Research Square

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The Characteristics of White Matter Hyperintensities in Patients With Migraine

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Abstract

Background

The presence of white matter hyperintensities (WMH) in migraine is well-documented, but the location of brain WMH in patients with migraine are insufficiently researched. Although recent semi-automatic software packages have been developed for calculating WMH, visual inspection remains the gold standard for measuring WMH. The goal of this study was to assess WMH in patients with migraine using a modified version of the Scheltens visual rating scale, a semiquantitative scale for categorizing WMH in the following brain regions: periventricular, lobar (frontal, temporal, parietal, occipital), basal ganglia, and infratentorial regions.

Methods

263 patients with migraine (31 male/232 female; mean age: 48.0) who were enrolled in the American Registry for Migraine Research from Mayo Clinic with a diagnosis of episodic (n = 46; 17.5%) or chronic migraine (n = 217; 82.5%) and who had brain magnetic resonance imaging were included in this study. Those with imaging evidence for gross anatomical abnormalities other than WMH were excluded. WMH were identified on axial T2 and FLAIR sequences by a board certified neuroradiologist. WMH were characterized via manual inspection and categorized according to the scale's criteria.

Results

95 patients (36.1 %: mean age: 41.8) had no WMH on axial T2 and FLAIR imaging and 168 patients (63.9%, mean age: 51.4) had WMH. Of those with WMH, 94.1% (n = 158) had lobar hyperintensities (frontal: 148/158, 93.7%; parietal: 57/158, 36.1%; temporal: 35/158, 22.1%; occipital: 9/158, 5.7%), 13/168, 7.7% had basal ganglia WMH, 49/168, 29.1% had periventricular WMH, and 17/168, 10.1% had infratentorial WMH. 101/168 patients (60.1%) had bilateral WMH and 67/168 (39.9%) had unilateral WMH (34 right hemisphere /33 left hemisphere). 30.0% of patients with WMH did not have WMH reported in their clinical radiology reports.

Discussion

Nearly 2/3 of patients with migraine had WMH. They were most common in the lobar regions, specifically in the frontal lobe. The categorization of WMH in migraine using the modified Scheltens visual rating scale could help in future studies to clarify the relationship between WMH and headache features and might be a useful method for developing classifiers that differentiate between migraine-specific WMH and other causes of WMH.

Key Findings

- Using T2 and FLAIR imaging, WMH were detected in the majority of migraine patients using a modified version of the Schelten's visual rating scale.

- Most of the lobar WMH were under 3 mm in size.
- When comparing migraine individuals with and without WMH, there was not a difference in the distribution of sex ratios (male vs female), presence or absence of aura, or ratios of episodic vs chronic migraine between cohorts.

Introduction

White matter hyperintensities (WMH) are a common finding on magnetic resonance imaging in people with migraine using T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences (1–4). A number of studies indicate that individuals with migraine have a higher likelihood of having WMH (5) and there is evidence that women with migraine have a higher incidence of deep WMH and show more rapid progression of WMH relative to non-migraine controls (6). Several studies have investigated correlations between WMH with 1) migraine subtypes (migraine with aura vs migraine without aura), 2), headache frequency, and 3) medication use(5, 7–9). However, conflicting study results have made it difficult to interpret whether WMH have clinical significance in migraine (4, 5, 8, 10–14). It is possible that discrepancies between studies may in part be due to variations in cohort selection, use of different MRI magnet strengths, and differences in techniques used for identifying WMH, as some studies have used semi-automated calculation of WMH (4, 6) whereas others identified WMH manually via routine visual identification or categorization (8, 10, 11, 13, 14). Furthermore, there are a lack of investigations into how WMH attributable to migraine might be distinguishable from those attributed to other etiologies such as small vessel ischemic disease and demyelinating disease.

The goal of this study was to assess WMH in patients with migraine using a modified version of the Scheltens visual rating scale (15), a well-known semi-quantitative rating scale for assessing WMH in the following brain regions: periventricular, lobar, basal ganglia, and infratentorial. (see Fig. 1). This study aimed to categorize WMH in patients with migraine by their size, and location, so as to allow *for future* differentiation of migraine-specific WMH from those attributable to other diseases such as small vessel ischemic disease and multiple sclerosis.

Methods

Subject Eligibility and Consent: Institutional Review Board approval was received from Mayo Clinic and all subjects completed signed consent prior to the start of this study. All migraine subjects between the ages of 18 and 80 years who were enrolled into the American Registry for Migraine Research (ARMR) from Mayo Clinic Arizona and who had brain magnetic resonance imaging (MRI) as part of their clinical care were selected for this study. ARMR methodology has been previously published (16). Subjects were included in this study if both FLAIR and T2 imaging sequences were available. Those patients that had only FLAIR or only T2 sequences were excluded from the analysis. Subjects were excluded if imaging reports identified brain abnormalities other than WMH due to migraine and if there were significant imaging artifacts due to motion, oral cavity fillings, or other etiologies.

Figure 2 shows a flow chart of the study design. Medical records were reviewed for 308 subjects. Thirteen subjects who had abnormal brain findings were excluded. Following imaging review, three patients were excluded for imaging artifacts, and twenty-nine patients were excluded who only had usable T2 or only had FLAIR imaging, thus leaving a total of 263 migraine subjects with good quality T2 and FLAIR imaging.

Brain MRI Evaluation: All images were read by a single, board certified neuroradiologist (BC) with 30 years of experience. As part of this study, to keep the radiologist uninformed of each patient's diagnosis, he was also given imaging of those with cluster headache and post-traumatic headache with and without WMH. However, data from patients with cluster headache and post-traumatic headache were not included in the analyses reported herein. All Images were read over a four-month period (September 2020-January 2021) using the desktop viewer QREADS (9) which was integrated with the picture archiving and communication system (PACS) (10). All imaging was conducted at Mayo Clinic, Arizona.

WMH were identified as hyperintense on both FLAIR and T2 images relative to the surrounding brain parenchyma. The widest dimension of the lesion was measured with digital calipers and the location was documented using a modified version of the Scheltens visual rating scale (15)(Fig. 1). The scale was modified to identify scanning sequences (those patients who only had T2 or only had FLAIR imaging were excluded) and to account for laterality of WMH (bilateral or unilateral), image quality and presence of insula WMH, although these were counted separately and were not included in the total scoring of lobar WMH, so as to not alter the scoring criteria of the original scale.

The Scheltens scale allows scoring of WMH by relative size and number of lesions. Periventricular hyperintensities are calculated for three main locations: occipital caps, frontal caps, and lateral bands. Each of these are scored as either, 0 (absent), 1 (≤ 5mm) or 2 (> 5mm). The total score for periventricular hyperintensities ranges from 0 to a maximum total of 6.

Lobar, basal ganglia, and infratentorial hyperintensities are scored using the following scaling criteria: 0 (absent), 1 (≤3mm and number of lesions ≤5), 2(≤ 3mm and number of lesions ≥6), 3 (> 3mm and number of lesions ≤ 5), 4(> 3mm and number of lesions ≥6), 5(≥10 mm and number of lesions ≥1), 6 (lesion formations are confluent). Lobar WMH are calculated for frontal, parietal, occipital and temporal regions. The total score for lobar WMH ranges from 0 to a maximum score of 24. Total scores for basal ganglia regions (caudate nucleus, putamen, globus pallidus, thalamus, internal capsule) ranges from 0 to a maximum score of 30. Infra-tentorial foci of hyperintensity are calculated for the cerebellum, mesencephalon, pons and medulla. The total score ranges from 0 to a maximum score of 24.

Statistical Interpretation: Subject demographics and headache characteristics and data that were recorded from the modified Scheltens Visual Rating scale were organized in Excel and exported to SPSS 26 (Released 2019. IBM SPSS Statistics for Macintosh, Version 26.0. Armonk, NY: IBM Corp) for statistical interpretation. Demographic information and data from the Scheltens visual rating scale were compared using two tailed t-tests or Fisher exact tests, or Chi square tests as appropriate. A binary

logistic regression analysis was used for a post-hoc analysis to explore the relationship between headache frequency and WMH.

Results

The 263 migraine patients (age ranges: 18–80) had an average age of 48.0 (SD = 15.0), and 88.2% were female. Average headache frequency reported within the electronic medical record was 18.7 (SD = 10.9) days per month. Forty-six had episodic migraine and 217 had chronic migraine. 117/263 (44.5%) had migraine with aura.

Classification according to a modified version of the Scheltens Scale:

95/263 (36.1 %: mean age: 41.8, SD = 13.4) had no WMH on axial T2 and FLAIR imaging and 168/263 patients (63.9%, mean age: 51.4, SD = 14.7) had presence of WMH. WMH were most common in lobar regions, 94.1% (n = 158) had lobar hyperintensities (frontal: 148/158, 93.7%; parietal: 57/158, 36.1%; temporal: 35/158, 22.1%; occipital: 9/158, 5.7%.

thirteen patients (7.7%) had basal ganglia WMH, 49 (29.1%) had periventricular WMH, and 17 (10.1%) had infratentorial WMH.

For patients with frontal lobe lesions, 87 patients (58.8%) had lesions of 3mm or less in size and 61 patients (41.2%) had lesions over 3mm in size (p = .0.09). 36 patients (63.2%) had WMH in the parietal lobe of 3mm or less in size and 21 patients (36.8%) had WMH over 3mm in size (p = 0.009).

For patients with temporal lesions, 24 (68.6%) had WMH of 3mm or less in size and 11 patients (31.4%) had WMH over 3mm in size (p = 0.001). Four patients had occipital WMH of 3mm or less in size. There were no patients who had occipital WMH that were over 3mm in size.

Twenty-one of 148 patients (14.2%) with frontal lobe WMH had WMH in the insula. Of those the majority of WMH of 3mm or less in size [17 patients (81%) had insular WMH of 3mm or less in size and 4 patients had insular WMH larger than 3mm (19%); p = 0.001].

101/168 patients (60.1%) had bilateral WMH and 67/168 (39.9%) had unilateral WMH (34 right hemisphere /33 left hemisphere). Figure 3 and Fig. 4, show representative migraine subjects with frontal WMH of typical size and distribution seen in the studied cohort. Table 1. Shows lobar (frontal, temporal, parietal, occipital) WMH and periventricular (frontal, occipital, and lateral bands) WMH categorized by lesion size. These descriptive data indicate that patients with larger WMH tended to be older. Fewer than 2% of patients who did not have WMH in the frontal lobe had WMH in the basal ganglia or infratentorial regions. 30.0% of patients with WMH did not have WMH reported in their clinical radiology reports. When comparing individuals with WMH to individuals without WMH the following was found: Individuals with WMH were significantly older than those without WMH (individuals with WMH: mean age = 51.5, SD =

14.7; individuals without WMH: mean age = 41.8, SD = 13.4; $p < 0.001$), but there were no difference in sex (individuals with WMH: 19 male and 149 female; individuals without WMH: 12 male and 83 female; $p = 0.84$) and there was not a difference in episodic vs chronic migraine (individuals with WMH: 28 had episodic migraine and 140 had chronic migraine; individuals without WMH: 18 had episodic migraine and 77 had chronic migraine; $p = 0.73$) or difference in aura status (individuals with WMH: 74 had migraine with aura and 94 had migraine without aura; individuals without WMH: 43 had migraine with aura and 52 had migraine without aura; $p = 0.89$) between individuals with WMH compared to those individuals without WMH, see Table 2. An exploratory binary logistic regression analysis indicated that there was no association between headache frequency (i.e., episodic vs. chronic migraine) and WMH (odds ratio (OR) .756; 95% CI, .339-1.686; $P = 0.494$). In the opinion of the neuroradiologist who reviewed the imaging, WMH tended to be round (punctate) in shape and not confluent.

Table 1
shows the mean ages of migraine patients with WMH for specific locations categorized by size. n/a = no WMH for that size and location.

Periventricular WMH per location	**≤ 5mm**	**> 5mm**
caps occipital mean age (SD)	53.5 (16.7)	62.1 (11.2)
caps frontal mean age (SD)	51.5 (14.7)	62.5 (12.2)
bands mean age (SD)	n/a	64.0 (10.9)
WMH per Lobar location	≤ 3mm	> 3mm
Frontal mean age (SD)	49.05 (13.5)	57.8 (14.0)
Parietal mean age (SD)	55.1 (15.6)	60.0 (10.2)
Occipital mean age (SD)	63.4 (8.9)	n/a
Temporal mean age (SD)	61.67 (12.2)	56.5 (11.7)
Insula Mean age (SD)	54.1 (14.2)	57.25 (9.5)

Table 2
Demographic information of individuals with patients with and without white matter hyperintensities.

	WMH *yes* (n = 168)	**WMH *no* (n = 95)**	**p-value**
Age (SD)	51.5 (14.7)	41.8 (13.4)	< 0.001
Sex, male/female	19/149 (11.3%/88.7%)	12/83 12.6%/87.4%	0.84
Episodic/chronic migraine	28/140 (16.7%/83.3%)	18/77 (18.9%/81.1%)	0.73
Aura, yes/no	74/94 (44.0%/56.0%)	43/52 (45.3%/54.7%)	0.89
WMH = white matter hyperintensities; SD = standard deviation.			

Discussion

WMH classification based on a modified version of the Scheltens visual rating scale indicated that a majority of migraine patients (63.9%) had WMH on T2 and FLAIR imaging which were most prominent in the frontal lobes. In fact, fewer than 2% of patients who did not have WMH in the frontal lobe had WMH in the basal ganglia or infratentorial regions and only 5.6% had WMH in the periventricular WM. WMH were mostly distributed bilaterally (61%) and right hemisphere and left hemisphere lesions occurred with equal frequency.

Our results are in accordance with those from Xiu and colleagues who assessed WMH in 69 migraine patients, 24 of whom had WMH. Similar to our results, Xiu reported WMH to be most prevalent in the frontal lobe (74.9%) followed by the parietal lobes. In our study, 14% of individuals (n = 21) with frontal lobe hyperintensities had WMH located in the insula which is an intriguing finding as the insula is a known ‘cortical hub’ and a key region of the salience network (17) involved in cognitive and interoceptive components of the pain experience (18) and an area known in migraine to demonstrate alterations brain functional connectivity using resting-state imaging (19–21). Furthermore, using positron emission tomography [^{11} C]HOwe(9) PBR28 imaging, Hadjikhani and collegues found increased binding of the 18 kDa translocator protein, a marker of glial activation, in individuals with migraine with aura in the bilateral insula (22). Furthermore, authors also noted a positive correlation between insula [^{11} C] PBR28 standard uptake ratio and migraine attack frequency further suggesting insula involvement in neuroinflammation and nociception.

In the present study, migraine patients who had WMH were significantly older compared to migraine patients who did not have WMH. Furthermore, those who were older tended to have larger WMH for lobar (frontal, temporal, parietal and occipital) and periventricular regions compared to younger patients.

Frazekas reported that 11% of symptom-free subjects (n = 87, ages 31–83) had WMH in the 4th decade of life which increased to 83% in subjects over the age of 70. This percentage was even higher in those with cardiovascular risk factors (23). It is possible that the larger WMH found in our study could be at least partially attributable to factors other than migraine.

There is substantial evidence that migraine is associated with an increased risk for WMH. However, more work is needed that defines the characteristics of WMH attributed to migraine (i.e. size, shape, number, distribution) and differentiates them from those associated with other diseases, such as small vessel ischemic disease, lacunar infarcts, or multiple sclerosis. The majority of lobar WMH were under 3mm in size. In the opinion of the neuroradiologist who reviewed the imaging WMH were most commonly punctate in shape. None of them were visible on T1-weighted imaging as hypointense, as can be seen with lacunar infarcts, small vessel ischemic white matter changes, and multiple sclerosis. Furthermore, none of the lobar lesions in our migraine cohort were confluent (i.e. none had a score of 6 on the Scheltens scale), as can be seen in these other three entities. An additional observation in our migraine cohort was that few patients had periventricular white matter lesions contiguous with the lateral ventricles or capping of the lateral ventricles. Similarly, few patients had involvement of the basal ganglia, brainstem, or other posterior fossa structures. These features might prove unique to migraine and be useful for differentiating WMH attributable to migraine from those due to other diseases. Interestingly, 30 % of those with WMH identified using the Scheltens scale did not have WMH identified in the clinical imaging report. Possible explanations for a negative clinical report in 30% of the cases could be that either the lesions were too small to be appreciated, or alternatively, WMH were not felt to be clinically relevant and therefore not described. As there are a paucity of studies that have used systematic methods to assess and compare WMH between disorders, at times it can be difficult in clinical practice to determine if WMH are due to migraine or if they are better explained by another etiology. (24). Classification of WMH using the modified Scheltens scale may contribute to a better identification and understanding of the distribution of migraine WMH which could help to clarify the relationship between WMH and headache features.

The distribution and size of WMH in our migraine cohort seems to differ from that of focal WMH associated with lacunar infarcts. Ryu et al. (25) used a modified version of the Scheltens scale to assess lacunar infarcts and found a left hemisphere dominance of WMH in the corona radiata, basal ganglia, thalamus and internal capsule. Lesions seen in lacunar infarcts are usually small lesions that are hyperintense on T2 and FLAIR and have low signal on T1, correlating with pathological descriptions of gliosis and encephalomalacia respectively (26). The absence of low signal on T1 in this migraine cohort might imply that these lesions are not due to encephalomalacia. Similar to lacunar infarcts, multiple sclerosis lesions are bright on T2 and FLAIR images and can demonstrate low T1 signal when the lesions are chronic (27). The absence of low T1 signal in lesions seen in our migraine cohort distinguishes the WMH lesions from lacunar infarcts and multiple sclerosis. It is interesting that even in older migraine patients WMH are not low signal and therefore may not represent a final common pathway of encephalomalacia that is seen with lacunar infarcts and demyelination.

Limitations

There are several limitations of our study. All subjects included in this study had brain MRIs ordered for clinical reasons. Thus, they might have specific characteristics that led the clinician to order an MRI (e.g. atypical symptoms, abnormal neurological examinations). Thus, the findings from this study might not be generalizable to the general migraine population. All subjects in this study were enrolled from a headache specialty clinic and the results might not be generalizable to the general population of people with migraine. It is not known whether some of the enrolled individuals had, vascular risk factors, or other conditions which might increase their risk of having WMH attributable to conditions other than migraine. Lastly, as the age range of this study cohort was broad, it cannot be ruled out that some of the WMH found in older subjects were age-related and not necessarily related to migraine.

Conclusion

63.9% of individuals with migraine had WMH which were most common in the lobar regions and were more commonly under 3mm in size. Periventricular WMH were uncommon, as were basal ganglia and infratentorial WMH, especially in the absence of frontal WMH. These and other characteristics might help the clinician to differentiate WMH attributed to migraine from those attributed to other diseases. Furthermore, WMH seen in migraine patients tended to be punctate (< 3mm in size) and not confluent. Future investigations should directly compare and contrast WMH associated with migraine from those associated with other diseases, with the goal of developing an easy-to-use model for classification of WMH attributed to migraine.

Abbreviations

BDI: Beck Depression Inventory

MRI: Magnetic Resonance Imaging

SD: Standard Deviation

WMH: White Matter Hyperintensities

Declarations

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none

Authors Contributions:

CC, TS, and BC designed the study. CC, TS, and BC collected and analyzed the data. CC, TS, and BC drafted the manuscript.

Ethics approval and consent to participate:

This study received approval from the Mayo Clinic Institutional Review Board. All subjects completed written informed consent prior to study participation.

Consent for publication:

not applicable

Availability of data and materials:

Researchers wishing to access data included in this study should send their request via email to the corresponding author (chong.catherine@mayo.edu) and the Mayo Clinic Institutional Review Board (IRBE@mayo.edu).

Competing interests: :

Catherine Chong has received research funding from Amgen, the U.S. Department of Defense, and the National Institutes of Health.

Todd Schwedt has served as a consultant for Abbvie, Allergan, Biohaven, Click Therapeutics, Eli Lilly, Equinox, Lundbeck, Novartis, and Tonix. He has stock options in Aural Analytics and Nocira. He has received royalties from UpToDate. He has received research funding from: Amgen, American Migraine Foundation, Henry Jackson Foundation, National Institutes of Health, Patient Centered Outcomes Research Institute, and U.S. Department of Defense. He serves on the Board of Directors for the American Headache Society and the International Headache Society. Meesha Trivedi declares no competing interests.

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Figures

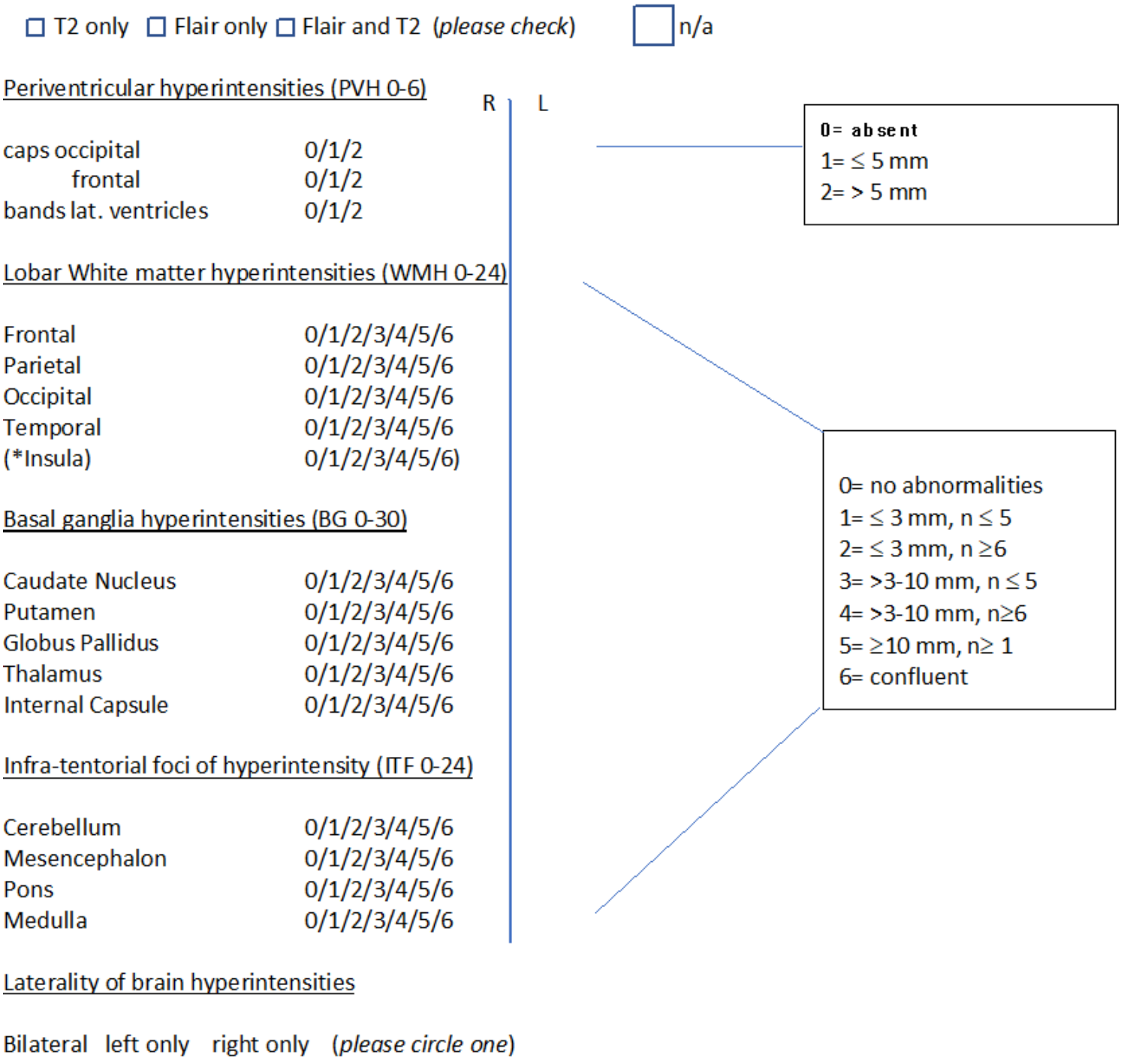

Figure 1

Modified Schelten's rating scale. Semiquantitative rating of signal hyperintensities for the following regions: Periventricular, lobar white matter hyperintensities (frontal, parietal, occipital, temporal), basal ganglia and infra-tentorial foci. * insular WMH were counted separately and were not included in the total of lobar WMH to remain consistent with the original rating of the scale. The number ranges in brackets indicate the range of the scale for each region. n= number of lesions; n/a =no abnormalities noted on scan. The scaling criteria for the regions is shown on the right side. Only those patients that had both Flair and T2 imaging were included in the analysis.

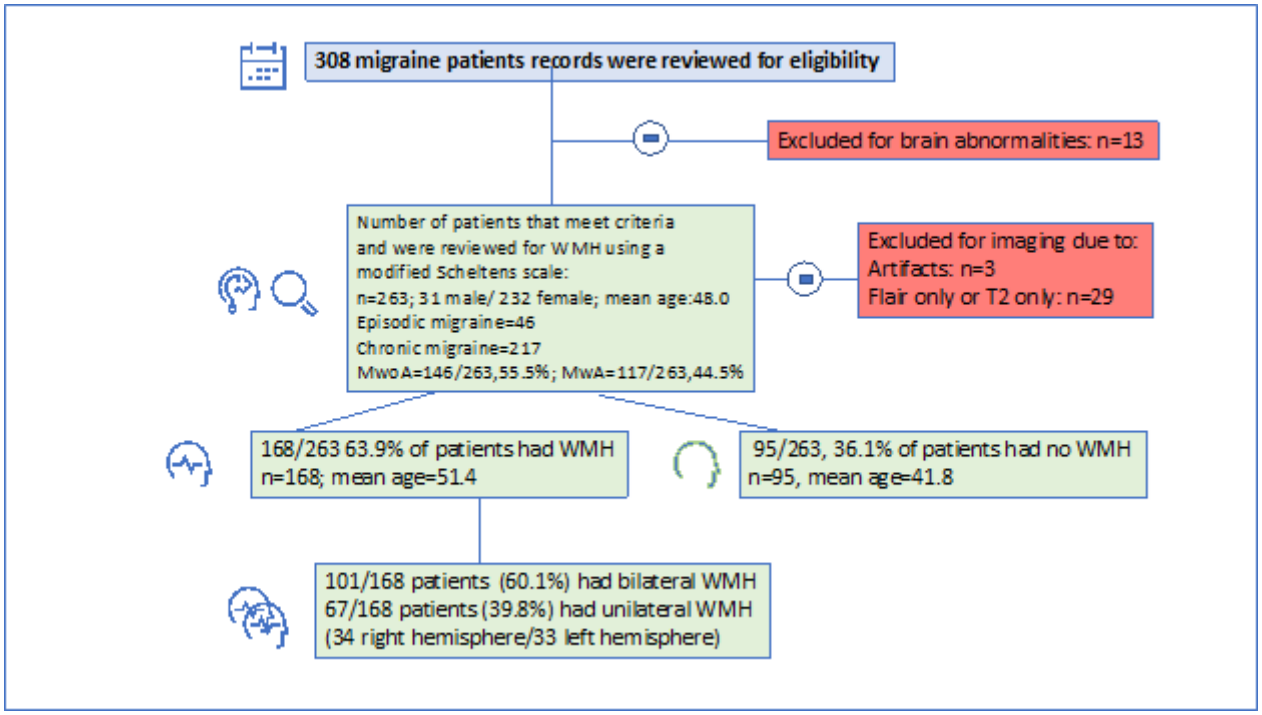

Figure 2

Flowchart indicating total number of subjects that were reviewed, number of patients that were excluded and number and demographic information for patients with and without white matter hyperintensities.

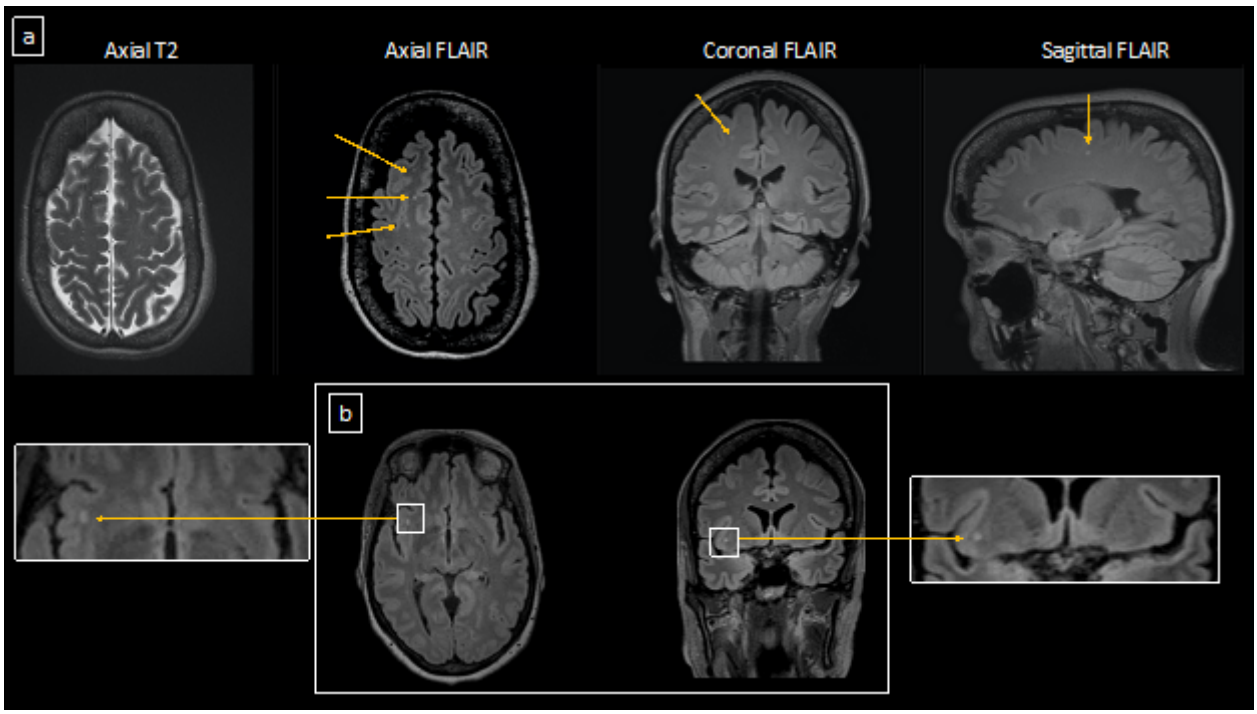

Figure 3

a: 64 year-old female with episodic migraine with aura who averaged 5 migraine attacks per month. No history of vascular risk factors. Axial FLAIR images show 3 of 9 right frontal white matter lesions all of which are small and punctate in contour. Lesions are less conspicuous on axial T2 images than seen on

FLAIR images. One of the lesions is depicted on coronal and sagittal FLAIR images b: Axial and coronal FLAIR images in the same patient show a punctate lesion in the right insular white matter.

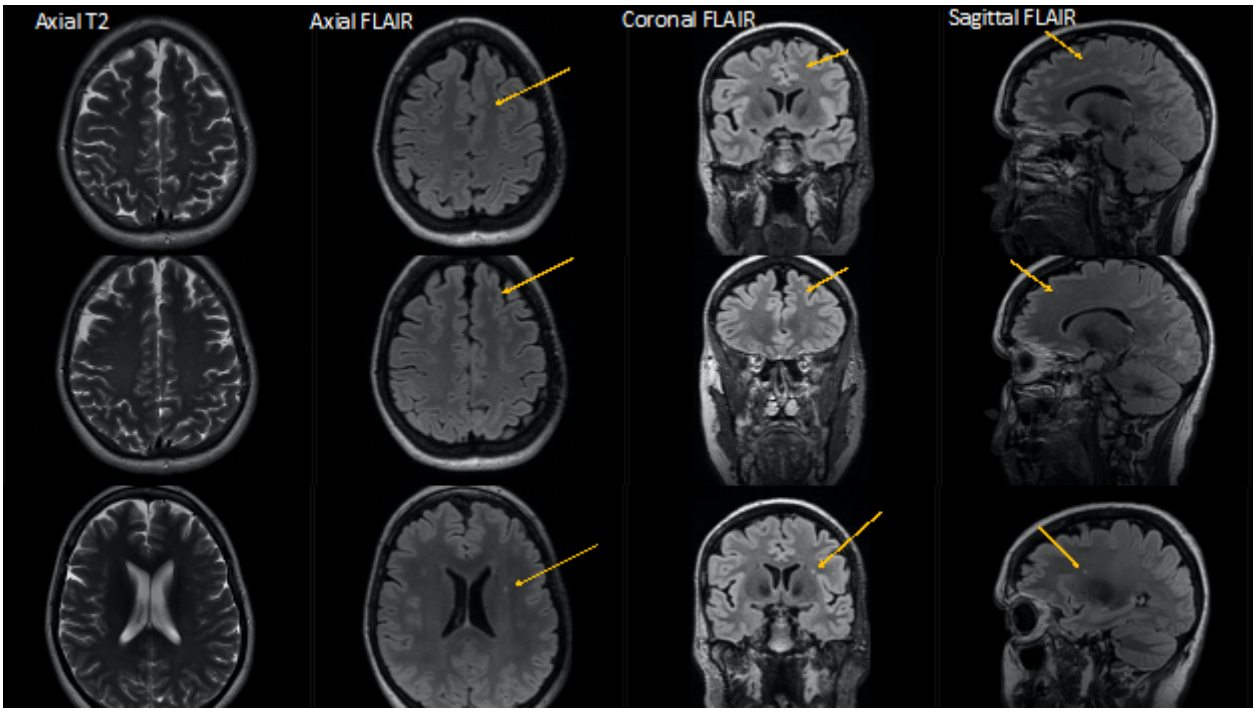

Figure 4

48 year-old female with chronic migraine, no aura. No history of vascular risk factors. Axial, coronal and sagittal FLAIR images show 3 left frontal white matter lesions all of which are small and punctate in contour. Lesions are difficult to appreciate on axial T2 images.