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Gadolinium Deposition in Neurology Clinical Practice

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Background: Magnetic resonance imaging (MRI) enhanced with gadolinium-based contrast agents (GBCAs) is an essential tool in the diagnosis and management of many neurologic diseases, including multiple sclerosis, brain tumors, and infections. The clinical utility of GBCAs is evidenced by their widespread use. GBCAs are produced in macrocyclic and linear forms. Since 2014, evidence has suggested that repeated administration of GBCAs can lead to gadolinium deposition in the brain.

Methods: We review the literature on gadolinium deposition, including both animal and human studies, as well as the literature on GBCA-associated health outcomes. Additionally, we summarize and discuss the updated medical society recommendations and perspectives on GBCA use in clinical practice.

Results: The first publication reporting gadolinium deposition in the human brain was published in 2014. Since that seminal report, multiple studies have demonstrated that exposure to linear GBCAs is associated with gadolinium deposition in the dentate nucleus and globus pallidus as seen on brain MRI. Macrocyclic GBCA exposure has not convincingly been associated with gadolinium deposition evident on brain MRI.

Conclusion: Clear evidence demonstrates that GBCAs lead to gadolinium deposition in the brain in a dose-dependent manner; however, only linear GBCAs have been associated with gadolinium deposition visualized on MRI. To date, no evidence links gadolinium deposition with any adverse health outcome. Updated medical society guidelines emphasize the importance of an individualized risk-benefit analysis with each administration of GBCAs.

Keywords: *Contrast media, gadolinium, magnetic resonance imaging*

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INTRODUCTION

Magnetic resonance imaging (MRI) enhanced with gadolinium-based contrast agents (GBCAs) is an essential component in the diagnosis and management of a wide variety of neurologic diseases, including demyelination, malignancy, and infections.[1] The US Food and Drug Administration (FDA) approved GBCAs for clinical use in 1988, and they are generally regarded as having had an excellent safety profile for the past 30 years. However, several recent papers (1995-2018) have indicated that gadolinium has the potential to deposit and persist within the body, particularly within the dentate nucleus (DN) and globus pallidus (GP) of the brain.[2-13] While the long-term clinical significance of gadolinium deposition remains unclear, this discovery has many in the medical community reconsidering the applications and necessity of GBCAs. In this article, we review the peer-reviewed data on GBCA safety and deposition. We also discuss the latest medical society recommendations and perspectives on GBCA use in clinical practice.

BACKGROUND, METABOLISM, AND EXCRETION

The first GBCA, gadopentetate, received FDA approval in 1988.[14] Since that time, eight other GBCAs have received FDA approval (Table 1).[14-18] By 2016, more than 300 million patients had received GBCAs.[19]

GBCAs are used clinically in the diagnosis and management of many neurologic diseases. In the central nervous system, GBCAs are used in contrast-enhanced MRI, perfusion imaging, and magnetic resonance angiography.[1] GBCAs are paramagnetic compounds that are imaged indirectly through their influence on the hydrogen relaxivity of surrounding tissue water molecules that is most readily visible on T1-weighted MRI sequences.[20-22] This change in hydrogen relaxivity allows visualization of pathologies that may not otherwise be apparent and can significantly increase the sensitivity of the MRI.[20] Increased T1 signal (or T1 shortening) after administration of a GBCA may reflect areas of neovascularity or disruption of the blood-brain barrier, as GBCAs do not cross the blood-brain barrier in significant quantities.[23,24] The pattern and distribution of this change in signal after GBCA administration, known as *enhancement*, can also increase the specificity of an MRI, as seen when MRI is used to differentiate between high- and low-grade gliomas.[24] Contrast-enhanced MRI also improves the diagnostic sensitivity of MRI in numerous disease processes, including multiple sclerosis (MS), malignancy, and

Table 1. US Food and Drug Administration–Approved Gadolinium-Based Contrast Agents[14-18]

Generic Name	Brand Name	Date Approved	Chemical Structure	Indication
Gadopentetate dimeglumine	Magnevist	6/2/1988	Linear	Central nervous system, extracranial/extraspinal, body
Gadoteridol	ProHance	11/16/1992	Macrocyclic	Central nervous system, extracranial/extraspinal
Gadoversetamide	OptiMARK	12/8/1999	Linear	Central nervous system, liver
Gadobenate dimeglumine	MultiHance	11/23/2004	Linear	Central nervous system, renal or aortoiliofemoral occlusive vascular disease
Gadodiamide	Omniscan	9/5/2007	Linear	Central nervous system, body
Gadoxetate disodium	Eovist	7/3/2008	Linear	Liver lesions
Gadofosveset trisodium	Ablavar (formerly Vasovist)	12/22/2008	Linear	Aortoiliac occlusive disease
Gadobutrol	Gadavist	3/14/2011	Macrocyclic	Central nervous system
Gadoterate meglumine	Dotarem	3/20/2013	Macrocyclic	Central nervous system

infections.[1,25-28] In addition to use in the central nervous system, GBCAs are also used in numerous body, cardiac, and musculoskeletal imaging applications.[1]

Gadolinium is a rare earth element.[16,20] GBCAs are composed of gadolinium with a chelating ligand in either linear[29] or macrocyclic[30] form (Figure 1) and are administered intravenously during a magnetic resonance examination.[1,16,20,31] The chelating ligand limits potential toxicity from ionized gadolinium (Gd^{3+})[3,21] that may otherwise have interfered with calcium-binding receptors.[32] Dissociation of chelated gadolinium occurs in the serum through a combination of dechelation and the ligand-metal (eg, zinc, copper, iron) exchange of transmetalation.[31,32]

The thermal and kinetic stabilities of each GBCA are thought to contribute to the differences in the rate of gadolinium deposition.[31,32] Macrocyclic GBCAs are thought to offer more secure binding of Gd^{3+} as evidenced by studies in animals[3,33] and in vitro studies in human serum[31] in which increased gadolinium dissociation and retention generally correlated with lower chemical stability of linear GBCAs. The increased stability of macrocyclic GBCAs may be related to a more rigid cage-like structure of the ligand with which to bind Gd^{3+}, leading to less dissociation of Gd^{3+} compared to linear GBCAs.[16,31] Because GBCAs are primarily cleared by the kidney (notably, gadoxetate disodium is equally cleared by renal and hepatobiliary routes), decreased renal function leads to prolonged GBCA exposure, allowing increased time for gadolinium deposition.[14,20,31]

EVIDENCE OF GADOLINIUM DEPOSITION IN TISSUE

Early Studies of Gadolinium Deposition

In 1995, Tweedle et al demonstrated that radiolabeled gadolinium distributes into the liver and bones of mice and rats, providing initial evidence that gadolinium might persist in tissue.[3] In 2006, White et al used inductively coupled plasma mass spectroscopy (ICP-MS) to demonstrate gadolinium deposition in human femurs 3-8 days after exposure to gadodiamide (linear GBCA; n=9 subjects) or gadoteridol (macrocyclic GBCA; n=10 subjects).[34] The study showed that although both agents resulted in gadolinium deposition, the group exposed to linear GBCAs had higher levels of gadolinium deposition as measured by ICP-MS, suggesting a different rate of deposition between macrocyclic and linear GBCAs.[34]

Studies of Gadolinium Deposition in the Animal Brain

In August 2015, Robert et al reported results of a rat study in which they found that gadodiamide (linear GBCA) administration led to deposition in the deep cerebellar nuclei of rats as measured by MRI and correlated with ICP-MS.[6] While the investigators did not detect gadolinium deposition on brain MRI in those exposed to the macrocyclic GBCA gadoterate, they did observe evidence of macrocyclic GBCA deposition in the brain when measured with ICP-MS.[6]

Two studies published in February 2016 examined the difference in gadolinium deposition between linear and macrocyclic GBCAs in healthy rats.[9,10] Groups led by Jost et al and Robert et al examined rats exposed to linear and macrocyclic GBCAs.[9,10] Both studies revealed increased signal on T1-weighted images on brain MRI in rats exposed to linear GBCAs but not in those exposed to macrocyclic GBCAs.[9,10]

Studies of Gadolinium Deposition in the Human Brain

The first report of suspected gadolinium deposition visualized on MRI in the human brain was a retrospective study published in 2014 by Kanda et al.[5] The authors examined 19 patients who had undergone between 6 and 12 GBCA administrations and found T1 shortening on brain MRI in the DN and GP compared to controls.[5] A study conducted by Errante et al examined patients with MS (n=38 subjects) and brain tumors (n=37 subjects) with normal renal function exposed to the linear GBCA gadodiamide and found similar evidence of T1 shortening of the DN on brain MRI in patients with more than 6 gadodiamide administrations.[35] Kanda et al published a follow-up study in June 2015 exploring the

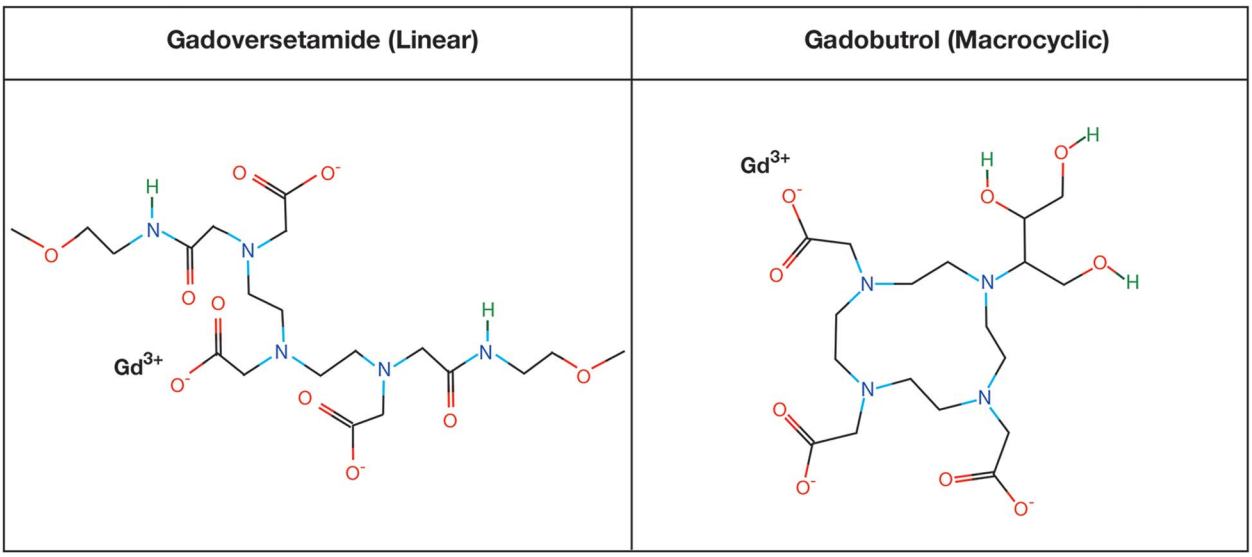

Figure 1. Chemical structures of example linear and macrocyclic and gadolinium-based contrast agents.[29,30]

difference between linear (n=23 subjects) and macrocyclic (n=36 subjects) GBCA gadolinium deposition in the brain.[4] Using brain MRI, the authors found a strong association between increased signal on T1-weighted images in the DN and linear GBCA exposure.[4] This finding was not observed with macrocyclic GBCAs.[4] In June 2015, Radbruch et al published a retrospective study examining subjects who had undergone at least 6 consecutive MRIs with either gadopentetate (linear; n=50 subjects) or gadoterate (macrocyclic; n=50 subjects).[36] Similar to Kanda et al, Radbruch et al reported a strong association between increased signal on T1-weighted images in those exposed to linear but not macrocyclic GBCAs.[4,36] In July 2015, 1 month after the publication of these studies by Kanda et al and Radbruch et al, the FDA announced it would investigate the health impacts of gadolinium deposition in the brain.[37]

In March 2016, Stojanov et al published a study examining gadobutrol (macrocyclic) administration in 58 patients with relapsing-remitting MS and in contrast to prior studies, reported that the macrocyclic gadobutrol led to increased signal on T1-weighted images in the DN and GP on brain MRI.[2] This study has been highly critiqued, with others expressing concerns about the validity of the results as noted in letters published in May 2016[38] and December 2015.[39] One of the primary drivers behind these concerns is the failure to account for prior GBCA exposures in this study.[2] A reproducibility study conducted by Radbruch et al was published in 2015 in which the same macrocyclic GBCA, gadobutrol, was studied in 30 patients with brain tumors.[40] In contrast to the study by Stojanov et al, Radbruch et al did not find evidence of signal increase in the DN and GP on T1-weighted brain MRI.[2,40] In contrast to Stojanov et al, Radbruch et al excluded all patients with more than 2 prior GBCA exposures.[2,40]

Quattrocchi et al published a retrospective study in 2015 examining 102 patients with meningiomas exposed to the linear agent gadodiamide that revealed increased signal on T1-weighted images in the DN after 6 or more contrast-enhanced MRIs, suggesting a dose response.[12] In this study, there were no reports of any significant neurologic complaints that the authors could associate with T1 shortening in the DN.[12]

From 2015 through 2016, 3 autopsy studies were conducted to assess for gadolinium deposition.[7,8,41] In 2015, McDonald et al examined autopsies of 13 patients with normal renal function exposed to 4-29 administrations of the linear GBCA gadodiamide.[7] At autopsy, tissue was examined for radiologic, spectrometric, electron microscopic, and histopathologic evidence of gadolinium deposition.[7] The authors found evidence of dose-dependent signal changes on brain MRI, as well as evidence of gadolinium deposition on ICP-MS and electron microscopy compared to controls.[7] One month after the McDonald study was published, Kanda et al published an autopsy study in which 5 subjects with normal renal function who had been exposed to linear GBCAs (gadopentetate and gadodiamide) were found to have gadolinium deposition through ICP-MS in the DN and GP.[41] In 2016, a study by Murata et al examined autopsies of 9 patients with normal renal function who had been exposed to GBCAs and found that all had demonstrated some degree of gadolinium deposition in the brain when measured with ICP-MS. In this cohort, 7 individuals had only been exposed to the macrocyclic GBCAs gadobutrol and gadoteridol.[8]

In 2018, Moser et al published a study of 119 patients with brain tumors who had been exposed to various forms of GBCAs and found that exposure to linear GBCAs led to increased signal on T1-weighted images, whereas similar changes were not observed with macrocyclic GBCAs.[13] Vergauwen et al conducted a retrospective study in a population of patients with either von Hippel-Lindau disease (n=28 subjects) or tuberous sclerosis complex (n=24 subjects) and discovered that both demonstrated increased signal on T1-weighted images in the DN and GP, although the increase in the tuberous sclerosis complex group did not reach statistical significance.[11] Notably, detailed records of the identity of contrast agents used for this study were not available,

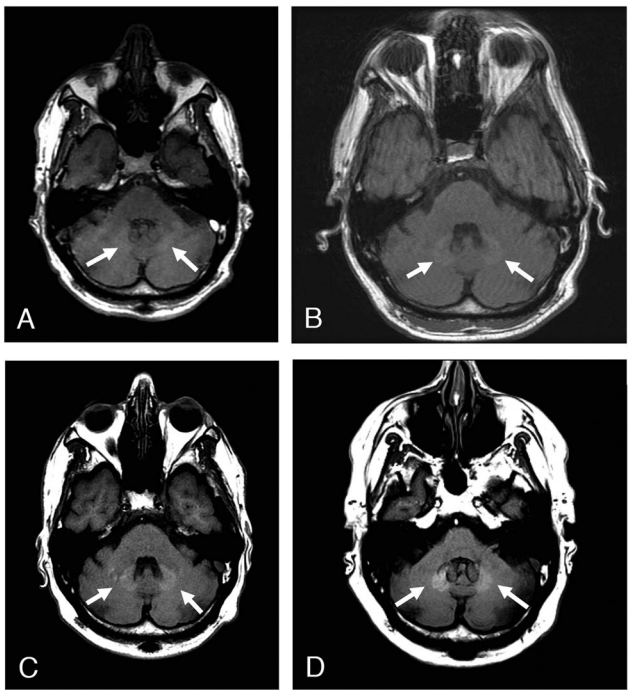

Figure 2. Sequential axial T1-weighted noncontrast magnetic resonance images through the posterior fossa of a 52-year-old male with history of multiple sclerosis demonstrate a progressive increase in signal within the dentate nuclei following repeated doses of gadolinium-based contrast agents in (A) December 2011, (B) June 2013, (C) September 2016, and (D) June 2018.

but basing a conjecture on the agents used by the hospitals where the MRIs were performed, linear GBCAs (gadopentetate, gadodiamide, gadobenate) were likely predominately used, with the recent introduction of gadoterate in 2016 (2 years prior to publication).[11]

In May 2017, the FDA announced that to date no harmful sequelae of gadolinium deposition in the brain had been identified but that reviews would continue.[42] In May 2018, the FDA announced that GBCAs would require new class warnings that detail the potential for gadolinium deposition.[18]

Summary of Evidence for Gadolinium Deposition in the Brain

Evidence shows that gadolinium is deposited in the DN and GP of the brain, as measured by autopsy, spectrometry, and MRI.[4-12,35,36,40,41] An example of the accumulation of gadolinium deposition is shown in Figure 2. Gadolinium deposition has been more prominently associated with linear than with macrocyclic GBCAs,[4,6,8-10,13,36,40] possibly because of differences in kinetic and thermal stabilities.[31,32] Additionally, evidence suggests a dose-dependent effect of gadolinium deposition.[7,12,35] Although studies have revealed mixed evidence of gadolinium deposition with macrocyclic GBCAs on MRI,[2,4,6,9,10,13,36,40] spectroscopic evidence suggests that macrocyclic GBCAs can result in gadolinium deposition.[6,8] One hypothesis to explain these findings is that the rate of macrocyclic GBCA gadolinium deposition is too low for detection via MRI but detectable by ICP-MS. Prior publications have hypothesized that the GP may be uniquely susceptible to metal deposition as seen in other metabolic disorders, such as hepatic dysfunction, Fahr disease, and Wilson disease.[5,7]

OTHER SAFETY CONSIDERATIONS

Since their introduction in 1988,[14] GBCAs have garnered a good safety record. In 2018, Behzadi et al conducted a metaanalysis to examine adverse reactions to GBCAs and discovered that the rate of immediate allergic-like reactions to GBCAs was 9.2 per 10,000 administrations and of severe allergic-like reactions was 0.52 per 10,000 administrations.[43] Furthermore, this analysis noted that linear nonionic GBCAs, such as gadodiamide in this metaanalysis, conferred the lowest risk of acute allergic reactions.[43] In terms of acute adverse reactions, GBCAs compared favorably with intravenous (IV) iodinated contrast for computed tomography scans. Common adverse reactions to iodinated contrast media include allergic-like reactions and cutaneous reactions (such as urticaria and/or rash).[19] The American College of Radiology (ACR) *Manual on Contrast Media* details overall adverse reaction rates ranging from 0.2%-0.7% depending on the study, while severe reactions to IV iodinated contrast have been reported at a rate of 4 per 10,000.[19]

In 2000, the first case series of nephrogenic systemic fibrosis (NSF), a scleroderma-like illness initially labeled nephrogenic fibrosing dermopathy, was published.[44,45] NSF was found to be associated with GBCA exposure in patients with decreased renal function (acute renal failure, chronic renal failure with glomerular filtration rate <30 mL/min/m^2).[44-46] The ACR classifies GBCAs based on their association with reported cases of NSF. The group I agents, consisting of gadodiamide, gadopentetate dimeglumine, and gadoversetamide, are all linear agents and associated with the greatest number of NSF cases.[47] The incidence of NSF has dramatically decreased in the past decade by limiting GBCA use in high-risk populations, using more stable GBCAs, and decreasing the dose of GBCAs for patients with poor kidney function.[46]

Ray et al published a population-based cohort study examining the association between MRI exposure during pregnancy and adverse fetal and childhood outcomes.[48] The authors found an increased risk of rheumatologic, inflammatory, infiltrative skin conditions and stillbirth or neonatal death in patients exposed to GBCAs during pregnancy.[48] They did not find an increased risk of conditions resembling NSF in the children exposed to GBCAs in utero.[48] At this time, GBCA use in pregnancy is typically contraindicated.

Despite the evidence of gadolinium deposition in the brain, evidence for adverse health effects resulting from gadolinium deposition is limited. In 2016, Semelka et al published an initial description of symptomatology following gadolinium exposure they termed "gadolinium deposition disease."[49] For this report, Semelka et al posted an online survey consisting of 18 questions to a private blog (MRI-Gadolinium-Toxicity Support Group) and a public MRI Gadolinium Toxicity Facebook page to identify symptoms of gadolinium deposition.[49] Inclusion criteria required self-reported normal renal function, onset of symptoms ranging from 1-365 days after gadolinium exposure, and self-reported laboratory evidence of gadolinium presence in the respondent's body.[49]

Table 2. Society Recommendations Regarding Gadolinium-Based Contrast Agent Use[16,19,51,52]

Society	Summary of Statements and Recommendations	Date
National Institutes of Health[16]	1. GBCAs should only be used when clinically indicated or when specified in an institutional review board–approved protocol. 2. When GBCAs are required, consider the use of a macrocyclic GBCA (eg, gadobutrol, gadoteridol, or gadoterate meglumine) rather than a linear agent. 3. For patients with documented sensitivity (eg, hives) to macrocyclic agents, it is appropriate to use linear agents when clinically indicated. 4. MRI protocols should always consider FDA label indications and dosing schemes for administration of GBCAs. 5. Encourage intradepartmental and interdepartmental research programs to evaluate T1 shortening in the brain and other organs in patients who have received multiple doses of GBCAs.	March 2016
American College of Radiology[19]	Would be prudent to consider the clinical benefit of the diagnostic information or treatment result that MRI or MRA may provide against the unknown potential risk of gadolinium deposition in the brain for each individual patient. Particular attention should be paid to pediatric and other patients who may receive many GBCA-enhanced MRI studies over the course of their lifetimes. If the decision for an individual patient is made to use a GBCA for an MRI study, multiple factors need to be considered when selecting a GBCA, including diagnostic efficacy, relaxivity, rate of adverse reactions, dosing/concentration, and propensity to deposit in more sensitive organs such as the brain. As this gadolinium deposition phenomenon remains a relatively undefined clinical phenomenon, and accurate and complete data may be useful as investigations proceed, the identity and dose of GBCA used should be recorded after each intravenous administration.	May 2016
International Society for Magnetic Resonance in Medicine[52]	1. The ISMRM urges caution in the use of any medical compound, including GBCAs. Per standard practice, use of GBCAs should be avoided when not necessary. The evidence on gadolinium deposition emphasizes but does 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 a contrast agent should understand the benefits and risks of the agent. 2. The clinical indication for which a GBCA is administered, the specific contrast agent used, its dosage, and other pertinent information should be documented in the patient's medical record. 3. Some commercially available macrocyclic agents might deposit less gadolinium than some linear agents; however, evidence shows that gadolinium deposition in the brain can also occur after the administration of macrocyclic agents. Evidence suggests differences in gadolinium deposition rates among macrocyclic agents and among linear agents, although some data are discordant. Relaxivity differences between contrast agents and between the potentially deposited chemical species can complicate the interpretation of differences in signal intensity. No evidence shows any harmful effects from the deposition of gadolinium, and therefore whether use of macrocyclic agents should be favored over linear agents is unclear. When choosing a contrast agent, many factors should be considered, including pharmacokinetics, relaxivity, efficacy, potential side effects (such as allergic reactions), patient age, probability of the need for repeated examinations, and cost. Institutions should weigh these factors and consider that some agents might have a greater propensity for deposition than others. 4. Given the importance of GBCAs for advancing scientific discovery and improving clinical care, the ISMRM Safety Committee supports the views of the National Institutes of Health, in that administration of GBCAs is appropriate in research settings under the guidance of protocols approved by an institutional review board, and that must include patient's informed consent. Because no risks are known to be associated with gadolinium deposition in the brain, the ISMRM is unable to make an overarching recommendation regarding disclosure of gadolinium deposition to research participants. Therefore, each institution must decide whether inclusion of information on the deposition of gadolinium in the brain is necessary and should be	July 2017

Table 2. Continued

Society	Summary of Statements and Recommendations	Date
	included as part of the consent form; if so, the institution must decide on the description to use. The circumstances under which the GBCA is administered, the unknown risks of gadolinium deposition, and the need to explain the deposition to participants in appropriate language should be taken into account. In the event that new data are available describing adverse biological or clinical effects associated with gadolinium deposition subsequent to this Personal View, it might be appropriate to include that information as part of the consent process. 5. Investigators reporting studies on gadolinium deposition in the brain should exercise meticulous disclosure of financial, consulting, and advising relationships with industries as potential conflicts of interest. Although proper disclosure of conflicts of interest must be done for all academic publications, transparency is particularly relevant for studies of gadolinium deposition. 6. Because of the potential confounding of disease-related signal intensity changes with gadolinium deposition, future studies should explicitly describe all relevant clinical history of participants, including treatment of the patients in the study.	
Consortium of Multiple Sclerosis Centers[51]	GBCAs do accumulate in the brain and to a much lesser degree with macrocyclic agents. While no known CNS toxicity has been identified with the use of GBCAs, these agents should be used judiciously, recognizing that gadolinium continues to play an invaluable role in specific circumstances related to the diagnosis and follow-up of individuals with MS. MS GBCA use is essential for • following a patient with highly active disease • when there is rapidly declining and unexplained and unexpected clinical worsening occurs • when there is concern regarding an alternative diagnosis other than MS MS GBCA use is optional for • the follow-up monitoring of patients with MS to detect subclinical disease activity that could lead to a change in therapy; the use of GBCA may be helpful within the first 2 years of treatment onset but is not required because new T2 MS lesions can be identified on well-performed MRI using a standardized protocol unless there is a large T2 lesion burden.	February 2018

CNS, central nervous system; FDA, US Food and Drug Administration; GBCA, gadolinium-based contrast agent; ISMRM, International Society for Magnetic Resonance in Medicine; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; MS, multiple sclerosis.

Forty-two individuals participated in the survey. Symptoms reported included pain, skin thickening and discoloration, joint stiffness, fatigue, persistent clouded mentation, dry eyes, and vision problems.[49]

In 2016, Burke et al published the results of a similar survey. This study (Semelka was a coauthor) also searched for adverse symptoms of gadolinium deposition based on survey questions posted to the private MRI-Gadolinium-Toxicity Support Group and the public MRI Gadolinium Toxicity Facebook page.[50] Fifty individuals participated in the survey, of whom a majority reported joint pain, headaches, flu-like symptoms, skin changes, digestive symptoms, difficulty breathing, and generalized whole-body symptoms.[50]

Both studies have several striking scientific limitations. Chief among them is the selection bias in targeting this survey to a study population comprised exclusively of individuals who a priori believe they have symptoms related to gadolinium exposure.[49,50] This selection bias undermines the results and calls into question the validity of any conclusions drawn by the authors. As a retrospective study, these studies were prone to bias and confounding even beyond the selection bias described. While Semelka et al included inclusion criteria, it is not clear that the participants were verified to have met these criteria.[49] Neither study included any exclusion criteria or a control group.[49,50] Furthermore, both surveys were conducted online, raising questions regarding the authenticity of the participants.[49,50] Semelka et al report that 3 random individuals were examined by a physician with experience in NSF, but no objective results of the examination are detailed.[49] Neither study reports the original indications for MRI, although the authors indicate that the symptoms reported in the survey are new since the respondents underwent contrast-enhanced MRI.[49,50]

Overall, while these studies have attempted to answer the ongoing question regarding the clinical significance of gadolinium deposition,[49,50] they fall short of the scientific standards of clinical investigation. We did not find a peer-reviewed report with sufficient scientific rigor to associate gadolinium deposition with adverse effects in humans.

SOCIETY RECOMMENDATIONS AND FUTURE DIRECTIONS

The ACR,[19] Consortium of Multiple Sclerosis Centers (CMSC),[51] International Society for Magnetic Resonance in Medicine (ISMRM),[52] and National Institutes of Health (NIH)[16] have made recommendations regarding GBCA use given recent evidence of gadolinium deposition (Table 2).

In January 2017, the CMSC released updated MRI guidelines for providers addressing GBCA accumulation in the brain and recommending judicious use given the invaluable role GBCAs can play in the diagnosis and management of individuals with MS.[53] The 2018 CMSC guidelines included more specific recommendations and distinguished between "essential" and "optional" uses of GBCAs. Essential uses include MRI surveillance in patients with highly active disease or rapid clinical worsening or for patients with diagnostic uncertainty.[51] Optional uses of GBCAs include follow-up monitoring of MS patients to detect subclinical disease activity.[51] Additionally, the CMSC notes that a well-performed noncontrast MRI may be used to detect new T2 lesions in patients without a high lesion burden.[51]

Similarly, the ACR published a position statement regarding gadolinium deposition in 2016 that was maintained in the 2017 *Manual on Contrast Media*.[19] This statement acknowledged that some GBCAs may be more likely to cause gadolinium deposition but that the potential adverse effects of this deposition, if any, remain to be elucidated and recommended that further research be done.[19,47] The ACR recommended weighing the clinical benefit of GBCA use with the unknown potential risk of gadolinium deposition[19,47] and documenting all GBCA administration in the patient's medical record, including the GBCA identity, dose, and date of administration.[19]

In 2016, the NIH published GBCA guidelines as well, noting that linear GBCAs may continue to be used in a limited fashion in individuals who are allergic to macrocyclic agents or in specific indications such as liver imaging.[16]

In 2017, the ISMRM published guidelines that echoed many of the above statements.[52] The ISMRM reinforced that the evidence for gadolinium deposition to date is not an indication to withhold GBCAs in a situation in which they are otherwise clinically indicated.[52]

Efforts are underway to develop alternative contrast agents to GBCAs, with manganese-based and iron-based complexes undergoing investigation.[54-56] Additionally, the use of different noncontrast magnetic resonance sequences as substitutes for GBCA administration are being explored.[57,58] In the future, these modalities may become viable alternatives to GBCA use.

CONCLUSION

Strong evidence shows that repeated GBCA exposure can lead to gadolinium deposition in the DN and GP in the brain. Evidence to date suggests that macrocyclic GBCAs are far less likely than linear agents to cause gadolinium deposition in brain tissue visible on T1-weighted MRI. Given this evidence, multiple medical societies have recommended preferential use of macrocyclic GBCAs instead of linear GBCAs. Despite the evidence of gadolinium deposition, no convincing data so far have linked gadolinium deposition with adverse health outcomes. Further investigation with scientific rigor is needed to explore this question.

Since 1988, GBCAs have been safely administered to millions of patients globally, and their use has undoubtedly benefited innumerable patients by enabling clinicians to make earlier and more accurate diagnoses of neurologic disease. Considering the benefits and unknowns of GBCAs, providers should use these agents judiciously and engage in shared decision-making with patients, with the discussion including an individualized risk-benefit assessment.

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