



and sex affect this relationship so we aim in the current study to find out the relation between the brain MRI findings and the type of the migraine as well the relation of these findings to the age or sex [20-22].

## Materials and Methods

This cross-sectional study was conducted at the outpatient neurology clinic in Al-Salam teaching hospital in Mosul city between July 2020 and January 2021, patients who complained of headache were evaluated by neurologists, then patients who met the International Classification of Headache Disorders-Third Edition (ICHD-3) diagnostic criteria for migraine (10) were asked to fill out a questionnaire which includes past medical history, drug history, some basic clinical information. Those who fulfill the study inclusion criteria have been invited to participate after full clarification of the study's objectives. In the same hospital, all the participants then had a brain MRI done to them, The MRI examination was performed by using Philips 1.5 T MRI scanner with a standard 16 channel phase array head coil, the sequences used are T1-weighted, T2-weighted as well FLAIR images. A radiologist and neurologists then examined the MRI records as 100 patients under the age of 18 and 100 patients aged 18-55 years were included in the sample. The Inclusion criteria included: Patients with newly diagnosed migraine, 55 years old or younger, a six month or more duration of symptoms, with no known history of cardiovascular, neurological, metabolic, inflammatory or infectious disease.

The exclusion criteria included: patients aged more than 55 years, short duration of symptoms (less than 6 months), presence of atherosclerotic disease or coexistence of cerebrovascular risk factors, patients who was discovered by MRI to have other pathology like brain tumor, ischemic infarction in the brain or vascular malformation, those with history of chronic drug use like contraceptive pills, or drug or alcohol abuse. All patients who refused the MRI examination were also excluded. 16 patients (6 over 55 years of age), 2 (short duration of symptoms), 5 (coexistence of cardiovascular

or neurological diseases), 2 (refusal of MRI), 1 female (contraceptive pill use) were excluded from the study. The study was approved by medical faculty's ethics committee of the Nineveh university. In the case of children, informed consent has been obtained from the participants or their guardians.

## Statistics

The data analysis was carried out using SPSS (Statistical Software Package for Social Sciences), version 22.0. For Windows descriptive statistics including frequency, percentage, range, mean, and standard deviation (Std. Dev), were used to summarize the demographic data. Pearson's chi-square test for independence is used to measures the dependency between the categorical variables, including MRI findings and aura, MRI findings and age group, as well MRI findings and sex. The strength of the association between two variables is then expressed in odds ratio. A non-parametric test is used to compare the mean in scale variables with no normal distribution P value below 0.05 was considered to be significant.

## Results

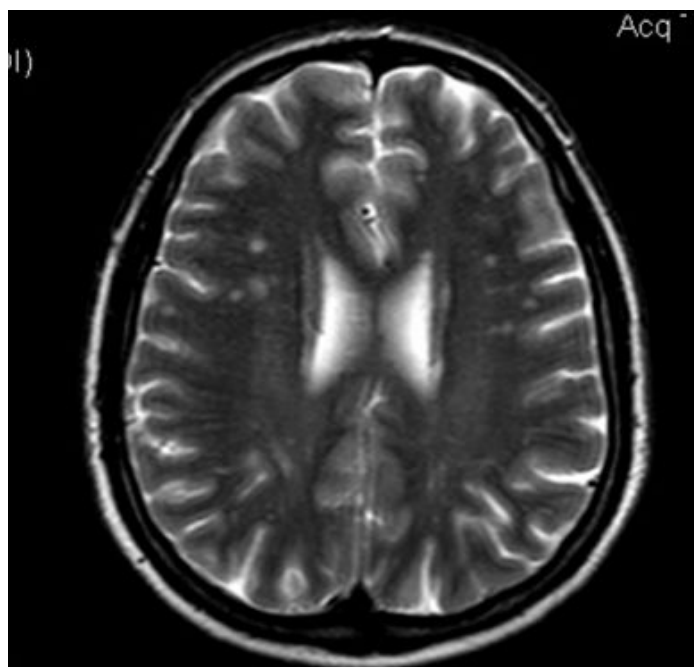
The studied sample includes two hundred patients (80 males and 120 females). The age range was (3-55 years) with a mean age of 22.7 years and standard deviation of 14.5 years. The positive MRI findings were observed in 51 patients (25.5%). Thirty-eight (19%) patients were presented with an aura (MA). Patients under 18 years of age (Group 1) (No=100), were 43 males (43%) and 57 females (57%), ranged from 3 to 18 years old, mean age was 10.36 years and 3.62 years of standard deviation 19 patients (19%) had positive MRI findings and 17 patients (17%) had MA. On the other hand, there were 100 patients aged 18 years or more (Group 2), 37 males (37%) and 63 (63%) females, their age ranged between 19 years and 55 years, the mean age was 35 years and 9.97 years of Standard deviation of whom 32 patients (32%) had positive MRI findings and 21 patients (21%) had MA, Table 1.

Characteristics	Group 1				Group 2			
	No.	Range	Mean	Std. Dev.	No.	Range	Mean	Std. Dev.
Age	100	3-18 y	10.36	3.62	100	19-55	35	9.97
	Frequency	Percent		P-value	Frequency	Percent		P-value
Gender								
Male	43	43		0.16	37	37		0.009
Female	57	57			63	63		
MRI findings								
Positive MR	19	19		0	32	32		0
Negative MR	81	81			68	68		
Type of Headache								
Aura	17	17		0	21	21		0
Without aura	83	83			79	79		

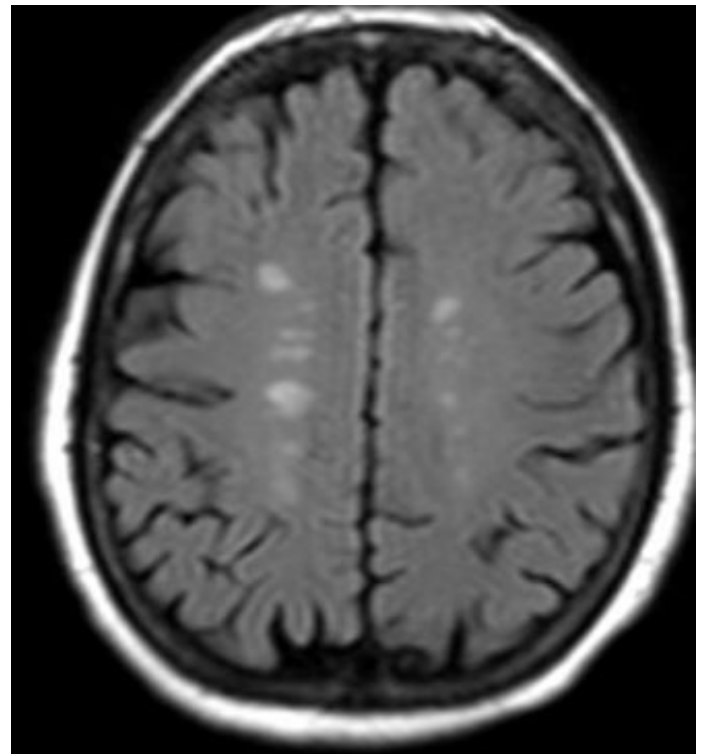
**Table 1.** Patient's demographics MRI findings and type of migraine headache in both groups. Group 1: Patients less than 18 years. Group 2: Patients of 18 years and older. y: Years.

Positive MRI findings were observed in 51 of the 200 patients in total (25.5%). The positive MRI findings were found to be in the form of WMHI (infra and supratentorial) and the total number was 120, of them 91 (75.8%) supratentorial and 29 (24.2%) infratentorial.

All WMHI were smaller than 5 mm, in any of the examined patients no brain infarct could be detected, multiple non-related incidental findings were also noted during the exam (Virchow-Robin spaces, arachnoid cyst, with extra cranial findings like sinusitis). The WMHI was found to be present in 32% in group 2 and 19% in group 1, with a statistically significant difference ( $p=0.035$ ), the average no. of WMHI found to be significantly higher in group 2 (18 years or above) compared to group 1 (below 18 years group) (1.9 per positive case for group 1 and 2.5 per positive case for group 2), with ( $P=0.04$ ). The presence of WMHI in MRI examinations of adult migraine patients is shown in Figure 1 and 2.



**Figure 1.** White matter hyper intensities T2 weighted MRI with multiple bilateral deep WMHI at the level of lateral ventricles.



**Figure 2.** White matter hyperintensities, FLAIR image showing WMHI at the supraventricular level bilaterally.

Compared to patients who do not have an aura, the presence of positive MRI changes in MA is shown to be significantly high ( $P$  value=0.00), as shown in Table 2, which demonstrates that 65.8% of patients with an aura had positive findings in MRI, compared with 16% only of patients without aura, with an odds ratio of 10.0 at 95% confidence interval.

Likewise if each age group (below 18 and above 18 years) has been separately analyzed, this difference is clearly noted, the odds ratio for having positive MRI findings in MA in the first group was 17, while in the second group was 6.7 at 95% confidence interval respectively Table 3.

Characteristics		Aura			Total
		MA	MW		
Positive	Count	25	26	51	
	%	65.80%	16.00%	25.50%	
Negative	Count	13	136	149	
	%	34.20%	84.00%	74.50%	
Total	Count	38	162	200	
	%	100.00%	100.00%	100.00%	

**Table 2.** Relation of MRI findings to the presence of aura. MA: Migraine with Aura; MW: Migraine without Aura.

Characteristics			Child			Adult		
			Type		Total	Type		Total
			MA	MW		MA	MW	
MRI	Positive	Count	11	8	19	14	18	32
		%	64.70%	9.60%	19.00%	66.70%	22.80%	32.00%
	Negative	Count	6	75	81	7	61	68
		%	35.30%	90.40%	81.00%	33.30%	77.20%	68.00%
Total		Count	17	83	100	21	79	100
		%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

**Table 3.** Relation of MRI findings to the presence of aura according to the age group. MA: Migraine with Aura; MW: Migraine without Aura.

## Discussion

Studying brain structural changes in migraine continues to be a subject of many recent studies, linking the presence of white matter changes and silent brain infarcts to migraine as there is still no clear relationship between migraine, presence of WMHIs and brain infarcts, vascular ischemic risks, and the clinical relevance of these WMHIs to migraine [23-25].

A meta-analysis study showed an increased risk of having WMHIs in migraines patients with an odds ratio of 3.9 [26]. In our study, the prevalence of positive MRI findings in form of WMHI was found to be 25.5% (32% in adult group and 19% in child and adolescent group) with a statistically significant difference between the two groups, this finding seems to be logical and consistent with the results of the previous studies which showed that the incidence of MRI WMHI generally increases with advances of age, and that its incidence in migraine patients also increases with advancing age [27-30].

Wide population based studies done in France, USA and Canada showed that females are more commonly affected by migraine than males [31-34] especially at reproductive ages the global burden of disease study in 2015 demonstrated that females are two or three times more commonly affected by migraine, this difference in prevalence may suggest that female hormonal factors may be a determinant factor for migraine risk and characteristics [33,35].

Furthermore some studies observed that decreasing estrogen in hormonal replacement therapy decreases the aura in postmenopausal migraines ladies [35]. In the current study the migraine is shown to be higher in females than in males in both adult and pediatric groups (57% in child and adolescents) (63% in adult group) respectively, however the statistical significance is noted in the adult group only, this finding is consistent with the result of a large study held in the US in 2003 on 40,892 participants and aimed to assess the age and gender prevalence of migraine, the study demonstrated that the one-year prevalence of migraine in boys and girls (until the age of puberty) is similar, then it became more common in females after this age [36].

There is still no clear association between sex and structural brain changes in migraine some studies suggest that the prevalence but not the progression of the structural brain changes in migraine including WMHI and brain infarcts is more common in others denied this association [22,25,37]. In our study WMHIs were identified in 51 of 200 cases (25.5%) of them 29 were female (56.8%), with no significant sex difference in MRI findings among migraine patients ( $p=0.5$ ). The previous literature showed that the percentage of aura among migraine patients ranged from 14%-54% [38-40]. In our study, 19% of the total 200 patients suffered from MA (17% in child, and 21% in adult), some studies including one large epidemiological study held by Rasmussen et al. demonstrated that migraines females are more commonly affected by aura than males [41]. In our study the percent of MA is higher in females than in males (60.5% vs. 39.5% respectively). However, no association between female sex and aura can be statistically proved.

The association of structural brain changes in migraine with aura is a subject of debates, several studies including meta-analysis study held by Bashir et al. demonstrated a strong association between MA and structural brain changes, including WMHs, silent brain infarct and volumetric changes in grey and white matter, others fail to prove such an association [9,17,42,43]. In our study, the presence of positive MRI changes among MA is shown to be significantly of high prevalence ( $p$ -value=0.00), compared to the patients who don't have an aura, with an odds ratio of 10.0. In the present study, the MRI findings are in the form of WMHI, supratentorial WMHIs are the commonest findings, no brain infarct or grey matter changes are noted in any of the studied cases, and these findings are comparable to Pavese et al. and Uggetti et al. The limitations of our study include the cross-sectional type of the study which may show relations between events but not the sequential effect. In addition, the strict exclusion criteria used in the selection of the patients may carry some bias, however their no. is considered small compared to the sample, so that it has only a minor impact on the results.

## Conclusion

Structural brain changes in form of WMHI are common MRI findings in the migraine patients. The presence of aura has

been shown to be strongly associated with an increased risk of getting WMHI in migraine. This theory can lead to the conclusion that the aura may be a strong sign of ischemic brain changes, thus further longitudinal studies are required to emphasize this relationship and to study the underlying pathophysiology. Also, this study makes us suggest that the presence of aura may be one of the indicators of neuroimaging for migraine patients. Advancing age and female sex in adult, but not in children, are other factors that have been shown to be associated with brain WMHI in migraine but however, to a lesser extent.

## Abbreviation

ICHD-3: The International Classification of Headache Disorders-Third Edition; MA: Migraine with Aura; MRI: Magnetic Resonance Imaging; MW: Migraine without Aura; No: Number; Std. Dev: Standard Deviation; TR: Time of Repetition; WMHI: White Matter Hyperintensities.

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