




The Association of MRI findings in migraine with the headache characteristics and response to treatment

La asociación de los hallazgos de la resonancia magnética en la migraña con las características del dolor de cabeza y la respuesta al tratamiento

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345

Abstract

Background: Migraine is associated with magnetic resonance imaging (MRI) changes as white matter hyper intensities (WMHI), which is interpreted as ischemic in origin, the clinical significance & pathophysiology of these lesions are not well understood. The aim of study: to investigate these lesions and to find the relationships to the character of the headache and the effect on the response to treatment.

Methods: a prospective, analytical study was conducted in Mosul city on 100 adult patients who were attending the neurological clinic, all fulfilled the migraine diagnostic criteria according to the Headache Classification Committee of the International Headache Society (IHS), the patients' demographics and the clinical characteristics of the headache were evaluated, all patients were examined by MRI, given treatment and followed up for three months.

Results: average age was 35.04 years, with the highest prevalence noted at 29-38 years, of all patients 36% were having WMHI in MRI (positive group), while 64% were having normal MRI study (negative group), the average headache frequency was 5.69 attacks /month, average severity was (3.6) according to GAMS (Global assessment of migraine severity), average disability was 14.29 according to migraine Disability Assessment Questionnaire (MIDAS), the average duration was 10.63 hours, the mean frequency, severity, disability and duration were all significantly higher in the positive group, compared to the negative groups, and all are significantly reduced after treatment, however (91.3%), of improved cases (n=23) were from the negative group.

Conclusion: migraine is associated with WMHI. Patients with WMHI showed a higher frequency, severity, disability as well as longer duration of the headache and a less favorable response to treatment.

Keywords: Headache, Migraine, MRI of Brain, Topiramate, White matter hyper intensities (WMHI).

Resumen

Antecedentes: la migraña se asocia con cambios en las imágenes de resonancia magnética (MRI) como hiperintensidades de la materia blanca (WMHI), que se interpreta como de origen isquémico, la importancia clínica y la fisiopatología de estas lesiones no se comprenden bien. El objetivo del estudio: investigar estas lesiones y encontrar las relaciones con el carácter del dolor de cabeza y el efecto sobre la respuesta al tratamiento.

Métodos: se realizó un estudio prospectivo y analítico en la ciudad de Mosul en 100 pacientes adultos que acudían a la clínica neurológica, todos cumplían los criterios diagnósticos de migraña según el Headache Classification Committee of the International Headache Society (IHS), la demografía de los pacientes y la Se evaluaron las características clínicas del dolor de cabeza, todos los pacientes fueron examinados por resonancia magnética, se les dio tratamiento y se les dio seguimiento durante tres meses.

Resultados: la edad promedio fue de 35,04 años, con la mayor prevalencia observada a los 29-38 años, de todos los pacientes, el 36% tenía WMHI en MRI (grupo positivo), mientras que el 64% tenía un estudio de MRI normal (grupo negativo), el dolor de cabeza promedio frecuencia fue de 5,69 ataques / mes, la gravedad media fue (3,6) según GAMS (Evaluación global de la gravedad de la migraña), la discapacidad media fue 14,29 según el Cuestionario de evaluación de la discapacidad de la migraña (MIDAS), la duración media fue de 10,63 horas, la frecuencia media, la gravedad, la discapacidad y la duración fueron significativamente más altas en el grupo positivo, en comparación con los grupos negativos, y todos se reducen significativamente después del tratamiento, sin embargo (91,3%). de los casos mejorados (n=23) fueron del grupo negativo.

Conclusión: la migraña está asociada con WMHI. Los pacientes con WMHI mostraron una mayor frecuencia,

gravedad, discapacidad, así como una mayor duración del dolor de cabeza y una respuesta menos favorable al tratamiento.

Palabras clave: dolor de cabeza, migraña, resonancia magnética de cerebro, topiramato, hiperintensidades de materia blanca (WMHI).

Migraine is a common debilitating neurological disorder¹. It is characterized by recurrent moderate to severe attacks of headache associated with autonomous nervous system dysfunction^{2,3}, about 15% of the general population are affected by migraine, females are more commonly affected².

On MRI Imaging, patients with migraine headache show a high prevalence of white matter hyper intensities (WMHI) and silent infarcts^{1,4,5}, where the migraine is regarded as a risk factor for these lesions, the pathophysiology; however, as well the clinical importance of these structural brain lesions is not well understood, they seem to be related to the disease and thought to be vascular in their origin⁵⁻⁷. These lesions are usually interpreted as ischemic lesions^{5,7}, some studies link the presence of the WMHI to advanced age and atherosclerosis as the main risk factors, in addition the long duration and the higher frequency of the attacks as well presence of comorbidities³.

The migraine is associated with impaired quality of life and disabilities, those are affecting work and daily activities, the management of migraine needs in addition to the pharmacological treatments, which is mostly in form of acute analgesics, bed rest which further decreases the patient's productivity^{8,9}, in addition, acute medication intake may lead to an overuse, that according to the studies may itself lead to chronic daily headache^{8,9}, on the other hand Preventive medications can play an important role in the management of migraine through reducing headache frequency and avoiding the potential risk of analgesic overuse⁸. Topiramate was approved first in 1996 as an antiepileptic drug and was later approved in 2004 for use as a prophylaxis of migraine in adults patients^{9,10}.

Our study aims to investigate brain MRI findings in migraine patients and to highlight the relationships to the character of the headache as well its effect on the response to treatment, were the same preventive treatment is given to all studied patients.

Patients and method:

A prospective, analytical study was conducted, in AL-Salam teaching hospital in Mosul city, ethical approval was obtained from the ethics committee of Ninevah University.

Patients who were attending the neurological consultation complaining of headache were enrolled in the study; the included patients were those older than 18 years and who fulfilled the migraine diagnostic criteria according to the Headache Classification Committee of the International Headache Society (IHS).

Patients younger than 18 years, with chronic diseases or comorbidities & those with demyelinating brain diseases, head trauma or any disease which might be associated with brain MRI changes, were all excluded from the study, added to the exclusion criteria are patients with a contraindication to the topiramate drug, like renal insufficiency, renal stone or glaucoma.

The included patients were all required to complete a questionnaire, that includes details about patients demographics, basic clinical information as well Migraine features including headache frequency in the last three months (mean number of attacks per month), duration (average duration of attacks in hours) and severity by using GAMS (Global assessment of migraine severity) and the degree of disability by migraine Disability Assessment Questionnaire (MIDAS)¹¹.

MIDAS assesses the disability caused by migraine within the most recent 3 months, this self-administered questionnaire consists of five -item questions, covering three domains that focus on lost time and reduction in the performance at school/work, household activities or family/leisurely activities, then the sum of these lost days will give us the MIDAS score that is given four grades of disabilities, grade I (0-5) for no or little disability, grade II (6-10) for mild disability, grade III (11-20) for moderate disability, and grade IV (21 or >) for severe disability, MIDAS has been widely used in many countries and translated into different languages^{11,12}.

For assessment of severity, Global assessment of migraine severity (GAMS) was used, it is a single question directed to the patient about the severity of the headache, with seven categories of the response from 1 (not at all severe) to 7 (extremely severe headache)¹¹.

All the participating patients were then sent to the Radiology department at AL-Salam teaching hospital, to be examined by MRI scan, using 1.5 T Philips Achieve MRI scanner and a standard 16-channel phased array head coil. with the following parameters: T1-weighted images TR 597 ms; TE 15 ms; matrix, 220*180; section-thickness 5 mm; FOV 23 cm, T2-weighted: TR 4870 ms, TE 110 ms, matrix 288*211, section thickness 5mm, FOV 23cm, FLAIR images were acquired with: TR, 6000 ms; TE, 120 ms; matrix, 220*160; section-thickness, 5 mm; FOV, 23cm, DWI:TR 3224 ms, TE 92ms, matrix 120*100, section thickness 5mm, FOV 24cm.

Results

according to the MRI findings, the patients were divided into two groups, those with positive MRI findings (positive group) & those with negative or normal MRI exam (Negative group), based on the reading of the MRI exam by radiologist & reviewing by a neurologist, the positive findings in MRI were in form of WMHI, mainly diagnosed at the T2/FLAIR images, these lesions were seen as iso or hypointensities in T1-weighted images.

All the patients then received the same preventive therapy in form of topiramate tablet 25 mg twice daily, of the total 100 participants included in the study, 20 were excluded due to either non-compliance of treatment or failure to keep on contact.

After three months from the start of the treatment, the patients were reevaluated by reassessment of the headache frequency, severity, disability as well duration taking the last month of treatment as the base.

We divided the patients according to the response to the given treatment into two groups, improved and non-improved group, we defined the improvement as a reduction of the mean migraine frequency by **50%50%** at the last month of the treatment from the baseline frequency. If the frequency of migraine otherwise increased or failed to reduce, or reduced by less than 50% then we regarded it as a non-improvement.

Statistical Analysis:

Data were analyzed by using SPSS 22, we used measures of central tendency (mean), measures of dispersion standard deviation (std. deviation) as well frequency and percentile to describe demographic and clinical characteristics. For the normally distributed continuous variables we used the student t-test, non-parametric tests were used for the variables, that failed to follow the normal distribution, we considered a P value of less than 0.05 to be statistically significant.

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total of 100 patients with an average age of 35.04 years old (range: 18-57 years old), enrolled in this study. Among these patients 44% were males,56% were females, the participants

were divided into four age groups, as shown in figure 1, with the highest prevalence of migraine headaches noted at 29-38 years old, figure 1.

Of the total 100 examined patients 36% were having positive findings in MRI in a form of WMHI, both supra and infratentorial (positive group), while 64% were having normal MRI study (negative group), on correlation to the age group, the percentage of positive MRI finding are shown to be increasing with the age, where 75% of the studied patients aged 49-57 years were showing positive MRI findings, the percentage is lower with the younger age group, figure 2.

Figure 1: distribution of migraine frequency among the age groups

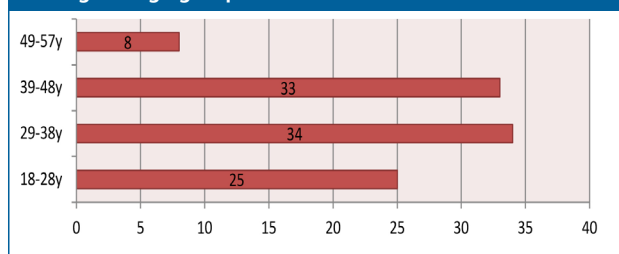
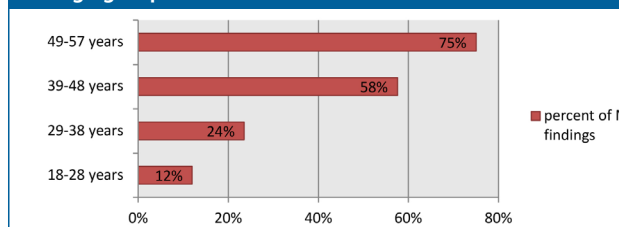


Figure 2: percent of positive MRI findings among the age groups



The range, mean as well standard deviation of migraine features including frequency (attacks/month), severity by GAMS, disability by MIDAS, in addition to headache duration in hours, before treatment and after three months of treatment, for whole patients were listed at the table 1, the P value of the statistical tests that compare the before with the after readings are also shown in the same table, it is noted that all the four parameters showed significant decrease in the mean after the given treatment.

Table 1. Descriptive statistics of migraine demographic, MRI findings and headache character, with comparison of mean frequency, severity, disability and duration before and after treatment in all patients.

		<i>Minimum</i>	<i>Maximum</i>	<i>Mean</i>	<i>Standard Deviation</i>	<i>No.</i>
Age		18	57	35.04	10.03	10
sex		<i>Frequency</i>	<i>Percent</i>		<i>P-value</i>	
M		44	44	0.23		
F		56	56			
Total		100	100			
MRI Findings		<i>Frequency</i>	<i>Percent</i>			
P		36	36			
N		64	64		0.005	
Total		100	100			
headache character	No.	<i>Minimum</i>	<i>Maximum</i>	<i>Mean</i>	<i>Standard Deviation</i>	<i>P-value</i>
frequency before Rx	100	3	10	5.69	1.66	0.000
frequency after Rx	80	0	9	4.18	1.98	
Severity before Rx	100	1	7	3.61	1.8	0.000
Severity after Rx	80	0	7	2.56	2.04	
Disability before Rx	100	2	28	14.29	7.45	0.000
Disability after Rx	80	0	21	7.69	5.39	
duration before Rx	100	4	72	10.63	11.77	0.000
duration after Rx	80	0	48	6.68	6.12	

M= Male, F=Female, P=Positive, N=Negative, No.=Number, Rx=treatment.

Before treatment:

Aiming to highlight the differences between the positive and the negative groups and to make baseline data for the future comparison, we compared the age between the two groups as well, the headache character at the first visit before starting treatment, The mean age of the positive group (n=36, mean age=41.2 years, std. deviation =8.2 years, range: 23-57 years), was shown to be significantly higher (P value=0.000), than in the negative MRI group (n=64, mean age=31.6 years, std. deviation =9.3, range:18-51 years) the mean frequency, severity, disability and duration were all noted to be significantly higher in the positive group, compared to the negative groups details were listed at table 2.

Table 2. comparison between the MRI positive group (1) and MRI negative group (2) regarding demographic and migraine features before starting treatment.

<i>Headache character</i>	<i>No.</i>	<i>Minimum</i>	<i>Maximum</i>	<i>Mean</i>	<i>Standard Deviation</i>	<i>P-value</i>
Age1	36	23	57	41.2	8.2	0
Age2	64	18	51	31.6	9.3	
Frequency1	36	3	10	6.5	1.5	0
Frequency2	64	3	10	5.2	1.6	
Severity1	36	2	7	5.2	1.3	0
Severity2	64	1	6	2.7	1.3	
Disability1	36	2	28	17.2	7.3	0.003
Disability2	64	2	28	12.7	7.1	
Duration1	36	4	70	13.8	14	0.007
Duration2	64	4	72	8.9	10	

After Treatment:

After three months of treatment, 80 patients were successfully followed up these include (30 patients of positive group & 50 patients of the negative groups), the character of the migraine headache compared again between the positive MRI group & the negative group & it is found that the mean frequency, severity, Disability as well duration of migraine headache findings is still significantly higher after the given treatment, in the positive group compared to negative group, Table 3.

Table 3. Comparison of the migraine features between the MRI positive (1) and MRI negative (2) groups after treatment.

<i>Headache Character</i>	<i>No.</i>	<i>Minimum</i>	<i>Maximum</i>	<i>Mean</i>	<i>Standard Deviation</i>	<i>P-value</i>
Frequency 1	30	3	9	5.8	1.6	0.000
Frequency 2	50	0	6	3.2	1.5	
Severity 1	30	2	7	4.8	1.4	0.000
Severity 2	50	0	4	1.2	0.7	
Disability 1	30	2	21	11.9	5.1	0.000
Disability 2	50	0	12	5.1	3.7	
Duration 1	30	4	48	9.9	8.7	0.000
Duration 2	50	0	10	4.7	2.4	

Focusing on the positive group only, who were 36 patients, 16 of them were males & 20 were females patients, the migraine character was compared before and after treatment within the same group, with a statistically significant reduction after the given treatment was noted in frequency, severity, Disability as well duration, the details shown in the table 4.

Table 4. positive group and comparison of the migraine headache before & after treatment.

Character of headache	No.	Minimum	Maximum	Mean	Standard Deviation	P-value
Frequency before Rx	36	3	10	6.5	1.5	0.001
Frequency after Rx	30	3	9	5.8	1.6	
Severity before Rx	36	2	7	5.2	1.3	0.002
Severity after Rx	30	2	7	4.8	1.4	
Disability Rx	36	2	28	17.2	7.3	0.000
Disability after Rx	30	2	21	11.9	5.1	
Duration before Rx	36	4	70	13.8	14.0	0.006
Duration after Rx	30	4	48	9.9	8.7	

Rx= treatment

Negative Group:

On the other hand the Negative group of 63 patients, of them 28males & 36 females patients, the migraine character was compared before and after treatment in this group, a significant reduction in the mean headache frequency, severity, disability as well duration, was noted, the details shown in the table 5.

Table 5. Negative group and comparison of the migraine headache before & after treatment.

Headache character	No.	Minimum	Maximum	Mean	Standard Deviation	P-value
Frequency before Rx	64	3	10	5.2	1.6	0.000
Frequency after Rx	50	0	6	3.2	1.5	
Severity before Rx	64	1	6	2.7	1.3	0.000
Severity after Rx	50	0	4	1.2	0.7	
MIDAS before Rx	64	2	28	12.7	7.1	0.000
MIDAS after Rx	50	0	12	5.1	3.7	
Duration before Rx	64	4	72	8.9	10.0	0.000
Duration after Rx	50	0	10	4.7	2.4	

Rx= treatment

Response to the treatment:

Both the positive and the negative group showed significant reduction in the mean frequency, severity, disability and duration of the headache from the baseline after the given treatment. However, the improved cases (n=23) were mainly seen in the negative group (91.3%), while only 8.7% of the improved cases were from the positive group, complete remission (absence of headache in the last month) were seen in four treated cases, all were of negative group, they were one male aged 20 years and three females of 34,37 and 36 years respectively.

Table 6. The distribution of improvement after treatment between the positive and negative group.

Group	No.	Non improved cases	Improved cases			Total improvement	percent
			50% reduction	>50% reduction	Complete remission		
Positive	36	34	2	0	0	2	8.7%
Negative	64	43	5	12	4	21	91.3%

Epidemiological studies have shown that the prevalence of migraine headache is affected by patients age, sex, sociocultural as well genetic factors³, The prevalence of migraine headache in previous international studies depending on HIS criteria as a diagnostic standard is reported to be 13-17%^{2,13-16}, Several studies have shown also that the most commonly affected age group by migraine, is in the age range of 20-

45 years^{14,15,17}, In our study, the highest migraine prevalence were shown to be in the age group of 29-38 years, a comparable results was obtained by a previous study held in Iraq by Al-Shimmary. On 200 adult patients & showed that the highest prevalence was noted to be between 30 and 39 years¹⁸.

There are many evidences that suggest a relationship between migraine headache and the sex hormones in the

females, and linked it to the fact that many of patients attacks of headache start at the age of menarche & continue throughout the time of menstruation, this may explain the highest prevalence of migraine among women, as many studies showed that (women are 2-3 fold more commonly affected than men by migraine^{3,13-17}, overall prevalence of migraine in our study, however did not show a significant sex difference and this may be attributed to the strict selection criteria, in our study the sex difference is statistically significant with female predominance at the age group of 29-38 years only (2.4 fold female to male prevalence).

WMHI on brain MRI are common nonspecific incidental findings in general population, that show increase incidence with advancing age, these lesions are thought to be caused by small vessels chronic ischemia, where the presence of coincidental vascular disease as stroke, coronary heart disease and vascular risk factors in a form of hyperlipidemia, hypertension, diabetes are all associated with increased prevalence of the WMHI¹⁹. migraine headache and the presence of WMHI in MRI is a well-known association, a meta-analysis by Swartz et al.²⁰ demonstrated that patients with migraine are at increasing risk of having WMHI on MRI, a finding which was confirmed in a young age group of migraine patients who did not have a co-incidental cardiovascular risk factor, another study by Toghae et al⁵. reported that there are four fold increase in the incidence of WMHI lesions in patients with migraine headache, some other studies agreed with this association, with the prevalence of WMHI in migraine reported to be 16-43%^{4,21,22}. In our study the prevalence of WMHI was 36%, this percent was noted to be significantly increasing with age, (75% of our patient who aged 49 years and older were showing WMHI), a finding which was also shown by cooney et al. study in which a statistically significant relation between WMHI frequency and age of the patients was noted²¹.

The mean age of the positive group (41.2 years), was shown to be significantly higher than in the negative group (31.6years) the finding is also reported by Xie et al².

Previous international studies reported different association of WMHI in migraine with gender, in some studies like Toghae et al. and Seneviratne et al. WMHI were more prevalent in women^{5,23}, in the current study the WMHI were more common in Women too, however with non-statistically significant difference from male (male: 16, female: 20) the result is comparable to Negm et al. who did not report any statistically significance sex difference²².

The relation of migraine frequency, severity and duration to the WMHI is conflicting. Many studies however show significantly higher migraine frequency among patients with WMHI as Xie et al. Seneviratne et al. Palm-Meinders et al.^{2,23,24}, some other studies as in study of Negm et al²² reported a more severe headache in the positive group.

Recognition of factors that may increase the risk of lesions in the brain of Migrainous patients, such as migraine type

and severity, may help identification of certain subgroups need to be treated²⁵. In our study the mean frequency, severity, disability and duration were noted to be significantly higher in the positive group than in the negative group, this finding leads us to the conclusion that migrainous patients with positive brain findings tend to have more severe headache.

The association between migraine headache and MRI detected intracranial lesion supports the idea that repeated attacks of migraine may be linked to cerebral ischemia and the resultant cerebral ischemia may be attack related²⁴, our study although lack the long term follow up and the large sample, however the frequency of the migraine is shown to be markedly higher among the positive MRI group (mean frequency measured as attack/month is 6.5 for positive group, versus 5.5 for the negative group), (P value is 0.000) the same finding is also reported by Kruit et al & Gozke et al.^{25,26}.

The hypothesis of increasing risk of brain lesions in association with the recurrence of migraine attacks may change the aim of treatment, where the prevention of migraine will be an important goal for secondary prevention in the population²⁵.

Topiramate is an antiepileptic drug²², its role as preventive treatment of the migraine is through multiple modes of action & it shows little interaction and only small percent of patients experience side effects^{22,27}. Topiramate efficacy and tolerability has been tested by many previous randomized clinical trials^{9,22,27,28}, the efficacy measured mainly by reduction of monthly frequency of migraine, decrease monthly disability days, decrease daily use of rescue medication^{8,9,27}, reduction of migraine severity and mean duration⁸, several randomized controlled clinical trials showed that the efficacy of the topiramate to be at the dose of 100-200 mg daily dose^{8,9,27}. Mei et al has noted that at 50mg daily dose of topiramate, there was a frequency reduction, but not to a statistical significance²⁷.

In our study; Topiramate at 50 mg daily dose, was an effective treatment in reducing mean frequency, severity, days of disability as well duration of migraine for all the treated patients. Both the positive and the negative groups showed significant reduction in the mean of these four features of the headache from the baseline after the given treatment; however, the improved cases (n=23) were mainly seen in the negative group (91.3%), versus 8.7% of the total improved cases are of the positive group, the complete remission (absence of headache in the last month) were seen in four treated cases (17% of the improved cases), all were of the negative group. So, the presence of WMHI may affect the efficacy of preventive treatment, Studies relating presence of WMHI to prognosis in migraine headache are little, one of the study held by Xie et al.² showed a comparative result to the current study and it showed that the presence of WMHI was as an important risk factor in non-improvement after migraine therapy.

We have demonstrated that migraine is associated with brain MRI changes in form of WMHI, migrainous patients with WMHI showed a higher frequency, severity, disability as well as longer duration compared to those without WMHI, the Preventive treatment is encouraged for migrainous patients with WMHI, which may prevent development of new lesions, however those patients may have a less favorable response than if WMHI were not present.

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