Gadolinium Deposition in the Brain: Summary of Known Science and Recommendations from the International Society for Magnetic Resonance in Medicine

Vikas Gulani, MD, PhD[1-4*], Fernando Calamante, PhD[5,6], Frank G. Shellock, PhD[7-9], Emanuel Kanal, MD[10], Scott B. Reeder, MD, PhD[11-15]

[1]Radiology, [2]Urology, [3]Biomedical Engineering, [4]Case Comprehensive Cancer Center, Case Western Reserve University and University Hospitals Case Medical Center, Cleveland, Ohio, USA
[5]Florey Institute of Neuroscience and Mental Health, Heidelberg, Victoria, Australia
[6]Florey Department of Neuroscience and Mental Health, University of Melbourne, Melbourne, Victoria, Australia
[7]Radiology, [8]Medicine, [9]National Science Foundation Engineering Research Center, University of Southern California, Los Angeles, California, USA
[10]Radiology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA
[11]Radiology, [12]Medical Physics, [13]Biomedical Engineering, [14]Medicine and [15]Emergency Medicine, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin, USA

* Address Correspondence to:
Vikas Gulani, MD, PhD
Director of MRI
Departments of Radiology, Urology, and Biomedical Engineering
Case Comprehensive Cancer Center
Case Western Reserve University
University Hospitals of Cleveland
11100 Euclid Ave., Bolwell B120
Cleveland, OH 44106-0500

Abstract:

Emerging evidence has linked MRI signal changes in deep nuclei of the brain with repeated administrations of gadolinium based contrast agents. Gadolinium deposits have been confirmed in brain tissue, most notably in the dentate nuclei and globus pallidus. While some agents of a particular chemical structure (termed linear) appear to cause greater signal changes, the deposition phenomenon has also been observed with other (macrocyclic) agents. There is variability among the agents in the degree to which this phenomenon has been observed. The chemical state of deposited gadolinium has not been determined, and no link to renal failure or other disease states has been established. The clinical significance of the retained gadolinium in brain, if any, remains unknown, as there are no data in humans or animals demonstrating a relationship between brain gadolinium deposition and adverse clinical effects. Recommendations are provided and will evolve as new studies are performed and disseminated.

Search and Study Criteria:

An extensive literature review was conducted in order to generate this manuscript. This consisted of Pubmed, Google Scholar, and ISI Web of Science searches on brain gadolinium deposition and gadolinium deposition, with extensive searches of papers referencing already published literature and also following all references in the publications found. Due to the large number of published papers on this topic, those of most importance to the community were selected for reference. Excluded from the manuscript were "research" manuscripts which provided only anecdotal evidence for conclusions. Papers with quantitative data were prioritized for inclusion, as were papers which sought to provide comparisons between agents.

A. Introduction

Magnetic resonance (MR) image signal intensity is affected by MR-specific tissue properties called T_1 and T_2 relaxation times. These are characteristic physical properties of each tissue, related to the behavior of the tissue in a magnetic field. Gadolinium based contrast agents (GBCAs) shorten the T_1 of water protons near the agent, and this phenomenon is exploited to produce images in which tissues with high concentration of GBCA are brighter than areas with lower GBCA concentration. Over 30 million doses are administered world-wide annually, and over 300 million doses have been administered since the introduction of these agents in 1987[1]. GBCAs are indispensable for diagnosis and treatment monitoring of many diseases, and in many research applications. Defined risks of GBCAs include allergic reactions, adverse reactions, and in patients with renal failure, nephrogenic systemic fibrosis (NSF). Allergic and adverse reactions are infrequent but can be serious[2,3]. NSF is a rare scleroderma-like illness that occurs in patients with severe renal disease and exposure to certain GBCAs. NSF has been effectively eliminated by curtailing the administration of GBCAs most closely associated with NSF in high-risk patient populations, and by minimizing GBCA dose.

Multiple recent reports detailed below indicate that there is residual brightness of tissue in deep brain nuclei of the brain, particularly the globus pallidus and dentate nucleus, in patients who have received gadolinium contrast, and additional reports showing that these signal changes are related directly to deposition of gadolinium in these regions. This raises concerns about the context in which gadolinium deposits in the brain, and whether this deposition is accompanied by harm to patients. On behalf of the International Society of Magnetic Resonance in Medicine (ISMRM), we summarize the known literature on this subject, place the material in context of experience with NSF, and provide recommendations for future use of the agents in research and clinical practice.

B. Gadolinium Deposition in the Brain

The presence of high signal on *unenhanced* T1-weighted images in the dentate nucleus and globus pallidus of patients who had undergone multiple GBCA enhanced MRI exams was first described in 2014[4]. Increased relative signal intensity correlated to the total number of gadolinium administrations. A comparison of signal intensities in a subgroup of patients who had undergone at least six contrast-enhanced exams with either gadopentetate dimeglumine or gadodiamide to patients who had undergone only non-contrast MRI, showed higher signal in these nuclei in patients who had undergone repeated GBCA injections. These findings were confirmed in a similar study involving gadodiamide[5] and in multiple subsequent studies[6-8]. Emerging case-report evidence suggests that this phenomenon also occurs in children, with a deposition pattern similar to that observed in adults[9,10].

Due to the association of NSF with renal failure, a natural question is whether gadolinium deposition in the brain is also related to renal failure. Signal intensities and postmortem tissue from brains of 13 patients who underwent at least 4 gadiodiamide enhanced exams were compared with 10 patients who did not receive gadolinium[7]. Gadolinium was confirmed in deep brain nuclei in patients who had undergone prior GBCA enhanced MRI exams, using inductively coupled plasma mass spectroscopy (ICP-MS). The signal intensity ratios had a positive correlation with the tissue concentration of gadolinium, definitively linking increased signal intensity ratios with gadolinium deposition and relative gadolinium concentration. X-Ray microanalysis also demonstrated gadolinium deposits in neuronal tissue. Gadolinium was observed in endothelial walls, but the authors also stated that "… gadolinium appears to have crossed the blood-brain barrier and been deposited into the neural tissue interstitium." Since all patients had normal renal function, gadolinium deposition (in non-diseased and non-irradiated brain tissue) appears to be unrelated to renal function.

Autopsy specimens from brains of five subjects without severe renal compromise who had undergone at least two administrations of linear GBCAs were compared to patients not receiving GBCAs, using ICP-MS[11]. Two subjects also received gadoteridol, one of whom had also received a dose of gadodiamide. Gadolinium was detected in all specimens from the GBCA group and in some specimens from the non-GBCA group at a much smaller concentration. The highest concentration in the GBCA group was in the dentate nucleus and globus pallidus. Gadolinium deposition in the brain was again confirmed in subjects with normal or near-normal renal function.

Quantitative measurements were made as part of an industry-sponsored study examining brains of rats after repeated doses of gadodiamide. This study demonstrated retention of 0.00019% of the dose at one week, and interestingly, clearance of 45% of the deposited gadolinium 20 weeks after deposition[12]. No neurotoxicity was observed.

An important question is whether the choice of contrast agent or agent class are factors in gadolinium deposition. GBCAs can be classified as nonionic and ionic, with ionic agents having greater thermodynamic stability though with an unclear relationship to relative safety. While thermodynamic stability and pH-corrected conditional stability are sometimes used, a better predictor of dissociation rates would likely be the kinetic stability, which provides the dissociation half-life of the gadolinium from its ligand[13]. GBCAs are also commonly classified as linear or macrocyclic, based on the chemical structure of the chelating agent bound to the gadolinium ion. Tables 1[14] and 2 provide summarize characteristics of various contrast agents, and comparative studies regarding the deposition phenomenon. Investigators have attempted to compare the effect of some linear and macrocyclic agents on gadolinium deposition. Patients who underwent six or more exams with gadopentetate dimeglumine (linear) were compared with patients given gadoterate meglumine (macrocyclic), showing that increases

in signal intensity ratios in dentate nucleus relative to the pons, and globus pallidus relative to the thalamus, were greater with gadopentetate dimeglumine, and there was no statistical increase in signal intensity ratio using gadoterate meglumine[6]. A similar study compared gadobenate dimeglumine (linear) with gadopentetate dimeglumine[15]. There was an increase in signal intensity ratio of dentate nucleus to pons, and dentate nucleus to CSF with gadobenate dimeglumine, but the change in dentate nucleus to CSF ratio was smaller for gadobenate dimeglumine, compared to gadopentetate dimeglumine, suggesting lower amounts of gadolinium deposition. A recent study of signal intensity ratios in the dentate nuncleus to pons or middle cerebellar peduncle included 33 patients who underwent 20 consecutive administrations of macrocyclic agents gadoterate meglumine and gadobutrol, showed no significant increase in the signal intensities in the dentate nucleus[16].

These authors hypothesized that differences in signal intensity ratios between linear versus macrocyclic agents were likely due to relative chemical stabilities of the two classes contributing differential amounts of unchelated gadolinium. This was based on the observation that gadolinium deposits measured in autopsy studies correlated with the observed signal intensity changes[7], and that some linear agents have lower thermodynamic stability than the macrocyclic agents currently in use. Thus, linear agents may release more gadolinium. Subsequently, it was reported that increased brain signal intensity ratio changes were observed in a subset of patients given gadopentetate dimeglumine, but not in patients given gadoteridol (macrocyclic)[17].

An industry-sponsored preclinical study investigated gadolinium deposition in rat models imaged serially while receiving over 20 injections of various GBCAs. Three groups were studied, including those administered gadodiamide (linear), gadoterate meglumine (macrocyclic), or hyperosmolar saline[18]. Repeated injections of gadodiamide resulted in progressively increased signal intensity ratio before

reaching a plateau. The authors also measured post-mortem gadolinium concentrations in the brain, and found that rats exposed to gadodiamide had higher gadolinium deposition than rats exposed to gadoterate meglumine. However, the gadolinium concentration in the subcortical brain was also significantly higher for the macrocyclic group than compared to control rats. Notably, the authors administered repeated behavioral exams found no abnormalities suggestive of neurological toxicity.

The same industry group studied gadoterate meglumine, gadopentetate dimeglumine, gadobenate dimeglumine and gadodiamide, and control animals injected with saline, using the previously described methodology with the addition of T1 mapping[19]. Signal intensity changes in the deep cerebellar nuclei were seen for gadodiamide and gadopentetate dimeglumine, but not gadoterate meglumine. Gadobenate dimeglumine showed a trend of increased signal but this was not significant. Quantitative measurements of gadolinium were highest for gadodiamide, followed by gadopentetate dimeglumine, gadobenate dimeglumine, and gadoterate meglumine, followed by saline. Concentrations in rats exposed to all three linear agents were significantly greater than both saline and gadoterate meglumine. Though there was a trend, no significant difference was observed between gadoterate meglumine and saline, pointing to a difference in the deposition of gadolinium between linear and macrocyclic agents. The fact that the concentrations of deposited gadolinium are higher for less thermodynamically and kinetically stable agents, supports the hypothesis that dechelation may play a role in gadolinium deposition. The authors also state that, “no obvious behavioral abnormalities were detected in rats, regardless of the GBCA administered.”

Human studies show considerable variation in observed signal changes among agents, with inconsistent data even for the same agent. For example, gadobenate dimeglumine has been associated with signal intensity changes in deep brain nuclei[15]. However, a study seeking to compare gadodiamide and

gadobenate dimeglumine, indicated that gadiodiamide is associated with signal intensity changes, while gadobenate dimeglumine is not, although there was a trend towards intensity changes in the dentate nucleus only and not in the globus pallidus[8]. The patients in the latter study received fewer doses of gadobenate dimeglumine on average. Recent work compared subjects who underwent at least three exams with gadobenate dimeglumine and who had prior exposure to multiple doses of gadodiamide, to a group who only underwent repeated gadobenate dimeglumine enhanced exams without prior exposure[20]. The group with prior gadodiamide exposure had higher baseline and follow-up signal intensity ratio of the dentate relative to the middle cerebral peduncle, and showed a trend towards an increased effect in patients who had prior gadodiamide exposure. The authors hypothesized a potentiating effect by gadodiamide, with a mechanism not yet understood.

Direct measurements of gadolinium deposition have been obtained in autopsy derived tissue from patients who had received various combinations of gadoteridol (macrocyclic), gadobutrol (macrocyclic), gadobenate dimeglumine, and gadoxetate disodium[21]. Gadolinium was found in all sampled brain regions, with all agents. This study showed that gadolinium from macrocyclic agents, as well as that from linear agents considered to be low NSF risk, does deposit in the brain. This phenomenon was documented after even a single dose. While the number of subjects was small, the work pointed to potential differences in levels of deposition between the macrocyclic agents investigated, with a higher rate of gadobutrol deposition than gadoteridol. Further, the degree of deposition observed for the two linear agents studied was less than that observed for agents previously implicated as carrying greater risk of NSF[14]. Both findings indicate that agent-specific characteristics such as protein interactions and chelate stability may play a role in the degree of deposition of gadolinium. Direct mapping showed Gadolinium deposition in a patient who had received 4 doses of Gadolinium [linear agents] over a lifetime, and showed no measureable signal intensity change[22]. This raises the question whether the

signal changes were absent simply due to concentration (though observed concentrations were similar to other studies), or if the form of deposited Gadolinium plays a role in the signal change. It is quite plausible that the chemical form of deposited agent may be different for linear and macrocyclic agents.

Based on the totality of data, we conclude that a simple division of agents into macrocyclic and linear classes is insufficient to classify the pharmacokinetic behavior of GBCAs with regard to gadolinium deposition and fails to take into account demonstrated clinically significant differences in relaxivity among the various GBCA, both linear and macrocyclic in nature[23].

Disruption of the blood brain barrier resulting from disease processes and/or treatment (e.g. radiation, chemotherapy) is a potential confounder, since most patients undergoing repeated brain MRIs typically have known or suspected neurological diseases. Signal intensity changes in the dentate nucleus and globus pallidus have been reported in patients with relapsing remitting multiple sclerosis who underwent repeated injections of gadobutrol[24]. Repeated injections over a shorter period resulted in greater signal intensity changes. Interestingly, a study from 2009 showed dentate nucleus signal intensity increases with disease progression in secondary progressive multiple sclerosis[25]. This raises the question whether disease progression is a confounding factor for, or potentiates, gadolinium deposition[26], and whether the disease subtype is important for the observed findings.

A study in patients with relapsing-remitting multiple sclerosis indicated that the observed phenomenon is independent of disease; relaxation times in the dentate nuclei were shortened even when controlling for disease related factors[27]. Another issue is whether the signal intensity changes in the dentate that correlate with disease progression occur in patients who underwent repeated MRI examinations. The authors note that changes persist even after controlling for disease progression, and that gadolinium

deposition from macrocyclic agents contributed to the observed signal changes[28]. However, two groups[29,30] report an increase in T1-weighted signal ratio between dentate and pons with gadopentetate dimeglumine but not with gadobutrol. Another group also found no significant increase in signal intensity in patients who had undergone repeated exams with gadobutrol[31], contradicting Stojanov et al.[24]

Finally, an industry sponsored group studied whether deposited gadolinium can be cleared after deposition, using a rat model[32]. The investigators studied the rat brain approximately 1 week and 20 weeks after up to 20 repeat doses of gadiodiamide or gadopentetate dimeglumine. The results showed the deposition of gadolinium as expected and gadodiamide deposited more than gadopentetate (0.00019% of the injected dose of gadodiamide was detected one week after dosing). The deposition of gadiodiamide decreased by approximately 43%, indicating a likely clearing phenomenon, with no indication of a saturation of this mechanism. Histopathological studies showed no neurotoxicity. The degree to which these results can be extrapolated to humans is unclear, but potential clearance of the already small amount of deposited gadolinium would be an important consideration if also true in humans.

C. Is There Evidence of Harm?

The clinical and biological significance of the retained gadolinium in brain, if any, remains unknown. No harm has been demonstrated in animal models of gadolinium exposure. No behavioral changes were reported in small animals undergoing repeated examinations with gadolinium agents over a very short period[18]. Burke et al. have reported a list of non-specific symptoms from a survey of patients who believe they suffer from gadolinium toxicity, though there is no corresponding controlled study[33].

Other than anecdotal reports, there are currently no peer-reviewed data linking adverse biological or neurological effects to gadolinium deposition in the brain. The principal physiological roles of the dentate nucleus, the site of deposition most often noted, include planning, initiation, and control of voluntary movements. No clinical conditions related to dysfunction of these roles have ever been associated with imaging findings in the retrospective studies published to date[6-8,11,15,17,20,24,27,29,31,34,35]. Specifically, no neurological symptoms have been reported that could relate to damage to those or other brain structures. Prospective controlled studies would be valuable to help draw more definitive conclusions, though very long periods of study may be required to draw conclusions regarding subtle neurological deficits.

D. Limitations of the Available Evidence

All clinical studies have been single-center and retrospective in design[6-8,11,15,17,20,24,27,29,31,34,35]. Patients were selected from hospital databases using a variety of selection criteria, and thus selection and information bias are possible. Some studies included prior scans with other GBCAs prior to studies acquired using the specific GBCA under investigation[6,15,31]. The hypothesized potentiation effect underscores the need for careful assessment of exposure history to various agents[20].

With some exceptions[27], investigators use signal intensity ratios between target and reference areas of the brain for quantitative analysis. The value of this ratio depends on a variety of physical and acquisition parameters that are system and site-dependent. Use of quantitative T1 mapping techniques rather than signal intensity ratios may be helpful to reduce variability between sites.

Free elemental gadolinium is known to be toxic, while chelated gadolinium is regarded as relatively safe. Many studies operate from the underlying assumption that gadolinium is deposited in an unchelated form, because some linear agents with lower thermodynamic stability are more strongly associated with this phenomenon. However, the chemical form of gadolinium deposits in brain remains unknown, and postmortem studies have been unable to address this issue[7,11,21,22]. Moreover, the presence and/or concentration of other substances with T1-shortening properties (eg. iron) has yet to been determined. Recently developed methodology to help determine speciation of gadolinium has not yet been applied to brain tissue[36].

E. Government Statements

The U.S. Food and Drug Administration (FDA) is evaluating the potential risk of brain deposits with repeated GBCA use[14]. The FDA stated that in order to "reduce the potential for gadolinium accumulation, health care professionals should consider limiting GBCA use to clinical circumstances in which the additional information provided by the contrast is necessary. Health care professionals are also urged to reassess the necessity of repetitive GBCA MRIs in established treatment protocols." Recently the Pharmacovigilance Risk Assessment Committee of the European Medicines Agency has recommended precautionary suspension of marketing authorizations for four linear agents gadobenate dimeglumine, gadodiamide, gadopentetic acid, and gadoversetamide, citing the fact that the linear structure makes these agents more likely to release gadolinium[37].

F. Recommendations and Conclusions

The data described above are representative of current knowledge. Based on these data, the current recommendations from the ISMRM Safety Committee are as follows:

1. The ISMRM urges caution in the utilization of any medication, including GBCAs. Per standard practice, GBCAs should be avoided when not required. The data on gadolinium deposition emphasize, but do not alter this practice, and GBCAs should not be withheld from patients with a clinical indication for gadolinium enhanced MRI. The physician responsible for the administration of contrast should understand the benefits and risks of the agent.

2. The clinical indication, specific agent, dose, and other pertinent information should be documented in the medical record.

3. While many studies indicate that at least some macrocyclic agents on the market currently may exhibit less deposition than at least some linear agents available today, the data document that gadolinium deposition in the brain does occur with macrocyclic agents as well. There are data, some of which are discordant, that suggest differences in gadolinium deposition rates among the macrocyclic agents and among the linear agents. Relaxivity differences between agents and between potential deposited species may complicate interpretation of signal intensity difference studies. In light of no known harm from the deposition phenomenon, it is unclear that all macrocyclic agents should be favored over all linear agents based on current data. There are many factors that should be considered when choosing a contrast agent, including pharmacokinetics, relaxivity, efficacy, potential or real side-effects including allergic reactions, patient age, probability of the need for repeated exams, and cost. Institutions must weigh these factors and the fact that some agents may exhibit a greater propensity for deposition, when choosing to use a specific agent.

4. Given the importance of GBCAs for advancing scientific discovery and for improving clinical care through research studies, the ISMRM Safety Committee, like the NIH[38], supports the view that it is appropriate to administer GBCAs for research under the guidance of IRB approved protocols that include informed consent. Because there are no known risks associated with gadolinium deposition in the brain at this time, the ISMRM is unable to make an overarching recommendation regarding disclosure of this phenomenon to research subjects. Therefore, each institution must decide whether inclusion of a description of this phenomenon in consent form materials is necessary and, if so, what content to use. Factors such as the circumstances under which the GBCA is being administered, unknown risks of gadolinium deposition, and the need to explain this phenomenon to subjects in appropriate language must be taken into account. In the event that new data are discovered describing adverse biological or clinical effects related to gadolinium deposition subsequent to this publication, it may be appropriate to include that information as part of the consent process.

5. Investigators publishing on this topic should exercise careful disclosure of financial, consulting, or advising relationships with industry that pertain to potential conflicts of interest (COI). While proper disclosure of COI should be performed for all publications, this is particularly relevant for the gadolinium deposition phenomenon.

6. Due to possible confounding of disease related signal intensity changes with gadolinium deposition related changes, future studies should explicitly describe all relevant clinical history, including treatment, of the patients included in the study.

7. The ISMRM supports rigorous data-driven research in all aspects of magnetic resonance, and will continue to urge and promote research and discussion on this subject at scientific meetings, workshops, journals and through pilot grant funding opportunities. As can be seen throughout, several issues remain unresolved. These include but are not limited to:

    (a) Is the deposited gadolinium accompanied by clinical adverse effects, and are these theoretical effects dose dependent? What are the frequencies and severities of adverse events (or perceived adverse events)?
    (b) What is the chemical state and structure of the deposited gadolinium?
    (c) What are the relative rates with which the phenomenon occurs with each gadolinium chelate? What is the role of dose or relaxivity in the severity of the phenomenon?
    (d) Are the observed differences between agents class or agent dependent? How do field strength, sequences and settings utilized and agent dependent differences in T_1 relaxivity impact our ability to pool large data sets?
    (e) Which groups of patients are more or less susceptible to the gadolinium deposition phenomenon?
    (f) How do treatments such as radiation or chemotherapy impact gadolinium deposition?
    (g) What is the mechanism of gadolinium deposition into the brain?

The existing data provide strong evidence for the deposition of gadolinium in deep nuclei of the brain, particularly after repeated exposures of GBCAs. While there are apparent differences among the agents and some differences by class, some data are contradictory. Additionally, there are agents with no reported data on this phenomenon. While the observation of gadolinium deposition in the brain should be taken very seriously, reliable data regarding clinical or biological significance, if any, are lacking.

Based on the available data, the recommendations above attempt to balance the potential (yet unknown) harm of gadolinium deposition with the proven clinical and research benefit of GBCAs. Further research is needed to elucidate the mechanisms and relevance of gadolinium deposition. As such data emerge, recommendations on the clinical and research use of GBCAs are expected to evolve.

Contributors

An initial draft was generated by Drs. Gulani, Calamante, and Reeder. All authors contributed to literature search, editing and the generation of recommendations. A longer form of the manuscript was reviewed by the ISMRM Safety Committee and after those comments were incorporated, the Board of Trustees of the organization reviewed the document, provided additional feedback, and eventually approved the document. The document was edited and shortened during the review and publication process. No funding was received for the generation of this manuscript. The relevant and non-relevant conflicts of interests of the authors and the ISMRM have been disclosed.

G. References

1. Runge VM. Commentary on T1-Weighted Hypersignal in the Deep Cerebellar Nuclei After Repeated Administrations of Gadolinium-Based Contrast Agents in Healthy Rats: Difference Between Linear and Macrocyclic Agents. *Invest Radiol* 2015; **50**(8): 481-2.
2. Prince MR, Zhang H, Zou Z, Staron RB, Brill PW. Incidence of immediate gadolinium contrast media reactions. *AJR Am J Roentgenol* 2011; **196**(2): W138-43.
3. Hunt CH, Hartman RP, Hesley GK. Frequency and severity of adverse effects of iodinated and gadolinium contrast materials: retrospective review of 456,930 doses. *AJR Am J Roentgenol* 2009; **193**(4): 1124-7.
4. 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 gadolinium-based contrast material. *Radiology* 2014; **270**(3): 834-41.
5. Errante Y, Cirimele V, Mallio CA, Di Lazzaro V, Zobel BB, Quattrocchi CC. 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**(10): 685-90.
6. 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**(3): 783-91.
7. McDonald RJ, McDonald JS, Kallmes DF, et al. Intracranial Gadolinium Deposition after Contrast-enhanced MR Imaging. *Radiology* 2015; **275**(3): 772-82.
8. 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**(3): 836-44.
9. Roberts DR, Holden KR. Progressive increase of T1 signal intensity in the dentate nucleus and globus pallidus on unenhanced T1-weighted MR images in the pediatric brain exposed to multiple doses of gadolinium contrast. *Brain Dev* 2016; **38**(3): 331-6.
10. Miller JH, Hu HH, Pokorney A, Cornejo P, Towbin R. MRI Brain Signal Intensity Changes of a Child During the Course of 35 Gadolinium Contrast Examinations. *Pediatrics* 2015; **136**(6): e1637-40.
11. Kanda T, Fukusato T, Matsuda M, 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.
12. Smith AP, Marino M, Roberts J, et al. Clearance of Gadolinium from the Brain with No Pathologic Effect after Repeated Administration of Gadodiamide in Healthy Rats: An Analytical and Histologic Study. *Radiology* 2016.
13. Port M, Idee JM, Medina C, Robic C, Sabatou M, Corot C. Efficiency, thermodynamic and kinetic stability of marketed gadolinium chelates and their possible clinical consequences: a critical review. *Biometals* 2008; **21**(4): 469-90.
14. Media ACoRCoDaC. ACR Manual on Contrast Media Version v10.1.2015; Available at http://www.acr.org/Quality-Saftety/Resources/Contrast-Manual. 2015 (accessed March 1, 2016 2016).
15. Weberling LD, Kieslich PJ, Kickingereder P, et al. Increased Signal Intensity in the Dentate Nucleus on Unenhanced T1-Weighted Images After Gadobenate Dimeglumine Administration. *Invest Radiol* 2015; **50**(11): 743-8.
16. 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**(3): 699-707.
17. 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**(3): 803-9.

18. Robert P, Lehericy S, Grand S, et al. T1-Weighted Hypersignal in the Deep Cerebellar Nuclei After Repeated Administrations of Gadolinium-Based Contrast Agents in Healthy Rats: Difference Between Linear and Macrocyclic Agents. *Invest Radiol* 2015; **50**(8): 473-80.
19. Robert P, Violas X, Grand S, et al. Linear Gadolinium-Based Contrast Agents Are Associated With Brain Gadolinium Retention in Healthy Rats. *Invest Radiol* 2016; **51**(2): 73-82.
20. Ramalho J, Semelka RC, AlObaidy M, Ramalho M, Nunes RH, Castillo M. Signal intensity change on unenhanced T1-weighted images in dentate nucleus following gadobenate dimeglumine in patients with and without previous multiple administrations of gadodiamide. *Eur Radiol* 2016; **26**(11): 4080-8.
21. Murata N, Gonzalez-Cuyar LF, Murata K, et al. Macrocyclic and Other Non-Group 1 Gadolinium Contrast Agents Deposit Low Levels of Gadolinium in Brain and Bone Tissue: Preliminary Results From 9 Patients With Normal Renal Function. *Invest Radiol* 2016; **51**(7): 447-53.
22. Roberts DR, Welsh CA, LeBel DP, 2nd, Davis WC. Distribution Map of Gadolinium Deposition within the Cerebellum Following GBCA Administration. *Neurology* 2017.
23. White GW, Gibby WA, Tweedle MF. Comparison of Gd(DTPA-BMA) (Omniscan) versus Gd(HP-DO3A) (ProHance) relative to gadolinium retention in human bone tissue by inductively coupled plasma mass spectroscopy. *Invest Radiol* 2006; **41**(3): 272-8.
24. Stojanov DA, Aracki-Trenkic A, Vojinovic S, Benedeto-Stojanov D, Ljubisavljevic S. 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 agent, gadobutrol. *Eur Radiol* 2016; **26**(3): 807-15.
25. Roccatagliata L, Vuolo L, Bonzano L, Pichiecchio A, Mancardi GL. Multiple sclerosis: hyperintense dentate nucleus on unenhanced T1-weighted MR images is associated with the secondary progressive subtype. *Radiology* 2009; **251**(2): 503-10.
26. 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? *European Radiology* 2015; **26**(3): 816-7.
27. Tedeschi E, Palma G, Canna A, et al. In vivo dentate nucleus MRI relaxometry correlates with previous administration of Gadolinium-based contrast agents. *Eur Radiol* 2016.
28. Stojanov DA. Reply to Letter to the Editor re: 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 agent, gadobutrol. *Eur Radiol* 2016; **26**(3): 818-9.
29. Cao Y, Huang DQ, Shih G, Prince MR. Signal Change in the Dentate Nucleus on T1-Weighted MR Images After Multiple Administrations of Gadopentetate Dimeglumine Versus Gadobutrol. *AJR Am J Roentgenol* 2016; **206**(2): 414-9.
30. Schlemm L, Chien C, Bellmann-Strobl J, et al. Gadopentetate but not gadobutrol accumulates in the dentate nucleus of multiple sclerosis patients. *Mult Scler* 2016: 1352458516670738.
31. 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**(12): 805-10.
32. Smith AP, Marino M, Roberts J, et al. Clearance of Gadolinium from the Brain with No Pathologic Effect after Repeated Administration of Gadodiamide in Healthy Rats: An Analytical and Histologic Study. *Radiology* 2017; **282**(3): 743-51.
33. Burke LMB, Ramalho M, AlObaidy M, Chang E, Jay M, Semelka RC. Self-reported gadolinium toxicity: A survey of patients with chronic symptoms. *Magnetic Resonance Imaging* 2016; **34**(8): 1078-80.

34. Quattrocchi CC, Mallio CA, Errante Y, et al. Gadodiamide and Dentate Nucleus T1 Hyperintensity in Patients With Meningioma Evaluated by Multiple Follow-Up Contrast-Enhanced Magnetic Resonance Examinations With No Systemic Interval Therapy. *Invest Radiol* 2015; **50**(7): 470-2.
35. Ramalho J, Ramalho M, AlObaidy M, Nunes RH, Castillo M, Semelka RC. T1 Signal-Intensity Increase in the Dentate Nucleus after Multiple Exposures to Gadodiamide: Intraindividual Comparison between 2 Commonly Used Sequences. *AJNR Am J Neuroradiol* 2016; **37**(8): 1427-31.
36. Birka M, Wentker KS, Lusmoller E, et al. Diagnosis of nephrogenic systemic fibrosis by means of elemental bioimaging and speciation analysis. *Anal Chem* 2015; **87**(6): 3321-8.
37. Agency EM. PRAC concludes assessment of gadolinium agents used in body scans and recommends regulatory actions, including suspension for some marketing authorisations. 10 March 2017. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2017/03/WC500223209.pdf. 2017 (accessed March 10, 2017 2017).
38. Malayeri AA, Brooks KM, Bryant LH, et al. National Institutes of Health Perspective on Reports of Gadolinium Deposition in the Brain. *J Am Coll Radiol* 2016; **13**(3): 237-41.
39. Kahn J, Posch H, Steffen IG, et al. Is There Long-term Signal Intensity Increase in the Central Nervous System on T1-weighted Images after MR Imaging with the Hepatospecific Contrast Agent Gadoxetic Acid? A Cross-sectional Study in 91 Patients. *Radiology* 2017; **282**(3): 708-16.

Generic Name	Brand Name	Manufacturer	Chemical Structure	Ionic vs Non-ionic	ACR NSF Safety Group	References Reporting Gadolinium Deposition		
						Signal Intensity Changes	T1 Changes	Gadolinium Detection
gadopentatate dimeglumine	Magnevist	Bayer	linear	Ionic	I	[4,6,9,17,19,29,30]	[19,27]†	[11,12,19]
gadoversetamide	Optimark	Mallinckrodt	linear	Non-Ionic	I			
gadodiamide	Omniscan	GE Healthcare	linear	Non-Ionic	I	[4,5,7,8,18,19,34]	[19]	[7,11,12,18,19] *
gadoteridol	Prohance	Bracco	macrocyclic	Non-Ionic	II			[11,21] *
gadoterate meglumine	Dotarem	Guerbet	macrocyclic	Ionic	II		[27]†	[18,19]
gadobutrol	Gadovist and Gadavist	Bayer	macrocyclic	Non-Ionic	II	[24]	[27]†	[21]
gadobenate dimeglumine	Multihance	Bracco	linear	Ionic	II	[8,15,19,20] #	[19]	[19,21]
gadoxetate disodium	Eovist	Bayer	linear	Ionic	III	[39]		[21]
gadofosveset trisodium	Ablavar	Lantheus	linear	Ionic	III			

Table 1: Contrast Agent, manufacturer, chemical structure, ACR designation for NSF risk, and reports associated with gadolinium deposition in the brain. The ACR designates three categories of contrast agent groupings by risk of NSF. Group 1 agents have been associate with the greatest number of NSF cases. Group II agents are associated with few, if any, unconfounded cases of NSF. Group III agents have only recently appeared on the market.

* Patients receiving gadodiamide and gadoteridol in ([11]) also received gadopentetate and thus results are confounded.

([8]) shows a trend for signal changes in gadobenate dimeglumine exposed patients

† ([27]) reported T1 changes but patients received combinations of three agents, and thus the results are confounded.

In addition, one paper shows direct evidence of gadolinium deposition with the patient receiving 2 doses of gadopentetate dimeglumine and 2 doses of either gadopentetate dimeglumine or gadodiamide[22]. Since these are confounded, this reference is not included in the last column.

Generic Name	gadopentatate dimeglumine	gadoversetamide	gadodiamide	gadoteridol	gadoterate meglumine	gadobutrol	gadobenate dimeglumine	gadoxetate disodium	gadofosveset trisodium
gadopentatate dimeglumine	*		19,32						
gadoversetamide		*							
gadodiamide			*			21			
gadoteridol	17,21		21	*		21	21	21	
gadoterate meglumine	6,19		18,19		*		15,19		
gadobutrol	29,30					*			
gadobenate dimeglumine	15,19		8,19,21			21	*		
gadoxetate disodium			21			21		*	
gadofosveset trisodium									*

Table 2: Studies with comparisons of gadolinium deposition in multiple gadolinium based contrast agents. For each entry, the agent depositing to a lesser degree (or not at all) is identified on the left (in red), and the agent depositing to a greater degree is identified above (in blue).