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FULL PAPER

A comparative MRI study for white matter hyperintensities detection: 2D-FLAIR, FSE PD 2D, 3D-FLAIR and FLAIR MIP

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Objective: The main objective of this study was to not only determine the most appropriate sequence for the analysis of white matter hyperintensities (WMH) on MRI but also to confirm the advantage of three-dimensional (3D) acquisition, as it has been suggested in previous studies, and to test the convenience of using maximum intensity projection (MIP) algorithms on 3D-fluid-attenuated inversion-recovery (FLAIR) images for a quicker evaluation of brain MR studies.

Methods: The number of WMH was compared in 40 patients and a control group of 10 volunteers using 4 different imaging modalities: two dimensional (2D)-FLAIR, 2D fast spin echo proton density (FSE PD), 3D-FLAIR and FLAIR MIP. Four experienced radiologists took part in the imaging analysis. All studies were performed on a 1.5-T whole-body MR unit.

Results: A statistically significant difference between the number of lesions detected on 3D acquisitions (FLAIR CUBE® or FLAIR MIP sequences) compared with those on 2D-FLAIR or 2D FSE PD was demonstrated. There is no significant difference between 3D-FLAIR and FLAIR MIP, therefore both of them can be used with similar results.

Conclusion: 3D-FLAIR sequences should replace conventional 2D-FLAIR and/or FSE PD sequences in the MR acquisition protocol when WMH are suspected. MIP reformat algorithms are less time consuming, therefore these can also be used to simplify the detection.

Advances in knowledge: 3D sequences are superior for WMH depiction. Moreover, MIP algorithms allow easier analyses with similar results.

White matter hyperintensities (WMH) are a common finding when sequences with long repetition time (TR) are used in brain MRI studies. Most of the time these hyperintensities do not have clinical significance or they are associated with a normal ageing brain.^{1,2} However, in some pathological processes, it is important to detect and quantify these lesions. Multiple sclerosis (MS) is a disease in which WMH depiction is important because many MS study groups employ diagnostic criteria for MS that take into consideration the number, location and evolution of these lesions.³⁻⁵ Brain ischaemic damage is another disease that is often expressed in MRI as hyperintensities on long TR sequences. The National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences criteria for the diagnosis of vascular dementia consider the presence of hyperintensities and lacunar infarcts⁶ as a useful tool for the differential diagnosis of other types of dementias.⁷ In summary, it is important to detect and quantify hyperintense brain lesions, especially when certain diseases are suspected.

Previous studies describe that with the three-dimensional (3D) fluid-attenuated inversion-recovery (FLAIR) sequence significantly higher contrast-to-noise ratios were achieved and significantly more lesions in patients with MS were detected compared with conventional two-dimensional (2D)-FLAIR.⁸ Furthermore, there is the additional advantage that multiplanar reformatting is possible by using a 3D acquisition.⁹ We hypothesize that with the use of maximum intensity projection (MIP) techniques, in a similar way as to how they are used for the counting of pulmonary nodules on CT,¹⁰ more WMH are detected when compared with 2D MR sequences and at least as good as on 3D-FLAIR viewing of non-post-processed images.

METHODS AND MATERIALS

Patients and controls

This study was performed on 40 randomly selected patients and 10 controls. The group of 40 patients (25 females and 15 males) comprised of 22 subjects with confirmed MS and 18 subjects with clinical isolated syndrome (CIS). The

mean age of the patients was 41.5 years (range, 24.6–56.6 years). The control group comprised ten volunteers (six females) with neither neurological disease nor clinical symptoms. The mean age was 32.7 years (range, 18–51 years) for the control group.

MRI acquisition parameters and post-processing

All studies were performed on a 1.5-T whole-body MR unit (Signa® Excite HDx; GE Healthcare, Milwaukee, WI) by using an eight-channel head coil. Each patient was imaged by using a standard 2D-FLAIR and 2D fast spin echo proton density (FSE PD) weighted sequence, as well as a single-slab 3D-FLAIR CUBE® (General Electric Healthcare, Milwaukee, WI). Sequence parameters and acquisition times are listed in [Table 1](#).

Reformat techniques were used on 3D-FLAIR CUBE sequences to generate the FLAIR MIP using the software Functool™ (GE XVI). Slice thickness was 2 mm, and the spacing was 3 mm. The whole brain was included in approximately 35–40 images on the FLAIR MIP reformat, as opposed to the 250–300 images that should be analysed on the 3D-FLAIR acquisition.

Image analysis

Four radiologists with image analysis experience documented the number and location of WMH.

All MR studies were divided into four groups containing ten patients each. Just one sequence, 2D-FLAIR, 2D FSE PD, 3D-FLAIR or FLAIR MIP, was assigned to every radiologist. Therefore, only one sequence was read following a rotating system (a different sequence per group of patients and for each radiologist) to avoid overlapping.

MR images of the control group were evaluated in the same way, and every radiologist documented the range of normal appearances and identified incidental lesions and artefacts. An example of a WMH analysis is shown in [Figure 1](#).

Lesions were counted and classified according to their location as either supratentorial (divided into three groups: periventricular, juxtacortical and other supratentorial locations) or infratentorial, based on the recommendations established by MS study groups.^{11,12}

- Juxtacortical lesions were those located within the grey matter or just within the subcortical white matter immediately adjacent to the grey matter.
- Periventricular lesions abutted the lateral ventricles or, rarely, third ventricle surfaces.
- Corpus callosum lesions, thalamus and basal ganglia lesions, and all the supratentorial white matter lesions that showed no contact with the ventricle or cortex were included in the supratentorial group.
- Infratentorial lesions were located in or along the surface of the cerebellum, medulla, pons or mid-brain.

Hyperintensities were only counted once when they appeared on multiple contiguous slices.

Statistical analysis

Because the data do not follow a normal distribution according to the Kolmogorov–Smirnov test, we used non-parametric tests to perform the analysis.

Interobserver reliability was checked using the Kruskal–Wallis and Bonferroni non-parametric tests.

To evaluate differences between the control group and the patients with proven MS and CIS, the Mann–Whitney test was used.

The repeated measures analysis of variance (ANOVA) test was used to detect statistically significant differences between the 2D-FLAIR, 2D FSE PD, 3D-FLAIR and FLAIR MIP sequences, for these items: supratentorial lesions, infratentorial lesions and total number of lesions.

Statistical software SPSS® v. 15.0 (IBM Corporation, Armonk, NY) was used for the analysis.

RESULTS

Study results support the hypothesis that 3D-FLAIR and FLAIR MIP are the best sequences for WMH detection, especially in the supratentorial compartment.

Table 1. MRI acquisition parameters for all sequences performed in this study

Parameter	2D-FLAIR	2D FSE PD	3D-FLAIR	FLAIR MIP
Repetition time (ms)	8000	20	6000	
Echo time (ms)	147	2000	126	
Inversion time (ms)	2000		1864	
Slice thickness (mm)	5	5	1.2	2
Slice gap (mm)	1	1	0.6	3
Number of images	24	24	256	43
Acquisition plane	Axial	Axial	Sagittal	Axial
Acquisition time (min)	3:12	2:04	5:39	

2D, two dimensional; 3D, three dimensional; FLAIR, fluid-attenuated inversion-recovery; FSE, fast spin echo; MIP, maximum intensity projection.

Figure 1. MRI without contrast of a patient with multiple sclerosis. (a) Fast spin echo (FSE) proton density, (b) fluid-attenuated inversion-recovery (FLAIR) two dimensional (2D), (c) 2D-FLAIR and (d) FLAIR maximum intensity projection (MIP; sequence parameters are listed in Table 1). The images show a periventricular lesion on the left side (arrow). This lesion is hardly seen on FSE proton density and 2D-FLAIR sequences. On the FLAIR MIP image there is a sharp contrast between the lesion and the surrounding parenchyma, which makes it easier to depict.

In order to validate this study is to achieve a good interobserver reliability. There were no significant differences between the observers when the total number of supratentorial hyperintensities (the sum of periventricular, juxtacortical and other supratentorial locations) was considered. This was also valid for the infratentorial and the total number of lesions. The interobserver reliability for the number of lesions counted separately in periventricular, juxtacortical and other supratentorial locations was poor. We only performed the analysis for these three different groups: supratentorial (the sum of periventricular, juxtacortical and other supratentorial locations), infratentorial and total.

Another important feature was detecting if there were any differences between the three subject types included in the study: proved MS, CIS and controls. As was expected, the Mann-Whitney test demonstrated a marked difference in the number of lesions between MS patients (mean, 16.6 lesions), patients with CIS (mean, 14.51) and the control group (mean, 0.5 lesion). Although the mean number of hyperintensities was higher in patients with MS, no statistical difference was observed between patients with MS and patients with CIS.

Finally, we compared the 2D-FLAIR, 2D FSE PD, 3D-FLAIR and FLAIR MIP sequences for the number of lesions detected on the supratentorial and infratentorial parenchyma and the total number of lesions.

Results were almost the same for the supratentorial and total hyperintensity groups. The ANOVA test demonstrated a statistically significant difference ($p < 0.05$) between the total number of lesions detected on 3D-FLAIR (mean 18.05 ± 10.16) or FLAIR MIP (mean 18.00 ± 9.58) sequences and those on 2D-FLAIR (14.87 ± 8.90) or 2D FSE PD (14.82 ± 7.54) sequences. No difference was detected between 2D-FLAIR and 2D FSE PD. When 3D-FLAIR and FLAIR MIP were compared, no significant difference was found (Figure 2).

Concerning the analysis of infratentorial compartment hyperintensities, the highest number of lesions was detected using (in descending order) FLAIR MIP, 3D-FLAIR, 2D FSE PD and 2D-FLAIR. However, there was no statistically significant difference between the sequences.

A schematic summary of the study design and the most important results are shown in Figure 3.

Figure 2. Boxplot representation of the total number of lesions detected using fluid-attenuated inversion-recovery (FLAIR) two dimensional, fast spin echo proton density (FSE PD), FLAIR three dimensional (3D) and FLAIR maximum intensity projection (MIP) reformat. The boxes show the lesions included between the lower and the upper quartile. The horizontal line represents the mean. The vertical lines mark the range of the number of lesions detected and therefore indicate the degree of dispersion and skewness in the data. The graphic shows that 3D-FLAIR and FLAIR MIP detect the highest number of white matter hyperintensities.

Figure 3. A summary of the study design and results. Four radiologists analysed the number and location of white matter hyperintensities (WMH) on four different sequences [two dimensional-fluid-attenuated inversion-recovery (2D-FLAIR), 2D-fast spin echo proton density (FSE PD), three dimensional (3D) FLAIR and maximum intensity projection (MIP) FLAIR]. The analysis demonstrated that 3D-FLAIR and MIP reformat images were superior for the detection of WMH with a good interobserver reliability. CIS, clinical isolated syndrome; MS, multiple sclerosis.

DISCUSSION

WMH are common findings on brain MR images, especially for the ageing brain, often without pathological significance. However, sometimes their number, location and characteristics, as well as the clinical condition, may suggest different brain diseases, such as MS. Therefore, a good tool that has no significant observer differences and that also serves as a reliable follow-up technique, seems to be necessary to detect WMH.

Based on this study, we recommend the use of MIP reformat images from 3D-FLAIR sequences as the best tool to detect WMH on MRI because when compared with classical sequences, more lesions are detected, the number of images is not so high because of the reformat parameters and the interobserver reliability is as good as for the other sequences. Unfortunately, acquisition time increases from approximately 3.12 to 5.39 min.

Since the first MR studies, technical development has allowed important improvements in the depiction of WMH. In earlier studies, 2D-FLAIR images were known to improve the detection of lesions when compared with conventional spin echo sequences.¹³ In 1998, the 2D double inversion-recovery technique was described. It combines two inversion pulses that suppress the signals of both cerebrospinal fluid and white matter, creating an image with a clear cortical delineation and demonstrated high lesion conspicuity.¹⁴ The advent of single-slab 3D methods, which use very long echo trains and refocusing pulses with variable flip angles, allowed 3D whole-brain acquisition on FLAIR and T_2 images. Some studies demonstrate how 3D imaging techniques improve the detection of MS plaques in different brain locations when they are compared against the conventional 2D sequences.^{9,15,16} Most of the 3D sequences employ a smaller slice thickness than 2D sequences, and this could be one of the reasons for 3D imaging techniques success.¹⁷ However, 3D methods result in an increase in the number of images which consequently becomes more time consuming. This is something similar to what happened with the development of multislice CT

compared with the conventional axial CT. The number of high quantity images could be reduced by increasing the thickness with reformat techniques; however, there is a risk of underestimating that lesions are smaller than the slice thickness.

Imaging with 3D-FLAIR CUBE consists of a single-slab 3D FSE imaging sequence that uses refocusing flip angles of $<180^\circ$, by modulating the refocusing flip angle the equilibrium between encoded longitudinal and transverse magnetization is achieved. At the beginning of the echo train, flip angles are rapidly reduced to store excess magnetization in an encoded longitudinal state. By increasing the flip angle, this sequence converts the slowly decaying longitudinal magnetization back to transverse magnetization to provide signal over a much longer train. This way, large 3D data matrices with thinner slices are acquired in a few echo trains, and an isotropic resolution is possible. Because all radio frequency pulses in the single-slab 3D sequences are non-spatially selective, the 3D slab was placed in the sagittal orientation, with read out in the head-to-feet direction to prevent infolding.¹⁸

In the MIP algorithm, only the highest attenuation voxels along lines projecting through the volume data set are selected to create the final image. MIP is a technique commonly used on CT scans, e.g. for pulmonary nodule depiction and different types of angiographic studies.¹⁹ On MRI, MIP images are used on many MR angiography and some breast studies; however, to the best of our knowledge, MIP has never been used for brain parenchyma analysis.

The MIP algorithm increases the slice thickness potentially with a risk of overlapping contiguous lesions; however, in our study, there was not a significant difference in the number of lesions detected in the 1-mm thickness 3D-FLAIR sequences and the 2-mm MIP reformat.

The fact that the same results were found in both the MS and CIS groups proved that the use of 3D sequences and MIP reformat

images are better for the diagnosis of white matter diseases than conventional 2D sequences, regardless of which pathology we are dealing with.

However, we did not obtain good interobserver reliability when supratentorial WMH were classified into periventricular, juxtacortical and other supratentorial locations, probably because the limit between those different areas is not clear and because some of the biggest lesions affect two or more different locations and

confuse the observers. The lack of infratentorial WMH in our patients did not allow for their statistical analysis.

CONCLUSION

According to our investigation, 3D-FLAIR sequences should replace conventional 2D-FLAIR and/or FSE PD sequences in the MR acquisition protocol when WMH are suspected. MIP reformat algorithm can be used to simplify its detection reducing the number of images with the same degree of reliability.

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