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T1 signal intensity in the dentate nucleus after the administration of the macrocyclic gadolinium-based contrast agent gadoterate meglumine: An observational study☆

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Abstract
Introduction and aims: Contradictory results have been reported about hyperintensity of the globus pallidus and/or dentate nucleus on unenhanced T1-weighted magnetic resonance (MR) images after exposure to various gadolinium-based contrast agents. This change in signal intensity varies with different gadolinium-based contrast agents. We aimed to determine whether signal intensity in the dentate nucleus is increased in unenhanced T1-weighted images in patients who have undergone multiple studies with the macrocyclic gadolinium-based contrast agent gadoterate meglumine. We thoroughly reviewed the literature to corroborate our results.
Materials and methods: We included patients who had undergone more than 10 MR studies with gadoterate meglumine. We quantitatively analyzed the signal intensity in unenhanced T1-weighted MR images measured in regions of interest placed in the dentate nucleus and the pons, and we calculated the dentate nucleus-to-pons signal intensity ratios and the differences between the ratio in the first MR study and the last MR study. We used t-tests to evaluate whether the differences between the signal intensity ratios were different from 0. We also analyzed the subgroups of patients who had been administered <15 and ≥15 doses of gadoterate meglumine. We used Pearson correlation to determine the relationships between the differences in the signal intensity ratios and the number of doses of gadoterate meglumine administered.

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Results: The 54 patients (26 men) had received a mean of 13.8 ± 3.47 doses (range, 10—23 doses). The difference in the dentate nucleus-pons signal intensity ratio between the first and last MR study was -0.0275 ± 0.1917 (not significantly different from 0; p = 0.2968) in the entire group, -0.0357 ± 0.2204 (not significantly different from 0; *p* = 0.351 in the patients who had received <15 doses (n = 34), and -0.0135 ± 0.1332 (not significantly different from 0; *p* = 0.655) in those who had received ≥15 doses (n = 20). Differences in signal intensity ratios did not correlate significantly with the accumulated dose of gadoterate meglumine (*P* = 0.9064; ρ = -0.0164 [95%]).
Conclusions: Receiving more than 10 doses of gadoterate meglumine was not associated with increased signal intensity in the dentate nucleus.

PALABRAS CLAVE
Gadolinium-based contrast agent;
Signal intensity;
Macrocyclic;
Linear;
Retention

Intensidad de la señal en T1 en el núcleo dentado tras la administración del agente de contraste con gadolinio macrocíclico gadoterato de meglumina: un estudio observacional

Resumen
Introducción y objetivo: Se han notificado resultados contradictorios sobre un aumento en la intensidad de la señal (IS) en las imágenes de resonancia magnética (RM) ponderadas en T1 no realzadas en el globo pálido y/o el núcleo dentado (ND) después de la exposición a varios agentes de contraste con gadolinio (ACG). Este cambio en la señal varía en función del ACG específico. Nuestro objetivo fue investigar si existe un aumento en la IS del ND en imágenes ponderadas en T1 no realzadas en pacientes sometidos a múltiples administraciones del ACG macrocíclico gadoterato de meglumina. Se realizó una revisión exhaustiva de la bibliografía para corroborar nuestros resultados.
Materiales y métodos: Se incluyeron pacientes que se habían sometido a más de 10 estudios de RM con contraste y administración exclusiva de gadoterato de meglumina. Se llevó a cabo un análisis cuantitativo mediante el uso de mediciones de regiones de interés en el ND y el puente en imágenes no realzadas ponderadas en T1. Se calcularon las proporciones ND-puente y las diferencias en las proporciones entre el inicio y la última RM realizada. Se utilizó una prueba de la *t* de una muestra para evaluar si las diferencias en la proporción de la IS difieren de 0. Se realizó un análisis de subgrupos de pacientes con <15 y ≥15 dosis. Se utilizó el análisis de correlación de Pearson para determinar las correlaciones entre las diferencias de las proporciones de la IS y el número de administraciones del ACG.
Resultados: 54 pacientes (26 hombres) recibieron una media de 13,8 dosis ± 3,47 (desviación estándar [DE]) (rango, 10—23 dosis). La diferencia en la proporción de la IS ND-puente entre la primera y la última exploración de RM fue de -0,0275 ± 0,1917 y no difirió significativamente de 0 *P* = 0,2968) en el análisis general y en el análisis de subgrupos [(<15 (n = 34), -0,0357 ± 0,2204, *P* = 0,351 y ≥15 (n = 20), -0,0135 ± 0,1332, *p* = 0,655)]. Las diferencias en la proporción de la IS no se correlacionaron significativamente Pon la dosis acumulada de gadoterato de meglumina (*P* = 0,9064; ρ = -0,0164 [95%]).
Conclusiones: Más de 10 administraciones de gadoterato de meglumina no se asoció a un aumento de la IS en el ND.

Introduction

Gadolinium-based contrast agents (GBCAs) have been used in MRI since 1988. The GBCA safety profile has been reported as excellent over the years.[1] There is incontestable evidence of its diagnostic value in clinical practice. Free gadolinium (Gd^{3+}) is toxic in humans and requires chelation to organic ligands to be used *in vivo* as a contrast agent. According to the molecular structure and its stability *in vivo*, GBCAs may be classified as nonionic linear, ionic linear, or macrocyclic. Macrocyclic chelates are more stable than nonionic linear chelates, and ionic linear chelates are more stable than nonionic ones.[2]

Over recent years, several reports have been published describing increased signal intensity (SI) in the globus pallidi (GP) and/or dentate nuclei (DN) on unenhanced T1-weighted images (WI) in patients with normal renal function and intact blood-brain barrier (BBB), after multiple administrations of

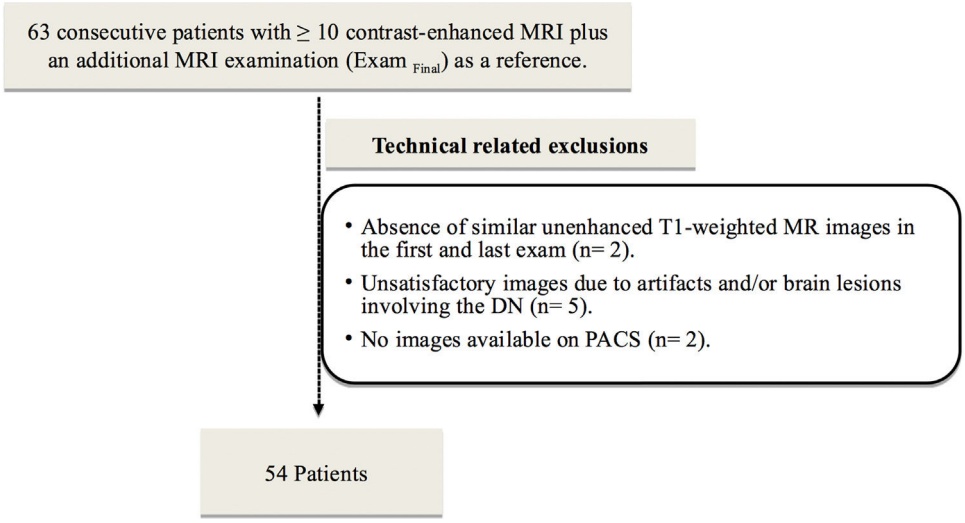

Fig. 1 Study flowchart of included and excluded patients.

a variety of GBCAs. Recent studies obtained histopathological confirmation of Gd deposition, establishing the link between MRI signal changes and Gd retention in brain tissue.

The majority of studies support the concept that hyperintensity in the DN and GP on unenhanced T1-WI are associated with the previous administration of linear, less stable, agents. A few studies have reported a SI increase after multiple exposures to macrocyclic GBCAs as well[3–10] challenging the hypothesis that signal increase is only associated with linear agents. Indeed, Gd in brain tissue has been confirmed after the administration of both classes of GBCA in human[11] and animal studies,[12,13] albeit in higher concentration with linear agents. To the best of our knowledge, there is no scientifically proven histological evidence of cytotoxic effects of gadolinium deposits in autopsy studies.[11]

Previous studies with gadoterate dimeglumine have reported conflicting results regarding visible deposition on MRI.[8–10,14–25] Our purpose was to investigate whether there is an increased SI of DN on unenhanced T1-WI in patients who underwent multiple (>10) administrations of the macrocyclic GBCA using a standardized protocol.

Material and methods

Patients

From our hospital database, we identified 63 consecutive patients with the diagnosis of a brain tumor who underwent at least 10 brain contrast-enhanced MRI exclusively with gadoterate meglumine (Dotarem; Guerbet, Aulnay-sous-Bois, France) between May 2005 and August 2017. All consecutive MR imaging examinations were performed in our department. Patients who underwent contrast enhanced MRIs outside our institution were not part of the study.

Patients without the same unenhanced T1- weighted MR sequences in the first and last exam (n = 2), without available exams in the PACS system (n = 2) or unsatisfactory images due to artifacts and/or brain lesions involving the DN (n = 5) were excluded. (Fig. 1) Our final population included 54 patients (28 female, 26 male; mean age, 40.9 ± 14.4 (standard deviation).

Forty-seven patients underwent appropriate radiation therapy. All patients had normal liver and renal function, as evaluated with routine laboratory tests. Abnormal liver function was defined by abnormal serum concentrations of aspartate aminotransferase, alanine aminotransferase, total bilirubin, or g-glutamyl transpeptidase. Renal function was assessed utilizing the estimated glomerular filtration rate. Only patients with an estimated glomerular filtration rate of > 60 mL/min/1.73 m2 were considered to have normal renal function.

The total number of administered doses of GBCA ranged from 10 to 23 (mean 13.8 doses ± 3.47 (standard deviation), and the interval between the first and last examinations ranged from 96 to 1905 days (mean 2235.5 ± 885.9 days). A summary of patient data is shown in Table 1.

Imaging protocol

Studies were acquired using a 1.5-T MR imaging system (Magnetom Avanto; Siemens, Erlangen, Germany) with a 12-element designed head matrix coil.

The MR imaging protocol for patients varied according to the clinical indications, but all protocols included fast spin-echo T1-weighted MR imaging performed with the following settings: repetition time msec/echo time msec, 623/13; echo train length, 1; section thickness, 5 mm; spacing, 1 mm; matrix size, 256 × 256; and field of view, 165 × 220.

A standard dose 0.1 mmol of gadoterate meglumine per kilogram of body weight was administered intravenously by using a power injector (Medrad, Pittsburgh, Pa) at a rate of 1.5–2.0 mL/sec and was followed by a 20-mL saline flush bolus administered at the same rate.

Table 1 Patients' demographics and examinations description.

Number of patients	54
Age	40.9 years ± 14.4 (SD)
Gender	28 female 26 male
Number of eMRIs	13.8 doses ± 3.47 (SD) (range, 10−23 doses)
Interval (days)	2235.5 ± 885.9
Diagnosis	Brain tumor (supra-tentorial in location): - Glioblastoma (n = 17) - Astrocytoma (n = 11) [Pilocytic (n = 2); Diffuse (n = 2), anaplastic (n = 6); gemistocytic (n = 1)] - Oligodendroglioma (n = 13) - Oligoastrocytoma (n = 4) - Meningioma (n = 3) - Metastasis (breast cancer) (n = 2) - Craniopharyngioma (n = 1) - Germinoma (n = 1) - Pineocytoma (n = 1) - Hemangioperycitoma (n = 1)

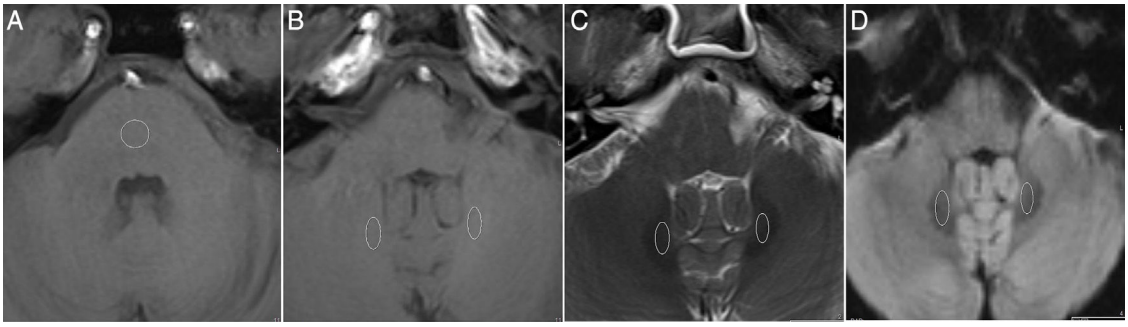

Fig. 2 Axial unenhanced T1-Weighted images at the level of the pons (a) and dentate nucleus (b) showing ROI placement. Axial T2-weighted (c) and diffusion weighted (d) images were used to guide the correct ROI placement.

Image and data analysis

All MR images were reviewed in our picture archiving and communication system (PACS) workstation Carestream PACS, version 11.0 (Carestream Health, Inc.; Rochester, NY USA).

Region of interest (ROI) placement was agreed upon by consensus of two readers (JR and TM with 13 years and 1 year of experience in neuroradiology, respectively). Oval ROIs were drawn around both DN (left and right) and central pons to include as much of each anatomic structure as possible, avoiding lesions, vessels, or artifacts on the first and last unenhanced T1-weighted images. (Fig. 2) Images from axial diffusion-weighted and axial T2-weighted sequences were used to guide the correct ROI placement.

Measurements were averaged for right and left DN, and the DN-to-pons SI ratio was calculated by dividing the mean SI of the DN by that of the pons. SI ratio differences were calculated by subtracting the SI ratio of the first from the SI ratio of the last MR examination. (Fig. 3)

All the procedures were conducted strictly following the Declaration of Helsinki. Since this is a single-center retrospective longitudinal observational study, in which collected data was stripped of all personal identifiers, informed consent was not obtained.

Statistical analysis

All statistical analyses were performed using a statistical software program (MedCalc, version 11.1.1.0; MedCalc, Mariakerke, Belgium). The Kolmogorov-Smirnov test tested the normality of quantitative data, and the choice of parametric versus nonparametric test statistics was made based on the outcome of this test.

A one-sample *t*-test was used to determine whether the SI ratio differences between the baseline and last MRI differed from 0. Pearson correlation analysis was used to examine whether the DN-to-pons SI ratio differences were influenced by the number of MR imaging examinations or the time interval between the first and the last GBCA application. A two-sample *t*-test and Pearson correlation also performed a subgroup analysis differentiating between patients with <15 and ≥ 15 GBCA administration. A *P* value of .05 was considered to indicate a significant difference for all statistical tests.

Results

Of the 106 evaluated MR imaging examinations (53 baseline, 53 fin. l), the right DN was excluded in 2 patients, and the

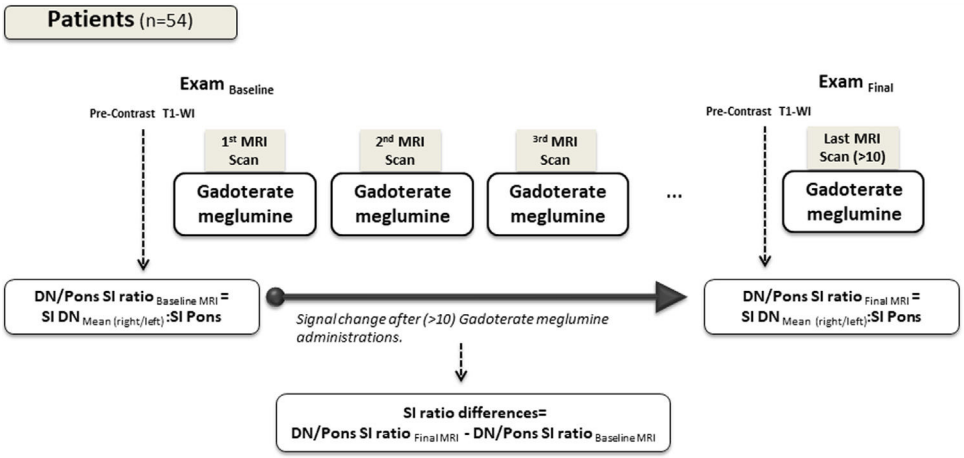

Fig. 3 Schematic representation of the study design.

left DN was excluded in 1 patient in both examinations due to the presence of artifacts or lesions involving these structures. In these patients, ratios were calculated based on the unilateral values alone without averaging. A total of 312 ROIs were drawn.

The distribution of the data was normal, according to the Kolgomorov-Smirnov one-sample test for normal distribution ($P > .01$).

The first and last DN-to-pons SI ratios differences in the entire study population and the two subgroups (<15 and ≥15 contrast-enhanced MR scans) are shown in Fig. 4. The SI ratio difference did not significantly differ from 0 in the overall study population -0.0275 ± 0.1917, $P = 0.2968$) as well as in the subgroup analyses, not only in the group with fewer than 15 contrast-enhanced MR scans (n = 34) −0.0357 ± 0.2204, P = 0.351), but also in the group with 15 or more contrast-enhanced MR scans (n = 20) −0.0135 ± 0.1332, $P = 0.655$). Table 2

No significant correlation was found between the DN-to-pons SI ratio difference and the mean number of contrast-enhanced MR scans (P = 0.9064; ρ= -0.0164 [95%]). The SI ratio differences did not significantly correlate with the cumulative dose of gadoterate meglumine ($P = 0.9064$; ρ= -0.0164 [95%]). The number of MR imaging examinations and time between the first and last exams did not have a significant influence on the SI ratio difference.

A non-significant trend towards SI stability was seen in patients with less than 15 doses and towards a decrease in SI ratio in more than 15 doses.

Discussion

We did not find a significant increase in SI in the DN after the administration of up to 23 doses of gadoterate meglumine. Our results are consistent with most studies, in that successive administrations of macrocyclic GBCA in adults are not associated with a significant increase in SI DN ratios on unenhanced T1-WI. Our results also corroborate the prior observations that macrocyclic GBCAs are less prone to dechelation and transmetallation due to their high kinetic and thermodynamic stability, which may ultimately contribute to Gd deposition in tissues that results in MR signal changes.

Macrocyclic agents currently available include the non-ionic agents' gadoteridol (ProHance; Bracco Diagnostics Inc. Italy) and gadobutrol (Gadovist; Bayer Healthcare, Berlin, Germany), and the ionic agent gadoterate meglumine (Dotarem; Guerbet, Aulnay-sous-Bois, France), the latter being the subject of the present study.

Previous studies in adults[26,27] and children[28] found no significant T1 SI changes after the administration of Gadoteridol. The majority of studies reporting on Gadobutrol in adult[16,29–34] and pediatric[28,35,36] patients, as well as healthy volunteers[37] also did not demonstrate T1 SI changes. Moreover, different approaches, such as relaxometry[38] and voxel-based whole-brain analysis,[39] did not demonstrate significant relaxation time T1 ratios or signal changes.

Regarding gadoterate meglumine, several studies did not find signal changes after repeated doses of this agent. Radbruch et al.[14] did not observe significant MRI changes after a mean of 7.06 doses, and Lee at al.[17] found similar results in 385 patients. Eisele et al.[15] and Salem Hannoun et al.[23] evaluated multiple sclerosis (MS) patients, and they did not obtain significant changes after 6–12 doses and up to 23 doses, respectively. Barbara Bennani-Baiti et al.[24] evaluated healthy women at high risk for breast cancer who underwent annual contrast-enhanced breast MRI screening. After exposure to relatively large cumulative doses of gadoterate dimeglumine, there was no T1 SI increase in deep brain nuclei. Comparable results were described in pediatric studies. Radbruch et al.[18] (mean of 8.6 doses), Pozeg et al.[25] (at least 10 doses), and Ryu et al.[20] (mean of 4.7 doses) found no significant increase in SI in the DN after gadoterate meglumine. Even patients who underwent MR cisternography with intrathecal administration of gadoterate meglumine showed no measurable T1 SI changes in the GP and DN.[40]

However, conflicting studies with macrocyclic agents reporting T1 signal changes after the administration of these agents in adult[3–8] and pediatric patients[9,10] have been published. Considering adult patients, Stojanov et al.[3] reported an increased T1 SI in DN and GP in MS patients with relapsing-remitting MS after successive administrations (4–6) of gadobutrol. However, the validity of these

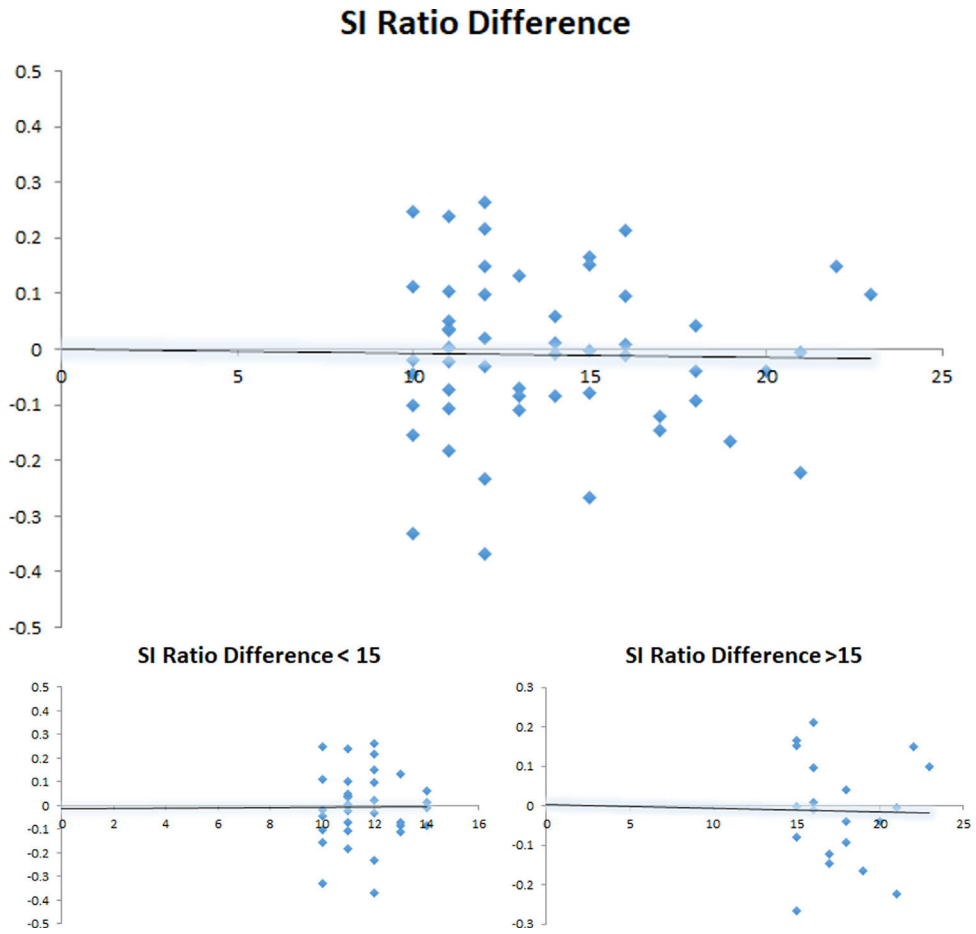

Fig. 4 Scatterplot representation of DN-to-pons SI ratio difference between the first and last MR examination in general analysis (a) and in subgroup analysis (b) (<15 and ≥15 contrast-enhanced MR scans).

Table 2 Mean, Standard deviation and results of One sample *T*-Test of the total population and subgroup analysis.

All patients (n = 54)	Mean ± SD	SI Ratio Differences ± SD	*T*-Test *P* value
DN/Pons SI Ratio $_{Baseline}$	2.034 ± 0.114	−0.0275 ± 0.1917	*P* = 0.2968
DN/Pons SI ratio $_{final}$	2.006 ± 0.1606		
Pts with <15 doses (n = 34)			
DN/Pons SI Ratio $_{Baseline}$	2.043 ± 0.1314	−0.0357 ± 0.2204	*P* = 0.351
DN/Pons SI ratio $_{final}$	2.007 ± 0.1864		
Pts with ≥15 doses (n = 20)			
DN/Pons SI Ratio $_{Baseline}$	2.0183 ± 0.0774	−0.0135 ± 0.1332	*P* = 0.655
DN/Pons SI ratio $_{final}$	2.004 ± 0.1076		

findings has been questioned, in particular, due to confounding factors and the absence of a control group of patients without MS.[41] Splendiani et al.[8] found increased SI on unenhanced T1-WI after a minimum of 4 administrations of gadoterate meglumine (n = 81) or gadobutrol (n = 77) in MS patients. Nevertheless, the differences were not statistically significant across the entire patient population. Moreno et al.[6] found an increase in SI in melanoma patients (n = 44) after 4–10 contrast-enhanced MRI studies performed with gadobutrol. Kang et al.[5] studied T1 relaxation time in the brains of 46 patients after receiving a mean of 9 doses of gadobutrol, using dynamic multi-echo MR imaging sequences. The authors found that exposure to gadobutrol was associated with T1 shortening in the GP. Kelemen et al.[7] calculated different SI-ratios, including pallidum, putamen, caudate nucleus, and pulvinar thalami (PTh) using PTh and frontal white matter (FWM) as references and DN using pons and FWM as reference. The study was conducted in patients with MS after the administration of multiple doses of gadobutrol. The authors found that minor Gd accumulation is possible if FWM was used as a reference area. Bjornerud et al.[4] studied 17 patients with high-grade gliomas who had received 10–44 administrations of gadobutrol and found a small, but statistically significant, dose-dependent

T1 SI increase in the DN. Interestingly the differences in SI between the baseline and last MR examination were more clear after 25 doses, which could explain the absence of signal changes in other series.

Considering pediatric patients and disagreeing with other studies,[18–21,25] Espagnet et al.[9] found an increased SI in DN and GP in 50 pediatric patients exposed to ≥6 administrations of gadoterate meglumine. Topcuoglu et al.[10] also noticed a significant T1 SI increase reflecting Gd retention in the brain of children with at least three gadoterate meglumine injections, in addition to a correlation between the number of administrations and the signal increase.

We consider that conflicting results in MRI studies may be related, among other things, to differences in technical aspects and/or the presence of confounding factors. However, as histological studies have shown the deposition of Gd of all types of GBCA,[11] it is clear that much of the deposited Gd remains undetectable on MRI. The explanation of why the retained Gd in macrocyclic agents remains undetected most likely relates to the fact that the amount may be small and below the level of MRI detection, where a threshold is present to appreciate hyperintensity on unenhanced T1-weighted images. However, the role or influence of the speciation, composition, and environment that results in a high signal is not established at present.

In a recent animal study, Frenzel et al.[42] investigated whether residual Gd is present as intact Gd complex or in other chemical forms, by using tissue fractionation and chromatography after administration of different linear and macrocyclic agents. The residual Gd after repeated administration of linear agents was present in 3 distinctive forms: 1) small soluble molecules, including the intact GBCA, 2) soluble macromolecules, and 3) insoluble forms. The Gd concentrations in the brain after administration of the macrocyclic agents were lower, and Gd was only present in small soluble molecules.

The presence of a sizable soluble fraction for all GBCAs probably explains their passive infiltration into the brain for all agents, which is not dependent on its chemical structure, GBCA stability, or ionic charge. In addition to a concentration difference in deposition between linear and macrocyclic classes, we hypothesize that the soluble macromolecular form of Gd, present with linear, absent with macrocyclic, likely contributes substantially to this difference. A high T1 signal of proteinaceous fluid observed on MR is explained by the higher tumbling rate of protons located in large proteins, which is the comparator for this observation. Additionally, MR agents with protein binding show higher T1 relaxivity because of this. MRI alone may be an imperfect measure for the amount of Gd deposited in the brain as Gd bound to protein is most visible, small soluble molecules moderately visible, and insoluble Gd likely invisible.

Lee at al.[17] and Rahatli et al.[43] found that patients with abnormal renal function showed a statistically significant increase in SI ratio differences, probably related to the reduced GBCA elimination and prolonged dwell time, allowing dissociation of linear GBCA complex to occur, resulting in a progressively higher fraction of soluble macromolecular form, even though the insoluble form also would increase. However, the effect of the former outweighing the latter. In our study, there were no renal impaired patients, so we were not able to assess this possibility. This finding suggests that even the macrocyclic GBCAs retained in the brain may produce SI changes on MRI, but this would be more likely with the agent with the lowest thermodynamic stability (*i.e.*, gadobutrol). In fact, most studies that have shown high SI following a macrocyclic agent have been reported with gadobutrol. It would be prudent though, to consider, based on conflicting data of SI change with macrocyclic agents, that we cannot exclude that higher number (>25) of gadoterate meglumine injections may result in a SI increase in the DN.

Interestingly, in our study, the mean DN-to-pons SI ratio showed a negative trend in patients with more than 15 doses of GBCA. Despite not achieving statistical significance, this trend may represent an ongoing elimination of Gd, as suggested by Frenzel et al.[42] In their study, they found that the Gd concentration of the soluble fractions from all agents showed a washout between days 3 and 24 after contrast injection. However, at present, this should be considered a preliminary observation. It remains to be determined whether underlying disease or disruption of the blood-brain barrier increases the risk of brain accumulation of Gd, the influence of the time interval between Gd administrations on T1 signal, and undoubtedly other factors that may affect these findings.

Our study has some limitations. The retrospective nature of the study always carries some limitations, in our case, probably minor regarding technical factors, as identical imaging protocol was applied to the same MR imager in all patients. However, system upgrades over time may have some minimal effect. Second, we did not take into consideration the potential confounding effect of treatment. However, the impact of radiation therapy on MR imaging SI changes has been addressed previously with differing results. Radbruch et al.[14] and Adin et al.[44] did not find any effect of radiotherapy on signal intensity ratios overtime, Lim et al.[45] found that radiation can induce R1 value increase in the brain parenchyma, which might suggest accelerated Gd accumulation due to damage to the blood-brain barrier. Regarding pediatric patients, results also show some variation. Rowe et al.[46] found that chemotherapy appeared to have no impact on the trajectory of T1 signal. In contrast, others[47,48] found that brain irradiation contributes to a higher dentate nucleus SI in pediatric patients with brain tumor independent of the administration of linear[48] or macrocyclic Gd-based contrast agents.[49] Third, patient age also influences the SI in deep brain nucleus, as demonstrated by Quatrocchi et al.[49] and Pozeg et al.[25] Fourth, we did not perform a qualitative analysis. However, in a recent study, quantitative analyses showed significant SI differences in overtime, and qualitative assessment of contrast-optimized images revealed visible DN enhancement in only two patients. These results suggest that ROI measurements may reveal subtle enhancement effects not evident with standard visual inspection.[4] Fifth, the choice of DN and the appropriate comparator. We used the DN-to-pons, based on the prior report of McDonald et al.,[50] who found 23 times more Gd in the DN than in the pons on postmortem brain tissue analysis. Sixth, as with most studies on GBCA, it

was impossible to exclude that our patients did not receive other GBCAs before the first study performed at our institution. We accounted for this potential bias by exclusively analyzing the SI ratio differences between the first and last MR imaging examinations and did not analyze absolute SI values.

Conclusions

More than 10 administrations of gadoterate meglumine did not result in an SI increase in DN. However, we cannot exclude that administration of more than 20 doses may eventually result in an SI increase in this structure.

Authorship

All authors have sufficiently and equally participated in the preparation of this manuscript, revised it before submission, and provide verbal approval for submission.

Conflict of interests

The authors declare that they have no conflict of interests.

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