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Original Article

Value of central vein sign in discriminating multiple sclerosis plaques from other white matter lesions

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ABSTRACT

Introduction: Susceptibility weighted (SW) magnetic resonance imaging (MRI) can visualize the vein/s around which multiple sclerosis (MS) plaques are centered. This study's purpose was to assess the ability of the central vein sign (CVS) to differentiate MS plaques from non MS white matter lesions (WMLs).

Methods: Out of 18 patients, 9 had MS, 3 had systemic lupus erythematosus, 4 had hypertensive microangiopathy and 2 had Behcet's disease. 3 T MRI examination was performed to obtain fluid attenuated inversion recovery (FLAIR) and the SW images. Lesions more than 3 mm were identified and analyzed for location and existence of the CVS.

Results: Out of 572 MS lesions, 281 lesions were positive for the CVS, while only 66 out of 279 non MS lesions were CVS positive with a statistically significant difference between the two groups ($p < 0.001$). As regards the percentage of perivenous lesions per patient; using a cutoff value of 30%, MRI accurately segregated all patients with MS and 8/9 non MS patients.

Conclusion: Though the CVS is not found solely in MS lesions it is more frequent in MS WMLs as compared to non MS WML and thus is reliable adjunctive tool in differentiation of MS plaques from WMLs of alternative etiologies.

1. Introduction

Multiple sclerosis is a chronic demyelinating central nervous system disease that commonly but not exclusively afflicts young and middle-aged adults [1]. More often than not, it results in permanent and chronic disability to the patients with life- long consequences. The need for a diagnostic method that ensures not just an accurate diagnosis but also a timely one is paramount to facilitate early initiation of appropriate therapy allowing rapid control of the disease process and better outcome to the patients in the long run [2].

Unfortunately, up till now there is no single diagnostic test for multiple sclerosis and this applies to magnetic resonance imaging (MRI) as well [3]. In classical and florid cases of MS, MRI can elegantly demonstrate typical WM matter lesions with MS – characteristic shape and pattern of distribution, as well as provide evidence of dissemination in space and time allowing a reliable diagnosis of MS to be made based upon 2010 revised McDonalds criteria [4,5]. However, MRI findings though sensitive are not specific to MS. In fact, white matter lesions can be found in a range of neurological diseases including small vessel disease, migraine, and vasculitis which may sometimes make differentiation between those entities and MS challenging especially in cases of early MS [6]. To overcome the lack of MR specificity the diagnosis of MS is currently dependent on presenting the proof of dissemination of central nervous system (CNS) lesions in time and space by a combination of clinical, imaging and paraclinical tests (i.e. cerebrospinal fluid analysis, evoked potentials) according to the 2010 revised McDonalds criteria [5]. However, diagnostic difficulties are still encountered sometimes, particularly during the early course of the disease and in those patients with delayed disease onset, as well as in patients with obscure or atypical clinical history leading to incorrect diagnosis and subsequently delayed implementation of the ideal treatment regimen [7]. If MRI could have improved specificity for MS lesions this would mean improved accuracy and reliability of MRI in diagnosing MS and could aid in making criteria for diagnosis of MS less complex in the future with less need for the multiple parameters currently in use [8].

Pathologically, plaques of inflammatory myelin destruction are considered the distinctive identifying feature of multiple sclerosis [9]. The existence of a small vein within the center of the majority of these plaques has been clearly shown long ago. This finding has greatly

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supported the theory that activated T lymphocytes and other chronic inflammatory cells pass out of the circulation, and gain access to the CNS where they induce an inflammatory reaction and local destruction of the myelin [8,10]. Among all the histo-pathological features characterizing the demyelinating process of MS and differentiating it from other white matter diseases the demonstration of theses plaques of myelin destruction encircling a central vein is the most specific for making a histo-pathological based diagnosis of MS [11].

Susceptibility weighted imaging (SWI) is a recently developed MR technique that exploits the susceptibility differences between tissues thus allowing enhanced depiction of smaller caliber veins, haemorrhage, and foci of iron deposition that will become out of phase with adjacent tissues at sufficiently long echo times [12,13].Thus, we hypothesized that the SWI would be able to visualize a central vein within MS plaques at a much higher frequency when compared to non MS white matter lesions (WML) hence improving the specificity with which MRI can diagnose MS.

The aim of this study was to assess whether the visualization of a central vein on SWI "so called central vein sign" (CVS) is specific to MS and whether it can be used to reliably discriminate between MS plaques and non MS white matter lesions.

2. Methods

The study was authorized by our department review board and informed consent was obtained from all patients who underwent the MR investigations.

2.1. Subjects

A total of 18 patients, referred from the neurology department in our hospital were included in this study. 9 patients with clinically definite MS (7 women, 2 men; mean age, 33 years; range, 26–45 years) were included. In addition, 9 patients (3 women, 6 men; mean age, 38 years; range, 29–60 years) with non MS WMLs, attributed to systemic lupus erythematosus (SLE) in 3 patients, hypertensive microangiopathy in 4 patients and Behcet's disease in 2 patients were also included. Diagnosis was made by referring neurologist based upon medical history, clinical picture and lab testing (where relevant).

2.2. MRI acquisition

MR imaging was conducted on a 3.0 Tesla (T) MAGNETOM Skyra scanner, (Siemens Healthcare, Erlangen, Germany). The sequence protocol included an axial FLAIR and a 3D SWI sequence. For the FLAIR-weighted sequence, the image parameters were: repetition time (TR), 9000 ms; echo time (TE), 108 ms; field of view (FOV), 25 cm; matrix, 320 mm; slice thickness, 3 mm; and acquisition time, 3 min (min), 56 s (sec). The SW sequence was obtained with a TE of 20 ms; TR, 27 ms; receiver bandwidth, 120 Hz; flip angle, 15°; FOV, 22 cm; acquired voxel size, $0.9 \times 0.9 \times 1.5$ mm; reconstructed voxel size, $0.86 \times 0.86 \times 1.5$ mm; acquisition matrix, 256 mm; slab thickness of minimum intensity projections (mIP), 12 mm (acquired, 1.5 mm); acquisition time, 4 min, 15 sec.

2.3. Image analysis

The MR data sets were co-analyzed by two experienced neuroradiologists who were unaware of all clinical details and patient identification data. Image interpretation was performed on a standard picture archiving and communication system workstation. FLAIR was used as gold standard for the identification of both MS-WMLs and non MS-WMLs. Only non confluent lesions measuring 3 mm or more were assessed for presence of a central vein. Each WML that met the size criteria was first identified on a FLAIR image and was classified as either periventricular (PV), deep white matter (DWM), juxtacortical (JC), or infratentorial (IT). Periventricular lesions were designated as those lesions contacting the ventricles with no tissue intervening between the ventricular wall and the WML. Lesions classified as juxtacortical were those involving the subcortical u- fibres. Lesions neither juxtacortical or periventricular in position were categorized as deep white matter lesions. Brain stem and cerebellar lesions were simply classified as infratentorial lesions. Subsequently each of the identified lesions on FLAIR were correlated to their equivalent on minimum intensity projection image of the SWI sequence and were evaluated for the presence of the central vein which could be visualized as either as a hypointense linear structure running through the lesion when the vein ran parallel to the imaging plane or as a centrally placed dot when it ran perpendicular to the imaging plane. In the latter case this centrally located dot had to be trailed to adjacent slices to ensure that it indeed represents a vein rather than simply iron deposition which is a common finding in multiple sclerosis plaques. Veins which ran eccentrically through the lesion (somewhere within the periphery) were not considered as a positive result. The synchronization tool of the PACS system was used to ensure co registration of SWI and FLAIR images. Lesions were only classified as positive for a central vein when it could be identified by both readers according to the above mentioned criteria. When the two readers agreed on the absence of a central vein, or if one of the readers disagreed about the presence of a central vein the lesion was considered as negative for central vein sign.

2.4. Statistics

Patients were classified into two groups; MS-WMLs and non MS-WMLs group. The total lesion load and the ratio and percentage of perivenous lesions (positive lesions) were calculated for both groups. Number of periventricular, juxtacortical, infratentorial and deep white matter lesions in each group and ratios and percentage of positive periventricular, juxtacortical, deep white matter, infratentorial lesions for each group were then calculated. Both groups were compared using the Z test. Furthermore the percentage of positive lesions was calculated for the 18 patients and a perivenous lesion percentage cutoff value that had the best sensitivity, specificity, PPV and NPV in discrimination of MS patients from non MS patients was determined. The data were analyzed using an IBM SPSS statistics (V. 24.0, IBM Corp., USA, 2016). Data were expressed as both number and percentage for categorized data. The probability of error (P-value) at 0.05 was considered significant, while at 0.01 and 0.001 was highly significant

3. Results

Our study was composed of a total of 572 MS-WMLs and 279 non MS –WMLs. Out of 572 MS lesions, 281 lesions (49.13%) were positive for the central vein sign, while 66 out of 279 non-MS lesions (23.6%) were positive for the central vein sign with statistically significant difference between the two groups ($p < 0.001$). Number and percentage of positive and negative lesions in different anatomical locations in both the MS and non MS group is summarized in Table 1. Examples of these lesions in both the FLAIR and corresponding SWI sequence can be seen in patients with MS (Figs. 1 and 2) and in a non MS patient (Fig. 3).

In the MS group the frequency of perivenous lesions was highest for the infratentorial region where 57.9% were positive for this sign, followed by the periventricular region (54.29%), then the deep white matter (49.3%) and finally the juxtacortical region (39.5%) (Fig. 4). In the non MS group the largest proportion of positive lesions were in the periventricular region (44.4%) followed by the deep white mater region (21.4%) (Fig. 5). (Fig. 6) compares the proportion of lesions positive for central vein sign in different anatomical locations in both MS and non MS groups.

Analysis of the percentage of positive lesions per patient revealed that for the MS group the percentage of positive lesions ranged from 31.6% to 57.7% (mean 47.2%, median 49.15%). While in the non MS