Quantification of Gadolinium Deposition in the Brain Using Quantitative MRI

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Abstract

Gadolinium depositions in the brain caused by Gadolinium Based Contrast Agents (GBCAs) represent a topical issue since depositions have been confirmed, but their potential effects remain unknown. The purpose of this study is to show that quantitative MRI provides an alternative to conventional MRI for detection of gadolinium depositions without the need for reference areas, while also avoiding methodological limitations associated with conventional MRI, facilitating future studies on the subject. This retrospective observational cohort study of longitudinally acquired data uses quantitative MRI to quantify gadolinium depositions in six areas of the brain; the dentate nuclei, globus pallidi, thalami, pons, white matter and frontal cortex grey matter of 43 patients who received two to five doses of Magnevist (a linear GBCA) from 2009 to 2015. R_1 was measured at baseline and after four years in the six areas of the brain of each patient. The changes in R_1 were examined using a Paired-Samples T test. The correlation between doses of Magnevist and R_1 was analysed using an Independent-Samples T test. There was a significant increase in R_1 ($p < 0.05$), consistent with gadolinium depositions in the dentate nuclei, globus pallidi and grey matter. No significant increase of R_1 was found in the thalami, white matter or pons. A correlation between doses of Magnevist and R_1 was found in the dentate nuclei and grey matter, but not in the globus pallidus. The results suggest that quantitative MRI is an alternative to conventional MRI for early detection of gadolinium depositions, while additionally providing quantitative measurements for comparison and follow-up.

Introduction

Gadolinium-based contrast agents (GBCAs) used for MRI are known to cause gadolinium depositions in several areas of the human body, including the brain, skin and bone (1). After the initial report in 2014 (2), gadolinium depositions in the brain have mainly been found in the dentate nuclei and globus pallidi, mostly associated with linear GBCAs (3, 4). There have also been studies indicating gadolinium uptake in the grey matter, thalami, pons and white matter (1, 5). Since 2014, studies on gadolinium depositions in the brain have focused on detection, distribution, potential toxicity and clinical consequences (1). This study focuses on the former, hopefully facilitating studies on the latter.

Various studies have shown that gadolinium depositions become detectable using conventional MRI after approximately four to six administrations of GBCAs, although most studies have been conducted on patients receiving far more than that (4). Previous studies on gadolinium depositions in the brain mainly used conventional T1-weighted MR images, where the affected areas were compared to reference areas using intensity ratios, and gadolinium depositions were detected by an increase in these intensity ratios. This method does not provide quantitative data on gadolinium depositions (T1 signal intensity depends on MRI parameters and does not provide linear associations) and the results cannot be compared over time or between different patients or populations. Furthermore, histopathological studies have shown that gadolinium retention is widespread and also occurs in brain regions that are often used as reference areas, such as the thalami (6).

In this study we use quantitative MRI to detect early gadolinium depositions after two to five (mean 3.4) doses of linear GBCAs without the use of reference areas. To our knowledge, so far, there have been only a few cross-sectional studies with quantitative MRI in the context of gadolinium retention (7, 8), and no studies on longitudinal data.

Our hypothesis is that using quantitative MRI, we can confirm the gadolinium depositions after fewer doses of GBCAs than generally seen on conventional MRI, without the need for reference areas, providing quantitative data

making comparison and follow-up in future studies on gadolinium depositions easier.

Results

Subjects and GBCA doses

Four different GBCAs were used in MRI exams before and during the study; the linear GBCAs Magnevist and Omniscan, and the macrocyclic GBCAs Dotarem and Gadovist. Only linear GBCAs were studied since macrocyclic GBCAs are not associated with signal intensity change on MRI (3, 4). The mean dose of Magnevist received by the 43 patients before the study was 0.14 (range 0–3), and the mean dose received during the study was 3.4 (range 2–5). The mean dose of Omniscan received before the study was 0.42 (range 0–2). No patients received Omniscan (or any other linear GBCA than Magnevist) during the study period (Table 1).

Table 1
Doses of GBCAs during or before the study period

Patient	Magnevist before	Magnevist during	Omniscan before	Omniscan during	Dotarem before	Dotarem during	Gadovist before	Gadovist during
1	0	3	1	0	0	0	0	0
2	0	3	0	0	0	0	0	1
3	1	3	0	0	0	0	0	0
4	0	4	1	0	0	0	0	0
5	0	3	1	0	0	0	0	1
6	3	4	2	0	0	0	0	0
7	0	4	0	0	0	0	0	0
8	0	4	0	0	0	0	0	0
9	0	4	0	0	0	0	0	0
10	0	4	1	0	0	0	0	0
11	0	3	0	0	0	0	0	0
12	0	5	0	0	0	1	0	0
13	0	2	0	0	0	0	0	0
14	0	3	0	0	0	0	0	0
15	0	2	1	0	0	0	0	1
16	0	2	2	0	0	0	0	0
17	0	3	0	0	0	0	0	0
18	0	4	0	0	0	1	0	1
19	0	4	0	0	1	0	0	0
20	0	3	0	0	0	1	0	0
21	0	3	0	0	0	0	0	0
22	0	4	0	0	0	0	0	0
23	0	4	0	0	0	0	0	0
24	0	3	1	0	0	0	0	0
25	0	3	0	0	0	0	0	0
26	0	3	1	0	0	0	0	0
27	0	3	1	0	0	0	0	0
28	0	4	1	0	0	1	0	0
29	0	3	1	0	0	1	0	0

Patient	Magnevist before	Magnevist during	Omniscan before	Omniscan during	Dotarem before	Dotarem during	Gadovist before	Gadovist during
30	0	3	2	0	0	1	0	0
31	0	4	0	0	0	1	0	0
32	1	3	0	0	0	0	0	0
33	0	4	0	0	0	0	0	0
34	0	3	0	0	0	0	0	0
35	0	3	0	0	0	0	0	0
36	0	4	0	0	0	0	0	1
37	0	3	0	0	0	0	0	1
38	0	3	0	0	0	0	0	0
39	0	3	0	0	0	0	0	0
40	0	4	0	0	0	0	0	0
41	0	4	0	0	0	0	0	0
42	1	3	1	0	0	0	0	0
43	0	4	1	0	0	1	0	0

Analysis of R_1 values

Measurements of the longitudinal relaxation rate R_1 in the dentate nuclei, globus pallidus, thalami, pons, white matter and frontal cortex grey matter revealed an increase in R_1 from 1.42 to 1.46 ($p < 0.001$) in the dentate nuclei, an increase in R_1 from 1.47 to 1.49 ($p = 0.04$) in the globus pallidi, and an increase in R_1 from 0.89 to 0.92 ($p = 0.005$) in the frontal cortex grey matter. There was no significant change in R_1 in the thalami (1.35 to 1.37, $p = 0.17$), pons (1.41 to 1.40, $p = 0.57$) or white matter (1.69 to 1.70, $p = 0.37$) (Fig. 1).

Independent-Samples T tests were performed for the three areas which showed a significant increase of R_1 ; the dentate nuclei, globus pallidi and frontal cortex grey matter, and since only increases in R_1 were found, one-tailed tests were performed.

The Independent-Samples T tests were used to compare the R_1 increase in each area for patients who received three or four doses of Magnevist respectively, since only a few of the patients received two or five doses. The tests showed a significant difference between three and four doses of Magnevist for the dentate nuclei ($p = 0.036$) and frontal cortex grey matter ($p = 0.026$). No significant difference was found for the globus pallidi ($p = 0.325$). (Fig. 2)

Discussion

This study is to our knowledge the first to use quantitative MRI (quantitatively measured longitudinal relaxation) in longitudinal data, measuring gadolinium depositions over time, in our case in six areas of the brain following 3.4 doses (mean) of linear GBCA administration.

Since the results are quantitative, the measured changes are directly proportional to the gadolinium concentration (12). In contrast, when using conventional T1-weighted MRI, the intensity changes due to gadolinium depositions will depend non-linearly on the change in R_1 (i.e. also non-linearly on the gadolinium concentration) (13). Additionally, quantitative MRI has fewer methodological limitations than conventional MRI, such as varying MRI parameters, repetition time, echo time, spin echo/gradient echo or systematic imperfections of RF and B0 inhomogeneities. Furthermore, as mentioned earlier, there is indication of potential gadolinium depositions in areas commonly used as reference areas (6). Arguably, quantitative data in combination with directly measuring areas without using reference areas may provide earlier detection of gadolinium depositions, since there are fewer confounding factors present. Comparisons of conventional and quantitative MRI in this regard could be a potentially interesting subject for future studies.

R_1 was significantly higher in the dentate nuclei, globus pallidi and frontal cortex grey matter following GBCA administration, whereas there was no difference in R_1 in the pons, thalami or white matter. These findings of an intensity increase in the dentate nuclei, globus pallidi and frontal cortex grey matter are consistent with previous findings (4, 6, 14, 15). They are also consistent with the findings of a recently published cross-sectional study using quantitative MRI for comparison of gadolinium depositions in MS patients and controls (8).

Our study did not show any intensity change in the thalami or pons, which has previously been reported (6, 16). However, GBCA doses in this study could potentially be too few to present as an intensity increase, since dose-dependent change in T1-weighted intensity is smaller in the pons and thalami compared to the dentate nucleus (6). Although studies (including ours) have shown no change in signal intensity in white matter, autopsies have shown gadolinium in all areas of the brain, indicating that MRI probably has a limited sensitivity to detect low levels of gadolinium depositions in the brain (5).

Subgroup analyses regarding correlation of GBCA doses and R_1 increase showed a dose-dependent association of GBCA doses and R_1 increase in the dentate nuclei and frontal cortex grey matter. No statistical significance was obtained in the globus pallidi, despite a tendency for R_1 increase between 3 and 4 doses seen in Fig. 2. Outliers in this group are a possible explanation for this result.

To confirm these findings, future studies including more patients and GBCA administrations should be performed, where using 3T MRI instead of 1.5T MRI can provide better image quality and accuracy of ROI placements.

Despite the numerous studies that suggest gadolinium deposition in the brain after multiple GBCA doses, few studies on the clinical manifestations correlated to each deposition area have been published, and those published have not been able to connect gadolinium depositions to signs of toxicity or clinical manifestations (17, 18). Nor have gadolinium brain depositions been proven to have any toxic effects in animal models (19, 20). Consequently, further studies are needed for evaluation of the clinical manifestations of gadolinium depositions. Our results suggest that the use of quantitative MRI can be beneficial for these future studies.

To conclude, quantitative MRI offers an alternative to conventional MRI for detecting and comparing gadolinium depositions in the brain, which can be useful in future studies regarding the distribution and toxicity of gadolinium

depositions. This method provides potentially earlier detection (compared to conventional MRI) without using reference areas which may be subjected to gadolinium depositions, in addition to providing quantitative data with fewer methodological limitations than conventional MRI.

Methods

The study was approved by the local institutional review board of the Swedish Ethical Review Authority in Linköping, and all methods were performed in accordance with the relevant guidelines and regulations. Informed written consent was obtained from all patients.

Study population

Forty-three patients who were earlier enrolled in a prospective longitudinal cohort study of early Multiple Sclerosis (MS) at the Department of Neurology at the University Hospital in Linköping, Sweden, were included. Originally, forty-six patients with a clinical suspicion of MS were consecutively enrolled and examined between October 2009 and May 2015. Three patients were excluded, one due to withdrawal of consent, one due to the finding of a trigeminal schwannoma, which explained the patient's clinical findings, and one due to missing quantitative MRI data. All patients had a normal Glomerular Filtration Rate during the study. Table 2 shows details of the patient demographics.

Table 2
Patient demographics

No. of subjects	43
Median age at inclusion (yr)	31 (range 21–62)
Sex (M/F)	9:34

MR imaging according to a standard clinical MS protocol with the addition of quantitative MRI (qMRI) before and after administration of Magnevist (gadopentate dimeglumine, 0.2 mL/kg body weight, Bayer HealthCare Pharmaceuticals) was performed at inclusion (baseline) and after one year, two years and four years.

In order to have as homogenous a group as possible, all studies used Magnevist as the contrast agent. Some of the patients had received other contrast agents before the study, and during the study when seeking emergency healthcare. However, none of the patients received another linear contrast agent during the study period (Table 1).

We have chosen six areas for our study; two areas that are most established as targets for gadolinium depositions (the dentate nuclei and globus pallidi), and additionally four areas that are often studied regarding gadolinium depositions (the thalami, pons, white matter and frontal cortex grey matter).

MR imaging acquisition

Images were acquired on a 1.5T MR imaging scanner (Achieva, Philips Healthcare, Best, the Netherlands) by using an eight-channel phased array head coil. The sequence parameters for conventional images have previously been described (9).

The quantitative sequence, QMAP (10, 11) is a multi-section, multi-echo, and multi-saturation delay qMRI technique, used with the following parameters in this study:

- qMRI (axial): FOV 230 x 182; 43 sections; in plane resolution 1.5 x 1.5 mm; TE, 14, 28, 42, 56, 70 ms; TR 4244 ms; TI 0.0974, 0.5846, 1.8511, 4.0919 seconds; saturation flip angle 120°; scan time 6:09 minutes (11).

All images had a section thickness of 3 mm without an intersection gap. Post-contrast qMRI images were acquired approximately 15 minutes after intravenous injection of Magnevist.

Post-processing

The qMRI sequence yields quantitative maps of longitudinal relaxation rate R_1 ($R_1 = 1/T_1$), transverse relaxation rate R_2 , and proton density (PD), which are used for measurements and to create quantitative images matching the conventional ones. The post-processing time of the raw image dataset was approximately one minute on an ordinary PC by using SyMRI Diagnostic software (SyntheticMR, Linköping, Sweden) to create quantitative maps of R_1 , R_2 , PD and synthetic T1, T2 and T2 FLAIR images.

Radiologic evaluation

Region of Interests (ROIs) were placed in the quantitative images (Fig. 3) in the area of the dentate nuclei, globus pallidi, thalami, pons, normal-appearing white matter and frontal cortex grey matter (Fig. 4). There were no MS lesions present in the areas of R_1 measurements. The segmentations were performed in MeVisLab (MeVis Medical Solutions AG, Bremen, Germany) by a radiology resident (A.L.L.), supervised by an experienced neuro-radiologist (I.B.). Conventional MR images were available for reference to confirm correct ROI placement. R_1 of the areas was measured in each MR study (the baseline study and the four-year control).

Statistical analysis

All statistical calculations were performed in IBM SPSS Statistics for Macintosh, Version 27.0 (IBM Corp, Armonk NY). A p-value of ≤ 0.05 was considered significant.

The R_1 value from the four-year control was compared to the R_1 value of the baseline study for each subject using a Paired-Samples T test, which was performed for each of the above-mentioned six areas in the brain. For areas with a significant increase of R_1 , an Independent-Samples T test was performed to correlate GBCA doses to the increase in R_1 in these areas.

List Of Abbreviations

GBCA Gadolinium-Based Contrast Agent

MS Multiple Sclerosis

ROI Region Of Interest

qMRI quantitative MRI

PD Proton Density

Declarations

Data availability statement

The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

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Contributions

A.L.L. wrote the main manuscript text. A.L.L. and A.T. prepared figures and tables. All authors reviewed the manuscript and participated in the study design.

Ethics declarations

Competing interests

The authors declare no competing interests.

References

1. Ramalho M, Ramalho J, Burke LM, Semelka RC. Gadolinium Retention and Toxicity—An Update. *Adv Chronic Kidney Dis* [Internet]. 2017;24(3):138–46. Available from: <http://dx.doi.org/10.1053/j.ackd.2017.03.004>
2. Kanda T, Ishii K, Kawaguchi H, Kitajima K, Takenaka D. High signal intensity in the dentate nucleus and globus pallidus on unenhanced T1-weighted MR images: Relationship with increasing cumulative dose of a gadoliniumbased contrast material. *Radiology*. 2014;270(3):834–41.
3. Radbruch A, Weberling LD, Kieslich PJ, Eidel O, Burth S, Kickingereder P, et al. Gadolinium retention in the dentate nucleus and globus pallidus is dependent on the class of contrast agent. *Radiology*. 2015;275(3):783–91.
4. Choi JW, Moon WJ. Gadolinium deposition in the brain: Current updates. *Korean J Radiol*. 2019;20(1):134–47.
5. Kanda T, Fukusato T, Matsuda M, Toyoda K, Oba H, Kotoku J, et al. Gadolinium-based contrast agent accumulates in the brain even in subjects without severe renal dysfunction: Evaluation of autopsy brain specimens with inductively coupled plasma mass spectroscopy. *Radiology*. 2015;276(1):228–32.
6. McDonald RJ, McDonald JS, Kallmes DF, Jentoft ME, Murray DL, Thielen KR, et al. Intracranial gadolinium deposition after contrast-enhanced MR imaging. *Radiology*. 2015;275(3):772–82.
7. Tedeschi E, Palma G, Canna A, Cocozza S, Russo C, Borrelli P, et al. In vivo dentate nucleus MRI relaxometry correlates with previous administration of Gadolinium-based contrast agents. *Eur Radiol* [Internet]. 2016;26(12):4577–84. Available from: <http://dx.doi.org/10.1007/s00330-016-4245-2>
8. Forslin Y, Martola J, Bergendal Å, Fredrikson S, Wiberg MK, Granberg T. Gadolinium Retention in the Brain: An MRI Relaxometry Study of Linear and Macrocyclic Gadolinium-Based Contrast Agents in Multiple Sclerosis. *Am J Neuroradiol*. 2019;40(8):1265–73.

9. Blystad I, Håkansson I, Tisell A, Ernerudh J, Smedby, Lundberg P, et al. Quantitative MRI for analysis of active multiple sclerosis lesions without gadolinium-based contrast agent. *Am J Neuroradiol.* 2016;37(1):94–100.
10. Warntjes JBM, Dahlqvist Leinhard O, West J, Lundberg P. Rapid magnetic resonance quantification on the brain: Optimization for clinical usage. *Magn Reson Med.* 2008;60(2):320–9.
11. Warntjes JBM, Dahlqvist O, Lundberg P. Novel method for rapid, simultaneous T1, T2*, and proton density quantification. *Magn Reson Med.* 2007;57(3):528–37.
12. Rohrer, Martin; Bauer, Hans; Mintorovitch, Jan; Requardt, Martin; Weinmann H-J. Comparison of Magnetic Properties of MRI Contrast Media Solutions at Different Magnetic Field Strengths. *Invest Radiol.* 2005;40(11):715–24.
13. Rinck PA. *Magnetic Resonance in Medicine.* 2019.
14. Kuno H, Jara H, Buch K, Qureshi MM, Chapman MN, Sakai O. Global and regional brain assessment with quantitative MR imaging in patients with prior exposure to linear gadolinium-based contrast agents. *Radiology.* 2017;283(1):195–204.
15. Khant ZA, Hirai T, Kadota Y, Masuda R, Yano T, Azuma M, et al. T1 shortening in the cerebral cortex after multiple administrations of gadolinium-based contrast agents. *Magn Reson Med Sci.* 2017;16(1):84–6.
16. Zhang Y, Cao Y, Shih GL, Hecht EM, Prince MR. Extent of signal hyperintensity on unenhanced T1-weighted brain MR images after more than 35 administrations of linear gadolinium-based contrast agents. *Radiology.* 2017;282(2):516–25.
17. Perrotta G, Metens T, Absil J, Lemort M, Manto M. Absence of clinical cerebellar syndrome after serial injections of more than 20 doses of gadoterate, a macrocyclic GBCA: a monocenter retrospective study. *J Neurol.* 2017;264(11):2277–83.
18. Welk B, McArthur E, Morrow SA, MacDonald P, Hayward J, Leung A, et al. Association between gadolinium contrast exposure and the risk of parkinsonism. *JAMA - J Am Med Assoc.* 2016;316(1):96–8.
19. Gulani V, Calamante F, Shellock FG, Kanal E, Reeder SB. Gadolinium deposition in the brain: summary of evidence and recommendations. *Lancet Neurol [Internet].* 2017;16(7):564–70. Available from: [http://dx.doi.org/10.1016/S1474-4422\(17\)30158-8](http://dx.doi.org/10.1016/S1474-4422(17)30158-8)
20. Hoggard N, Roditi GH. T1 hyperintensity on brain imaging subsequent to gadolinium-based contrast agent administration: What do we know about intracranial gadolinium deposition? *Br J Radiol.* 2017;90(1069).

Figures

Figure 1

Title: Increase in R1 in each area of the brain Caption: R1 of ROIs at baseline and the four-year control, after 3.4 (mean) doses of Magnevist. *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$, ns (non-significant).

Figure 2

Title: Scatter plots of R1 differences correlated to doses of Magnevist
Caption: The scatter plots show the R1 difference for patients receiving two, three, four or five doses of Magnevist in the dentate nuclei, frontal cortex grey matter and globus pallidi. Patients receiving two or five doses of Magnevist were too few to be included in the statistical analyses. A tendency for an increase between patients receiving three and four doses of Magnevist can be seen in all three areas. A significant difference between increase for three and four doses was found in the dentate nuclei and frontal cortex grey matter.

Figure 3

Title: Synthetic grey-scale images and quantitative maps
Caption: This figure illustrates the synthetic grey-scale images and quantitative maps derived from one six-minute scan of one of the patients. In the top row from left to right: synthetic T1WI, synthetic T2WI and synthetic T2FLAIR. In the bottom row from left to right: quantitative R1-map, quantitative R2-map and PD-map. All images, both grey-scale and quantitative maps, are derived from the same scan, meaning that the ROI only needs to be placed once, and is then registered in the same place for all images, since the spatial coding is the same for all images.

Figure 4

Title: ROI placement Caption: Regions of Interest (ROIs) were placed in the quantitative images in the areas of the dentate nuclei, globus pallidi, thalami, pons, white matter and frontal cortex grey matter. The figure shows the ROI placements for one slice of each region.