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Update on brain MRI for the diagnosis and follow-up of MS patients

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Abstract

Over the past decades, MRI has become a major tool in the diagnosis and the follow-up of patients with multiple sclerosis (MS), especially for monitoring the effectiveness of therapy. The recent international recommendations issued for the standardization of neurological and radiological clinical practices converge on many points. In this setting, recommendations made by the "Observatoire Français de la Sclérose En Plaques", the French MS registry, can be distinguished by its interdisciplinary complementarity, its longevity, its size, and its positions in direct connection with the clinic. Hence, after suspicions of gadolinium deposition in the brain, with multiple warning from the American and European health authorities, a national consultation took place and resulted in limitation to useful injections. The precautionary principle prevailing, the patient receives a limited quantity of contrast product even if no clinically harmful manifestation has been detected to date. The result of this round table bringing together neurologists and neuroradiologists from specialized centers was published in the form of a recommendation in early 2020. The interest of this project also lies in the constant improvement of the management of patients with MS and the possibility of developing advanced techniques to assist the clinician.

The aim of this review is to explain to the neurologist, the interest of following this imaging protocol both in his/her clinical practice and in the possibilities that this opens up.

Introduction

Since the introduction of MRI in the early eighties, Magnetic Resonance Imaging has been used to identify, quantify, and follow patients with Multiple Sclerosis (MS). Rapidly, MRI has become a standard clinical exam in MS to help the diagnosis and follow the natural progression of the disease[1]. All recent recommendations include MRI measures to evaluate infra-clinical disease activity and provide a set of quantifiable measures to help selecting the most accurate disease modifying treatment (DMT) for their patients. MRI being by nature “non-invasive”, MRI screening can be performed with a relatively high frequency and thanks to the physics behind, different biological functions can be highlighted through the image, using complementary sequences. Lots of recent groups reviewed in detail the technics available and how they can be used by clinicians, as well as researchers, to better understand MS and improve the patient’ care. MRI is crucial to establish the diagnosis of MS. Overtime, the major interests of MRI for the neurologist are to compare the burden of the disease including T2/FLAIR lesion load and brain atrophy and to follow the efficiency of DMTs.

MRI shows great interest in patients with a first demyelinating event, as it can provide sufficient information on dissemination in space and in time to confirm early the diagnosis of MS[2]. MRI has also taken a pivotal position in following the potential serious adverse events associated with some DMTs, as it is the case for multifocal leukoencephalopathy (PML)[3]. MRI is a minimally invasive, reproducible, affordable technique, more sensitive than the clinical observations, which makes it possible to objectively assess the efficacy and risks of a treatment. Its use to optimize therapeutic strategies and appears profitable for the civil society[4]. Treating patients as early as possible in the natural history of the disease is the most efficient way to delay accumulation of disability in the long term [5]. Controversies have existed on the possibility of making a

diagnosis too early [6], but the current recommendations with regular use of MRI considerably improve the accuracy of the diagnosis, and clinical management. [3,5,7]. MRI is nowadays an essential part on the neurological criteria [8] especially for the ability to depict the changes over time of the demyelinating lesions in number, size and activity. Rio and al.[9] and Sormani and al.[10] studies linked MRI lesions to long-term disability and proposed a classification of the patients based on the relapse occurrence and with two or more new or enlarging T2 lesions. To fulfill the needs for following up patients and monitor safely the evolution of the pathology, current guidelines recommends an annual MRI[11,12]. In addition to the use of the actual state of the art T2/FLAIR sequences[13], MRI can also provide other assets such as atrophy[14], cortical lesions [15] or even optical nerve[16] which can also provide useful information.

For a disease like MS with life follow-ups, reproducible protocol is a mandatory to ensure a good quality of care from center to center, physicians to physicians over a long period of time. Acquiring systematically the same protocol across centers, with the less variability as possible on the data, allows to build big databases like the project in France achieved by a group of neurologist and radiologist specialized in MS organized into the “Observatoire Français de la Sclérose en Plaques” (OFSEP) (<http://www.ofsep.org/>) [17]. Those databases are the first step to conduct epidemiological studies and to develop deep learning algorithms that can benefit patients, doctors, industrial and regulators.

Value of MRI with contrast: from diagnostic to international concern.

Diagnosis and treatment

The physiopathology of MS is complex. MS is defined as a chronic inflammatory and demyelinating disease of the central nervous system (CNS) with multiple biological implications and clinical manifestations [2,18,19]. A hallmark of the pathology is the presence of lesions which can appear throughout the CNS and which include focal areas of demyelination, inflammation, and glial reaction. Fortunately, MRI can sensitively identify MS lesions with standard acquisitions and is now a privileged tool for neurologist to assess the progression of MS.

MRI lesions were firstly introduced to assess dissemination in both space and time in 2001 MacDonald criteria for MS. The contributions of MRI have improved the sensitivity of the diagnosis of MS; the latter can be carried out earlier and earlier, while limiting the risks on specificity, which makes it possible to avoid diagnostic errors. Since then, to improve diagnostic accuracy, updates on the criteria were published in 2005 [20], in 2010 [21] and 2017 [8]. In parallel, groups of experts regularly updated the good practices of MRI to unify, standardize MRI procedures. Better detection of lesions, changes over time and better comparability of examinations have become of crucial importance in follow-up of for MS patients under therapy. Among these, the referring group of MAGNIMS edited in 2016 their guidelines [22–25]; a retrospective study conduct within this network on 368 clinically isolated syndrome (CIS) patients, to determine if a CIS patient will develop MS over a period of 36 months, has report comparable sensitivity (0.93 vs 0.91) and specificity (0.32 vs 0.33) of the 2016 MAGNIMS

from 2010 version[11]. Those early recommendations have been established to allow an early diagnosis of MS and measure the response to a DMT.

Loss of brain volume has been a decades-long recognized MRI marker of neurodegeneration in MS but is not yet used clinically because many changes at the individual level make it difficult; the first recommendations were made in 2013 [26] and updated with a focus on cerebral and spinal atrophy, recently in 2020 [27]. To be use as a clinical imaging biomarker to evaluate effectiveness of a treatment across time, unification, and standardization of all the clinical imaging practice is the first step. Even so, limitations including age, lifestyle factors and comorbidities make essential the need for a global database as a benchmark essential. In these respects, the initiative of OFSEP' clinicians to unify their clinical and imaging practice, in line with the international consortium, appears to be a breakthrough[12,17,28].

The range of therapeutics opportunities continues to expand with a dozen of DMTs available to the neurologist with a better outcomes for patients which become evident over the years[5]. However, initiating those DMTs has early as possible is important to avoid long-term disability[29]. The benefits-risk of the DMT for MS patients have been balanced [30–32]and leads to an increase of the quality of life for MS patients[33]. An example of good practice is given by treatment with natalizumab: with an efficient risk stratification policy, involving frequent MRI check-ups and a systematic use of John Cunningham virus (JCV) serologic test results, the risk of PML drastically decreases[34].

Gadolinium deposition' warning

Gadolinium based contrast agents (GBCA) have been used in clinical practice for decades. Focal enhancing in the brain on T1 sequences is the consequence of a blood-brain barrier (BBB)

disruption. In MS, GBCA mainly enhance new lesions (< 2 weeks) due to the BBB rupture induced by the MS-related inflammatory demyelination[35]. The GBCA-enhancement in MS lesions is a marker of the blood-brain barrier breakdown which is a surrogate for recent and active inflammation. The evidence of enhancing lesions provides important assets, to 1- establish the initial diagnosis; 2- determine “dissemination in time” when comparing multiple scans. As introduced above, diagnosis is dependent of the dissemination in time and in space of the lesions. MRI is extremely sensitive to detect demyelinating lesion and active lesion is define as an enhanced lesion by GBCA, but a new lesion on the most recent exam has been an active lesion between at some point[36],

Although essential[37], GBCAs, mostly linear agents, have recently been implicated in a radiological controversy due to accumulation of the ion gadolinium into the body and more specifically in the brain[38–42]. Although no clinical implication of brain deposition of gadolinium has been described yet, the concerns for patient safety impose to establishment of a risk management threat[42]. This is of particular importance in MS patients, with their frequent lifelong MRI follow up has to be protected to any potential harmful effect. Following warning from US and European regulatory agencies, MRI guidelines has been established to limit to essential the use of gadolinium in the clinical practice to monitor MS patient. In 2017, a Swedish working group has completed a 2016 publication from a consortium of MS task force [43] to help clinicians regarding the use of GBCA and with GBCA injection for follow-up scan. In 2020, OFSEP updated its MRI recommendations by limiting the number of injection to necessary as mention below [12] and almost on the same time a UK group from the national health service [44] converged with the French protocol in term of frequency, type of sequences and the standardization of the practice. The main divergence between the two groups is the

systematic injection of gadolinium for the UK's group whereas OFSEP' approach limit the injection of the scrutiny. Another major difference is the injection priorly to a 3D FLAIR sequence for the OFSEP which has benefits to have better washout of the contrast for the 3D GDCA-enhanced T1 sequence and a better detection of the focal leptomeningeal enhancement on the 3D FLAIR[12].

Imaging MS patients in the 2020s: the OFSEP' recommendations

2020' recommendations is an update of the initial national protocol[45] with the emphasis of threefold: 1- respect of the 2017 MacDonald criteria for the neurologist; 2- protocol compatible with clinical practice in a busy radiology department; 3- patient safety with regards to the GDCA.

As mentioned above, GDCA has no equivalent to highlight current disease activity by enhancing MS recent inflammatory lesions. Neurologists and radiologists may have interest to see GDCA-MRI during the follow-up of treated MS patients, in the following situations:

- 1- Absence of previous MRI or poor quality of previous MRI
- 2- Baseline when starting a new DMT and 6 months after to rebase (drug action time or time to adjust in regard of the marketing authorization applications of the drug)
- 3- Brain side-effect or other disease appearing during the follow-up like PML
- 4 Optionally, in case of relapse

For the follow up of clinically stable patient, the comparison of two consecutive 3D millimetric FLAIR allows to the physicians to detect any new lesions. If new lesions appear when compared to the baseline MRI with or without clinical signs, treatment may need to be adjusted. In this situation, the case #2 above should be considered.

As mentioned above, it should be noted that not all active lesions are enhanced since the timing is key to image them; Cotton and al. shows that the average window to detect inflammatory lesion by GDCA MRI is only two weeks[46]. However, all new lesions between two consecutive scans has been once inflammatory It has been admitted that, in absence of clinical event, a yearly screening in MRI is the best cost efficiency to detect potential activity of the disease and indeed make treatment decisions. The OFSEP recommendations go in this direction of monitoring patients every year in the absence of an MS outbreak as shown in the figure 1, adapted from [12]. This figure also summarizes the situation when the gadolinium should be used systematically, when it is recommended to use for re-baselining (before the drug is fully active, some lesions may appear and the comparison with baseline can be subject to question) and when it is not necessary for the screening. In the case of GBCA injection, only macrocyclic agents could be used as recommended by the European Medicines Agency (EMA)[47] and must be injected with a dose of 0.1 mmol/kg. By acquiring the most clinically efficient standardized protocol in term of sequences, orientation and frequency, algorithms can be developed to help the physician in time consuming tasks as detection of the active lesions especially if they are numerous or small. Recent machine learning technics has already been developed to help the clinician in that routine of detection or characterization[48,49].

The spine cord lesions recently gained renewed interest in assessing severity of the disease and monitoring the effectiveness of the treatment. Cerebral cord atrophy has been recently described

as an early indicator of the disease evolution[2,27], but remains used only in research at this stage. The OFSEP imaging group recommend an entire spine examination every 3 years at minima. The acquisition of the spine will follow the brain complete exam with GDCA injection

To ensure optimal coordination between neurologists and radiologists, the OFSEP provides national procedures and disseminates standardized protocols available on its website. Technical reproducibility across centers and in-time are guaranteed by the availability of the exam cards developed by the four main MRI manufacturers (Siemens, Philips, GE and Canon) on demand directly through the web site (<http://www.ofsep.org/en/professionals/imaging/mri-protocol>). The 3D sequences should have isotropic resolution, ideally millimetric or better, with no gap to allow reconstruction in all plans and direction according to physician will. Reconstruction of the MRI in the subcallosal plane (lower edge of the rostrum and lower edge of the splenium of the corpus callosum) has been retained over other planes, such as AC-PC plane, for its better reproducibility for MS studies [50].

The Figure 2 shows a proper example of acquiring a patient with all the sequences required for the baseline for a treatment in order: 3DT1 Unenhanced, 2D PD/T2, Diffusion, injection of a dose of Gadolinium, 3D FLAIR and 3DT1 Enhanced. The entire scan time of the protocol is 20 minutes. The acquisition of the 3D sequences allows to retrospectively reconstruct the sequences in different axes. Same sequences are used on the yearly follow-up protocol on the same patient but the injection of the GDCA neither the DP/T2 with a scanning time of 14 minutes as shown on Figure 3. A short version of this follow-up protocol can be used for patients at high-risk of developing PML (treated with natalizumab and JCV+) for whom frequent acquisition (3 to 4 months) is recommended with a short protocol including diffusion and 3D FLAIR [51]. On Figure 4 a 46 treated woman with a relapsing remitting MS form for 11 years and with an EDSS

4 has been imaged with the follow-up protocol including: A- 3D T1, B- 3D FLAIR, C- Diffusion. The 3D sequences were acquired with iso-millimetric spatial resolution and the Multiplanar reconstruction (MPR) can be carried out easily according to the needs. The FLAIR sequence shows an important lesion load on the supra and infratentorial part of the brain and in the brainstem. Comparing each lesion over time is necessary to follow the progress of treatment but can be highly time consuming if the number of lesions is high and some computer assisted technique can help for this task. Since all the acquisition was standardized, in the Figure 4D, a simple subtraction of the two last FLAIR with 18 months apart was performed and do not show any new lesions. More advanced techniques in image analysis, whether in image processing or in AI, may soon also provide other information such as atrophy.

Figure 5 illustrate the benefice to acquire the same protocol in the time, with a comparable sequence. The same patient was scanned with 64 months apart as shown on the scan on the left and middle. During that time, upgrades may occur in the sequences or on the hardware, patient can move to another center or anything nonrelated to MS events. Here the same sequence, namely 3DFLAIR, was acquired at 3T. Direct comparison with a simple subtraction is then feasible; IA software can help the physician to enhance the statistically different voxel and superimpose color heatmap that highlight new contrast enhancement as shown on the right panel with a new lesion appears in red (yellow arrow).

Discussion

By consulting the neurologists and radiologists in its network, and by issuing standards to be followed, and by coordinating the actions of the various disciplines at the national level, OFSEP plays a leading role in the standardization of care practices for patients suffering from MS. But

its role does not stop there. The OFSEP aims to provide a high quality multimodal collection of standardized data for the scientific community[17]. Upon validation by a scientific board of the research projects and data access requests submitted to the national coordination center of the OFSEP, the access of patients of interest in the cohorts are available to all academic and industrial researchers who request them, constituting a step forward in research on MS. The data collected by the OFSEP have a high clinical value (clinical, biological and MRI data) with the evolution of patients over time. Epidemiologic studies carried out on retrospective clinical data make it possible to attest to the effectiveness of good practices; for example, recently highlights patient stratification benefits and the drastic decrease of the MS patient under natalizumab that develop PML [52]. On the other side, MRI analysis around MS are often limited to studying lesions due to the spectacular ability of the method to demonstrate the demyelinating activity linked to the pathology[2]. However, progress in image processing have enabled the development of new biomarkers, such as brain or spine alteration[53–55] to follow the effect of the treatment [56–59] and have recently been included on the most updated recommendations[27].

Thanks to the recent progress in AI[60,61], deep learning technics can be successfully applied to various applications that can directly benefit to the clinical routine such as detection, automated image quality evaluation[62], segmentation and classification of the lesions[48,49] among others. Recently, deep learning method was even employed to predicting enhancing lesions from T1 unenhanced, T2 and FLAIR out of a thousand patients cohort and obtain a 70% accuracy with high hope to increase it with more data [63]. This group has also pinpoint out the impact of number of patients needed to deploy adequate solution[64]; if only ten proper segmented brain can be enough to develop a solution to obtain white (WM) and grey matter (GM), 50 is a

minimum to get decent score on lesions segmentation. Using their cohort of 1,000 patients to assess the impact of using multi-contrast MRI to segment GM, WM, and lesions, this team achieved comparable performance using all available contrasts and using the FLAIR sequence only as input[65]. Another AI model has been successfully developed to predict the two-years EDSS score with only FLAIR sequences and basic demographic information, all available on the OFSEP database[66]. While these advanced AI techniques are potentially very effective on local data, scaling them up can only be considered by learning, testing and validating these algorithms on a real databases; those must reflect a diversity of acquisitions (manufacturer, fields strength, equipment set-up) and with all the variations, even infantile ones, of the pathology which can only be observed at national or international level and which can only be captured by projects such as the one carried out by OFSEP.

Conclusion

The standardization of MR protocols in clinical practice are the cornerstone of the recent recommendations while ensuring the best possible care in the safest conditions for the patient. Independent groups of specialists converge on several diagnostic criteria, follow-up and even on a minimum set of radiological information for correct practice. OFSEP's positioning was precursor and is in line with other international recommendations with a more cautious approach to the use of gadolinium contrast agents. Another part of the OFSEP' MRI protocol is that it is also designed to conduct research studies, especially in data science either for statistics, image processing or artificial intelligence (AI).

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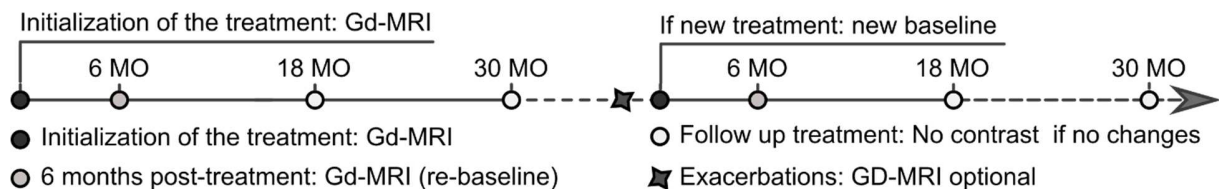
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Figures:



In accordance with the suggestions made by the European Medicines Agency and the French National Agency for Drug Safety, the OFSEP recommends the use of macrocyclic agent at the dose of 0.1 mmol per kilogram of body weight.

Figure 1: Time to perform GDCA-MRI during the follow-up of patients under treatment

OFSEP's imaging recommendation of use of GDCA: diagnosis and introduction of a new therapy. Re-baseline scan is also highly recommended to avoid pseudo progression effect. For follow-up scan of stable patient, good quality 3D-FLAIR is required.

Adapted from Brisset et al. Journal of Neuroradiology Volume 47, Issue 4, June 2020, Pages 250-258

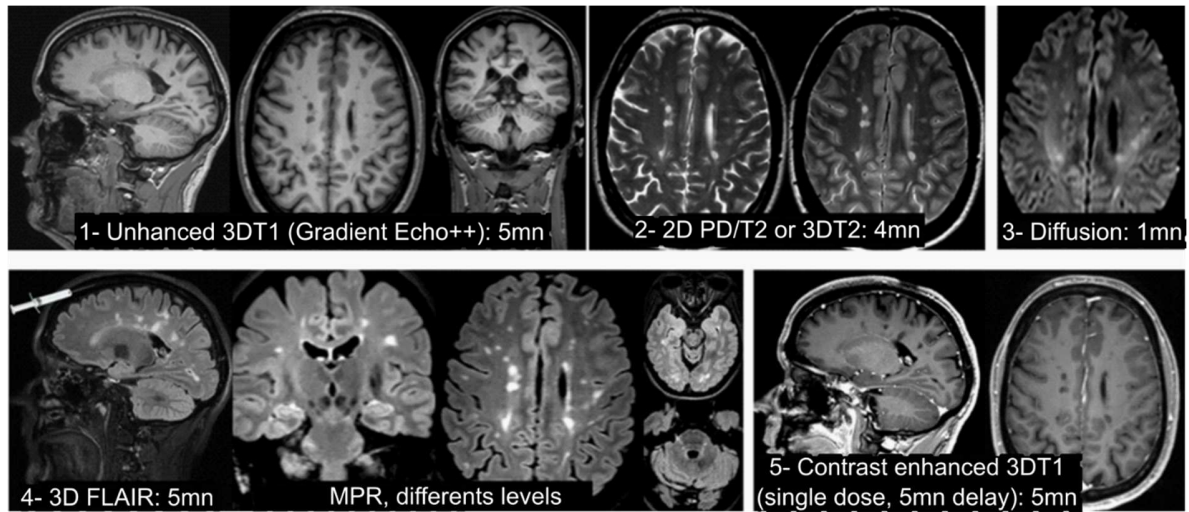


Figure 2: Example of MRI protocol for MS patient at baseline

Typical acquisitions for GDCA MRI as recommended by the OFSEP, here on a 3T scanner. This baseline protocol includes: 1- a non-contrasted 3D T1; 2- a T2 sequence either a 3D T2 or a dual 2D Proton Density/T2; 3- a diffusion sequence and the DTI/ADC map; a gadolinium injection at 0.1mmol/kg; 4- a post contrast 3D FLAIR and a post-contrast 3D T1. The time of acquisition of this entire protocol is 20 min. Optional sequences can complete this exam at the discretion of the practitioner as a SWI sequence. All the 3D sequence must be acquired at a spatial resolution of 1mm isotropic et thus can be reconstructed in different plans (MPR: Multiplanar reconstruction) without loss.

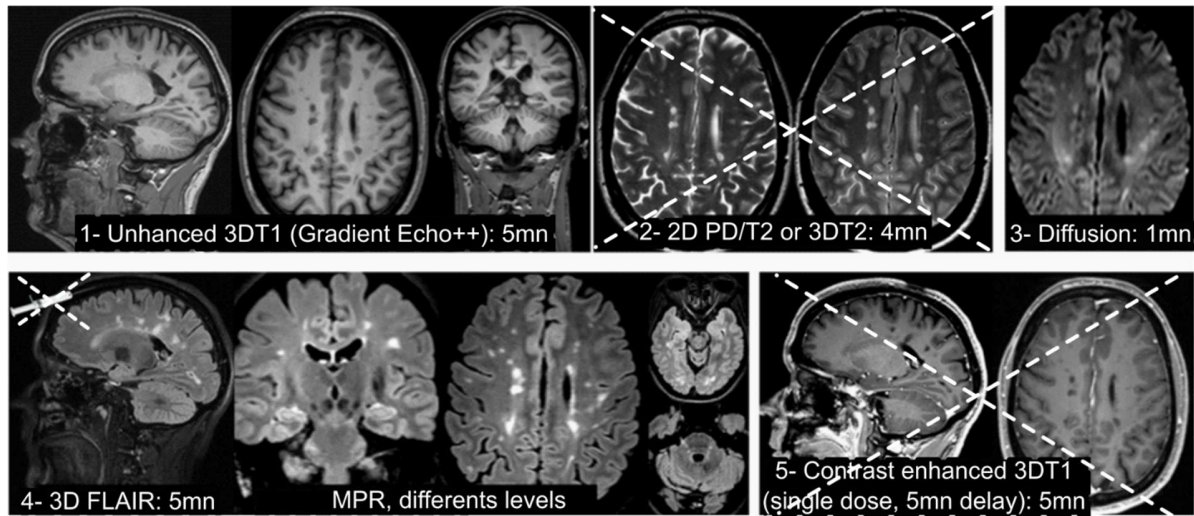


Figure 3: Example of the follow-up MRI protocol for treated patient

Typical acquisitions for follow-up MRIs as recommended by the OFSEP, here on a 3T scanner. This follow-up protocol includes: 1- a 3D T1; 2- a diffusion sequence and the DTI/ADC map; 3- a 3D FLAIR. Time of the acquisition is divided by 2 compared to baseline (14 min). As for the baseline protocol, all the 3D sequence must be acquired at high spatial resolution (1mm iso) and can be reconstructed in different plans (MPR: Multiplanar reconstruction)

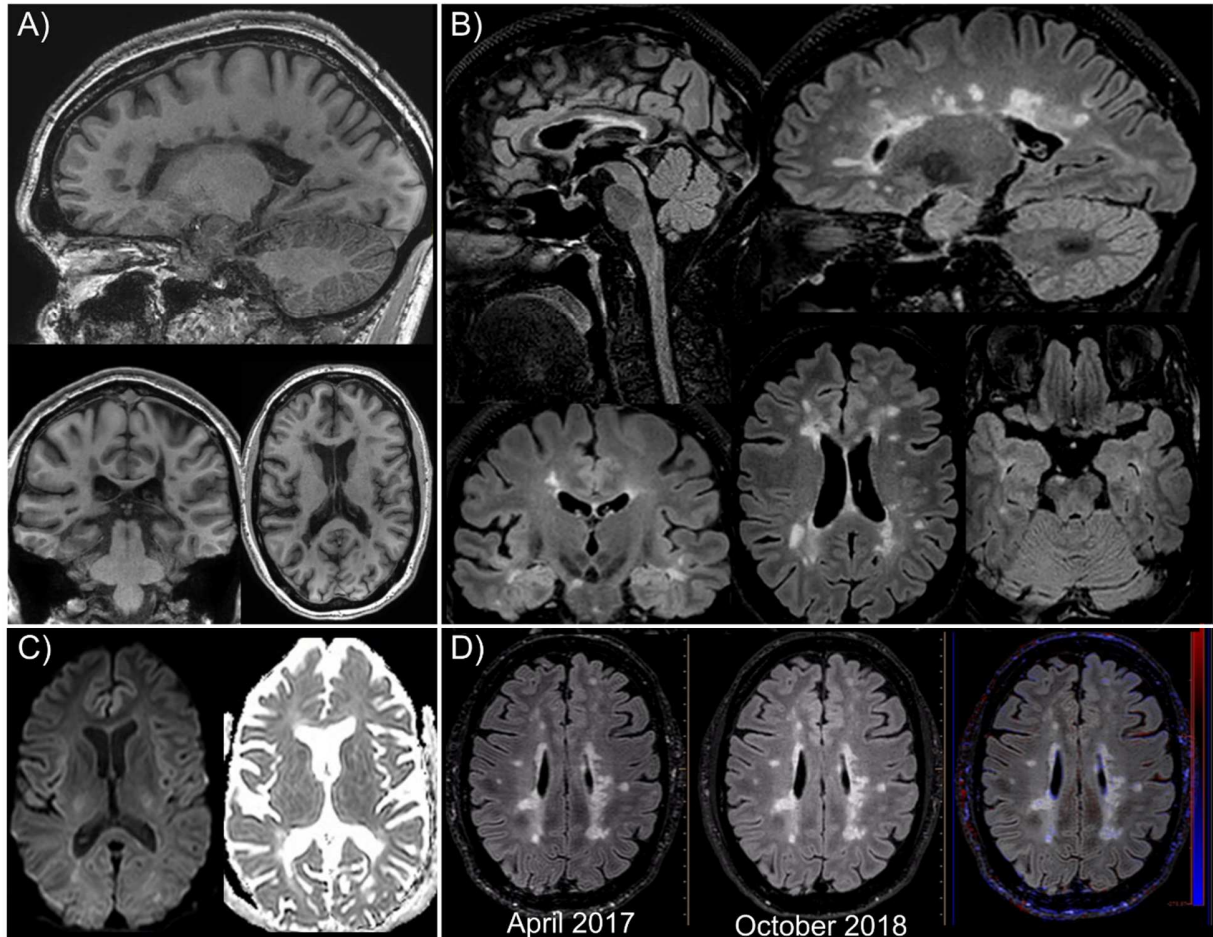


Figure 4: Follow up of a 46-year-old woman with a Relapsing-remitting form of MS for 11 years with EDSS 4

Patient with Relapsing-Remitting Multiple Sclerosis (RRMS) screened with the following protocol: A) Isotropic millimetric 3D Gradient Echo T1 without contrast agent and two subsequent Multiplanar Reconstruction Plan (MPR) in axial and coronal. B) Isotropic millimetric 3D FLAIR with different MPR. On this sequence, a significant lesion load with lesions can be observed on the supra and infratentorial part of the brain and in the brain stem. C) Diffusion sequences at

b=1000 s/mm² and Apparent Diffusion Coefficient map. D) Two FLAIR acquisitions at 18 months apart with a subtraction on the right that do not highlight new lesions

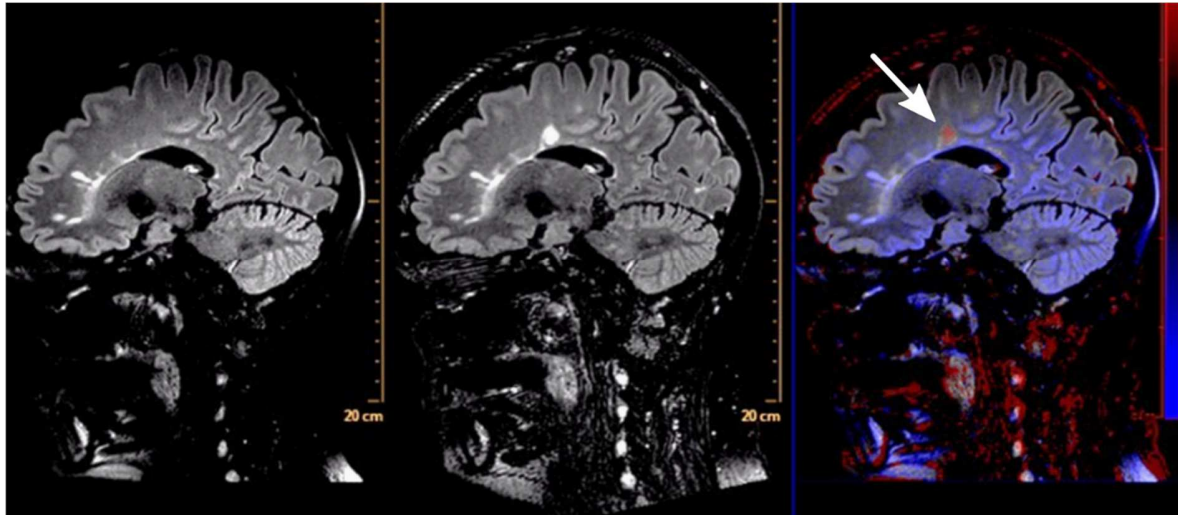


Figure 5: Follow up of a 30-year-old woman with a Relapsing-remitting form of MS

Same Relapsing-Remitting Multiple Sclerosis (RRMS) patient acquired twice with 64 months interval (Left: May 2013, Center: September 2018). The two protocols were acquired at 3T and includes 3D FLAIR. The orientation was standardized and sequences comparable. On the right, an automatic subtraction can help to depict new lesion (in red as pointed by the arrow)