Evaluating the Role of Central Vein Sign as an Imaging Biomarker for Developing Multiple Sclerosis

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ABSTRACT

**Background:** Multiple sclerosis (MS) is considered as one of the common chronic disorders. It affects young population which is commonly observed as inflamed lesions and caused by demyelination of the myelin sheath. It might consequently lead to loss of myelin sheath. These lesions are not specific to MS but could mimic several pathological conditions. They are hardly undifferentiated by medical imaging techniques. With the increased number of MS patients, who may have an actual disability. Therefore, the accurate diagnostic imaging of MS lesions has been highly demands.

**Aims:** This paper aims to review the role of magnetic resonance imaging (MRI) sequences to detect the central vein sign (CVS). Also, to evaluate the capability of CVS in differentiating MS from other cerebral vascular diseases (CVD) and, attempting to find the relation between the CVS and MS progression based on the literature review of the recent studies.

**Methodology:** This study is a qualitative literature review for the selected published articles from 2010 to 2020. The following database and searching engine were used: PubMed database, Saudi digital library, and google scholar. Several keywords were applied to search for these articles, such as: “multiple sclerosis and central vein sign,” “Multiple sclerosis and progression,” “central vein sign and susceptibility-weighted image.”

**Summary of this review:** According to the recent published article presented in our review paper, the CVS positive lesions found in MS patients were higher than those found in non-MS patients. The MS lesions with CVS had been observed in different MS stages, including clinically isolated syndrome (CIS), relapsing-remitting MS (RRMS), and secondary progressive MS (SPMS). Recent detected lesions have a larger diameter compared with well-established lesions. There is a high correlation between CVS lesions and MS progression. The CVS plays a significant role in MS diagnostic and differentiating between MS and other mimicking diseases. In addition, the CVS could be easily investigated using T2* WI sequences, including SWI, SWAN, FLAIR*. While the T2*-WI with EPI achieved higher detection abilities for CVS lesions. The chronic active MS lesions detected with CVS at the follow-up MR imaging may indicate MS progression.

**ABBREVIATIONS:** MRI: Magnetic Resonance Imaging; MS: Multiple Sclerosis; CVS: Central Vein Sign; CVD: Cerebral Vascular Diseases; CIS: Clinically Isolated Syndrome; RRMS: Relapsing-Remitting MS; SPMS: Secondary Progressive MS.
to MS but can be showed up with several pathological conditions and mostly undifferentiated by imaging examinations [2]. With the increase of MS patients in the world and the excessive use of immunity suppression medications which have long term side effects on MS patients. The diagnostic accuracy of MS disease has been highly demands [3]. However, the multiple sclerosis disease confronts some diagnosis challenges in mimicking diseases that have a pattern similar to MS [4].

Magnetic resonance imaging (MRI) has been considering as appropriate choice for brain imaging to evaluate and diagnose uncertain MS plaques [5]. Although conventional MRI has provided high sensitivity to demonstrate the MS lesions, however, it also has a low specificity [6]. MS lesions have been characterizing by dissemination in space (DIS), which refers to the ability of inflammatory lesions to build up in a different area of CNS, and dissemination in time (DIT), which referred to the inflammatory recurrent accumulating over time. At the early stage of MS, the fulfillment of DIS and DIT by McDonald’s criteria application can minimize the MS diagnosis time and improve the sensitivity [7,8]. However, the wrong implementation of these criteria in the presence of mimicking disease may result in a wrong diagnostic and leads to low specificity in patients with non-specified MS finding [4].

The ability of the T2 weighted images and FALIR weighted images in the detection of the central nervous system lesions is apparent [2]. However, the need for a solid and easy imaging sign or biomarker that can help to diagnose MS patients and distinguish between MS and mimicking diseases is still a mandatory [3]. The white matter (WM) lesions are either related to MS disease or another vascular disease. It can grow up around the small veins [9,10]. In MS lesions, the conspicuous of these veins may indicate the inflammation caused by the demyelination process [11]. These veins have been clearly observed at the center of WM lesions [9]. They can be detecting using various T2* weighted imaging sequences [6] such as 3D T2*- gradient echo [3], susceptibility-weighted image [12], and T2*-WI with EPI [11]. They are known as central vein signs and show up as a line having low signal intensity [6]. Some studies have performed at variable strength of MR scanners such as 1.5 T, 3T, and 7T. These studies demonstrate the presence of CVS in MS patients more than in other vascular disease patients [10]. Hence, the CVS can be the imaging sign that can be helpful to distinguish between MS lesions and other vascular disease lesions [3].

This review study aims to determine the magnetic resonance imaging (MRI) sequences that could detect the central vein sign (CVS). Also, to evaluate the capability of CVS in differentiating MS from other cerebral vascular diseases (CVD) and also, attempting to find the relation between the CVS and MS progression.

Methodology for Reviewing Published Articles

Our study is a qualitative literature review for articles from 2010 to 2020. Web of Science, PUBMED/MEDLINE, Saudi digital library, and google scholar were used to search for articles using “multiple sclerosis and magnetic resonance imaging”, “multiple sclerosis, and central vein sign”, “central vein sign and susceptibility-weighted image”. Several keywords used to search for these articles involve: “multiple sclerosis and magnetic resonance imaging,” “multiple sclerosis and central vein sign,” “Multiple sclerosis and progression,” “central vein sign and susceptibility-weighted image.” The selected articles must meet the following criteria: studies written in English; studies including patients with MS; studies evaluating CVS. We excluded from this review any studies applied to animals and pediatrics.

Moreover, for each study used to evaluate the CVS abilities in MS diagnosis, we also reported the study design; the number of patients in the MS cohort and the control group differential diagnosis; magnetic field strength; sequence used in the evaluation of the CVS; use of contrast agent; threshold of the CVS in MS lesions and rule used. Also, the diagnostic performance of CVS in terms of median and range of CVS frequency; CVS proportion in MS and control group; The sensitivity; specificity have been reported. The studies used to evaluate the performance of MRI sequences in CVS detection, the MRI strength; type of sequence; parameters, and CVS proportion in percentage have been reported and listed in the table. In our study, we reviewed MRI pulse sequences used to detect CVS. This had been applied to compare their sensitivity to evaluate such lesions. Studies have been evaluated to find a relationship between the central vein sign and MS progression, containing information about lesions morphological changes, new active lesions, chronic active lesions, CVS diameter; type of study, either longitudinal or cross-sectional have been reported.

McDonald Criteria and CVS

Whereas DIT and DIS have characterized the MS at MR images, fulfilling these criteria by combining the MR imaging results and clinical investigation will provide a robust MS diagnosis [13]. That is called McDonald's criteria, which clarifies the probability of MS disease occurring in a patient who had an attack and demonstrated the type of MS. Considering that, the clinician could not find a better explanation for the case [14]. The early MS diagnostic can prevent MS patient's disability and minimize the chance of relapsing onset by providing appropriately modified therapies. The application of McDonald’s criteria can offer an early and accurate MS diagnosis. McDonald criteria was published in 2001 and revised many times until 2017 [7]. Improvement of McDonald’s criteria has aimed to integrate the MRI results. In addition, it becomes more helpful in clinical use than the earlier [15].

McDonald’s criteria depend on the number, size, and location of MS lesion [16]. The conventional MR images, including T2-WI, FLAIR, T1-weighted images pre and post-contrast, can visualize the MS lesions and demonstrate their distribution [13]. Using T2-WI, the lesions could be appreciated as a small ovoidal shape with a diameter that reaches 2 cm, and the length of the long axis is at least 3 mm.

Applying 2017 McDonald criteria, the DIS could be defined by detecting at least one T2 lesion in at least two different areas of the central nervous system. These lesions could have found in the juxtacortical, periventricular, infratentorial, and spinal cord [7,8,17]. The DIT was explained by detecting new lesions at the follow-up MRI, whether in contrast-enhanced or non-enhanced lesions in at least two attacks with at least 1-month interval. The oligoclonal bands Detection/finding of oligoclonal bands in CSF analysis in cerebrospinal fluid analysis can be used if the DIT does not fulfill the criteria [17]. Different types of MS have extracted by combining the McDonald criteria with MR images results including [18,19]:

a) Relapsing-remitting MS (RRMS) is describing by the time of recover that follows by severe exacerbations of the disease with a stable interval time between them.
b) Clinically isolated syndrome (CIS) explained when the patient had single symptomatic onset similar to MS symptoms, but the MRI results do not conform to RRMS criteria.

c) Radiologically isolated syndrome (RIS), explained by any detected abnormalities related to MS in a first MRI examination. This usually observed for patients complaining from headache or another pathology without noticeable MS symptoms.

d) Primary progressive MS (PPMS) indicates the progressively degrading in the neurological function since the disease initiated.

e) Secondary-progressive MS (SPMS) is a gradual degrading in neurologic functions affecting the same CNS areas that [20] have been affected during the relapsing course. SPMS affects 40% of RRMS patients after 20 years from the first symptomatic onset of the relapsing course.

The disability of MS patients can be measured using the Expanded Disability Status Scale (EDSS), which ranges between 0.0 to 10.0. The patient who has a normal motor and cognitive ability, the disability has measured at 0.0. For the patient who needs assistant to walk, the disability has measured at 6.0. The disability range for the patient who cannot walk, and he is using a wheelchair will be 7.0, the range starting from 8.0 to 9.0 using to measuring the disability of bedridden patients. While the EDSS equal to 10.0 indicates patient death. The MS also has been classified according to disease severity into [14]:

a. Benign MS disease indicates the patient with no significant disability for ten years since the incidence of the first symptoms.

b. Malignant MS disease indicates the patient suffering a significant disability because of rapidly developing the disease in a short duration time.

c. The aggressive MS disease the patient was getting worse rapidly.

Although The benefit of the 2017 McDonald criteria application is a diagnosis of MS after the first clinical isolated syndrome in a short time with high Sensitivity [14], it has limited specificity in the presence of CVD. In addition, the wrong implementation of this criteria may result in a wrong MS diagnostic [4]. Finding a robust imaging biomarker can improve the sensitivity, specificity, and accuracy to exclude these issues. Recently the CVS is a potential promising imaging biomarker under investigation. Therefore, it should be included in the future classification of McDonald criteria [21].

Definition of Central Vein Sign

The MS lesions can grow up around the small veins that may indicate inflammation and motivation of metabolic activity [22]. There is a difficulty in detecting the small vein in MS lesions. The T2*-WI has been used to detect these veins utilizing the sensitivity of T2* - weighted GRE to deoxygenated blood [23]. The CVS has been observing in all MS stages as a hypo-intense line or dot caused by paramagnetic substances and a contrast agent [13]. According to North American Imaging in Multiple Sclerosis guidelines that's recommends standardization to define the CVS, as the following [11,12]:

a) Lesions appear as a centric hypo-intensity, as a central line or central dot according to the slice's position, either parallel or perpendicular to the vein.

b) Vein must be crossing the lesion center.

c) Vein diameter must be less than 2 mm.

d) Vein diameter more than 3 mm, confluent lesions, and unwell discernible lesions were not including.

The loss of signal caused by deoxygenated blood presenting in CVS can be significantly detected using 7T, 3T and less visualized in 1.5T [23]. Blinded raters can follow different diagnostic rules to detect the central vein sign using T2*-WI, including:

a) The threshold of 40% was applied for patient who has more than ten lesions; if the rater detects more than 40% of lesions in perivenular space, that indicates MS. If the number of lesions with CVS ≤ 40% means non-MS [15].

b) The rule of 6 that used if more than 6 WM lesions have been detected in general, and the rater identifies at least 6 with CVS, indicating MS patient. While, if the lesions with CVS were less than 6, that means non-MS patients. If the T2* images have less than 6 WM lesions in general, and the rater identifies 50% or more with CVS, that indicates MS patient. While, if the identified CVS less than 50%, that means non-MS patients [24].

c) The rule of 3 used when the rater selected and assessed 3 MS lesions randomly at the subcortical, deep white matter, and juxtaocular areas. If the CVS had been detected in all selected lesions, that indicates MS [25].

Current MR Imaging Sequences to Detect CVS

Multiple sclerosis can be diagnosed using conventional MR techniques that provide lesion identification and good anatomical visualization [26]. Conventional MR sequences including T2-weighted images, T2-fluid attenuated inversion recovery (FLAIR), and T1- weighted images pre-and post-contrast enhancement. They are available in all MRI centers and can be performed even at relatively low MRI strength, such as 1.5T. The DIS criteria of MS has been demonstrated, and lesions detected as hyperintense areas at T2-WI and T2 FLAIR WI [23]. The T2-FLAIR image has been considered the most important sequence in MS MRI protocol (Figure 1). That is because of the high sensitivity to detect the perivenicular and the juxtaocular lesions [27]. The T1- weighted image pre-and post-contrast enhancement (Figure 2) has been used to provide suitable anatomical structures for defect area, which appears as hypointense on the T1-WI. The post-contrast enhancement lesions provide localization of the inflammation. Investigate the defective Blood Brain Barrier (BBB) that might lead to detect the gadolinium extravasation. Contrast enhancement starts after 5 min following the injection. The hyperintensity in some lesions is mainly combined with the central black hole related to the axonal loss process. In addition, the enhanced lesions define the DIT and indicate the MS activity [28].

The Advanced MR sequences performing at a high magnetic field have an increased sensitivity to assess the MS lesions progression. In addition, it is providing different biomarkers that can be contributing to MS diagnostic. These sequences including, Diffusion Tensor Imaging (DTI), Magnetic Resonance Spectroscopy (MRS), and Magnetization Transfer Imaging (MTI) [26]. The Short tau inversion recovery (STIR) sequence has the ability to detect the CVS at the cervical spine region [16,29], the paramagnetic properties of deoxygenated blood make the T2*-WI the choice sequence. This imaging technique could be used to detect central vein signs and iron accumulation [16].
Figure 1: Axial FLAIR (a) and SWAN image (b1). Both images for the same MS patient and the same level. (b2) demonstrate the magnified SWAN image. A row head indicate the central vein as hypointense line in MS lesions [30]. [Reproduced with courtesy of Lummel N; T Boeckh Behrens, et al. [30] “Presence of a central vein within white matter lesions on susceptibility weighted imaging: a specific finding for multiple sclerosis?”

Figure 2: Zoom in section from axial T1-weighted post contrast (a) and SWI images (b), both images for the same MS patient. In (a) and (b) the white arrow indicates the inactive lesions. Black arrow in (a) and (b) indicate the active lesion. These two images are demonstrating the CVS in both inactive and active lesions [2] [Reproduced with courtesy of Lamot UJ; Avsenik et al. [2]. “Presence of central veins and susceptibility weighted imaging for evaluating lesions in multiple sclerosis and leukoaraiosis.”

Figure 3: Axial plan (a) and sagittal plan (b). (a) and (b) demonstrating the MS lesions with central vein sign at 3D T2*-Wi-EPI [31]. [Reproduced with courtesy of Oh J; NL Sicotte [31]. “New imaging approaches for precision diagnosis and disease staging of MS”]
Various T2* sequences have been used to detect and evaluate the CVS with noticeable efficiency in differentiating MS from non-MS disease. The sequences widely used in MS diagnosis including 3D T2*- GRE [3], SWI [12], T2*-WI with EPI (Figure 3) and, SAWN. In addition, the use of optimized sequences in attempting to increase the diagnostic efficiency including, FLAIR* that is resulted from a combination between T2-FLAIR and T2*-WI by using post-processing software. Also, the SAWN- venule is an optimized 3D-SWAN sequence performing after contrast administration (Figure 4) [5,9].

The CVS as an Imaging Biomarker to Distinguish MS From Non-MS

White matter lesions might occur due to many factors for example, increasing the patient’s age or other CNS diseases, that may be compromising the MS diagnosis. CNS lesions can be presented in the same areas that have been affected by MS lesions. In addition, it has a similar pattern in MR images and fulfilling the DIS criteria. These may lead to inaccurate diagnosis between MS and other non-MS diseases such as small vessel diseases (SVD) [32].

The appearance and distribution of the CVS in white matter lesions (WMLs) for MS and CSVD patients were under investigation retrospectively in Sparacia et al. [6] study. Two groups consist of 19 MS patients, and 19 CSVD patients have been examined at a 1.5T MR scanner using T2-WI and FLAIR. The images were analyzed according to the presence and localization of WMLs. The number of lesions with CVS had been reported in both groups using SWI. The results showed that, the number of MS lesions with CVS was 128 /313 (40.9%), while in CSVD patients was 22 / 75 (29.3%). In addition, most of them were periventricular distribution. Sparacia et al. [6] results were confirmed by a prospective study performed by Anan et al. [12] applied the same MRI strength and imaging sequences which had been used in Sparacia et al. [6] to discriminate between MS and CSVD lesions. The number of CVS has been detected in MS lesions was 223 / 453 (49.22%). While the number of CVS in CSVD lesions was about 37/144 (40.5%), which was lower than that found in MS patients. Anan et al. [12] found that the CVS detection played a significant role in MS diagnosis with 83.3 % sensitivity and 70 % specificity.

While the neuromyelitis Optica spectrum disorder (NOMOSD) has been characterizing by WMLs presenting similarly to the MS disease. It is crucial to differentiate between them accurately. The prospective study acquired by Cortese et al. [33] aimed to assess the CVS value to distinguish the MS from neuromyelitis NMOSD. Two groups of patients have been selected. The first group was 18 patients with NMOSD; the second group was 18 patients have RRMS. All groups have been examined by SWI sequence at 3T scanner, and the occurrence of CVS was recored. The CVS proportion in MS lesions was 80% and 32% in non-MS lesions. The high CVS proportion in MS lesions was similar to the results Sparacia et al. [6]; Anan et al. [12] studies. Noticeable relation between lesions with CVS and MS diagnosis prediction has been observed. These results indicate that the CVS has a value in distinguishing MS from NMOSD.

The determination of CVS’s presence is influenced by MS lesions activity, and if the CVS can be utilized as a specific biomarker for the MS were investigated in 2017 by Lamot et al. [2]. MS patients’ group and ischemic patients group were examined retrospectively at 3T MR scanner by applying FLAIR and T2-WI to identify the lesions’ location. SWI has been used to determine the presence of CVS. In contrast, the T1-WI post gadolinium was involved for MS activity evaluation. The results of this study include the number of CVS proportion in ischemic lesions was 144/204, which is more than the proportion of CVS in MS lesions, that was (370 / 601). The CVS has been detected in 16 active MS lesions out of 29 and 167 out of 226 inactive MS lesions. These results were not supporting previous studies such as Sparacia et al. [6]; Anan et al. [12]; Cortese et al. [33].

In general, Lamot et al. [2] showed that the visualization of CVS with MS lesions was not related to MS activity. Also, the presenting of CVS not specific to MS; it can be detected with other CNS disease lesions. The drop in CVS proportion with MS may be caused by mismatching the slice thickness between FLAIR and SWI, and in some cases, suffered from iron accumulation. In addition, the method that has been used may play a role in affecting the CVS assessment. Lummel et al. [30] was performed a prospective study in 2011 using the same MR strength and protocol that have been used in Lamot et al. [2]. The investigation resulted in 80% of CVS proportion in MS lesions higher than non-MS lesions that were 78%. While both studies have the same conclusion that suggesting presenting a CVS in a WMLs is not a specific finding in MS patients, it can be related to other diseases [2,30].

A prospective study was acquired by Maggi et al. [1] to assess the occurrence of MS lesions around the small veins against the lesion related to systemic autoimmune diseases. Two groups have

**Figure 4:** Comparison between the SWAN-venule (a) and, SWAN (b). Arrows indicate the lesions in SWAN-venule and the same place at SWAN image [9] (Reproduced with courtesy of Gaitan Mi; P Yanez et al. [9], “SWAN-Venule: An Optimized MRI Technique to Detect the Central Vein Sign in MS Plaques.”)
been investigated consist of Central Nervous System Inflammatory Vasculopathies patients and relapsing MS patients. The MRI sequences have been performed for both groups after contrast administration, including T2*WI with EPI and FLAIR. 1.5T and 3T MR scanners at multi centers have been contributing to this study. Images have been analyzed to detect and evaluate the CVS depending on the consensus criteria of the magnetic resonance imaging in multiple sclerosis (MAGNIMS). This investigation showed that the median frequency of CVS in MS lesions was 88%. At the same time, the median frequency of CVS in CNS vasculopathy lesions was 14%. No interference between the exams has been performed at different MR scanners. At the 50% threshold, the CVS has 100% accuracy in differentiating between MS and inflammatory vasculopathy. The median frequency of CVS has been reported by Guisset et al. [24] was 71% in MS patients, which was significantly lower than Maggi et al. [1]. That may be related to the gadolinium administration that has been used by Maggi et al. [1] before imaging acquisition which enhanced the MR imaging performance in detecting the CVS.

The 2017 McDonald criteria for MS diagnoses were impacting the earlier MS diagnosis with higher sensitivity and lower specificity. The overlapping between MS and MS-mimics disease might happen. The cross-sectional study performed by Sinnecker et al. [4] aimed to evaluate the CVS lesions’ sensitivity and specificity to discriminate the MS and non-MS diseases such as migraine and systemic lupus erythematosus (SLE). Different imaging sequences have been used in this study, including the T2*WI or SWI at 3T MRI. This investigation resulted in 68.1% sensitivity and 82.9% specificity for differentiating between the MS from non-MS using a 35% CVS threshold. The sensitivity was 61.9%, and specificity was 89.0% when a third CVS rule was used. The 100% Sensitivity and the 92% specificity at the 40% CVS threshold were the results of a retrospective study performed by Maggi et al. [34]. These results were significantly higher than Sinnecker et al. [4] results. That may be related to the methods that have been used by Maggi et al. and Clarke et al. [10,34] have been performed prospectively to assess the CVS accuracy in cases with unclear MS diagnosis. The results have been agreed with Maggi et al. [34]in the same sensitivity of 100%. In contrast, the specificity was 73.9%, which is lower than Sinnecker et al. and Maggi et al. [1,4] using a 40.7% threshold. Lower specificity may be related to the lack of multicenter, and the evaluation of the CVS depended only on T2*WI with EPI.

**Table 1:**

<table>
<thead>
<tr>
<th>Study</th>
<th>MRI</th>
<th>Sequence</th>
<th>Parameters</th>
<th>1CVS %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oh et al. [31]</td>
<td>3T</td>
<td>3D T2*-WI - EPI</td>
<td>Sagittal 3D T2*-W - EPI: coil=20 channels, TR=64, TE=35, FA=10°, NEX=L, slice thickness=0.65mm, in-plane resolution=0.65 × 0.65mm³, and number of slices=265.</td>
<td>75%</td>
</tr>
<tr>
<td>Clarke et al.</td>
<td>3T</td>
<td>3D T2*-WI - EPI</td>
<td>3D T2*-W GRE, coil=32 channels, EPI factor=15, TR=54ms, TE=29ms, matrix=448 × 448 × 336, voxel size=0.54 × 0.54 × 0.55mm, FA=10°, and acquisition time=4.15 minutes.</td>
<td>51%</td>
</tr>
<tr>
<td>Dixon et al.</td>
<td>3T</td>
<td>IS0. 3D T2*- WI-EPI</td>
<td>Coil=8 channels, TE = 20ms, TR = 150ms, FA = 14°, SENSE factor = 2, EPI factor = 3, isotropic voxels= 0.8 mm, stacks overlap= 3mm, volumed covered= 192 × 164 × 95.2mm³, and acquisition time=7.2 min.</td>
<td>56%</td>
</tr>
<tr>
<td></td>
<td>7T</td>
<td>IS0. 3D T2*- WI-EPI</td>
<td>Same ISO parameters with some optimization involves, TE=25ms, voxel size=0.57 × 0.57 × 1.05mm³, TR=150 ms, FA = 14°, EPI factor=3, and acquisition time=7.2 min.</td>
<td>82%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OPT. 3D T2*- WI-EPI</td>
<td>Go=16 channels, TE = 20ms, TR = 150ms, FA = 14°, SENSE factors = 2, EPI factor = 3, isotropic voxels= 0.5mm, stacks overlap= 5mm, volumed covered= 192 × 164 × 85 mm³, and acquisition time=8.8 min.</td>
<td>89%</td>
</tr>
<tr>
<td>Lumel et al.</td>
<td>3T</td>
<td>SWAN</td>
<td>Same ISO parameters with some optimization involves, TE=15ms, voxel size=0.32 ×0.32 ×0.90 mm³ TR = 150ms, FA = 14°, EPI factor=3, and acquisition time=8.8 min.</td>
<td>95%</td>
</tr>
<tr>
<td></td>
<td>3T</td>
<td>3D T2*-WI</td>
<td>3D T2*-W GRE pulse sequence, coil=8 channels. TE=25.4ms, BW = 62.5kHz, FA = 20°; TR=43ms; matrix size=364 × 364mm; FOV=200 × 200mm; slice thickness=2.6mm; 60 slices; and acquisition time=5min 48s.</td>
<td>80%</td>
</tr>
<tr>
<td></td>
<td>3T</td>
<td>SWAN</td>
<td>Coil= 32 channels, 3D T2*-W GRE, voxels size = 43 × 43 × 1.5mm, matrix= 416 × 416 × 48, TE=25ms, TR=38ms, BW=110Hz, and acquisition time=10.33 min.</td>
<td>40%</td>
</tr>
<tr>
<td></td>
<td>3T</td>
<td>SWAN</td>
<td>Coil= 32 channels, 3D T2*-W susceptility-weighted angiography, voxels size = 43 × 43 × 1.0mm, matrix= 400 × 400 × 94, TE=24ms, TR=39ms, BW=240Hz, and acquisition time=7.16 min.</td>
<td>55%</td>
</tr>
<tr>
<td></td>
<td>3T</td>
<td>3D T2*-WI - EPI</td>
<td>Coil= 32 channels, 3D T2*-W GRE, EPI factor=15 echoes, sagittal plane, matrix = 448 × 448 × 336, voxel size = .55 × .55 × .55mm, Parallel imaging factors=2, FA=10°, TE=29ms, TR=54ms, two averages, and acquisition time=4.23 min.</td>
<td>64.50%</td>
</tr>
<tr>
<td>Lamot et al.</td>
<td>3T</td>
<td>SWI</td>
<td>Coil= 32 channels, TR=28ms, TE, 20ms, BW=120Hz, FA=15°, FOV=200mm, the voxel size= 0.8×0.8×1.5mm, matrix= 256×228mm, slice thickness= 1.5mm, slices= 72, and acquisition time=4.46 min.</td>
<td>62%</td>
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**MR imaging sequences vs. the proportion of lesions with CVS**

According to Flippi et al. [16], the perivenular lesions still under research. Different MRI strengths, including 7T, 3T, and 1.5T, can detect the CVS. In addition, 3D T2*-EPI WI, FLAIR*, SWI, and SWI with contrast administration can be used. The studies listed in Table 1 involved sequence, parameters, and the CVS proportion in MS lesions. The heterogeneity between the results may be related to the different imaging acquisition parameters and how each investigator evaluates CVS.
Central vein sign and MS progression

MR imaging can provide important details about the tissue structure and integrity. The phase changing in MS lesions may indicate the changing in the stage of the active inflammation. MS lesion morphology was investigated by Bozin et al. [36], using cross-sectional study. Two groups of patients were examined, 17 MS patients with short MS duration and 11 MS patients with long MS duration. The groups include CIS, RRMS, and PPMS patients. All images were acquired at 7T MRI using T2*-WI, SWI, and 3D T1-W magnetization -prepared -rapid gradient echo (MPRAGE). Images were analyzed to detect the CVS and inflammatory lesions. This study resulted in phase changes were detected in 126/192 lesions. At the same time, Phase changes related to the central vein have been detected in 83/192. In addition, the number of detected lesions that’s have phase changing was less in the patients with long MS duration than the patients with short MS duration. In general, the phase changing in MS lesions can be detected in short and long MS duration. The longitudinal MR imaging studies have a significant role in detecting the activity and the development of MS lesions stages [36].

CVS changes have been investigated using a cross-sectional study was performed by Gaitan et al. [37] to investigate the veins sizes in MS patients group, healthy controlled group, and cerebrovascular disease patients group. The MS group includes RRMS, SPMS, and PPMS patients. The images were acquired at 3T MR scanners, using the following imaging protocol: MPRAGE, 3D-T2 FLAIR, and 3D T2*-WI with gadolinium administration. The CVS has been classified into intralesional, perilesional, and extralesional. The exact vein location was identified in non-MS patients. The smaller intrallesional veins diameter might be caused by external inflammatory compression, the thick wall of the vein, and perivasular space. In addition, these veins are narrower in MS than in non-MS or healthy controlled cases. These results have been supported by a longitudinal study acquired by Dal-Bianco et al. [22]. Both studies conducted by Gaitan et al. [37] and Dal-Bianco et al. [22] resulted in a noticeable change in CVS diameter has been detected over time.

The reason for acquiring longitudinal studies such as Dal-Bianco et al. [22] was to evaluate the CVS size in MS lesions initially founded and the new MS lesions presented and related them to the controlled group. The MS group and controlled group have the same age and under-investigated over 3.5 years. The investigation was performed at 7T MRI using SWI co-registered with FLAIR images and T1-W (MPRAGE). All the patients were examined over 3.5 years annually. MRI of the brain was acquired for each patient as a cross-sectional study. Two groups of patients were examined, 17 MS patients with short MS duration and 11 MS patients with long MS duration. The longitudinal MR imaging studies have a significant role in detecting the activity and the development of MS lesions stages [36].
sequences were performed again for follow-up. The FLAIR* was performed and analyzed to detect the CVS, which was either chronic active or shrinking the vein diameter at the baseline and after 12 months were calculated. The total number of lesions with CVS was 222/389. The number of chronic active lesions was 48, while the number of non-enhancing shrinking lesions was 48 also, and the number of non-enhancing stable lesions was 126. The diameter size of the CVS at the baseline MRI was relatively the same in all lesion types. While, at the follow-up MRI, the CVS diameter size in chronic active lesions, shrinking lesions, and stable lesions were (0.92 ± 0.15 mm), (0.90 ± 0.19 mm) (1.10 ± 0.18 mm) respectively. This study was also agreed with Gaitan et al. [37] whereas, the narrower CVS in MS lesions may indicate the chronic inflammatory process. In addition, the fibrosis; thickening of collagen and increase the oxyhemoglobin have a role in MS lesions changing.

This review was limited due to the lack of some results such as, the studies that have been used to evaluate the CVS as imaging biomarker were suffering from results heterogeneity. Some studies provided their results as sensitivity and specificity. Also, some of the results offered as median CVS frequency or proportionality of lesions with CVS. The different parameters that have been used for the same sequence at a different study may lead to difficulties in evaluating the results. Also, the differences between the methods that have been used for each study may affect the last results. A small number of studies were obtained from search engines to investigate the central vein sign and MS progression relation. We recommend that more research must be done in this field. Finally, in this review, we only investigated the brain MS lesions; spine MS may be investigated in other studies.

The CVS is a promising imaging biomarker in MS diagnostic and differentiating between MS and other mimics diseases. In addition, the CVS able to be detected using T2*-WI sequences, including SWI, SWAN, FLAIR* While the T2*-WI with EPI reveals the best detection of CVS which shows promises in detecting more CVS lesions. the detected chronic active and new lesions with CVS at the follow-up MR imaging exam may indicate the MS disease progression.

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