Gadoterate Meglumine Administration in Multiple Sclerosis has no Effect on the Dentate Nucleus and the Globus Pallidus Signal Intensities

Salem Hannoun, PhD, Rayane Issa, MD, Nabil K. El Ayoubi, MD, Ribal Haddad, MD, Marwa Baalbaki, MD, Bassem I. Yamout, MD, Samia J. Khoury, MD, Roula Hourani, MD

Abbreviations

BBB brain blood barrier

CP central pons

CSO centrum semiovale

DN dentate nucleus

GBCAs gadolinium-based contrast agents

Gd− patients without gadolinium injections prior to MRI1

Gd+ patients with one or more suspected gadolinium injections prior to MRI1

GP globus pallidus

MS multiple sclerosis

N Patients' number

Rationale and objectives: Previous studies on possible accumulation of gadolinium-based contrast agents (GBCA) in the brain suggest that macrocyclic GBCA are less likely to accumulate than linear GBCA. However, conflicting results have been reported, especially in MS. The aim of this study is to investigate retrospectively the correlation between gadoterate-meglumine (macrocyclic GBCA) use and T1 signal intensity changes (SI) in the dentate nucleus and the GP on unenhanced T1-weighted images in a large cohort of MS patients.

Materials and methods: Unenhanced T1-weighted images of 232 MS patients who previously received multiple intravenous administrations of 0.1 mmol/kg of gadoterate-meglumine were reviewed. The change in T1 SI ratios of dentate nucleus/central pons (DN/CP) and globus pallidus/centrum semiovale (GP/CSO) was calculated between the first and last MRIs and correlated with age, number of injections, time interval between MRIs, disease duration, activity, and therapy.

Results: DN/CP ratio showed no significant changes whereas the GP/CSO ratio showed a significant decrease ($p < 0.0001$) between the first and last MRIs. Multivariable analyses of both ratios, controlling for age, disease duration, and time interval between MRIs, showed no significant correlation between the number of gadolinium injections and the differences in DN/CP (standardized beta = −0.018, $p = 0.811$) or GP/CSO SI ratios (standardized beta = −0.049, $p = 0.499$).

Conclusion: Repeated administration of gadoterate-meglumine in MS patients did not result in increased T1 SI in the DN or the GP. The significant decrease of GP/CSO ratio between the first and last MRIs is not due to gadolinium accumulation but rather to varying MR parameters.

Key Words: Multiple sclerosis; Macrocyclic gadolinium-based contrast agents; Gadoterate-meglumine; Dentate nuclei; Globus pallidus.

Acad Radiol 2019; 26:e284–e291

From the Nehme and Therese Tohme Multiple Sclerosis Center, American University of Beirut Medical Center, Beirut, Lebanon (S.H., N.K.E.A., R.H., M.B., B.I.Y., S.J.K.); Abu-Haidar Neuroscience Institute, Faculty of Medicine, American University of Beirut Medical Center, Beirut, Lebanon (S.H., S.J.K.); Department of Diagnostic Radiology, American University of Beirut Medical Center, Beirut, Lebanon (R.I., R.H.). Received October 16, 2018; revised November 9, 2018; accepted November 15, 2018. **Address correspondence to:** R.H.
e-mail: rh64@aub.edu.lb

https://doi.org/10.1016/j.acra.2018.11.010

SD
standard deviation
SI
signal intensity

INTRODUCTION

MRI is one of the safest, noninvasive and highly informative diagnostic imaging modalities. Coupled with gadolinium-based contrast agents (GBCAs), MRI assesses variable brain pathologies and provides clinical information that are often undetectable on unenhanced MRI. Nonetheless, GBCAs administration safety, in terms of brain deposition and secondary neurotoxicity, has been one of the most debatable topics, ever since the first report of increased signal intensities (SI) in the dentate nucleus (DN) and globus pallidus (GP) (1). To our knowledge, besides the issues reported by Semelka et al. that lack scientific evidence (2), there have been no observed adverse clinical symptoms associated with gadolinium tissue deposition and the clinical impact remains unclear.

The free gadolinium ions are highly toxic and thereby require chelation to a ligand to remain stable in the human body. Based on the chemical structure of the ligand, GBCA can be either linear or macrocyclic (3). The difference between both ligands is the structural stability of the gadolinium chelate. The tighter the gadolinium ion is bound to the chelating molecule, the less likely it is to dissociate from it. However, when dissociated before elimination, the released gadolinium ion could be picked up by a variety of anions and cation-binding proteins circulating in the blood and deposited in certain regions of the brain (4). Gadolinium deposition was shown to increase T1 SI in the DN and GP. This was significantly associated with linear rather than macrocyclic GBCAs (1,5−12). The macrocyclic ligand structure cages the gadolinium ion in a preorganized cavity rendering its dissociation rate slower than the linear ligands, thus making it more stable in the human body, most likely to be excreted intact, and less likely to be deposited (3,13).

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system. It is the most common cause of nontraumatic neurologic disability in young adults (14). GBCAs will improve the accuracy of MRI in staging MS disease activity by differentiating enhanced active from unenhanced nonactive lesions (15). Any abnormal enhancement in the brain parenchyma would therefore reflect a disrupted brain blood barrier (16). This sensitivity implies that MS patients are subjected to, at least, yearly contrast-enhanced MRI evaluation, thereby increasing the possibility of gadolinium deposition. Several studies already assessed the effect of GBCAs in MS patients. However, most had many limitations i.e. small sample size, and heterogeneity of study samples, which lead to conflicting results. Indeed, findings of increased SI after serial administrations of linear (17) and macrocyclic GBCAs (18) were reported in the DN and GP of MS patients. In contrast, Eisele et al. showed no intensity increase in the DN after repeated administration of a macrocyclic GBCA (Dotarem) in MS patients (19).

The paucity of research and evidence-based conclusions on this topic showed a need for further investigations. Since our institution is a major referral center for MS patients, in Lebanon and Arab countries, we proposed to do a retrospective study of our patients, assessing the effect of gadoterate-meglumine (Dotarem) on T1 SI change in the DN and GP of MS patients.

MATERIALS AND METHODS

Subjects

In this retrospective study, 250 adult patients diagnosed with clinically definite MS according to the 2010 McDonald's criteria (20) were enrolled from our institution's longitudinal cohort database. Patients were included if they had at least two brain MRI studies performed (first MRI referred to as MRI1 and last available MRI referred to as MRI2 in this study) between 2009 and 2017. Exclusion criteria included a history of intravenous steroids or MS relapse within the past 4 weeks prior to MRI, pregnancy, history of dementia or other neurodegenerative diseases, neuromyelitis optica, or poor MR image quality. Clinical and demographic variables included age, gender, disease duration, disease course (relapsing-remitting vs progressive MS), number of attacks and steroids courses until MRI1 and between MRI1 and MRI2, MS treatments, number of new gadolinium-enhancing and nonenhancing lesions between MRI1 and MRI2, number of gadolinium injections prior to MRI1 (including nonbrain MRI), number of gadolinium injections between MRI1 and MRI2 (including nonbrain MRI), interval between MRI1 and MRI2 in months. Patients were divided into two subgroups: patients without gadolinium injections prior to MRI1 (Gd−) and patients with one or more gadolinium injections (Gd+) at other centers (of unknown GBCA structure) prior to MRI1 at our institution. This retrospective study was approved by the Institutional Review Board of our institution that waived the requirement to obtain informed consent from patients.

Acquisition

All patients had both their MRIs performed between October-2008 and April-2017. MRI acquisitions were performed on a 3T Philips Ingenia System (Philips Healthcare, Best, The Netherlands) using a 16-channel head coil. MRI protocol consisted of: 2D gradient-echo (GE) axial T1-weighted (TR/TE: 260/204ms; Flip angle 80°; slice thickness 3 mm); 3D sagittal

T1-weighted with and without gadolinium injection (0.1 mmol/kg of gadoterate-meglumine) (TR/TE: 8.3/3.8 ms; Flip-angle 8°; slice thickness: 1 mm); 3DFLAIR (TR/TE/TI: 4800/302/1650 ms; slice thickness: 0.97−1.1 mm). For the purposes of this study, only unenhanced T1-weighted (2D or 3D depending on the availability) and 3DFLAIR images were used. The MRI protocol for MS patients in our center has been updated to include 3D T1-weighted images instead of 2D images in 2016. Thus, most MRI1 were acquired with a 2D GE T1 and all MRI2 were acquired using 3D T1. Only 18 patients had both MRI1 and MRI2 acquired with 3D T1.

Image Analysis

A quality control step was first performed by an experienced operator with more than 10 years of experience on all MRIs to rule out and exclude any images with major artifacts that could implicate an error during the manual and automatic segmentation processing steps. Of the 250 MS patients, 18 were excluded due to movement or susceptibility artifacts in at least one of their MRIs that rendered the images unfit for processing.

Quantitative analysis was performed on a total of 464 unenhanced-T1 images (232 patients, 2 MRIs for each patient, MRI1 and MRI2). Image processing started with applying a bias field correction on all T1 images using the N4-algorithm in 3DSlicer (https://www.slicer.org/), followed by a whole-brain extraction using the Brain Extraction Tool of the FMRIB Software Library (FSL5.0) (21). The resulting images were nonlinearly registered to the MNI152 space using Nifty-Reg (https://cmiclab.cs.ucl.ac.uk/mmodat/niftyreg/). Once registered, an average T1 image of our cohort was created to serve as reference for the histogram matching step performed using 3DSlicer (Fig. 1). This final step will correct the variations in scanner sensitivity due to differences in scanner performance thereby reducing the variations in WM intensities.

ROI in the DN, central pons (CP), GP, and centrum semiovale (CSO) were manually delineated by an experienced operator with more than 10 years of experience. Delineation was carried out on FLAIR images of ten randomly selected patients with various stages of the disease. DN and GP hypointense signal on FLAIR makes them easier to delineate when compared to T1 images. Delineation was performed on both left and right hemispheres. Only the central part of the ROIs was delineated to avoid any contamination from partial volume effects with the surrounding tissue. FLAIR images and the corresponding masks were then nonlinearly registered to the MNI space. ROIs were next merged, averaged and then eroded to cover only the central part of each structure, thereby excluding any voxels that could introduce bias to the signal quantification due to partial-volume effects. The resulting masks were finally applied on all unenhanced-T1 images to extract the intensity values within each ROI (Fig. 2). Manual delineation being time-consuming, we segmented the ROIs on ten patients since only the central section of the ROIs was used. There was therefore, no need to be very thorough in the delineation.

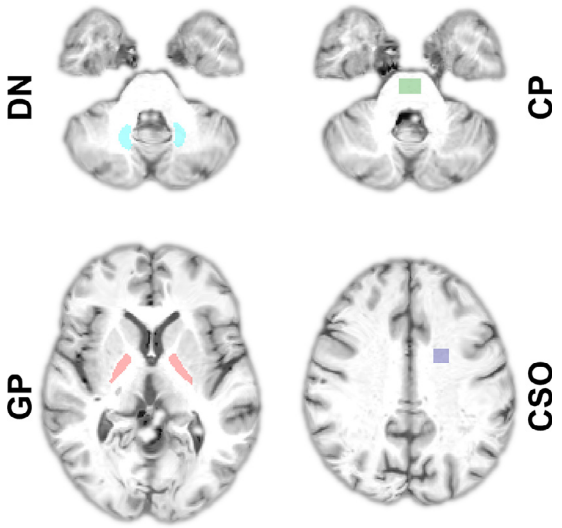

Figure 2. Regions of interest used for the extraction of the dentate nuclei (DN), globus pallidus (GP), central pons (CP), and centrum semiovale (CSO) signal intensities. (Color version of figure is available online.)

Prior to value extraction, FLAIR images of all patients were checked for any lesion occurrence at the ROI locations. In case of a lesion occurrence, ROIs were adjusted and placed away from any lesion visible on T1 images. Out of the 464 MRIs, 69 DN, 60 CP, 45 GP, and 91 CSO had lesions that were corrected. Furthermore, unenhanced-T1 images of both first and last MRIs were reviewed by two experienced

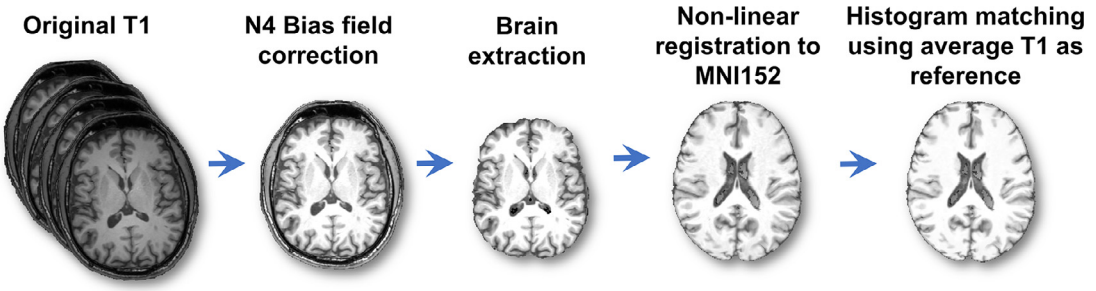

Figure 1. Processing pipeline for the measurement of the DN/CP and the GP/CSO ratios. CP, central pons; CSO, centrum semiovale; DN, dentate nucleus; GP, globus pallidus. (Color version of figure is available online.)

neuroradiologist (with more than 10 and 20 years of experience) for any visually apparent hyperintense signal in the DN and/or GP as well as calcifications or lesions within these structures. The inspecting neuroradiologist was blinded to the number of gadolinium injections received between MRI1 and MRI2.

Statistics

Statistical analysis was performed using the Statistical Package for Social Sciences software (IBM Corp. IBM SPSS Statistics for Windows, Version 25 Armonk, NY: IBM Corp.). The normality of distributions was evaluated through the Shapiro-Wilk test. A two-sided p value of less than 0.05 was considered significant. Mean (SD) and counts (proportions) were reported for the clinical and demographic variables, including the number of gadolinium injections before and between the included MRIs. DN/CP and GP/CSO SI ratios were calculated for each of MRI1 and MRI2, as well as the difference in the SI ratio between both MRIs.

DN/CP and GP/CSO SI changes were explored between MRI1 and MRI2 as continuous variables, using paired samples t tests or the nonparametric Wilcoxon Signed ranks test, as appropriate. One-way ANOVA was used to evaluate if the extent of the difference in SI ratios from MRI1 to MRI2 was unequal between specific subgroups of patients. Linear mixed effects models were performed with random intercept and slope, examining the effect of cumulative gadolinium exposure on MRI signal intensity ratio as outcomes (DN/CP ratio, GP/CSO ratio), controlling for, age, disease duration, and interval between first and last MRI. Other covariates were explored as well, including: sex, number of previous gadolinium injections, number of steroids between first and last MRI, number or gadolinium enhancing lesions between the first and last MRI, number of attacks between first and last MRI. Furthermore, given the possibility of exposure to unknown types of GBCA among patients who underwent gadolinium injections at other centers prior to MRI1, we repeated the analyses controlling for age, disease-duration, and time interval between the MRIs, among the subgroup of patients with no history of gadolinium exposure until MRI1, and another subgroup with one or more doses of gadolinium received prior to MRI1. Similarly, these sensitivity analyses were done on the subgroup of patients with RRMS as well as those with progressive MS.

RESULTS

In this study, 232 (209 relapsing-remitting MS and 23 progressive MS) patients were included, with a mean (SD) age of 33.2 (11.6) years and mean (SD) disease duration of 104.4 (90.7) months. The mean (SD) interval between MRI1 and MRI2 was 36.5 (27.8) months. One hundred and seven (46.1%) patients had no gadolinium injections prior to MRI1 (Gd−), while 125 (53.9%) received at least one gadolinium injection (Gd+) at other centers (of unknown GBCA structure) prior to MRI1 at our institution. Clinical and demographic characteristics of the studied patients are shown in Table 1.

TABLE 1. MS Patients Demographics

Characteristics	Mean ± Standard Deviation	Min−Max
Age (years)	33.17±11.63	11−75
Disease duration (months)	104.40±90.73	1−519
Time interval between MRI1 and MRI2 (months)	36.48±27.78	1−101
Attacks between MRI1 and MRI2	0.56±1.06	0−6
Gadolinium injections before MRI1	2.03±3.29	0−18
Gadolinium injections between MRI1 and MRI2	3.09±2.87	0−23
New lesions between MRI1 and MRI2	1.86±3.69	0−32
Enhancing lesions until MRI2	1.91±3.41	0−25
Steroid courses between MRI1 and MRI2	0.88±1.75	0−13
Steroid courses before MRI1	1.39±3.57	0−49

There was no significant change in the DN/CP SI ratios between MRI1 and MRI2. Howe`ver, there was a statistically significant decrease in GP/CSO ratios between MRI1 and MRI2 (Table 2, Supplementary Table 1), with no differences in the extent of decrease in the SI ratios between Gd− and Gd+ patients.

Using a mixed effects model to control for age, disease duration, and time interval between the first and last MRI, there was no association between number of gadolinium injections and the DN/CP ratio (coefficient = −3.08, 95% confidence interval: −0.073 to 0.73, $p = 0.933$) or the GP/CSO ratio (coefficient = 0.0003; 95% confidence interval: −36.03 to 36.04; $p = 1.0$) over time (Fig. 3).

Time interval between MRI1 and MRI2 was the only statistically significant variable (standardized beta = −0.296, $p < 0.0001$) that was associated with the decrease in GP/CSO ratios between MRI1 and MRI2. Since the drop in GP/CSO ratio was not explained by age, disease-duration, or number of gadolinium injections between MRIs, but rather by the interval between MRIs, sensitivity analyses were performed including only patients who had 3D MRIs at both MRI1 and MRI2. This was done to determine if the change in GP/CSO ratio was related to technical differences between 2D and 3D MRI acquisitions. Eighteen patients were available for this subgroup analysis, showing no changes between MRI1 and MRI2 for either DN/CP (MRI1 = 0.9994±0.0129 vs MRI2 = 0.9979±0.0136; $p = 0.407$) or GP/CSO (MRI1 = 0.9868±0.0098 vs MRI2 = 0.9826±0.0149; $p = 0.144$) ratios.

TABLE 2. Paired-Samples Differences in DN/CP and GP/CSO Ratios Between MRI1 and MRI2

Ratio	N	MRI1	MRI2	MRI2-MRI1	*p* Value[1]
DN/CP	232MS	0.9988±0.0100	0.9974±0.0100	−0.0014±0.0118	0.083
	107Gd−	0.9981±0.1151	0.9969±0.0103	−0.0012±0.0124	0.301
	125Gd+	0.9993±0.0086	0.9979±0.0097	−0.0015±0.0114	0.158
GP/CSO	232MS	0.9990±0.0089	0.9865±0.0131	−0.0125±0.0127	$p < 0.0001$
	107Gd−	0.9992±0.0078	0.9851±0.0119	−0.0142±0.0111	$p < 0.0001$
	125Gd+	0.9987±0.0096	0.9877±0.0139	−0.0110±01362	$p < 0.0001$

CP, central pons; CSO, centrum semiovale; DN, dentate nucleus; GP, globus pallidus; Gd−, patients without gadolinium injections prior to MRI1; Gd+, patients with one or more suspected gadolinium injections prior to MRI1; N, patients number.

[1] Paired-samples *t* test.

Upon visual inspection, an increased SI on MRI2 compared to MRI1 was reported in the DN of 17 patients (7.3%) and in the GP of 4 patients (1.7%).

The presence/absence of a hyperintense signal detected upon visual inspection, as well as the numbers of gadolinium injections before MRI1, new lesions and steroid courses between MRI1 and MRI2, enhancing lesions until MRI2, and steroid courses before MRI1, showed no statistically significant relationship with the differences in SI ratios in the regression analyses.

The quantitative changes in SI ratios between MRI1 and MRI2 were also explored among patients based on their clinical MS course, whereby no statistically significant changes were observed in any of DN/CP (209 relapsing-remitting MS: MRI1 = 0.9984 ± 0.0098 vs MRI2 = 0.9973 ± 0.0101; 23 progressive MS: MRI1 = 1.0021 ± 0.0113 vs MRI2 = 0.9980 ± 0.0086) and GP/CSO ratios (209 relapsing-remitting MS: MRI1 = 0.9989 ± 0.0088 vs MRI2 = 0.9862 ± 0.0127; 23 progressive MS: MRI1 = 0.9995 ± 0.0089 vs MRI2 = 0.9891 ± 0.0160) in each clinical form.

DISCUSSION

Our retrospective observational study showed no significant SI increases within the DN and GP on unenhanced T1 images in MS patients, following multiple injections of the macrocyclic GBCA, gadoterate-meglumine (Dotarem). The relatively large sample of patients included in this study added power to our conclusion that was in accordance with previous reports (5,7,9,19). Although there was a significant decrease of GP/CSO ratio, neither related to GBCA administrations before MRI1, nor to the total cumulative dose, we noted that this result was mostly influenced by the MRI acquisition type (2D or 3D).

Our study showed no increased SI in the DN or GP of MS patients even when controlling for age (taking into account the increased T1 signal in the basal ganglia secondary to age-related calcifications), disease-duration, the mean interval between MRI scans, and the mean number of gadoterate-meglumine injections. This finding is consistent with previous studies reporting no SI increase in the DN and GP even with increased cumulative doses of macrocyclic GBCA and time (7−10,19,22−25). Stojanov et al. reported increased T1 SI in the DN following macrocyclic GBCA (gadobutrol) administration in MS patients (26). However, this study had a number of confounders that could have influenced the results (27).

Interestingly we found a significant decrease of GP/CSO ratio over time at the bivariate level. However, multivariate analysis showed that this decrease was not associated with the number of GBCA administrations, nor age, nor disease-duration, but rather

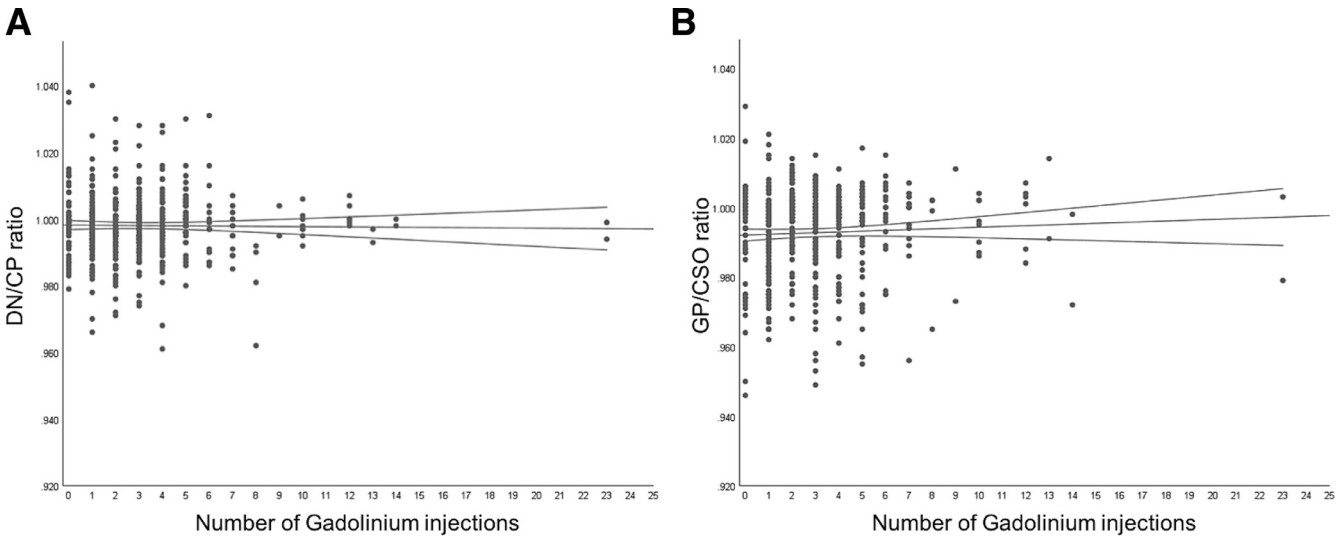

Figure 3. Signal intensity ratios of DN/CP (A) and GP/CSO (B) in function of the number of gadolinium injections exposure.

with the time interval between MRIs. A sensitivity analysis was therefore required to determine whether this change was related to technical differences between 2D and 3D MRI acquisitions. Indeed, when analyzing patients with only 3DT1 sequences at MRI1 and MRI2, GP/CSO ratio changes were no longer significant ($p = 0.144$). Hence, acquisition type (2D vs 3D) plays a major role in data processing. On one hand, 2D TSE and/or gradient-echo sequences have excellent tissue contrast and high in-plane spatial resolution but are affected by the relatively thick slices. On the other hand, 3D images can reduce these negative effects through fast acquisitions, thin continuous slices, and isotropic voxels that enable a multiplanar reconstruction (28). The main difference observed between GE 2D and 3D imaging is the signal-to-noise ratio, which is determined by the voxel size and detection volume, the pulse sequence, and the field strength. Thus, the observed differences could be the resultant of slice thickness and voxel resolution differences. Additionally, a recent study by Moser et al. (12) also showed an unexpected significant decrease of DN/CP ratio between the initial and last MRIs. Authors attributed this result to clearance of previously deposited GBCA from prior unknown administration before the date of the initial MRI ("gadolinium holiday" theory). However, this theory does not apply to our study, since the analysis of both Gd− (N = 107) and Gd+ (N = 125) patients showed no significant difference in the extent of decrease in GP/CSO ratios between the two groups.

DN hyperintensities have also been reported in secondary progressive MS patients (29). In order to mitigate the confounding effect of MS subtypes, we statistically analyzed our MS patients based on their clinical course. No significant intensity increases were detected neither within the 209 relapsing-remitting MS patients nor the 23 progressive MS patients. Moreover, visual checking of T1 SI in progressive MS patients also confirmed the quantitative results by highlighting the lack of any hyperintensities in the DN or GP. In contrast to the report by Roccatagliata et al., we did not find an association between DN hyperintensity and secondary-progressive MS subtype, number of new or enhancing lesions, or steroid treatment, thus raising the possibility that the reported association may have been driven by the type of GBCAs (linear or macrocyclic) or the number of gadolinium administrations (29).

The anatomic locations that seem to retain and accumulate the greatest amount of gadolinium on pathologic examinations are the DN and GP. We selected the CP and CSO as reference regions for the DN and GP respectively. Both regions are less affected by image artifacts and easier to reproduce and correct in case of lesion occurrence (7,17). Previous studies used the thalamus as a reference for the GP (31). However, the thalamus may be affected by demyelinating lesions and antero-retrograde degeneration in MS that could make it a possible confounder (32).

The small percentage of residual gadolinium, if dissociated in vivo, has a long biologic residence time. Thus, it might have the potential to lead to chronic toxic effects. Acute toxic effects may be caused by the ability of gadolinium to interfere with calcium-mediated cellular processes through the modulation of the immune system via induction of cytokine expression and inhibition of the mononuclear phagocyte system. Unlike the known acute toxicities of gadolinium and GBCAs, there is less evidence of chronic GBCA-mediated toxicities after intravenous administration. However, although gadolinium retention is lower in the brain than in bones or skin, there are concerns about metal toxicity in the brain and developing organs (30).

Our study had several limitations that could have impacted our results. The retrospective nature of our study is a limitation. Another limitation is the long interval over which the MRIs were obtained that impacted the choice of acquisition type (2D vs 3D). Nonetheless, Ramalho et al. reported no significant differences between 2D and 3D sequences (33). Image resolution difference was another limitation, since 2D images had greater slice thickness compared to 3D images. Indeed, voxel size and therefore the resolution depend on the matrix size, the field-of-view, and the slice thickness. However, biases related to partial volume effects and region-delineation errors were avoided by normalizing all images to the MNI space and using a single ROI for all patients. Almost half of our cohort (Gd+ = 125) had received at least one or more gadolinium injections of unknown structure outside of our institution. This could be considered as a major limitation especially since the structure of the injected agent (linear or macrocyclic) could not be accounted for. However, since the analysis of these patients showed no significant differences in either the DN/CP or the GP/CSO ratios, this limitation could be considered negligible. The ROI delineation on the FLAIR images of ten randomly selected patients with various stages of the disease could be questionable in view of the anatomical variations. However, since all the patients' T1 images as well as the manually delineated ROIs were nonlinearly registered to the same MNI152 standard space, the bias introduced by the anatomy alterations between patients is greatly reduced.

The long-term impact of gadolinium deposition on public safety in the brain remains unknown. Our paper along with previous reports reported no signal intensity increases using the macrocyclic GBCAs gadoterate-meglumine (contrarily to linear GBCAs). Future studies should continue to investigate histopathological gadolinium deposition on autopsy specimen using more sensitive techniques like inductively coupled plasma mass spectrometry introduced by McDonald et al. (6) that can detect small amounts of accumulated macrocyclic gadolinium in the brain not detectable by MRI. According to the "NIH perspective on reports of gadolinium deposition in the brain," it appears prudent at this time to use macrocyclic agents for their favorable safety profile, higher in vitro and in vivo stability and longer dissociation half-lives, and a low risk of potential long-term deposition within normal tissue (34). NIH also recommended the use of GBCASs only when clinically indicated (use of macrocyclic rather than linear agent) or when specified in an institutional Review Board approved protocol. Additionally, MRI protocols should always consider FDA label indications and dosing

schemes for administration of GBCAs. Finally, a research roadmap is crucial and needed to improve our understanding of gadolinium retention and its clinical importance (30,35).

CONCLUSION

In conclusion, we found no increased T1 SI in the dentate nuclei and globus pallidus regions susceptible to gadolinium deposition after multiple administrations of the macrocyclic GBCA gadoterate-meglumine.

ACKNOWLEDGMENT

The authors would like to thank the Nehme and Therese Tohme Multiple Sclerosis Center at the American University of Beirut Medical Center for funding this study.

REFERENCES

1. Kanda T, Ishii K, Kawaguchi H, et al. High signal intensity in the dentate nucleus and globus pallidus on unenhanced T1-weighted MR images: relationship with increasing cumulative dose of a gadolinium-based contrast material. Radiology 2014; 270:834–841 doi:10.1148/radiol.13131669.
2. Semelka RC, Ramalho M, AlObaidy M, et al. Gadolinium in humans: a family of disorders. Am J Roentgenol 2016; 207:229–233 doi:10.2214/AJR.15.15842.
3. Olchowy C, Cebulski K, Łasecki M, et al. The presence of the gadolinium-based contrast agent depositions in the brain and symptoms of gadolinium neurotoxicity—a systematic review. PLoS One 2017; 12: e0171704doi:10.1371/journal.pone.0171704.
4. Kanda T, Nakai Y, Oba H, et al. Gadolinium deposition in the brain. Magn Reson Imaging 2016; 34:1346–1350 doi:10.1016/j.mri.2016.08.024.
5. Cao Y, Huang DQ, Shih G, et al. Signal change in the dentate nucleus on T1-weighted MR images after multiple administrations of gadopentetate dimeglumine versus gadobutrol. Am J Roentgenol 2016; 206:414–419 doi:10.2214/AJR.15.15327.
6. McDonald RJ, McDonald JS, Kallmes DF, et al. Intracranial gadolinium deposition after contrast-enhanced MR imaging. Radiology 2015; 275:772–782 doi:10.1148/radiol.15150025.
7. Kanda T, Osawa M, Oba H, et al. High signal intensity in dentate nucleus on unenhanced T1-weighted MR Images: association with linear versus macrocyclic gadolinium chelate administration. Radiology 2015; 275:803–809 doi:10.1148/radiol.14140364.
8. Radbruch A, Weberling LD, Kieslich PJ, et al. Gadolinium retention in the dentate nucleus and globus pallidus is dependent on the class of contrast agent. Radiology 2015; 275:783–791 doi:10.1148/radiol.2015150337.
9. Radbruch A, Weberling LD, Kieslich PJ, et al. High-signal intensity in the dentate nucleus and globus pallidus on unenhanced T1-weighted images: evaluation of the macrocyclic gadolinium-based contrast agent gadobutrol. Invest Radiol 2015; 50:805–810 doi:10.1097/RLI.0000000000000227.
10. Ryu YJ, Choi YH, Cheon JE, et al. Pediatric brain: gadolinium deposition in dentate nucleus and globus pallidus on unenhanced T1-weighted images is dependent on the type of contrast agent. Invest Radiol 2018; 53:246–255 doi:10.1097/RLI.0000000000000436.
11. Ramalho J, Castillo M, AlObaidy M, et al. High signal intensity in globus pallidus and dentate nucleus on unenhanced T1-weighted MR images: evaluation of two linear gadolinium-based contrast agents. Radiology 2015; 276:836–844 doi:10.1148/radiol.2015150872.
12. Moser FG, Watterson CT, Weiss S, et al. High signal intensity in the dentate nucleus and globus pallidus on unenhanced t1-weighted mr images: comparison between gadobutrol and linear gadolinium-based contrast agents. Am J Neuroradiol 2018; 39:421–426 doi:10.3174/ajnr.A5538.
13. Langner S, Kromrey M-L, Kuehn J-P, et al. Repeated intravenous administration of gadobutrol does not lead to increased signal intensity on unenhanced T1-weighted images—a voxel-based whole brain analysis. Eur Radiol 2017; 27:3687–3693 doi:10.1007/s00330-017-4777-0.
14. Confavreux C, Vukusic S. Natural history of multiple sclerosis: a unifying concept. Brain 2006; 129:606–616 doi:10.1093/brain/awl007.
15. Filippi M. Enhanced magnetic resonance imaging in multiple sclerosis. Mult Scler J 2000; 6:320–326 doi:10.1177/135245850000600505.
16. Berghoff SA, Düking T, Spieth L, et al. Blood-brain barrier hyperpermeability precedes demyelination in the cuprizone model. Acta Neuropathol Commun 2017; 5:94 doi:10.1186/s40478-017-0497-6.
17. Errante Y, Cirimele V, Mallio CA, et al. Progressive increase of T1 signal intensity of the dentate nucleus on unenhanced magnetic resonance images is associated with cumulative doses of intravenously administered gadodiamide in patients with normal renal function, suggesting dechelation. Invest Radiol 2014; 49:685–690 doi:10.1097/RLI.0000000000000072.
18. Stojanov DA, Aracki-Trenkic A, Vojinovic S, et al. Increasing signal intensity within the dentate nucleus and globus pallidus on unenhanced T1W magnetic resonance images in patients with relapsing-remitting multiple sclerosis: correlation with cumulative dose of a macrocyclic gadolinium-based contrast age. Eur Radiol 2016; 26:807–815 doi:10.1007/s00330-015-3879-9.
19. Eisele P, Alonso A, Szabo K, et al. Lack of increased signal intensity in the dentate nucleus after repeated administration of a macrocyclic contrast agent in multiple sclerosis. Medicine (Baltimore) 2016; 95:e4624 doi:10.1097/MD.0000000000004624.
20. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol 2011; 69:292–302 doi:10.1002/ana.22366.
21. Smith SM, Jenkinson M, Woolrich MW, et al. Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage 2004; 23:S208–S219 doi:10.1016/j.neuroimage.2004.07.051.
22. Lee JY, Park JE, Kim HS, et al. Up to 52 administrations of macrocyclic ionic MR contrast agent are not associated with intracranial gadolinium deposition: multifactorial analysis in 385 patients. PLoS One 2017; 12: e0183916 doi:10.1371/journal.pone.0183916.
23. Radbruch A, Haase R, Kickingereder P, et al. Pediatric brain: no increased signal intensity in the dentate nucleus on unenhanced T1-weighted MR images after consecutive exposure to a macrocyclic gadolinium-based contrast agent. Radiology 2017; 283:828–836 doi:10.1148/radiol.2017162980.
24. Radbruch A, Haase R, Kieslich PJ, et al. No signal intensity increase in the dentate nucleus on unenhanced T1-weighted MR images after more than 20 serial injections of macrocyclic gadolinium-based contrast agents. Radiology 2017; 282:699–707 doi:10.1148/radiol.2016162241.
25. Young JR, Qiao J, Orosz I, et al. Gadolinium deposition within the paediatric brain: no increased intrinsic T1-weighted signal intensity within the dentate nucleus following the administration of a minimum of four doses of the macrocyclic agent gadobutrol. Eur Radiol 2018: 1–8 doi:10.1007/s00330-018-5464-5.
26. Stojanov DA, Aracki-Trenkic A, Vojinovic S, et al. Increasing signal intensity within the dentate nucleus and globus pallidus on unenhanced T1W magnetic resonance images in patients with relapsing-remitting multiple sclerosis: correlation with cumulative dose of a macrocyclic gadolinium-based contrast age. Eur Radiol 2016; 26:807–815 doi:10.1007/s00330-015-3879-9.
27. Agris J, Pietsch H, Balzer T. What evidence is there that gadobutrol causes increasing signal intensity within the dentate nucleus and globus pallidus on unenhanced T1W MRI in patients with RRMS? Eur Radiol 2016; 26:816–817 doi:10.1007/s00330-015-4019-2.
28. Kijowski R, Gold GE. Routine 3D magnetic resonance imaging of joints. J Magn Reson Imaging 2011; 33:758–771 doi:10.1002/jmri.22342.
29. Roccatagliata L, Vuolo L, Bonzano L, et al. Multiple sclerosis: hyperintense dentate nucleus on unenhanced T1-weighted MR images is associated with the secondary progressive subtype. Radiology 2009; 251:503–510 doi:10.1148/radiol.2511081269.
30. McDonald RJ, Levine D, Weinreb J, et al. Gadolinium retention: a research roadmap from the 2018 NIH/ACR/RSNA workshop on gadolinium chelates. Radiology 2018; 289:517–534 doi:10.1148/radiol.2018181151.
31. Forslin Y, Shams S, Hashim F, et al. Retention of gadolinium-based contrast agents in multiple sclerosis: retrospective analysis of an 18-year longitudinal study. Am J Neuroradiol 2017; 38:1311–1316 doi:10.3174/ajnr.A5211.
32. Hannoun S, Durand-Dubief F, Confavreux C, et al. Diffusion tensor-MRI evidence for extra-axonal neuronal degeneration in caudate and

thalamic nuclei of patients with multiple sclerosis. Am J Neuroradiol 2012; 33:1363–1368 doi:10.3174/ajnr.A2983.
33. Ramalho J, Ramalho M, AlObaidy M, et al. T1 signal-intensity increase in the dentate nucleus after multiple exposures to gadodiamide: intraindividual comparison between 2 commonly used sequences. Am J Neuroradiol 2016; 37:1427–1431 doi:10.3174/ajnr.A4757.
34. Malayeri AA, Brooks KM, Bryant LH, et al. National Institutes of Health Perspective on Reports of Gadolinium Deposition in the Brain. NIH Public Access, 2016; doi:10.1016/j.jacr.2015.11.009.
35. Levine D, McDonald RJ, Kressel HY. Gadolinium retention after contrast-enhanced MRI. JAMA–J Am Med Assoc 2018; doi:10.1001/jama.2018.1336.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.acra.2018.11.010.