Southeast-Asian J. of Sciences: Vol. 7, No 2 (2019) pp. 178-189

OVERVIEW: STUDYING THE CHANGE OF WHITE MATTER ASSOCIATED WITH MIGRAINE DESEASE BY MAGNETIC RESONANCE IMAGING

Tran Thi Kim Lan*, **Ly Anh Tu***
and
Nguyen Truong Thanh Hai†

* *Department of Applied Science*
University of technology-VNU HCM City, Vietnam
email: kimlantran.bme@gmail.com lyanhtu@hcmut.edu.vn

† *University Montpellier, Montpellier city, France*
email: thanhhai7486@gmail.com

Abstract

Migraine is a common neurological disorder. It influences the quality of personal life and also brings economic and social drawbacks. Studies on the change of white matter associated with migraine disease by magnetic resonance imaging (MRI) have been investigating in many places around the world. Early detection of white matter changes in migraine patients determines its relationship with migraine severity, type and duration[1].

At present, the general method of studying on the change of white matter associated with migraine disease is using magnetic resonance imaging. Research groups gathered migraine patients in different ages. They excluded smokers and patients with hypertension, cardiac disease, diabetes mellitus, endocrine dysfunction, oncological and hematological diseases, infectious diseases, demyelinating disorders, and Alzheimer disease because the repeated attacks of migraine were the only known risk factors for the change of white matter. Magnetic resonance images of same patient groups were captured in same MRI scanners and acquisition protocols in a period of time to investigate functional and structural abnormalities of white matter due to the effects of the repeated migraines.

Key words: Migraine, brain white matter hyperintensity, quantitative 3.0-Tesla MRI, volumetry, longitudinal analysis

The results of studies by magnetic resonance imaging method show that there are white matter hyperintensities (WMHs) and white matter lesions (WMLs) associated with migraine and the status of these changes depend on the frequency of the repeated migraine attacks.

1. Introduction

According to WHO, migraine affects about 15% of world population. This is the most popular neurological disorder and it ranks 12^{th} in women and 19^{th} in population for the level of disablement. Normally, migraine is considered as a benign disorder which does not cause long-term consequences for brain. Neurologists have usually evaluated that patients suffer migraine to exclude the secondary causes of headache.

However, researchers have recently investigate the brain activation pattern when migraine attacks and symptoms such as nausea, vomiting, and sensitivity to light, sound, or smell to find out basic mechanism. There are more evidences that migraine is unpredictable and the repeated attacks leads to structural and functional abnormalities, finally chronic headaches.

Using MRI technique has pointed out that migraine is not just a disorder related to continuous pain or not but a process of the structural and functional brain changes through time. In the last decade, several ordinary changes were proved such as gray matter (GM) and white matter (WM). This helps to improve treatments as well as monitor treatment effectiveness in an objective and non-invasive way.

Migraine is an independent risk factor for brain white matter lesions (WMLs) and silent posterior circulation territory infarcts [2],[3].Both the disease duration and the attack frequency have an important role in the lesion evolution, and the effects of comorbid diseases may also lead to the development of lesions. While quantitative magnetic resonance imaging (MRI) study of chronic supratentorial white matter hyperintensities (WMHs) in migraine patients demonstrated tissue damage with axonal loss, decreased glial cell density with impaired energy metabolism, an enlarged extracellular space with an increased extracellular water fraction and decreased blood flow and volume.10 WMHs could be the consequence of a microvascular ischemic injury in migraine. The WMHs appeared most frequently in the deep white matter in the anterior circulation territory, mainly in the frontal and parietal lobes, with a similar average WMH size in all hemispheric lobes [5].

Examination of white matter change associated with migraine patients can be performed by functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI) because of its high specification and sensitivity. Commonly used to detect changes in brain function and structure in the central nervous system. Thereby, neuroimaging provides new insights into brain function and structure that can provide objective signs of the disease.

2. Methodology

Method

We searched and review the reference articles studying white matter change by magnetic resonance imaging in migraineurs, based on title, in the period 2013-2018. The search was limited to English-language publications and studies of humans. We also reviewed the reference lists of relevant primary articles and reviews. Diagnostic criteria for migraine were carefully reviewed. Studies used the International Classification of Headache Disorders for MO and MA. We included the following imaging techniques: T1- and T2-weighted and fluid-attenuated inversion recovery MRI, diffusion tensor imaging (DTI), and voxel-based morphometry (VBM). Studies performed at 1.5 and 3.0 T were included. All articles were screened for content, methodology, and design carefully.

Patient

Research groups gathered migraine patients in different ages. They excluded smokers and patients with hypertension, cardiac disease, diabetes mellitus, endocrine dysfunction, oncological and hematological diseases, infectious diseases, demyelinating disorders, and Alzheimer disease because migraine was the only known risk factor for the change of white matter.

They also divided patients into two major types: migraine without aura and migraine with aura. Migraine without aura is a clinical syndrome characterized by headache with specific features and associated symptoms. Migraine with aura is primarily characterized by the transient focal neurological symptoms that usually precede or sometimes accompany the headache. Depending on criteria, all patients were be diagnosed and coded [6].

There were differences about number, age groups, gender, migraine type as well as the study period (Table 1)

I. Diagnostic criteria of migraine without aura [6]

A. At least five attacks1 fulfilling criteria B-D;

B. Headache attacks lasting 4-72 hours (when untreated or unsuccessfully treated);

C. Headache has at least two of the following four characteristics:

1. unilateral location;
2. pulsating quality;
3. moderate or severe pain intensity;
4. aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs).

D. During headache at least one of the following:

1. nausea and/or vomiting;
2. photophobia and phonophobia.

E. Not better accounted for by another ICHD-3 diagnosis.

II. Diagnostic criteria of migraine with aura [4].

A. At least two attacks fulfilling criteria B and C;

B. One or more of the following fully reversible aura symptoms:
1. visual;
2. sensory;
3. speech and/or language;
4. motor;
5. brainstem;
6. retinal;

C. At least three of the following six characteristics:
1. at least one aura symptom spreads gradually over 5 minutes;
2. two or more aura symptoms occur in succession;
3. each individual aura symptom lasts 5-60 minutes;
4. at least one aura symptom is unilateral [2];
5. at least one aura symptom is positive [3];
6. the aura is accompanied, or followed within 60 minutes, by headache;

D. Not better accounted for by another ICHD-3 diagnosis.

There were differences about number, age groups, gender, migraine type as well as the study period (Table 1)

Table 1. Studies of white matter changes on migraine patients.[5][7][8]

Authors	MRI scanners	Patients				Migraine Type		Time period
		Number	Gender		Age groups			
			Male	Female		With aura	Without aura	
Szilvia et al.[5]	3.0-Tesla Magnetom TIM Trio, Siemens Medical Solutions, Erlangen, Germany) with a 12 channel phased-array head coil was used for MR measurements.	17	2	15	22-68	x	x	3 years
Jixin et al.[7]	3.0-Tesla Signa GE scanner (GE Healthcare, Milwaukee, WI) with an 8-channel phase array head coil at the Huaxi MR Research Center in Sichuan, China	21			22.6± 2.0 years	x		1 year
Mohamed Negm et al.[3]	1.5 Tesla MR Imager (Achieva; Philips Medical Systems, Best, Netherlands)	65	48	17	18-50	x	x	

MR Scanning Protocol

Experiments were carried out in brain MRI techniques such as T1- weighted, T2-weighted, fluid-attenuated inversion recovery MRI (FLAIR), diffusion tensor imaging (DTI), and voxel-base morphometry (VBM). The most common MRI sequences are T1-weighted and T2-weighted scans. T1-weighted images are produced by using short TE and TR times. The contrast and brightness of the image are predominately determined by T1 properties of tissue. Conversely, T2-weighted images are produced by using longer TE and TR times. In these images, the contrast and brightness are predominately determined by the T2 properties of tissue. In general, T1- and T2-weighted images can be easily differentiated by looking the CSF. CSF is dark on T1-weighted imaging and bright on T2-weighted imaging. A third commonly used sequence is the Fluid Attenuated Inversion Recovery (Flair). The Flair sequence is similar to a T2-weighted image except that the TE and TR times are very long. By doing so, abnormalities remain bright but normal CSF fluid is attenuated and made dark. This sequence is very sensitive to pathology and makes the differentiation between CSF and an abnormality much easier.

Studies performed at 1,5 to 3T MRI scanners with 8 to 12 channel phased array head coil for MR measurements. To capture high resolution images, the sequence parameters were used for different performances. For each brain MRI techniques, sequences were done with the following parameters: Repetition time (TR), Echo time (TE), Slice thickness, Field of view, Matrix or diffusion weighted (DW) images with the b value.

Imagine Analysis

Original images were transferred to a work station. Data were fed to a computer and analyzed by software of analysis tools for FMRI, MRI and DTI brain imaging data. There are many different steps involved in a neuroimaging analysis and there is not just one order in which to perform them. Depending on the researcher, the paradigm at hand, or the modality analyzed (sMRI, fMRI, dMRI), the order can differ. Some steps may occur earlier or later or may be left out entirely. Nonetheless, the general procedure for analysis can be divided into the following three steps: preprocessing, model specification and estimation, statistical inference. Preprocessing is the term used to for all the steps taken to improve our data and prepare it for statistical analysis such as slice timing correction, motion correction, artifact detection, coregistration, normalization, smoothing, segmentation. Model specification and estimation is to test our hypothesis on our data we first need to specify a model that incorporates this hypothesis and accounts for multiple factors. Statistical inference making inferences about the estimated parameters using appropriate statistical methods.

Szilvia et al used Matlab software's curve fitting toolbox and a self-written program code (The MathWorks Inc., Natick, MA, USA) software to analyze T1,

T2, and diffusion data processing while perfusion analysis was carried out by the Siemens Perfusion software (Siemens Medical Solutions, Erlangen, Germany). The arterial input function was determined by an experienced radiologist. The free-hand ROIs were drawn on hyperintense lesions on T2* images by referring to T2-weighted and FLAIR images [5].

Jixin et al used the Brain (FMRIB)'s Diffusion Toolbox (FDT) 2.0 and parts of the FMRIB Software Library (FSL) 4.1.9 (Oxford Centre for Functional Magnetic Resonance Imaging of the Brain Software Library, www.fmrib.ox.ac.uk/fsl/). FSL is a comprehensive library of analysis tools for FMRI, MRI and DTI brain imaging data. It runs on Apple and PCs (both Linux, and Windows via a Virtual Machine), and is very easy to install. Most of the tools can be run both from the command line and as GUIs ("point-and-click" graphical user interfaces) [7,9,10].

Mohamed Negm et al transferred all original DICOM images to Philips workstation. Data were analyzed by the same radiology consultant. He detected white matter hyperintensities through high-signal-intensity punctate foci on T2WI and FLAIR images [8].

Statistical analysis

Data were usually analyzed by the IBM SPSS Software version 20. They used different tests such as Mann- Whitney test (for abnormally distributed quantitative variables, to compare between two studied groups with and without aura to each other), Wilcoxon's test (to compare the baseline and follow-up values), Kruskal Wallis test (for abnormally distributed quantitative variables, to compare between more than two studied groups, and Post Hoc "Dunn's multiple comparisons test" for pairwise comparisons) Spearman's correlation (to investigate the relationship between the number of migraine attacks and the hyperintensity number) and Pearson's chi-square test (to evaluate changes of size of hyperintensity categories)., the Bonferroni correction was used to reduce type 1 error [5,8].

3. Result

The study of Szilvia et al.1 included 17 patients with migraine. Their age ranged from 22 to 68 years. 15 patients (88.24%) were females, and 2 patients (11.76%) were males. 10 patients (58.82%) of the patients had migraine without aura and 7 patients (41.18%) had migraine with aura. 17.65% of the studied patients had migraine for less than 20 years, and 8 (47.06%) patients had migraine for 20-30 years, while 4 patients (23.53%) had migraine for 30-40 years, and 2 patients (11.76%) had migraine for more than 15 years. The average of attack frequency per month was 3.35 in both 2009 and 2012 and the highest was 10 times. There were 4 patients attacked less, just one case attacked more while the rest was unchanged.

Changes in Number of WMHs

From 2009 to 2010, almost patients experienced an increase of the number of WMHs, the only exception was a forty-three years old patient. It can be seen that the number of WMHs of two male patients were higher than those of female. The average number of WMHs was 22 in the year 2009 and was 29 in the year 2012. The proportion of patients whose number of WMHs were about 20-40 and over 40 grew from 35.29% and 17.65% to 47.05% and 23.25% while the percentage of patients having less than 20 WMHs fell for 17.61%.

Changes in Size of WMHs

Most of the WMHs became larger after the 3-year long follow-up period. All patients had at least 1 WMH with an increased volume (Table 1). Only the minority of WMHs had the same size at baseline and 3 years later. A total of 91 WMHs had a smaller volume at follow-up and all patients had at least 1 WMH that became smaller.

Changes in Prevalence of WMHs

The number of newly developed hyperintensities (n = 130) was higher than the number of disappeared ones (n = 22), (Tables 1). Whereas 16 patients had at least 1 newly developed WMH, only 6 patients who had at least 1 disappeared WMH were identified (Table 1). The age of patients having disappeared WMHs ranged from 35-68 years (Table 2) Figure 1 shows the changes of size, the presence of hyperintensities through tree-year period from 2009 to 2012. Axial fluid-attenuated inversion recovery brain MRI images of 2 migraine patients show changes between the baseline and the follow-up studies regarding the white matter hyperintensities. These include unchanged right frontal and larger left fronto-parietal bright signal intensities and appearance of a new frontal hyperintensity (A), and a disappeared frontal hyperintense lesion (B). Images are presented in radiological convention (left = right).

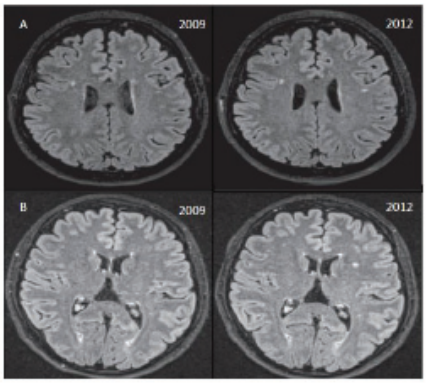

Figure 1. The changes of white matter hyperintensities through tree-year period from 2009 to 2012 [5]]

Table 2. Clinical and White Matter Hyperintensity Data of Migraine Patients.[1]

Patient	gender	Age	Migraine type	Disease Duration (years) 2012	Attack Frequency/ Month		Total number of WMHs		Comparison Between 2009 and 2012 (Number of WMHs)				
					2009	2012	2009	2012	Unchanged size	Increase in size	Decrease in size	Disappeared	Newly Developed
1	Female	22	With aura	8	3	3	17	25	0	16	1	0	8
2	Female	28	Without aura	13	8	8	7	11	0	2	5	0	4
3	Female	35	Without aura	17	2	1	21	23	1	10	6	4	6
4	Female	41	Without aura	31	2,5	4	46	55	0	37	7	2	11
5	Female	43	Without aura	23	3	2	5	5	1	3	1	0	0
6	Male	44	Without aura	24	2	2	54	65	0	41	7	6	17
7	Female	46	Without aura	28	10	10	5	9	0	2	1	2	6
8	Female	46	With aura	27	1	1	14	18	0	10	4	0	4
9	Female	47	Without aura	29	3,5	3,5	22	27	2	11	9	0	5
10	Female	47	With aura	31	6	4	28	33	5	17	6	0	5
11	Female	48	With aura	28	4	4	39	46	2	23	14	0	7
12	Female	49	With aura	29	5	5	2	7	0	1	1	0	5
13	Female	50	Without aura	28	8	8	12	23	0	9	3	0	11
14	Female	51	Without aura	37	4	4	31	39	1	19	11	0	8
15	Male	54	With aura	40	1	1	21	33	0	14	5	2	14
16	Female	56	Without aura	38	2,5	1,5	20	23	0	15	5	0	3
17	Female	68	With aura	48	0,5	0,5	46	56	1	34	5	6	6

The study of Mohamed Negm et al. [8] showed that white matter hyperintensities are detected as high-signal-intensity punctate foci on T2WI and FLAIR images and the most common areas of white matter was the centrum semiovale while the converse of deep white matter was seen like small high-signal-intensity lesions due to ischemic brain changes. There were two patients groups: those with white matter hyperintense punctate foci and those without any lesions. There were about the haft of migraine patients who had white matter hyperintense punctate foci (43.1%). 9.2% of them had one lesion (figure 2), 13.8%) patients had 2 lesions (figure 3) and the rest had more than

2 lesions. Figure 2 illustrates Axial FLAIR MRI image of 50-year-old female patient, not known to have any chronic illness, presented with migraine with aura for 10-year duration of grade III severity. It shows small single bright focus at the right centrum semiovale (arrow) while Axial FLAIR MRI image of 25-year-old female patient, not known to have any chronic illness, presented with migraine without aura for 6-year duration of grade II severity, not responding to medical treatment shows two left frontal white matter hyperintense lesions (arrows) (figure 3).

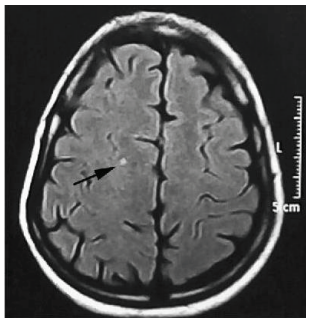

Figure 2. Axial FLAIR MRI image shows small single bright focus at the right centrum semiovale (arrow)[8]

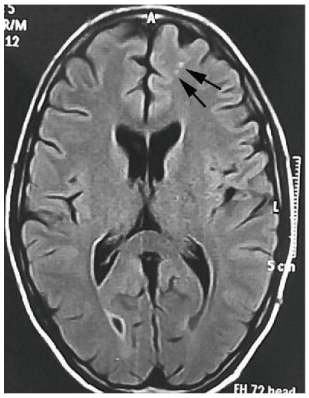

Figure 3. Axial FLAIR MRI image shows two left frontal white matter hyperintense lesions (arrows)[8]

The study of Szilvia et al compared between data in 2009 (the baseline study) and data in 2012 (follow-up study), A significantly higher number of WMHs was detected than in the baseline study (498 vs 370, $P < .001$). In all locations, the hyperintensity number was higher in the deep white matter ($P < .001$), the subcortical ($P = .012$), and the periventricular ($P = .021$) locations. Large hyperintensities significantly increased in size more often than medium-

sized or small hyperintensities (P < .002), while size decrease was most common in small hyperintensities (P < .002). The number of increased or decreased-sized hyperintensities did not correlate with age, the disease duration, or the frequency of migraine attacks (correlation coefficients: 0.160, 0.360 and -0.470, P > .05, respectively). The number of newly developed hyperintensities did not correlate with age, the disease duration, or the frequency of migraine attacks (correlation coefficients: 0.196, 0.261, and -0.286, P > .05, respectively). While the number of disappeared hyperintensities did not correlate with the age and disease duration (correlation coefficients: -0.014 and 0.158, P > .05), the number of disappeared WMHs negatively correlated with the attack frequency at baseline (coefficient: -0.517, P = .034). Meanwhile, according to multivariate analysis of the study of Mohamed Negm et al , neither gender nor duration of attack had statistically difference, but age, migraine severity grade, pain intensity during attack, nausea, disability, and tolerability had a highly statistically significant difference, while migraine duration and resistance to treatment had a statistically significant difference.

4. Discussion

In these studies, scientists investigated a studied migraine group with brain WMHs performing the same quantitative MRI measurements for a period time. The only known risk factors were the recurrent headache attacks, which could be the cause of progression in the tissue impairment inside the WMHs or could lead to the volume change of hyperintensities and the formation of new hyperintensities. The size of WMHs did not remain constant. The majority of them increased in size while the proportion of the decrease was lower. The quantity of new WMHs formation were higher than the disappearance. As a result, the number of WMHs rose. As a result, migraine may be a risk factor for structural brain changes including white matter abnormalities, infarct-like lesions, and volumetric changes in the white matter regions. The higher hyperintensity number associated with higher cerebral and lobar hyperintensity volumes. A higher number of newly developed hyperintensities were detected than disappeared hyperintensities. The repeated headache attacks with different attack frequency and attack intensity may have a different impact on changes of white matter hyperintensities. Based on these findings, patients with disappeared hyperintensities had a low migraine attack frequency at baseline.

Since these studies varied in sample size, participant selection, headache characteristics, test methodology, timing of study, and data interpretation, the authors suggested additional longitudinal studies with a broad range of attack frequency and severity for better understanding the association between migraine and structural brain changes and to clarify the association to attack frequency and disease duration and the difference led to the increase of the cerebral hyperintensity count.

There still were study limitations such as the size of patient groups, the criteria selection, the control of potential unpredicted factors and the quality of MRI scanners. The small sample size is a consequence of the longitudinal design and strict selection criteria. Unfortunately, small sample size did not allow extensive correlation of WMH characteristics with clinical headache parameters including investigation of differences among migraine subgroups, neither control for potential confounding factors.

5. Conclusion

The number of migraine patients is increasing, and need appropriate and effective treatments. Many causes have been implemented to effectively diagnose and treat migraine. Therefore, studying the relationship between white matter and migraine is necessary to improve the effect of identification of migraine and to avoid wrong examination of the symptoms. This method requires modern accurate MRI scanners, imaging techniques such as T1- weighted, T2-weighted, fluid-attenuated inversion recovery MRI (FLAIR), diffusion tensor imaging (DTI), and voxel-base morphometry (VBM). Age, presence of aura, nausea, and disability during attack, resistance to treatment, and severity of headache and duration of migraine are considered a risk factor for development of WMHs. Based on the studies, migraine is commonly associated with the change of white matter. However, the association between migraine and structural brain changes and the relationship between properties of migraine attack and disease condition is complicated by differences in interaction mechanisms, it is necessary to clarify. There are important limitations of studying such as the size of patient groups, timing of study, the criteria selection, the control of potential unpredicted factors and the quality of MRI scanners, which can effect the accuracy of results.

To elucidate the nature of the relationship between migraine headaches and white matter changes found, it is able to use DTI for research as DTI is a powerful support tool at present. It may help people better understand the progression of migraine and implicate its treatment.

References

[1] T.J Schwedt et al., *Advanced neuroimaging of migraine,* Lancet Neurol, vol. 8 (2009), 560-568.

[2] A. Bashir et al., *Migraine and structural changes in the brain: A systematic review and meta-analysis,* Neurology, vol. 81 (2013), 1260-1268.

[3] M.C. Kruit et al., *Migraine is a risk factor for subclinical brain lesions,* JAMA, vol. 291 (2004), 427-434.

[4] M. Aradi et al., *Quantitative MRI studies of chronic brain white matter hyperintensities in migraine patients,* Headache, vol. 53 (2013),752-763.

[5] E. Szilvia et al., *Changes of Migraine-Related White Matter Hyperintensities After 3 Years: A Longitudinal MRI Study,* Headache, Wiley Periodicals, pp. 55-70, Jan. 2015.

[6] "Headache Classification Committee of the International Headache Society", The International Classification of Headache Disorders, 2nd edn. Cephalalgia, 2014.

[7] L. Jixin et al., *Migraine-Related Gray Matter and White Matter Changes at a 1-Year Follow-Up Evaluation,* The Journal of Pain, **14** (12) (Dec 2013), 1703-1708.

[8] N. Mohamed et al., *Relation between migraine pattern and white matter hyperintensities in brain magnetic resonance imaging,* The Egyptian Journal of Neurology, Psychiatry and Neurosurgery, 2018.

[9] S.M. Smith et al., *Advances in functional and structural MR image analysis and implementation as FSL,* NeuroImage, **23**(S1) (2004), 208-219.

[10] M. Jenkinson et al., *FSL,* NeuroImage, **62**(2012), 782-90.