



Research article

Diagnostic value of 3DFLAIR in clinical practice for the detection of infratentorial lesions in multiple sclerosis in regard to dual echo T2 sequences



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ABSTRACT

Background and purpose: The aim of this prospective study is to investigate and evaluate in clinical practice the diagnostic impact of 3DFLAIR in regards to 2DT2/PD in terms of infratentorial lesions detection in multiple sclerosis (MS).

Material and methods: 164 MS patients from the OFSEP database were reviewed retrospectively. MR examinations were performed on 1.5T or 3T systems from four different centers. Infratentorial lesions were counted and allocated to different regions of the posterior fossa by three raters independently (junior resident, resident with an expertise in neuroradiology, and senior neuro-radiologist) on the 3DFLAIR and 2DT2/PD. Both sequences do not have the same spatial resolution but reflect what is recommended by most of the consensus and done in clinical practice.

Results: With an overall number of 528 for Rater-1 and 798 for Rater-2 infratentorial lesions, 3DFLAIR had a significantly higher number of lesions detected than 2DT2/PD (303 for Rater-1 and 370 for Rater-2). The prevalence of trigeminal lesions detected by using 3DFLAIR was also significantly higher than 2DT2/PD. ROC analysis showed 3DFLAIR to be more specific and sensitive than 2DT2/PD. An overall difference between all three Raters has been observed. The more the Rater is experienced the more lesions he detects.

Conclusion: Along with the radiologist ability to detect lesions based on his level of experience, the OFSEP optimized 3DFLAIR can significantly improve infratentorial lesion detection in MS compared to 2DT2/PD. This is important in MS follow-up that takes into account new lesions number to adapt patients' treatment.

Abbreviations: AUC, area under the curve; DIR, double inversion recovery; OFSEP, French Observatory of Multiple Sclerosis; PD, proton density; PSIR, phase-sensitive inversion recovery; ROC, receiver operating characteristic

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1. Introduction

MS is considered as an autoimmune neuro-inflammatory demyelinating disease of the CNS. It is one of the most common causes of disability in young adults. MS lesions sometimes called scars, are produced when myelin sheets are attacked by the immune system. Depending on the lesions' location and type, normal functioning is inhibited and MS symptoms and relapses are manifested. Even if in some cases scarring heals and normal functioning is restored, over time the continual scarring can cause permanent damage to motor and sensory functions [1]. MRI has become an essential tool for the establishment of a definite MS diagnosis. The identification of typical lesions on MRI remains a challenge. Indeed, lesions localization, shape and size, provide the best view yet of tissue injury, lesion activity, and disease accumulation. Moreover, MS lesion follow-up serves as a monitoring tool for their dissemination in space and time. Studies have in fact shown that patients selected with the aid of MRI for immunomodulatory-therapy benefit more from this treatment [2]. Thus, efficient tools for high sensitivity in lesion detection are necessary using MRI.

The French Observatory of MultipleSclerosis (OFSEP) aims to provide a major epidemiological tool for the scientific community in France and abroad. This tool will help answer large number of questions concerning MS causes and mechanisms, prognostic factors of disease progression, etc. The acquisition of the standardized OFSEP MRI protocol in MS [3] still vary between centers, reflecting local availability of equipment (magnet field, head coils...). Indeed, constraints related to acquisition time in a national cohort with clinical care conditions will depend on the sequences parameters, such as acceleration factor, parallel imaging or sequences type selection.

MS lesions manifest as high signal foci against the low signal background of WM on T2WI. Although important and informative, T2-hyperintensities are indistinguishable from adjacent CSF at periventricular levels. Lesions contrast can be improved with proton density (PD) because of its lower CSF signal. Nonetheless, this problem is much easily overcome with FLAIR imaging which suppresses CSF signal, while maintaining good contrast between lesions and WM [4]. For these properties, FLAIR became a standard sequence for MS imaging.

Despite this advantage, the only drawback of 2DFLAIR is its inferior lesion detection quality in the posterior fossa and spinal cord where 2DT2/PD are preferred. More recently, 3DFLAIR has become available and allowed high spatial resolution with good SNR as well as multi-planar reconstruction that improves scanning efficiency, spatial resolution, and generates a large isotropic image volume in feasible time. Hence increasing lesion detection quality in the posterior fossa and spinal cord.

Infratentorial lesions have been considered as clinically eloquent sites that may have major impact on clinical disability in MS [5]. Indeed, they might be related to long-term prognosis for MS patients and thus help identify high risk patients for earlier occurrence of clinically relevant disability [6]. Better outcomes for infratentorial lesion detection were obtained when routinely applying dual T2/PD [7]. However, the application of 3DFLAIR significantly increased detection quality and efficiency of whole-brain lesions [8]. Thus, acquiring both sequences might be redundant and time consuming in routine exams [3,8]. The aim of this prospective study is therefore to investigate and evaluate the diagnostic impact of 3DFLAIR compared to 2DT2/PD in terms of infratentorial lesions load.

2. Materials and methods

2.1. Patients

Through the systematic longitudinal follow-up of patients with MS and combination of clinical data with biological samples and neuro-images, the OFSEP aims to foster clinical, basic and translational research in MS. OFSEP's neuro-imaging working-package have

implemented an optimal and standardized MRI protocol [3] for MS patients follow-up. Acquired MR data are anonymized and saved in a centralized database along with the patients anonymized clinical records and biological samples. For the purposes of this study, 164 patients with clinically definite MS according to the McDonald's criteria [9] (108 women, mean age 41.5 ± 11.0 years; 56 men, mean age 41.0 ± 10.8 years) were selected from the OFSEP imaging database. These patients were followed at four different neuroradiology centers in France: Center-1 (21 patients), Center-2 (58 patients), Center-3 (2 patients) and Center-4 (83 patients). All patients signed an informed consent form approved by the national commission on informatics and liberty (CNIL:DR-2015-212).

2.2. Data acquisition

The OFSEP MRI brain protocol was implemented, tested and validated on seven MRI machines in four French centers. It comprised recommended conventional MR sequences (3DT1WI with and without gadolinium injection, axial DWI, axial dual-TSE 2DT2/PD or 3DT2, and 3DFLAIR (or 2DFLAIR if 3D is not available)) and some optional sequences (DTI and 2D gradient echo T2 for a first diagnosis). In this study, only patients that have both 2DT2/PD and 3DFLAIR sequences acquired were included (164 MS patients; 139 at 1.5T and 25 at 3T). Sequences parameters for each MRI and center are detailed in Supplementary Table 1. Within the framework of MRI recommendations, centers had a certain freedom of choice of the MR sequences parameters including the possibility to use multichannel coils and parallel imaging. By doing so, MRI data acquired within the OFSEP framework could be performed routinely in clinical and private centers; it is therefore a national clinical cohort and not a research study.

2.3. Image analysis

The selected anonymized MR data were first downloaded from the OFSEP database, after the OFSEP scientific committee approval. Quality of images (artifacts and image homogeneity) was assessed for each sequence. MITK-3M3 (Mint Medical, Germany) was used for analysis and visualization of radiological data. Image analysis was independently performed by three raters in consensus (Rater-1, junior resident with 3-years of experience; Rater-2, resident with 5-years of experience; and Rater-3, senior neuro-radiologist with 20-years of experience). Rater-3 performed the analysis on 30 patients whom lesion count differences between the first and the second raters were the highest. Raters were blinded to patients' number and never checked both sequences one after the other. 3DFLAIR images were analyzed in the three orthogonal planes while 2DT2/PD images were only analyzed in axial slices. For each subject and for each sequence, infratentorial lesions were counted based on their anatomical location: cerebral peduncle, tegmentum of midbrain, tectal plate, pons, floor of the 4 ventricle, superior, middle and inferior cerebellar peduncles, and cerebellum. Raters gave special and careful attention to lesions in the trigeminal nerves in both its intra-pontine and transisternal parts.

2.4. Statistical analysis

Statistical analysis was performed using the Data Analysis and Statistic Software (STATA, v9.2, stataCorp, Texas, USA). The matched-pairs Mann-Whitney test (two-sample Wilcoxon rank-sum) for non-parametrical data was first applied to compare infratentorial lesions' number in 2DT2/PD vs 3DFLAIR images in all previously mentioned anatomical regions for both Raters-1 and -2, and to test the difference between both sequences when separating patients' MRIs acquired at 1.5T and 3T. The same test was also used to compare lesions count between all three Raters for the 30 MS patients. The receiver operating characteristic (ROC) curve analysis was then applied to test the specificity and the sensibility of 2DT2/PD compared to 3DFLAIR. ROC

Table 1
Lesions number accounted for on 2DT2/PD and 3DFLAIR, in all ten anatomical locations.

Anatomical locations	Rater-1		Rater-2	
	2DT2/PD	3DFLAIR	2DT2/PD	3DFLAIR
Cerebral peduncle	23	31	28	45*
Tegmentum of midbrain	8	13	20	41*
Tecta plate	2	3	2	8
Trigeminal root	5	49***	7	66***
Pons	35	67**	68	151***
Floor of 4th ventricle	6	9	5	11
Superior cerebellar peduncle	14	45***	16	40***
Middle cerebellar peduncle	40	69	30	66***
Inferior cerebellar peduncle	11	19	30	50*
Cerebellum	159	223	164	320***
Total	303	528**	370	798**

* p < 0.05.
** p < 0.01.
*** p < 0.001.

analysis was performed on the total number lesions regardless of their anatomical location. Area under the curve (AUC) was also reported. A p-value < 0.05 was considered significant.

3. Results

Lesions count in the different anatomical locations for Rater-1 and 2 is reported in Table 1. Overall, the total number of lesions accounted for on 3DFLAIR (N = 528 (Rater-1) & 798 (Rater-2)) was significantly higher than on 2DT2/PD (N = 303 (Rater-1) & 370 (Rater-2)). At the anatomical locations level, 3DFLAIR lesions count was always higher than 2DT2/PD, but was only significant in the trigeminal root (p < 0.001), pons (p < 0.01), and superior cerebellar peduncle (p < 0.001) for Rater-1, and in the cerebral peduncles (p < 0.05), tegmentum of midbrain (p < 0.05), trigeminal root (p < 0.001), pons (p < 0.001), superior (p < 0.001), middle (p < 0.001) and inferior (p < 0.05) cerebellar peduncles and cerebellum (p < 0.001) for Rater-2.

In both 1.5T and 3T groups, 3DFLAIR also showed higher lesion count than 2DT2/PD (1.5T (139 patients): 2DT2/PD = 246 for Rater-1 & 295 for Rater-2; 3DFLAIR = 456 for Rater-1 & 692 for Rater-2; 3T (25 patients): 2DT2/PD = 57 for Rater-1 & 75 for Rater-2; 3DFLAIR = 72 for Rater-1 & 106 for Rater-2). Only 2DT2/PD lesion count differences were significant for both Raters (p < 0.001).

Lesions count performed by Rater-3 was significantly higher than both Raters-1 and -2 (Table 2). No significant differences were observed when comparing Rater-1 lesion count to Rater-2 for the 30 MS patients.

ROC analysis was performed to test the specificity and the sensitivity of 3DFLAIR compared to 2DT2/PD in detecting infratentorial lesions. In all three raters AUC illustrated in Fig. 1 (AUC_{Rater-1} = 0.641; AUC_{Rater-2} = 0.794; AUC_{Rater-3} = 0.938) suggested that 3DFLAIR is more sensitive and more specific to detect lesions than 2DT2/PD.

4. Discussion

As MR imaging in MS is evolving, several consensus guidelines recommended the standardization of MRI protocols based on evidence of optimal practice [7,10–15]. 3DFLAIR is in many recommendations but is not requested as a core sequence [16]. Taking time into account in clinical practice, 2DFLAIR is privileged over 3DFLAIR. However, 2DFLAIR is always associated with 2DT2/PD because of its low lesion detection rate [3,12]. The aim of this study was therefore to investigate and evaluate in clinical routine, on both 1.5T and 3T systems, the diagnostic value of 3DFLAIR compared to 2DT2/PD in terms of infratentorial lesion detection.

In the line of this study, 3DFLAIR was proved to be more sensitive in

Table 2
Lesions number accounted for on 2DT2/PD and 3DFLAIR of 30 MS patients performed by the three raters.

Anatomical locations	2DT2/PD			3DFLAIR		
	Rater-1	Rater-2	Rater-3	Rater-1	Rater-2	Rater-3
	Cerebral peduncle	8***	9***	33	9***	16***
Tegmentum of midbrain	2***	10***	56	4***	17***	70
Tecta plate	0	2	2	1**	3	9
Trigeminal root	1	2	2	13**	18*	32
Pons	9***	15***	83	20***	63***	183
Floor of 4th ventricle	2***	3***	31	4***	6***	45
Superior cerebellar peduncle	5	5	6	11*	13*	25
Middle cerebellar peduncle	12***	10***	56	19***	21***	93
Inferior cerebellar peduncle	2*	7	10	6*	16	18
Cerebellum	54*	60*	116	79*	120	168
Total	95***	123***	395	166***	293***	692

p-values when comparing Raters-1 and -2 lesion count to Rater-3: *p < 0.05; **p < 0.01; ***p < 0.001. No significant differences were reported between Rater-1 and -2.

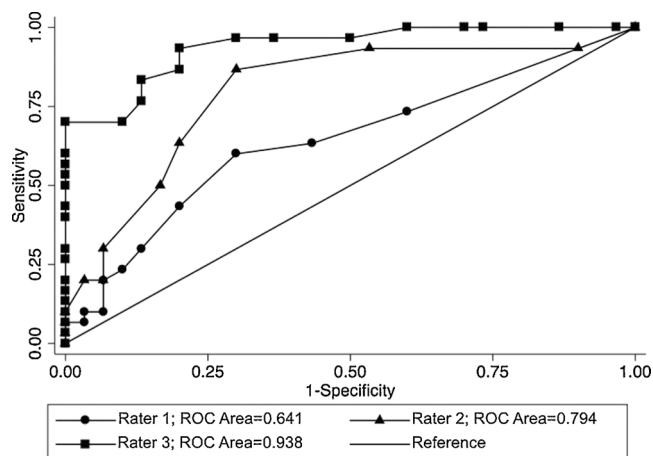


Fig. 1. ROC analysis performed by three raters for the total number of lesions suggests that 3DFLAIR is more sensitive and more specific to lesions detection than 2DT2/PD. (Rater-1: resident, Rater-2: resident with an expertise in neuroradiology, and Rater-3: expert).

detecting infratentorial lesions than 2DT2/PD. Raters-1 and -2 found in average 32% more lesions on 3DFLAIR. This is most probably due to 3DFLAIR higher spatial resolution that allowed a better detection of smaller lesions (Fig. 2). Many lesions which appear to be one or confluent lesions on 2DT2/PD, were found to be several distinct lesions on 3DFLAIR. The absence of CSF and blood flow artifacts in 3DFLAIR, in addition to the acquisition of thin slices without intersectional gaps, improves visualization of infratentorial lesions [17]. Indeed, by decreasing slice thickness (1 mm for 3DFLAIR vs 3 mm for 2DT2/PD), and increasing spatial resolution (less partial volume effects), the sensitivity of lesion detection would increase. To this end, 2DT2/PD has been considered optional due to the high sensitivity of 3DFLAIR [14].

To our knowledge, no other study has attempted to check 3DFLAIR superiority in terms of detecting trigeminal lesions. Previous studies have compared 3D to 2DFLAIR [18] and showed 3DFLAIR to have higher sensitivity for lesions detection. Indeed, even if some infratentorial regions were not significantly different, 3DFLAIR always had the higher lesions count. When compared to previous findings, our study showed a higher trigeminal lesions prevalence (33% vs 23%) (Fig. 2) [19], which could be explained by the relatively larger sample size.

Based on the ROC analysis (Fig. 1), 3DFLAIR was always more

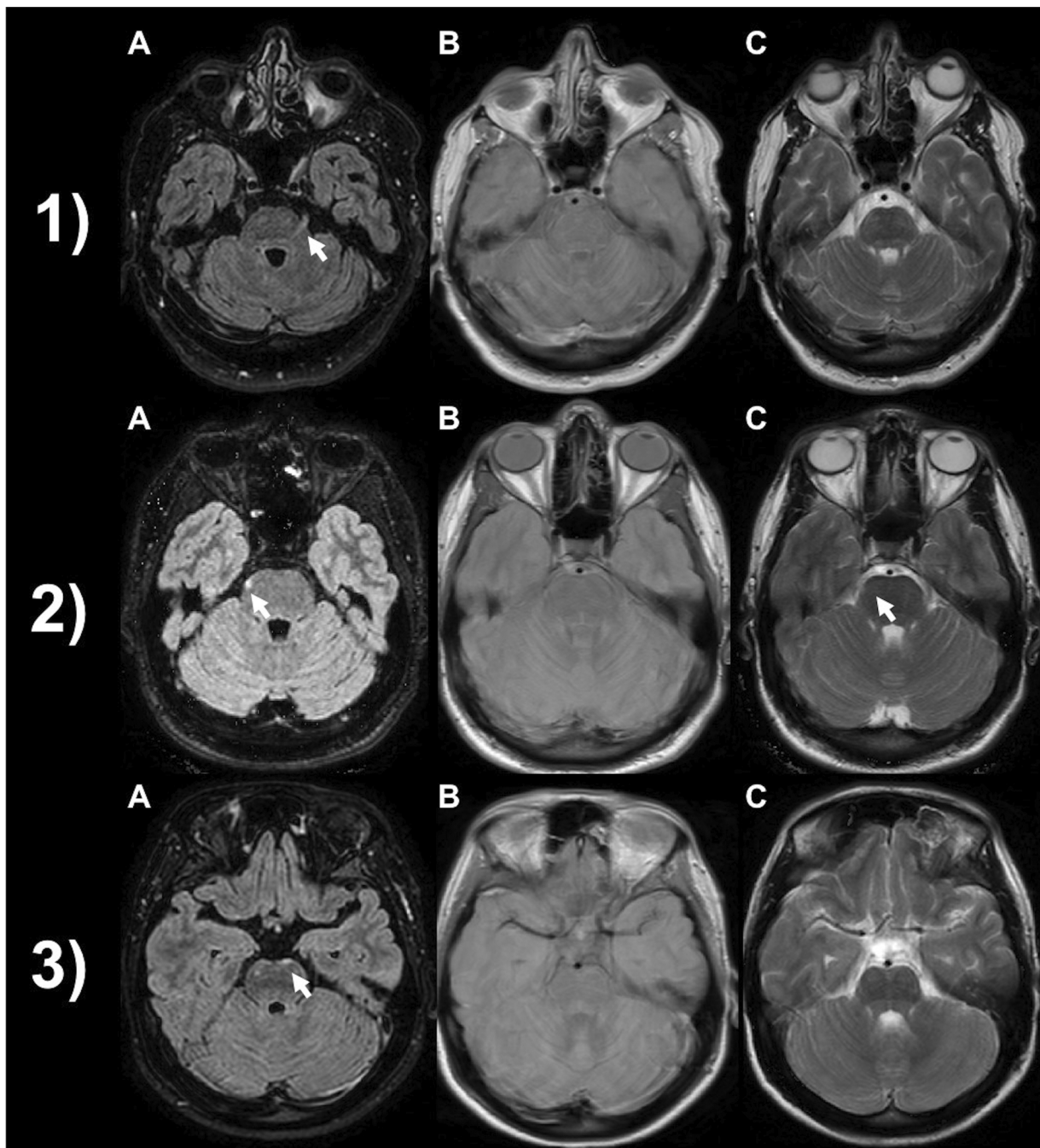


Fig. 2. Axial slices of (A) 3DFLAIR, (B) PD, and T2WI (C). 1) Trigeminal root entry zone and tract lesion (marked with arrow on A) is exclusively visible on 3DFLAIR; 2) Lateral pontine lesion clearly distinguished on the 3DFLAIR image than on T2WI image, and undetected on the PD image; 3) Curvilinear lesion of pons visible on the 3DFLAIR but not on the 2DT2/PD.

specific and more sensitive to lesion detection than 2DT2/PD. Interestingly, Rater-1 had the lowest specificity/sensitivity to detect lesions while Rater-3 had the highest values (Table 2). Hence, the more the rater is experienced the more lesions he could detect. This point is even more important for patients' follow-up that takes into account new lesions number to adapt patients' treatment [20]. Indeed, decisions to put patients under a certain therapy are based on the radiological occurrence of a new lesion [21]. For some regions such as the trigeminal root, lesion count was similar between raters while others such as the floor of the 4 ventricle and the tegmentum of midbrain, lesion count differed significantly. The sensibility to detect lesions therefore depends on the radiologist degree of expertise and neuroanatomy knowledge, which puts into perspective the results interpretation on which therapeutic decision are based on. To this end, radiologists need to converse with

the technical aspects of their equipment and that sub-specialists involve themselves where possible in the development and implementation of new innovations. Moreover, they must act as clinicians and understand the clinical features, natural history and treatments of the diseases that they are requested to investigate [22].

Gramsch et al. [8] previously demonstrated that 3DFLAIR is more sensitive in the lesion detection than PD/T2. However, the results of their study are somewhat limited by the relatively small number of patients (20 patients vs 164 patients recruited in our study). Additionally, their paper studied the infratentorial lesion load as a whole instead of separating them into subdivisions.

The higher sensitivity of 3DFLAIR to detect lesions raises some questions. Detectable lesions could be the result of an inflammatory demyelinating and neurodegenerative MS attack, or it could be related

to the patients age. Indeed, WM lesions are commonly seen on MR images of elderly people [23]. However, this is not the case in our study since all patients were relatively young (41.0 ± 11.0 years). The use of two different field strengths, 1.5T and 3T, could be seen as a limitation in this study. However, since lesion load comparison was performed intra-individually using a paired *t*-test, the field strengths are not crucial for the comparison. When analyzing both fields separately, 3DFLAIR was also more sensitive to detect infratentorial lesions, more specifically at the trigeminal root region. However, these results were only significant in the 1.5T group due to the small sample of the 3T group ($N = 25$). Another limitation that could intervene is the heterogeneity of the sequences parameters that could affect the quality of 3DFLAIR. By suppressing the CSF signal, and by providing a better spatial resolution, FLAIR images WM lesions detection is improved. Thus, by applying the common OFSEP MRI protocol, specifically designed for MS and validated by the three main constructors, 3DFLAIR quality is normalized in all patients. However, since OFSEP is mostly a national clinical cohort and not a research study, centers' radiologists were left a certain freedom of choice of the sequences parameters. Indeed, this study is based on the comparison of sequences with different slice thickness and different acquisition parameters (TE, TR, ...). However, since the aim of this study was to evaluate the diagnostic value of 3DLAIR compared to 2DT2/PD, the sequences' parameters of the protocol had to be compared as a whole. Nonetheless, the clinical importance of precise lesion detection in the infratentorial regions, added to the significant superiority of 3DFLAIR compared to 2DT2/PD, are sufficient arguments for the replacement of the conventional sequence by the new 3DFLAIR in MS MRI protocols.

Future studies may try to replace 3DFLAIR with even more sensitive and specific sequences such as double inversion recovery (DIR), phase-sensitive inversion recovery (PSIR), or synthetic MR imaging. The latter enables images production with almost any contrast-weighting, including DIR and PSIR, by virtually adjusting the TR, TE, and TI after quantifying T1 and T2 relaxation times and the PD [24]. A recent study showed that synthetic MR imaging detected more intra-cortical and mixed WM-GM lesions than conventional MR imaging [25]. DIR however, provides two different inversion pulses, that suppress the CSF signal and simultaneously show the synergism of T1 and T2, thus achieving a superior delineation between GM and WM [26]. Using DIR, studies have shown a higher sensitivity to detect lesions even in the infratentorial regions when compared to FLAIR and T2WI [27]. Future studies would have to verify these findings in infratentorial regions of MS patients, and study their feasibility in a clinical setting.

5. Conclusion

In conclusion, our study showed that optimized 3DFLAIR can significantly improve infratentorial MS lesion detection compared to 2DT2/PD, on both 1.5 and 3T systems. Also, the more the radiologist is specialized and experienced, the more his sensibility to detect lesions is optimized. This is important in MS follow-up that takes into account new lesions number to adapt patients' treatment.

Author declaration

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have

followed the regulations of our institutions concerning intellectual property.

We further confirm that any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

We understand that the Corresponding Author is the sole contact for the Editorial process (including Editorial Manager and direct communications with the office). He is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.ejrad.2018.03.017>.

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