Are Periventricular Lesions Specific for Multiple Sclerosis?

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Abstract

Background: The presence of periventricular lesions (PVL) on MRI scans is part of the revised McDonald multiple sclerosis (MS) diagnostic criteria. However, PVL can be found in other neurological diseases including stroke and migraine. Migraine is highly prevalent in patients with MS.

Objective: To determine if PVL are specific for patients with MS compared to stroke and migraine.

Methods: We studied patients diagnosed with clinically isolated syndrome (CIS), relapsing-remitting MS (RRMS), migraine, and ischemic stroke. The number, location and the volume of PVL were identified on brain MRI scans and analyzed.

Results: The number and volume of PVL adjacent to the body and the posterior horn of the lateral ventricles were significantly increased on fluid-attenuated inversion recovery MRI in RRMS compared to migraine. There were no significant differences in the total number and volume of PVL in ischemic stroke patients compared to the age-matched RRMS patients nor in the number and volume of PVL adjacent to the anterior and temporal horns of the lateral ventricles on FLAIR images in migraine compared to CIS or RRMS.

Conclusion: In contrast to PVL adjacent to the body and the posterior horn of the lateral ventricles, PVL adjacent to the anterior and temporal horns of the lateral ventricles may not be specific for CIS/RRMS when compared to migraine, the disease highly prevalent among patients with MS. PVL are not specific for MS when compared to ischemic stroke.

Keywords: Multiple sclerosis; Migraine; Stroke; MRI

Abbreviations: CIS: Clinically Isolated Syndrome; FLAIR: Fluid-attenuated Inversion Recovery; MS: Multiple Sclerosis; PVL: Periventricular Lesions; ROC: Receiver Operating Characteristic; RRMS: Relapsing-Remitting MS; T2WI: T2-weighted Images

Introduction

The presence of periventricular lesion (PVL) has been considered a hallmark of multiple sclerosis (MS) and was included in the 2010 revised McDonald MS criteria of "dissemination in space" [1] based on observation of Swanton et al. [2]. The original study used a population of young patients presenting with their first clinically isolated syndrome (CIS). However, "The performance of the MRI diagnostic criteria in patients …with other multifocal diseases of CNS white matter have not been systematically addressed" as was noted by Montalban et al. [3]. PVL were reported in a number of neurological disorders which can mimic MS such as vitamin B12 deficiency [4], migraines [5] and stroke, especially in women [6]. The prevalence of migraine in patients with MS is approximately 25% [7-9]. In this study, we performed a retrospective analysis of brain MRI and clinical records of patients in order to determine if PVL presence, volume and location are specific for patients with CIS and relapsing-remitting MS (RRMS) as compared to migraine or stroke.

Methods

Patients

In this study we identified records of patients who were recently seen in the Department of Neurology at Robert Wood Johnson Medical School and had a clinical diagnosis of CIS as per CHAMPS criteria [10] (without migraine or stroke), clinically-definite RRMS as per Poser criteria [11] (without migraine or stroke), migraine (without MS, CIS or stroke) or ischemic stroke (without CIS, RRMS or migraine).

Additionally, these patients had to have brain MRI available in Digital Imaging and Communications in Medicine (DICOM) format. The study population included patients between the ages of 18 and 60. Exclusion criteria were: history of neurological disease affecting the CNS other than ischemic stroke, migraine, CIS or clinically-definite RRMS or clinical history or laboratory tests consistent with systemic disease associated with demyelinating lesions in the CNS such as Lyme, vitamin B12 deficiency, sarcoidosis, lupus, syphilis, rheumatoid arthritis or diabetes mellitus. The study was approved by the local IRB. The final patient pool consisted of CIS (n=10), RRMS (n=36), migraine (n=32) and ischemic stroke (n=18). Their demographic characteristics are depicted in Table 1 (CIS, RRMS and migraine) and Table 3 (stroke).

Patient Group	Number of patients	(Male/Female Ratio)	Age, Mean ± SD	Minimum Age / Maximum Age
RRMS	36	(5/31)	39.44 ± 9.81	22 / 58
CIS	10	(3/7)	34.8 ± 13.81	19 / 58
Migraine	32	(9/23)	39.97 ± 9.57	22 / 57

Abbreviations: RRMS = Relapsing-Remitting Multiple Sclerosis, CIS = Clinically Isolated Syndrome

Table 1: Age and Gender Data for RRMS, CIS and Migraine Patient Groups.

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Neuroimaging analysis

We analyzed the lesion number (count) and volume of PVL distributed across four areas of the lateral ventricles: anterior (frontal) horn, the body of the lateral ventricles, posterior (occipital) horn and temporal horn, as defined in Dr. Lawrence B. Stack's, Head CT Scan Interpretation: An Organized Approach to Seeing Inside the Head (2007)__(http://www.accessem.com/login.aspx). Both T2-weighted images (T2WI) and fluid-attenuated inversion recovery (FLAIR) MRI images performed on 1.5 T MRI machine were analyzed using JIM version 5.0 software (Xinapse systems, UK, http://www.xinapse.com/) to compile PVL volumes that spanned multiple axial views of the brain MRI for both FLAIR and T2WI. This manual outlining technique yielded lesion volumes as well as lesion counts for each of the four anatomical areas of the lateral ventricles. Supplemental Figure 1 depicts the example of lesion outline using JIM for axial images. Since conventional MRI cannot differentiate nonspecific frontal capping from small white matter lesions that are a result of multiple sclerosis, periventricular "caps" around the frontal horns and hyperintense outlines of the ventricles were included [12]. PVL were identified if there was no normal-appearing white matter between the lesion and the border of the ventricle. If there was normal-appearing white matter appreciated between two PVL, and it was evident on all axial views depicting those lesions, then the lesions were counted separately [12].

GraphPad Prism software (LaJolla, CA, http://www.graphpad.com/) was used for statistical analysis of collected data using unpaired t-tests. Using SYSTAT Software (http://www.systat.com/), we could also determine what lesion volume or count for particular MRI modality (e.g., FLAIR or T2WI) would yield the highest accuracy of a correct differentiation between MS or migraine diagnosis. SYSTAT's two-step approach included its binary logistic regression and receiver operating characteristic (ROC) curves [13] that generated cutoff points, or thresholds, for each of the data sets that were compared (e.g., total PVL volumes of CIS versus migraine) [14]. Once the thresholds were generated, we calculated the corresponding accuracy using ROC's sensitivity and specificity data. The threshold that aligned with the maximal accuracy was then used to create a Model classification table. The Model classification table enabled us to see how many patients were classified correctly or incorrectly as being CIS, RRMS or migraine.

Results

First, we compared the volume and the number (count) of the PVL in the four anatomical regions of the lateral ventricles in CIS and RRMS versus migraine. (Table 1) depicts our patient groups' data and characteristics. These three groups were predominantly females.

As shown in (Table 2), not all anatomical periventricular areas were equally specific for CIS/RRMS patients as compared to migraine on FLAIR and T2WI.

The maximal difference identified between patient groups was seen when comparing the volume of PVL adjacent to the body of the lateral ventricles and the posterior horn. In those two anatomical areas, the average volume of these PVL was between 1.9 to 6.2 times greater in RRMS patients (p<0.033) and 3.3 to 8.9 times higher in CIS patients

PVL Location	PVL Volume** or Count	RRMS (n=36)		CIS (n=10)		Migraine (n=32)
		Mean ± SEM (mm³)	P-value (RR-MS vs Migraine)	Mean ± SEM (mm³)	P-value (CIS vs Migraine)	Mean ± SEM (mm³)
T2WI						
Anterior Horn	Volume	268.2 ± 39.04	0.2589	225.7 ± 64.84	0.7788	200.8 ± 44.87
Anterior Horn	Count	1.583 ± 0.1457	0.3477	1.600 ± 0.3712	0.5376	1.375 ± 0.1665
Posterior Horn	Volume	470.4 ± 90.61	0.0325***	829.5 ± 437.6	0.0228	250.6 ± 31.32
Posterior Horn	Count	1.306 ± 0.1248	0.2228	1.500 ± 0.2687	0.9127	1.531 ± 0.1346
Body of Lateral Ventricles	Volume	838.5 ± 178.8	0.0005	857.5 ± 509.6	0.0149	138.3 ± 30.90
Body of Lateral Ventricles	Count	2.444 ± 0.3198	0.0002	1.500 ± 0.4534	0.1657	0.9375 ± 0.1735
Temporal Horn	Volume	16.28 ± 9.756	0.133	15.53 ± 11.06	0.4066	69.92 ± 35.79
Temporal Horn	Count	0.139 ± 0.070	0.0097	0.2000 ± 0.1333	0.1986	0.5313± 0.1346
FLAIR						
Anterior Horn	Volume	415.7 ± 43.26	0.256	393.5 ± 108.3	0.3946	498.6 ± 59.35
Anterior Horn	Count	2.250 ± 0.1220	0.5494	2.100 ± 0.2769	0.4309	2.375 ± 0.1724
Posterior Horn	Volume	1405 ± 314.8	0.0011	1311 ± 725.9	0.0132	253.6 ± 56.20
Posterior Horn	Count	1.528 ± 0.1290	0.0037	1.200 ± 0.3266	0.3999	0.9063 ± 0.1641
Body of Lateral Ventricles	Volume	1802 ± 384.3	0.0005	2578 ± 1538	0.0096	290.1 ± 55.70
Body of Lateral Ventricles	Count	2.944 ± 0.2899	0.0019	2.000 ± 0.5774	0.5351	1.625 ± 0.2831
Temporal Horn	Volume	49.17 ± 21.29	0.3043	543.7 ± 543.7	0.086	21.15 ± 15.79
Temporal Horn	Count	0.2500 ± 0.09237	0.4207	0.1000 ± 0.1000	0.6666	0.1563 ± 0.06521

* PVL = Periventricular Lesions

** T2WI and FLAIR images were analyzed using JIM version 5.0 software to measure PVL volume. Unpaired t-test was used for statistical analysis and calculation of p-value.

*** P-values in bold are considered statistically significant.

Table 2: Comparison of PVL* Volume and Count for Four Anatomical Regions for RRMS and CIS versus Migraine Patients.

(p<0.023) as compared to migraine for both FLAIR and T2WI. Greater PVL volume difference between CIS/RRMS and migraine was seen using FLAIR sequence as opposed to T2WI. With regard to PVL count, significant statistical difference was identified for RRMS but only for lesions adjacent to the temporal horn and body of the lateral ventricles (as seen on T2WI) and the posterior horn and body of the lateral ventricles (as seen on FLAIR). There were no significant differences between the number and volume of PVL adjacent to the anterior horns of the lateral ventricles among all three groups of patients on both imaging sequences. Additionally, there was no statistical difference in the volume of PVL adjacent to the temporal horns of the lateral ventricles on either sequence. Interestingly, patients with migraine had increased numbers of PVL adjacent to the temporal horn of the lateral ventricles on T2WI (P < 0.0097) compared to RRMS, this trend was not seen on FLAIR. The earliest clinical presentation of RRMS is CIS. There was no significant difference between RRMS and CIS in PVL count or volume for any anatomical region analyzed in Figure 2.

In the next part of the study, we applied binary logistic regression analysis, as described in the methods section, to identify the maximal accuracy and its corresponding threshold for both lesion counts and lesion volume that would differentiate migraine from RRMS and CIS. This was done separately for the count and the volume of lesions adjacent to the posterior horn, the body of the lateral ventricles, total lesion count as well as total lesion volume for both FLAIR and T2WI. The highest accuracy to correctly diagnose CIS vs. migraine was reached when comparing the volume of PVL adjacent to the body of the lateral ventricles, 0.857, for FLAIR images and for the posterior horn and body of the lateral ventricles, both at 0.833, for T2WI. The highest accuracy to correctly diagnose RRMS vs. migraine was reached when comparing the volume of PVL adjacent to the body of the lateral ventricles, 0.75, for FLAIR images. The corresponding volume or count threshold yielding the maximal accuracy to distinguish between RRMS and CIS versus migraine is provided in Supplemental Table 1.

As for the count of PVL, the highest accuracy to correctly diagnose RRMS counting the number of PVL adjacent to the body of lateral ventricles was 0.662 on FLAIR (2 or more PVL) and 0.721 on T2WI (3 or more PVL). The highest accuracy to correctly diagnose RRMS counting the number of PVL adjacent to the posterior horns of lateral ventricles was 0.662 on FLAIR (1 or more PVL) and 0.603 on T2WI (2 or more PVL). In all cases, counting the total number of PVL adjacent to all four anatomical areas of PVL provided equal or inferior accuracy as compared to analyzing PVL adjacent to the body of the lateral ventricles.

In the last part of our study, we compared PVL in patients with RRMS and ischemic stroke. All our stroke patients were between 37 and 58 years old. The mean age of patients with stroke (51.1 years) was significantly higher as compared to patients with CIS (34.8 years) or RRMS (39.4 years) (Table 1). Thus, from the total group of 36 RRMS patients we excluded patients younger than 37 years of age. The final RRMS group consisted of 19 patients, as depicted in Table 3. The mean ages (±SEM) of "age-matched" RRMS and stroke were 46 ± 7.2 and 51.1 ± 6.9, respectively.

As shown on Table 4, there were no significant differences in the total number and volume of PVL in ischemic stroke patients as compared to the age-matched RRMS patients.

Additionally, there were no significant findings for any of the anatomical areas regarding both lesion count and volume; this was consistent in both T2WI and FLAIR (Supplemental Table 2).

Discussion

The recent MS criteria [2,3,15] incorporate the presence of PVL on brain MRI for MS diagnosis among young subjects with CIS. However, the specificity of PVL for MS among patients with neurological diseases has not been systematically addressed [3]. FLAIR provides increased sensitivity of demyelinating lesion detection especially in the periventricular location as it can differentiate the signal from the CSF, in the lateral ventricles, from the lesion itself [16-18]. Another important issue is the presence of nonspecific T2 hyperintensities adjacent to the frontal horns of the lateral ventricles in healthy subjects, so-called frontal capping, which can be mistakenly counted as PVL [12].

Our results strongly suggest that PVL adjacent to the anterior and temporal horns of the lateral ventricles are not specific for patients with CIS/RRMS as compared to patients with migraine. In contrast, the volume of PVL adjacent to the posterior horn and body of the lateral ventricles was significantly increased in both RRMS and CIS using different MRI modalities (e.g., FLAIR and T2WI). As related to PVL count, only the FLAIR modality showed significantly increased count of PVL adjacent to both the posterior horn and the body of the lateral ventricles in RRMS. The PVL count was not significantly different between CIS and migraine in any anatomical region.

Based on the binary logistic regression analysis, the highest accuracy in distinguishing between RRMS and migraine was seen when using volume of PVL adjacent to the body of the lateral ventricles instead of PVL count. However, using PVL volume may not be a practical approach in the clinical setting because volumetric analysis software may not be available. Based on our analysis, a reasonable accuracy in distinguishing between RRMS and migraine could be reached by using the following MRI criteria: one or more PVL adjacent to posterior horns as seen on FLAIR, two or more PVL adjacent to the body of the lateral ventricles as seen on FLAIR or three or more PVL adjacent to the body of the lateral ventricles as seen on T2WI (Supplemental Table 1). The recent recommendation by Montalban et al. and the 2010 revised McDonald MS diagnostic criteria [1,3] have decreased the number of PVL from three to one to prove MS dissemination in space as compared to original Barkhof's criteria and the 2005 revised McDonald MS diagnostic criteria [19,20]. This change has significantly simplified criteria for MD diagnosis but is raising concerns about the specificity of the 2010 criteria among patients with migraine. The prevalence of migraine in woman with MS may reach 29% [9].

Patient Group	Number of patients (Male/Female Ratio)	Age, Mean ± SD	Minimum Age / Maximum Age
RRMS	19 (4/15)	46.7 ± 7.2	37 / 58
Stroke	18 (11/7)	51.1 ± 6.9	37 / 58

Table 3: Age and Gender Data for Age-Matched RRMS and Stroke Patient Groups.

Neuroimaging Parameters	RRMS (n=19)	Stroke (n=18)	RRMS vs. Stroke (P-value**)
T2WI			
Total PVL Volume	1583 ± 341.2*	2154 ± 854.7	0.531
Total PVL Count	4.895 ± 0.5402	4.444 ± 0.5437	0.5608
FLAIR			
Total PVL Volume	3831 ± 912.8	5311 ± 1956	0.49
Total PVL Count	6.842 ± 0.5936	7.333 ± 0.4501	0.5174

* Values are the Mean ± SEM
** Unpaired t-test was used for statistical analysis and calculation of p-value.

Table 4: PVL Volume and Count in Age-Matched RR-MS and Stroke Patients.

We and others have reported that acute demyelinating lesions in patients with RRMS may have restricted diffusion and may be non-enhancing on brain MRI similar to patients with acute stroke [21,22]. Comparison of age-matched ischemic stroke and RRMS patients provided no significant differences in both volume and count of PVL adjacent to any of the four anatomic regions and in total PVL volume and count (Table 4). To our knowledge, this finding has not been previously described. The middle-aged patients presenting with acute symptomatic periventricular lesion may represent a diagnostic challenge in clinical practice.

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