Original article

3 Tesla three-dimensional Fluid Attenuated Inversion Recovery MR imaging in multiple sclerosis

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SUMMARY: Aims. *Magnetic resonance brain evaluation in multiple sclerosis must be made by sequences that enable you to display the largest possible number of lesions. In our study, carried out with a 3 Tesla equipment, we compared a new three-dimensional fluid attenuated inversion recovery sequence with the conventional ones in order to establish whether it can be used, instead of the other, for the multiple sclerosis patients evaluation.*
Materials and methods. *The sequences used were proton density, fast spin echo T2-weighted, two- and three-dimensional fluid attenuated inversion recovery. Preliminarily, we acquired these sequences in 5 healthy volunteers and subsequently in 40 patients with clinically definite multiple sclerosis. The impact of any artefacts in all 4 sequences was evaluated. Afterwards the contrast resolution between lesions and the surrounding tissue was compared among all the sequences. Finally the number of lesions visualized with the 4 sequences was evaluated: both the total number of plaques and partial subgroups, according to lesions location and size.*
Results. *In some cases (6/40) artefacts in three-dimensional fluid attenuated inversion recovery sequences were present both in volunteers and in patients. The contrast resolution was similar between fast spin echo T2-weighted, two- and three-dimensional fluid attenuated inversion recovery, whereas it was significantly lower in the PD images. Finally, as regards the number of lesions displayed, three-dimensional fluid attenuated inversion recovery sequences proved better than the other in all brain locations and especially as regards the small lesions assessment.*
Conclusions. *The three-dimensional fluid attenuated inversion recovery sequences, in 3 Tesla magnetic resonance studies, may be considered as the best choice for the multiple sclerosis patient study.*

KEY WORDS: *Fluid attenuated inversion recovery sequence, Magnetic resonance, Multiple sclerosis.*

INTRODUCTION

Magnetic resonance evaluation of patients with multiple sclerosis should be more accurate and sensitive as possible, either at the onset of clinical symptoms and in subsequent examinations. It is necessary to ensure the proper differential diagnosis with other diseases as the MS clinical debut can often be vague; while in control studies the aim is to assess the lesions evolution and correlate with the clinical aspect or with any residual neurological deficits and to evaluate the therapy results. The morphological data delivered by MR images are particularly important in experimental studies that evaluate the new drugs effectiveness[1,12,13].

For all these reasons it is extremely important to use an examination technique that identifies the maximum number of lesions with the highest resolution.

Fluid attenuated inversion recovery sequence is considered to be the best technique for cortical and

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Progress in Neuroscience 2020; 5 (3-4): 37-45. *ISSN: 2240-5127*

LIST OF ACRONYMS AND ABBREVIATIONS: **2D** = Two-dimensional; **3D** = Three-dimensional; **CSF** = Cerebral Spinal Fluid; **CR** = Contrast Resolution; **DIR** = Double Inversion Recovery; **FLAIR** = Fluid Attenuated Inversion Recovery; **FOV** = Field Of View; **FSE** = Fast Spin Echo; **IR** = Inversion Recovery; **MPR** = Multi Planar Reformatting; **MR** = Magnetic Resonance; **MS** = Multiple Sclerosis; **PD** = Proton Density; **ROI** = Region Of Interest; S_B = Signal Background; S_I = Signal Intensity; **TE** = Time to Echo; **TR** = Time of Repetition; **TSE** = Turbo Spin-Echo.

periventricular MS lesions evaluation because signal hyperintensity of cerebral spinal fluid is saturated. The FLAIR sequences adoption enabled to assess that in previous years the number of cortical lesions truly presents in MS patients had been underestimated[8,10].
3D FLAIR sequences have recently been introduced into clinical procedures and they enable to obtain quick high contrast-resolution images and ultra-thin slices in all spatial planes[15].
Lately the use of MR unit with the 3 Tesla static magnetic field is spreading even in the hospital setting for clinical use and not only in research centers; as a matter of fact the diagnostic sensitivity and specificity of these equipments in different neurological applications are still in a developmental phase.
Aim. The aim of our work was to carry out a 3 Tesla MR comparative study among different T2-weighted sequences in patients with certainly established multiple sclerosis, in order to assess the best one to obtain a faithful evaluation of brain lesions number, location and morphological aspect.

□ MATERIALS AND METHODS

In the first part of the study 5 healthy volunteers (3 females and 2 males, aged between 25 and 43 years) without neurological symptoms and with no history of neurological diseases were examined, using the 4 sequences of a protocol in order to evaluate the images characteristics especially with regard to the assessment of any artefacts.
Subsequently a prospective study, including 40 patients with clinically definite MS, was performed (24 patients had a relapsing-remitting course of MS, 13 a secondary progressive one and finally 2 patients were affected of primary progressive type of MS); 24 patients were females and 16 males, aged between 22 and 59 years, average age 44.3 years.
Informed consent was obtained for each patient in each examination.
The study was performed according to the World Medical Association Declaration of Helsinki.
Since the study was performed using sequences perfectly compatible with a clinical protocol for the MS without any harm to patients, no ethics board was needed.
The studies were carried out from March 14th 2012 to November 26th 2012, all of them with a 3 Tesla MR Unit (*Magnetom Verio, Siemens*), with 45 mT/m gradients, 200 mT/m/s slew rate, phased array volume coil.
The following sequences were included in the study protocol:
- axial IR fast FLAIR T1-weighted sequence: (TR 2400 ms, TE 9 ms, TI 1001 ms), FOV 230 mm, matrix 230 x 320, slice thickness 4 mm, acquisition time 3:50 minutes;
- axial TSE T2- weighted and PD sequence (TR 2110 ms, TE 11 and 95 ms), FOV 230 mm, matrix 252 x 448, slice thickness 4 mm, acquisition time 3 minutes;
- axial IR (fast FLAIR) T2-weighted sequence (TR 9000 ms, TE 100 ms, TI 2499 ms), FOV 230 mm, matrix 256 x 256, slice thickness 4 mm, acquisition time 3:20 minutes;
- sagittal IR (fast FLAIR) 3D T2-weighted sequence (TR 5000 ms, TE 395 ms, TI 1800 ms), FOV 230 mm, matrix 256 x 256, slice thickness 1 mm, acquisition time 5:50 minutes. In post processing axial and coronal 1 mm MPR images were reconstructed;
- axial and coronal fast FLAIR T1-weighted sequences after contrast media administration (0.2 mmol/kg) were also acquired in all cases.

The total acquisition time of the entire protocol was 15 minutes and 20 seconds.
Two expert neuroradiologists carried out the image evaluation on a workstation (*Syngo VB17, Siemens*).
The inter-observer variability was assessed by calculating "inter-observer agreement index".
The comparative evaluation was assessed among the following sequences:
1. PD;
2. TSE T2-weighted;
3. 2D Fast FLAIR T2-weighted;
4. 3D Fast FLAIR T2-weighted, including also the axial, sagittal and coronal MPR images.

First of all the artefacts impact in all of the sequences was evaluated.
Then the CR of the lesions and the normal tissue

surrounding them, was calculated with the following formula: $(S_I-S_B)/S_B$, where: S_I was the lesion signal intensity value and S_B is the signal intensity value of the perilesional tissue.

For each patient at least three measurements were carried out, using ROI consisting of at least 24 pixels, all of them placed in the same position for each sequence, using an automatic system.

Then the arithmetic average of the CR values of all the ROIs in all patients for each sequence were calculated and a statistical analysis, using t-test, of the difference among the 3D FLAIR sequences average CR value and the other three was carried out. Statistically significant difference was achieved if $p < 0.05$.

Finally the lesions number, shown with the 4 sequences, was evaluated in order to determine which of these sequences was able to identify the greatest number of MS plaques.

Firstly the total lesions number visualized with each sequence was evaluated. Then 6 subgroups according to the lesions site (cortical, subcortical, periventricular, basal ganglia, centrum semiovale white matter and posterior cranial fossa, i.e. cerebellum and brain stem) were extrapolated from the total. Finally other 4 subgroups, based on the size of the lesions: small (3-5 mm), medium (6-10 mm), large (> 10 mm) and confluent, were considered.

□ RESULTS

Healthy volunteers had well tolerated the MR exam without artefacts in PD, TSE T2-weighted and 2D FLAIR sequences. Instead in 3D FLAIR images posterior cranial fossa artefacts have been identified in 1/5 cases. These artefacts appeared as patchy hyperintense lines.

In PD, TSE T2-weighted and 2D FLAIR sequences artefacts have not been detected in all 40 patients; instead, in 6 out of 40 patients, in the 3D FLAIR sequences posterior cranial fossa artefacts (the same as those seen in healthy volunteers) were present.

The "inter-observer agreement index" was 97.6 for PD images, 97.5 for TSE T2-weighted, 98.0 for 2D Fast FLAIR T2-weighted and 97.4 for 3D Fast FLAIR T2-weighted, while as regards the lesion number evaluation the "inter-observer agreement index" was 97.5 for PD images, 97.3 for TSE T2-weighted, 98.1 for 2D Fast FLAIR T2-weighted and 97.6 for 3D Fast FLAIR T2-weighted.

As concerns contrast resolution, in PD sequences quite low values were showed, instead the other three sequences (TSE T2-weighted, 2D and 3D FLAIR) values were very close to each another and considerably higher than the first one (Figure 1).

The statistical analysis showed a statistically significant difference ($p < 0.005$) only between the contrast resolution means of the 3D FLAIR and PD sequences. Contrarily a statistically significant difference ($p > 0.005$) was not proved between 3D FLAIR and TSE T2-weighted sequences and between 3D FLAIR and 2D FLAIR ones (Figure 2).

Finally regarding the overall lesions number displayed with the 4 sequences superiority of 3D FLAIR images over the other ones was observed, especially towards PD and TSE T2-weighted sequences (Figure 3).

Even regarding the lesions number evaluation, related to the site, 3D FLAIR sequences were more diagnostic than the others (Figure 4). In fact the PD sequences exhibit good diagnostic ability for periventricular and centrum semiovale lesions, while they are less diagnostic for cortical and basal ganglia lesions. TSE T2-weighted sequences showed similar results (good diagnostic ability in periventricular and centrum semiovale lesions and less reliability for cortical and basal ganglia lesions) but with better quantitative values compared to PD. Instead regarding 2D FLAIR sequences the findings were nearly always excellent, except for basal ganglia lesions, even better compared with TSE T2-weighted sequences (Figure 4).

Instead as for the number evaluation related to the lesions size, the 3D FLAIR advantage only concerning small lesions was proved, while regarding the medium, large and confluent lesions visualization, overlapped results among the 4 sequences were showed (Figure 5). The prevalence of 3D FLAIR images for little lesions visualization was clear, especially compared with PD and TSE T2-weighted sequences (Figure 5).

According to these results 3D FLAIR images were superior or equivalent to the other sequences as regards the lesions detected; however, this advantage was more clearly seen in certain types of lesions rather than in others.

□ DISCUSSION

Recently the interest for the cortical gray matter lesions has increased considerably according to a

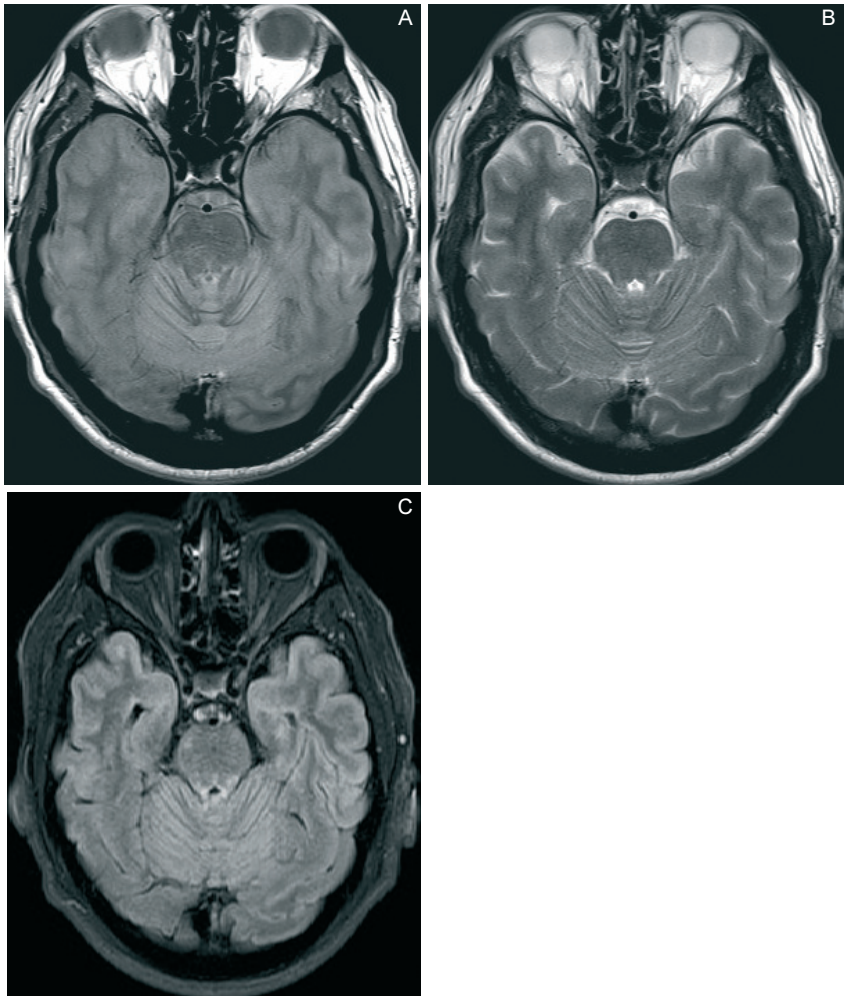

Figure 1. A-D. Artefact. Proton density (A), FSE T2-weighted (B), 2D FLAIR (C) and 3D FLAIR (D) images. Only in 3D FLAIR image the artefact was evident (*arrow*), while the others sequences were free of artefacts.

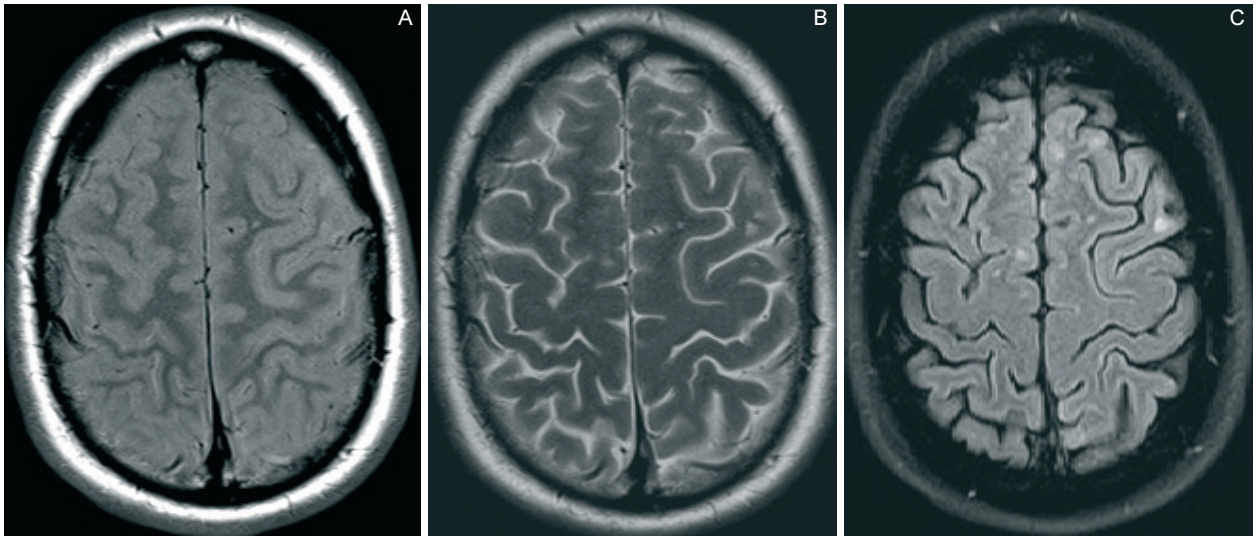

Figure 2. A-D. Cortical MS lesion. Proton density (A), FSE T2-weighted (B), 2D FLAIR (C) and 3D FLAIR (D) images. The cortical lesion, evidenced with the *arrow*, is only visible in the 3D FLAIR sequence (D), while in the other sequences can not be displayed.

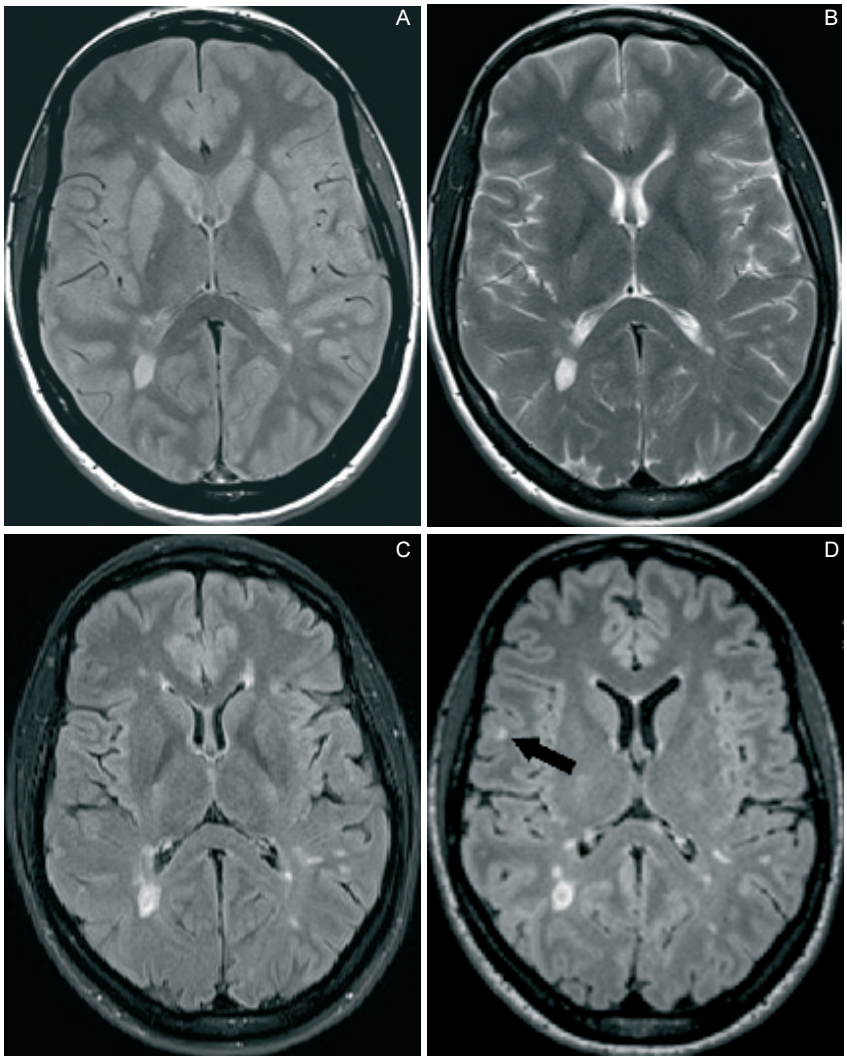

Figure 3. A-D. Subcortical MS lesion. Proton density (A), FSE T2-weighted (B), 2D FLAIR (C) and 3D FLAIR (D) images. Also the subcortical lesion, evidenced with the *arrow*, is only visible in the 3D FLAIR sequence (D), while, even in this case, in the other sequences can not be displayed.

better understanding of MS pathophysiology and evolution and a precise MR visualization of the cortex lesions has become significant[3,9,16].

FLAIR and DIR are the sequences that permit to display better cortical MS lesions, because they are the ones with the best contrast resolution between the lesions and surrounding tissues[8,10,19]. In a recent study, however, it has been shown that the DIR sequences are often inaccurate with regard to the correct identification of cortical lesions[18]. In addition to this, as thin as possible scans must be used because cortical MS lesions are often small. FLAIR sequences, unlike the DIR, can also be acquired with 3D technique, with the advantage to get then ultrathin multiplanar scans (even less than 1 mm.) with high CR; for this reason it is reasonable to assume that this type of sequence is very effective for the detection of gray matter lesions, as well as for the identification of all other lesions located in other brain areas as already well known from previous studies in literature[4,17].

Moreover, since the static magnetic field strength is directly proportional to the signal intensity, generated with a sequence, it is logical to assume that diagnostic gain, using a 3 Tesla MR equipment, can be obtained with lower magnetic fields units, for multiple sclerosis patients' brain lesions evaluation[21].

Furthermore some safety guidelines recommend not to expose the patient to 3 Tesla magnetic field for more than an hour at once. For this reason it is necessary to optimize MR imaging of multiple sclerosis patients in order to obtain relevant information to assess the disease status and its possible evolution in the shortest time possible[14].

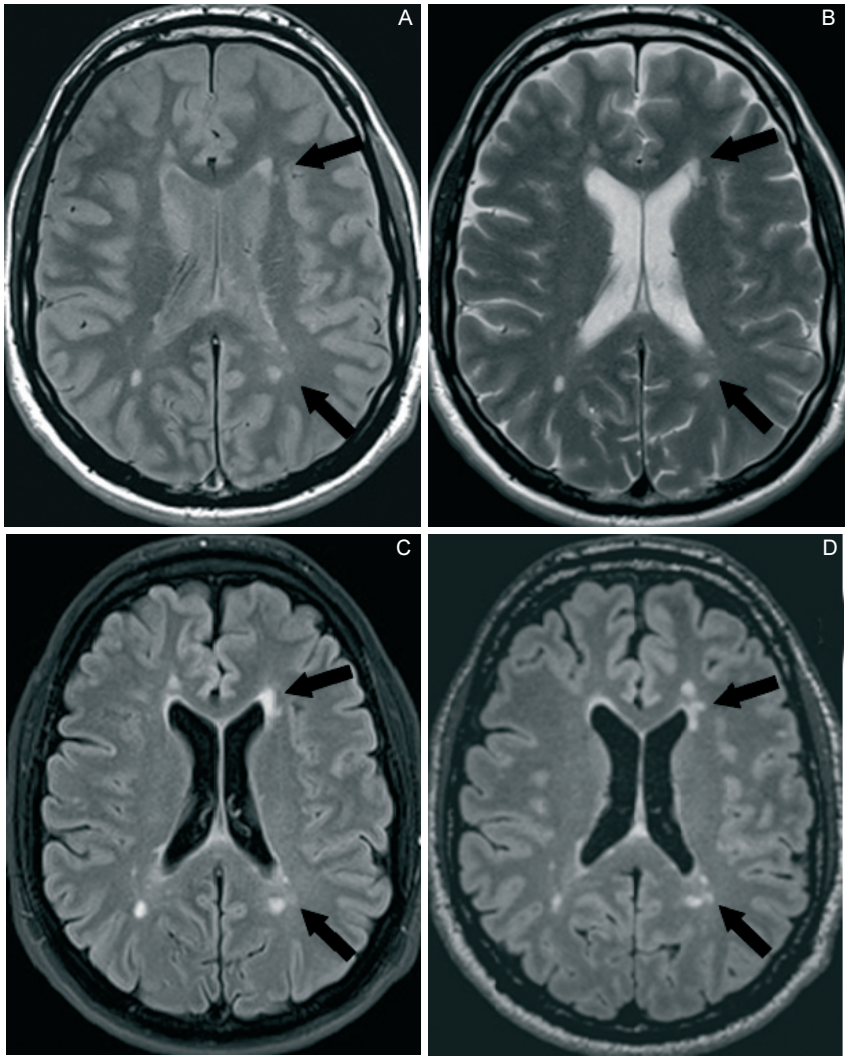

Figure 4. A-D. Periventricular MS lesions. Proton density (A), FSE T2-weighted (B), 2D FLAIR (C) and 3D FLAIR (D) images. Only the thin slice 3D FLAIR image (D) displays optimally periventricular lesions (*arrows*).

Although in the last years many articles were published regarding the use of advanced MRI techniques (for example, spectroscopy and diffusion imaging) the imaging protocols for the study of multiple sclerosis, for the disease diagnosis and for the anatomical evaluation over the time are still based on morphological MRI sequences[1]. FLAIR is the best MRI sequence to define the number, morphology, and lesion load in multiple sclerosis plaques. In fact, due to the CSF signal saturation of both cisters and cerebral ventricles, the FLAIR sequence, is highly sensitive to the detection of brain lesions especially in the periventricular and cortical districts(10). Furthermore, in order to avoid partial volume artefacts and in order to properly define the lesions morphology, which often are contiguous to each other, it is necessary to use images with layer thickness as thin as possible[4,17]. The conventional 2D sequences however have a limit, the signal / noise ratio decreases with the use of thin-layer sequences, so ultra-thin scans cannot be used. On the contrary, the 3D sequences do not have this limitation because the signal is generated from all the acquired volume and the final images are obtained in postprocessing. That's why with the latter technique can be obtained with ultra-thin scans (even a millimetre) without penalizing the signal to noise ratio[15]. Moreover, the 3D sequences allow to obtain multi-planar reconstructions also on coronal and sagittal planes only in postprocessing, with a single data acquisition. For this reason the FLAIR sequences (characterized by high contrast resolution) acquired with 3D technique (characterized by high spatial resolution) might represent the gold standard to evaluate the brain in multiple sclerosis patients, both at

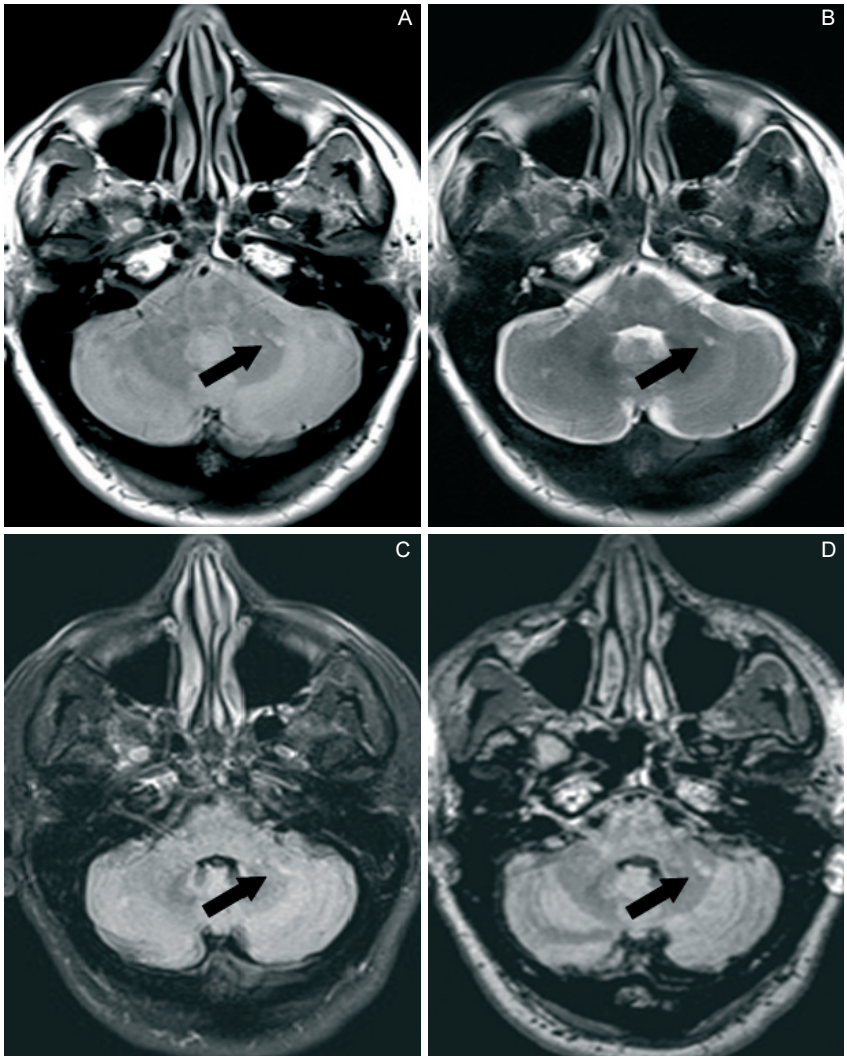

Figure 5. A-D. Cerebellar MS lesions. Proton density (A), FSE T2-weighted (B), 2D FLAIR (C) and 3D FLAIR (D) images. Also in this case only the thin slice 3D FLAIR image (D) displays optimally the lesions (*arrows*).

the time of first diagnosis and in controls over the time. Finally, the third element of our study protocol creates a framework for considering the technique tested by us as optimal for the morphological study of multiple sclerosis using a 3 Tesla MR equipment. It is known that the static magnetic field intensity, in a MR unit, is directly proportional to the signal intensity generated by any sequence[21]. For this reason the use of high field equipment improves the sensitivity and diagnostic specificity in multiple sclerosis and now considered an essential element for the study of the disease, as demonstrated by numerous studies in the literature[7,11,21-23].

So there are all theoretical assumptions to account for the 3D FLAIR sequences, acquired with 3 Tesla equipment, as ideal for morphological evaluation of multiple sclerosis plaques.

Our protocol (lasting 15 minutes) was well tolerated by all patients with a low incidence of voluntary motion artefacts. A check of the 3D FLAIR sequence characteristics was carried out through the comparison with the standard sequences that currently are used for the MS' study.

Our study results have shown that 3D FLAIR sequences are superior to the others to identify MS plaques in all anatomical areas of the brain but especially in cortical areas; furthermore they have been proven to be particularly useful for the detection of small lesions.

The main 3D sequences advantage, is therefore the possibility to obtain, with a single acquisition, high resolution brain images in all planes of space. Also in the longitudinal evaluation of patients the comparison among examinations, carried out at different times, is

easier. In fact, the final images obtained with the 3D sequences can be aligned through post-processing techniques, with a best tolerance to possible scanning planes positioning errors[20].
The possibility to obtain images of studies carried out at different times, with the same spatial orientation and located in the same cranial-caudal position, allows the comparison among them by means of overlapping and digital subtraction techniques that allow to visualize immediately any differences in lesion load in the same patient[20].
The 3D sequences, compared to 2D acquisitions, can also have some disadvantages. The first is the need for a greater space for data archiving. In addition, the larger number of image processing, takes a longer time reporting than 2D sequences. Finally, the 3D sequence acquisition time is a little longer than a 2D one.
It would be in any case easy to overcome disadvantages that do not limit the use of these sequences, if they were accepted as the gold standard for MS.
The available studies in literature agree that the FLAIR sequences (both 2D and 3D) are superior to TSE T2-weighted for the assessment of cortical lesions, while in some of them it is highlighted a limitation with regard to the evaluation of subcortical lesions[2,5,6,10,15]. In fact, the 3D FLAIR sequences are characterized by a lower contrast resolution between gray and white matter compared to the 2D TSE T2w and this may prevent a proper display of the lesions[2,5,6,10,15]. However, in our study we showed that even in the subcortical, 3D FLAIR sequences are superior to others.
Finally an important drawback, related to the use of 3D FLAIR sequences, that we identified in our study is the occasional presence of artefacts in the posterior fossa. However, despite this limitation, also for the evaluation of the posterior cranial fossa lesions, 3D FLAIR sequences have proved better than conventional.

□ CONCLUSIONS

Based on our study results, the 3D FLAIR sequence MRI at 3 Tesla allows to display a greater number of MS lesions compared with conventional sequences. There is no difference among the various brain anatomical areas, as in all areas the superiority of the 3D FLAIR sequences has been demonstrated. This sequence is also characterized by an acquisition time fully tolerated by all patients. It therefore represents an essential diagnostic tool for the MS diagnosis in the first MR examination and is also the optimal sequence for disease temporal evolution evaluation of the brain.

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Disclosure. *The Authors declare that aren't in receipt of any founding, and they aren't contractually or otherwise obliged to, or in receipt of personal or institutional financing from firms whose products are mentioned in the text.*