. These investigations have also proven that the risk factors for white matter hyper intensities include advanced age, a prolonged disease course, and frequent migraine attacks. Patients were also categorized on the frequency of attack. We made five groups, 1st group with patients who had less than four attacks per year, 2nd group with 5-10 attacks per year, 3rd group with 1-2 attacks per month, 4th group with one attack per week and 5th group with more than one attack per week.

Such meticulous grouping was done to observe the patients in detail. On the analysis of MRI scans of group 1st, 16.6% patients had white matter hyper intensities while was in 84.4% did not have white matter hyper intensities. In group 2nd, 25% patients had white matter hyperintensities while as it was absent in 75% patients. In group 3rd. 37.5% patients had white matter hyper intensities and it was absent in 62.5% patients.

From the patients of group 4, white matter hyper intensities was present in 60% patients and absent in 40% patients. In the group 5 patients 69.2% patients showed white matter hyperintensities while as 30.8 patients did not show white matter hyperintensities. Upon analyzing this data, we can infer than white matter hyper intensities increase as we go from the group with lowest frequency to the group with highest frequency of attack.

white matter hyper intensities was found least (16.6%) in the group with less than four attacks a year and highest (69.2%) in the group with more than one attack per week. The results of our study are in correlation with those of the studies done by Jasemet al. and Hasnaoui at el. These investigations have also demonstrated that migraine episodes often, older age, and longer duration of illness are risk factors for white matter hyper intensities.

Patients were divided into four groups on the basis of intensity of pain in migraine. Grouping was done into mild, moderate, intense and very intense, depending on the severity of pain.

When we corelated the MRI scans with this grouping, it was found that in patients with mild pain 10% had white matter hyper intensities while as 90% did not show any presence of it. In patients with moderate pain 36.4% had white matter hyper intensities while as 63.6% did not show presence of it. 58.3% patients with intense pain had white matter hyper intensities while as 41.7% did not have white matter hyper intensities. In the last group of patients with very intense pain 75% had white matter hyperintensities while as it was absent in 25%. Only 10% patients with mild pain had white matter hyperintensities on the other had 75% with intense pain showed white matter hyper intensities in their MRI scans. This signifies that the severity of pain in migraine has a role in white matter hyper intensities.

Using MIGSEV scale we graded the patients into three group on the basis of the severity of migraine. Grade I being least severe and grade III being most severe. 13.3% patients of grade I severity had white matter hyper intensities while as 86.7% had no white matter hyper intensities. In patients of Grade II severity 44.4% showed the presence of white matter hyper intensities while as 55.6% did not show the presence of it. In Grade III patients 71.4% had white matter hyperintensities and 28.6% did not.

This statistical analysis shows that in patients with Grade III migraine (very severe) 71.4% had white matter hyper intensities, which is a very significant number. We can infer that as the severity of migraine increases according to MIGSEV Scale, the occurrence of white matter hyper intensities also increases.

The results of our study coincide with the study carried out by Jasem et al and Hasnaoui at el. These studies have also confirmed that older age, longer disease duration and frequent attacks of migraine are risk factor for white matter hyper intensities.

During our study we found some special cases. A 32 male, with migraine history of 5 years was included in this study. He had Grade I severity of migraine as per MIGSEV Scale. He was advised to go for MRI scan. His MRI scan revealed sub arachnoid cyst. However, there were no white matter hyperintensities.

A 47-year-old female came with the complaint of headache. She fulfilled migraine criteria as per ICHD3. She was advised for MRI. Her MRI Scan revealed meningioma and periventricular hyperintensities.

In our study two patients, a 25-year-old female and 19-year-old female, who were fulfilling migraine criteria as per ICHD3. These two patients had a background history of seizure disorder. MRI scan of these patients revealed hyperintensities in frontal and parietal lobes.

Figure legend

Fig 1. Axial FLAIR image of brain showing focal discrete hyper intensity in corona radiata of Right pariatal lobe.

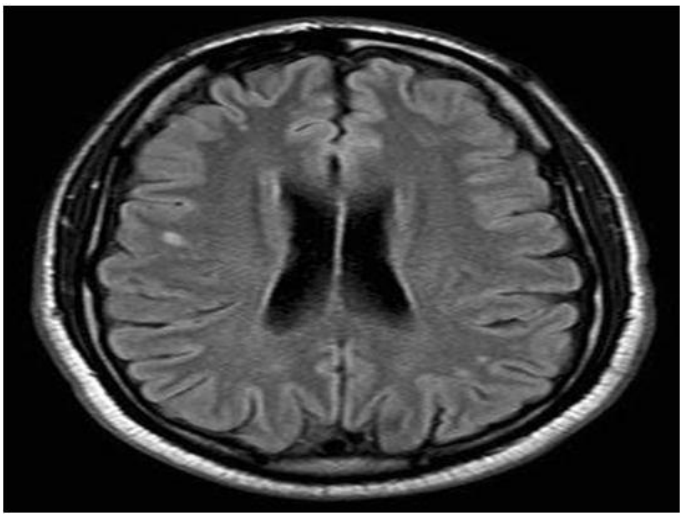


Fig 2: Axial FLAIR of brain showing focal white matter hyperintensity in left high frontal lobe.

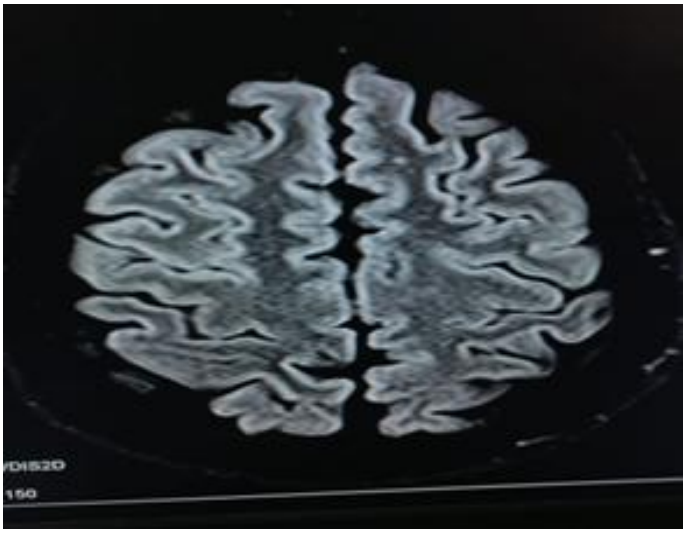


Fig 3: Axial FLAIR image of brain showing few focal discrete white matter hyperintensities in bilateral frontal lobes.

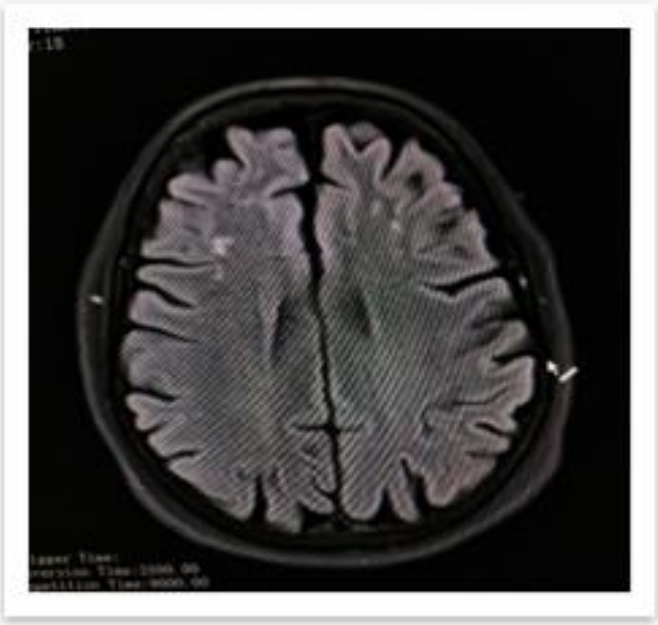
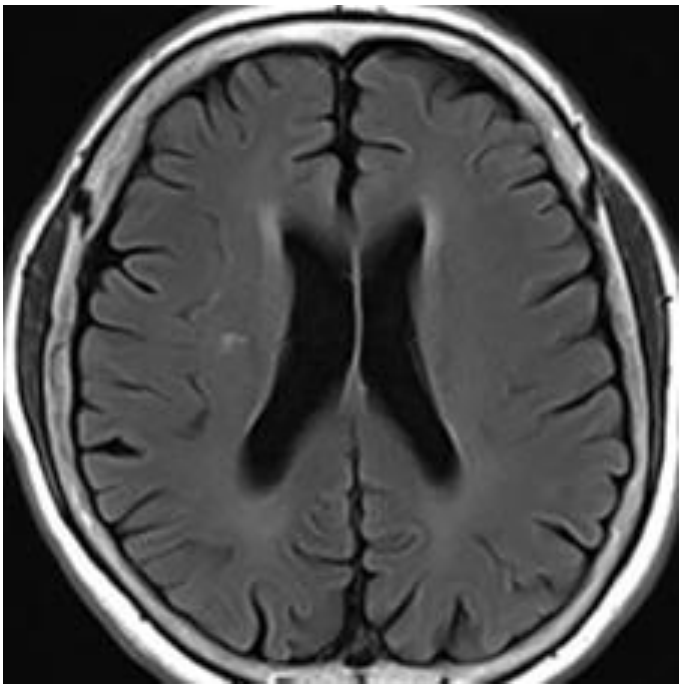


Fig 4: Axial FLAiR image of brain showing extra axial hyperintense lesion in left occipital lobe in para sagittal location with associated buckling of cortex. Post contrast images revealed heterogeneous enhancement and Dural tail sign (not shown). Imaging features were suggestive of meningioma.

Fig 5: Axial FLAIR Image of brain showing peri ventriclar hyper intensities in bilateral frontal lobes.



Conclusion

In this study we tried to ascertain the Clinico - radio logical relation between migraine and white matter hyper intensities in brain. We used MRI as the main tool of investigation. Our study concludes that age, duration of migraine, intensity of pain, nausea/ vomiting, aura, frequency of attacks, duration of attacks, intensity of migraine as per MIGSEV scale have a role in the presence and absence white matter hyper intensities. Our study found that the presence of white matter hyper intensities has more chances in patients who are aged, have frequent attacks of migraine, have intense pain, feel highly nauseated, have longer duration of attacks and have Grade III migraine on MIGSEV scale.

However further studies are required to further investigate it.

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