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Presence of central veins and susceptibility weighted imaging for evaluating lesions in multiple sclerosis and leukoaraiosis

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ABSTRACT

Purpose: The process of demyelination in multiple sclerosis (MS) is reflected in lesions of the central nervous system (CNS), which are found in an abundance of different diseases and are frequently radiographically indistinguishable. Our aim was to determine whether the perivenous distribution of MS lesions identified on susceptibility weighted images (SWI) could be used as a specific radiographic sign for MS, and also to determine whether the visibility of the central vein (CV) is affected by the activity of MS lesions.

Methods: We retrospectively examined 34 subjects with MS and 19 subjects with ischemic lesions, which underwent a 3 T MRI investigation. According to FLAIR and T2-weighted sequences the lesions were categorized regarding location. The presence of CVs was determined on SWI. Gadolinium enhanced T1-weighted sequence was included for the evaluation of MS lesion activity.

Results: A total load of 601 MS and 204 ischemic lesions was identified. We found significantly more lesions with CVs in the group with ischemic lesions compared to the group with MS lesions ($p < 0.001$). Similarly, significantly more supratentorial peripheral ischemic lesions had CVs (p=0.011), whereas in supratentorial periventricular and intratentorial lesions we found no significant difference between the two groups (p=0.377 and p=0.615). Comparing the active and inactive MS lesions regarding CVs, we found no significant difference between the groups (p=0,472).

Conclusions: We can conclude that the presence of a CV is not a specific radiographic sign for MS. CVs can also be identified in lesions caused by various other diseases.

1. Introduction

Multiple sclerosis (MS) is a chronic, neurodegenerative disorder of the central nervous system (CNS), which is histopathologically characterized by multiple inflammatory demyelinating lesions (Osborn, 2012; Lummel et al., 2011; Kau et al., 2013). However, lesions in the CNS are a common finding in various other diseases and are frequently radiographically indistinguishable (Lummel et al., 2011; Mistry et al., 2013). One of the most common of these diseases is hypertensive microangiopathy, which leads through arteriolosclerosis to ischemic lesions, which may also be identified in elderly people who are clinically healthy (Lummel et al., 2011; Kau et al., 2013; Enzinger and Fazekas, 2015; Harvey and Zieve, 2012).

At present, there is no specific test that is diagnostic for MS, including MRI (Mistry et al., 2013). The diagnosis remains clinical and is achieved with a combination of clinical signs and diagnostic examinations (laboratory, electrophysiologic and imaging), which are used for demonstrating the dissemination of lesions in space and time and are applied to the revised McDonald scheme to achieve an early diagnosis (Kau et al., 2013; Polman et al., 2011; McDonald et al., 2001).

MRI is the examination of choice for both initial evaluation and treatment follow-up (Osborn, 2012; Ge et al., 2011). T2- weighted and fluid-attenuated inversion recovery (FLAIR) sequences are highly sensitive in the detection of hyperintensities in the CNS, which correspond to a wide spectrum of pathologies ranging from oedema, inflammation, gliosis, demyelination to complete necrosis, so the lack of specificity of these two sequences must be taken into consideration (Osborn, 2012; Kau et al., 2013; Ge et al., 2011; Filippi and Rocca, 2011). While a T1-weighted sequence is not sensitive for detecting lesions in the CNS, a Gadolinium-enhanced T1-weighted sequence provides information about vascular inflammation, which is a marker of lesion activity in MS lesions (Ge et al., 2011; Suzuki et al., 2011).

Histopathological post-mortem studies have suggested that the

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localization and shape of MS lesions can be attributed to their perivenous distribution (Lummel et al., 2011; Mistry et al., 2013). In acute MS lesions, the periluminal region of the central veins (CVs) is hypercellular, which is in accordance with the hypothesis that the autoreactive T cells and macrophages enter the brain parenchyma from systemic blood vessels and induce inflammation, which causes destruction of myelin (Osborn, 2012; Mistry et al., 2013; Graham and Lantos, 1997).

Recently, new MRI techniques have been developed to display the perivenous localization of MS lesions (Lummel et al., 2011; Kau et al., 2013). One of them is susceptibility weighted imaging (SWI), which is a flow compensated three-dimensional gradient echo sequence (Haacke et al., 2009; Gasparotti et al., 2011; Romarić et al., 2014). SWI exploits the differences in magnetic susceptibility of various tissues with paramagnetic properties (for example, venous blood) and uses this information as a source of contrast enhancement (Lummel et al., 2011; Kau et al., 2013; Ge et al., 2011; Haacke et al., 2009; Gasparotti et al., 2011; Romarić et al., 2014).

One key factor that is presumed to affect the visibility of CVs and needs to be addressed in the evaluation of CVs in MS lesions is the different stages of lesion evolution (Osborn, 2012). Significantly reduced visualization of periventricular white matter veins on SWI has been reported in patients with chronic MS lesions, probably due to decreased levels of venous deoxyhemoglobin in the chronic altered tissue, compared to control subjects (Kau et al., 2013).

The purpose of our study was to determine whether the perivenous localization of MS lesions on SWI images could be used as a specific radiographic sign for MS and, secondly, to determine whether the visibility of the CVs is affected by the activity of the MS lesions.

2. Materials and methods

We declare that our study has been approved by the National Medical Ethics Committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

2.1. Subjects

In our retrospective study, the sample group consisted of 34 subjects (25 females and 9 males; mean age 39.6 years, range 21–66 years), who were assigned a clinical diagnosis of MS. In 20 of these patients, MRI examination showed only inactive demyelination lesions, while in 14 patients, active demyelination lesions were also depicted. Patients who were diagnosed with cardiovascular and/or cerebrovascular disease, other neurological disorders, a history of malignant disease, severe kidney disease or previous allergic reactions to gadolinium contrast medium were excluded from the study.

We also included 19 patients (11 females and 8 males; mean age 71.4 years, range 46–89 years) with ischemic lesions, probably due to hypertensive microangiopathy. All the patients in this group had confirmed clinical history of chronic hypertension, without any other conditions, including: prior brain stroke, severe cortical atrophy, a history of malignant disease or manifest neurological deficit (including patients with signs and symptoms suggestive of MS) Patients with any of the mentioned conditions were also excluded from this group.

2.2. MRI acquisition

MRI imaging was performed on a 3.0 T system (MAGNETOM Trio, A Tim System, Siemens AG, Erlangen, Germany) using a 32-channel head coil. All patients underwent a brain MRI examination with a uniform protocol (FLAIR, T2-weighted sequences in different planes and a SWI to determine the presence of CVs). In the group of patients with MS, the protocol included a gadolinium enhanced T1-weighted sequence.

The FLAIR sequence was acquired with the following imaging parameters: repetition time (TR), 5000 ms; echo time (TE), 392 ms; inversion time (TI), 1800 ms; flip angle, 120°; averages, 1; NSA: 2; field of view (FOV), 240 mm; acquired voxel size, 0.9×0.9×0.8 mm; matrix, 258×256 mm; slice thickness, 0.8 mm; slices, 192; and acquisition time, 7 min 2 s. The imaging parameters for the T2-weighted sequence were: TR, 6000 ms; TE, 120 ms; flip angle, 120°; averages, 2; NSA: 1; FOV 220 mm; acquired voxel size, 0.8×0.6×3 mm; matrix, 266×384 mm; slice thickness, 3 mm; slices 42; and acquisition time, 3 min 8 s. The imaging parameters for the T1-weighted sequence were: TR, 2000 ms; TE, 20 ms; flip angle, 120°; averages, 1; NSA: 3; FOV 220 mm; acquired voxel size, 1×0.9×3,0 mm; matrix, 256×169 mm; slice thickness, 3 mm; slices, 42; and acquisition time, 4 min 42 s.

The SWI sequence was acquired with: TR, 28 ms; TE, 20 ms; receiver bandwidth, 120 Hz; flip angle, 15°; FOV, 200 mm; acquired voxel size, 0.8×0.8×1.5 mm; acquisition matrix, 256×228 mm; slice thickness, 1,5 mm; slices, 72; acquisition time, 4 min 46 s.

2.3. Image analysis

MR data was analysed by two experienced neuroradiologists who were blinded to patients' identification and clinical data. FLAIR and T2-weighted images were used for the identification of both MS and ischemic lesions.

Each lesion was first identified on FLAIR and T2-weighted images and then defined as supratentorial periventricular, supratentorial peripheral or infratentorial. Only lesions ≥3 mm in size were included. Periventricular lesions were classified if lesions had a border ≤5 mm of the venticules and all other supratentorial lesions were classified as peripheral. For the evaluation of the activity of demyelination lesions in the group of patients with MS, the protocol included gadolinium enhanced T1-weighted images. Lesions with vascular inflammation, which is a known marker of lesion activity, showed enhancement after contrast application and were defined as active lesions (Ge et al., 2011). In the group of patients with ischemic lesions, we only included patients who had lesions classified according to the Fazekas scale as 0–2. Patients with lesions classified as Fazekas 0 represented single punctate lesions, lesions classified as Fazekas 1 were defined as multiple punctate lesions. Lesions classified as Fazekas 2 also include some lesions which were beginning to confluent. In these group we excluded confluent lesions and only punctate lesions, if present, were evaluated.

In terms of the angle of the slice, a CV (on SWI) was identified as a hypointense linear structure running through the centre of the lesion (if parallel to the plane) or as a small hypointense central dot (if oriented perpendicular to the plane). Only when both evaluators were in agreement in the identification of a CV did we assign the lesion to the group with CV positive lesions.

2.4. Statistics

For each group of patients (with MS and ischemic lesions), we calculated descriptive statistics. We next calculated the ratios between the number of lesions with CVs and the total number of lesions for each patient, in both groups. In addition, we calculated the same ratios for lesions in terms of their location (supraventricular peripheral, periventricular and infratentorial). The ratios between the number of active MS lesions with CVs and the total number of active lesions and the ratio between the number of inactive lesions with CVs and the total number of inactive lesions were also calculated.

Variables were compared between the groups (MS and ischemic lesions, active and inactive MS lesions) using the Mann-Whitney *U* test (total number of lesions, supratentorial peripheral, supratentorial periventricular and infratentorial). The data was analysed using SPSS® (Version 20.0, SPSS Inc., Chicago IL, USA, 2011) statistical software. A value of $p < 0.05$ was considered statistically significant.