





Gadolinium Deposition Safety: Seeking the Patient's Perspective

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Gadolinium is a rare-earth metal of the lanthanide series; it is represented by the symbol Gd, and its atomic number is 64.^{1,2} At room temperature, Gd is paramagnetic, meaning that it enhances nuclear relaxation rates, making it useful as a contrast agent for MR imaging. In clinical practice, Gd ions are administered to patients in the chelated form as gadolinium-based contrast agents (GBCA).^{1,2}

GBCA were first introduced in the late 1980s. Because of the intrinsic toxicity of Gd salts, initial clinical trials focused on the stability of the complex between the Gd ion and the chelating agent. Early studies pointed out that the stability constant was much higher for macrocyclic (or cryptelates, as they were initially called) than for linear agents.^{1,3} These concerns never received much attention because all linear and macrocyclic agents appeared to be safe and well-tolerated. Moreover, because macrocyclic GBCA were only available in Europe and not in North America, there appeared to be little scientific incentive to study these concerns further. In fact, GBCA were considered so safe that they were used in large volumes as intra-arterial contrast agents for conventional angiography in patients with iodine allergy.⁴ Indeed, double-dose GBCA were also commonly applied for gadolinium-enhanced MR angiography studies. These practices all changed in 2006, when a possible causation was identified between GBCA and nephrogenic systemic fibrosis (NSF).⁵ NSF is characterized by fibrosis of the skin and internal organs, and the symptoms are somewhat reminiscent of scleroderma or scleromyxedema, though the underlying pathology is different. In this respect, credit should be given to Cowper et al⁶ for a very early and brilliant description of NSF.

The first cases of NSF had already been described earlier, but the possible causation between NSF and GBCA in patients with renal insufficiency was first reported in 2006.⁵ Next, in 2006, the FDA restricted the use of GBCA in patients with a glomerular filtration rate of <60 mL and <15 mL/min/1.73 m²;⁷ the cutoff then proposed in 2007 was <30 mL/min/1.72 m².

Due to these measures, NSF has become very rare, and GBCA were, once again, considered very safe agents in patients with normal renal function.

Brain Gadolinium Deposition

New concerns have been raised in the past 5 years due to mounting evidence of unexpected central nervous system gadolinium deposition after serial administrations of GBCA.⁸⁻¹¹ The phenomenon was found to be greater in the dentate nucleus of the cerebellum and the globus pallidus of patients exposed to several

doses of GBCA with a linear structure.^{9,12,13} In fact, GBCA with a macrocyclic structure are known to have higher thermodynamic, kinetic, and conditional stability with respect to the linear ones, and these features have been suggested to mitigate the tendency of deposition.^{14,15} Given that there are differences in the rates of deposition between linear and macrocyclic agents, slight differences among macrocyclic GBCA have been suggested in studies based on murine models.^{13,16} Specifically, lower gadolinium concentrations were found after exposure to gadoteridol compared with gadoterate and gadobutrol, especially in the cerebellum, cerebrum, and kidneys.¹⁶

Despite the higher degree of gadolinium deposition, nonionic linear GBCA (eg, gadodiamide) showed the lowest rate of immediate allergic adverse events compared with ionic linear and nonionic macrocyclic GBCA.¹⁷

On the basis of the global use of GBCA and the concern for gadolinium deposition into brain tissue, different countries have implemented various strategies. The European Union removed the GBCA with a linear structure for general use from the market in 2017 after a 3-year multistage evaluation process.¹⁸ In Japan, linear ligands were proposed only as an alternative when macrocyclic agents were contraindicated for clinical reasons.¹⁹ In many other countries, such as the United States and China comprising most of the world's population, instead there have been no formal changes in the regulatory standing of the use of GBCA other than education and notices/warnings of the potential retention with unknown and unclear clinical relevance, if any, together with a call for more research on the issue.

In parallel, imaging scientists from academia and industry have developed new avenues of research, endeavoring to understand the mechanism of the phenomenon and to mitigate gadolinium deposition. Three main topics currently are the following: 1) the validation of alternative contrast molecules not containing gadolinium;²⁰ 2) unenhanced MR imaging techniques with quantitative image analysis, aiming to carry gadolinium-analog information;^{21,22} and 3) synthetic enhanced MR imaging using very low doses of available GBCA.²³ These approaches are valid and will take brain MR imaging various steps forward in the years to come. However, the main issue is what to do about brain gadolinium deposition or, even more important, providing answers to what matters most to patients, in terms of clinical consequences on their neurologic function or the clinical effects in other sites such as skin, liver, kidney and bone.

Indeed, what remains to be proved, of great importance to patients, is whether there is any impact on cell/tissue function from the small amounts of gadolinium deposited. The current available data on clinical consequences are mainly based on clinical retrospective studies involving large cohorts (ie, 99,739 patients receiving at least 1 dose of GBCA)²⁴ or those including highly exposed patients (ie, 4 patients receiving at least 50 injections of GBCA).²⁵ These studies failed to demonstrate an association of brain gadolinium deposition with worsening of neurologic or neuropsychological status.^{24,25} Also, studies applying imaging techniques to evaluate brain microstructural and functional integrity, such as sodium MR imaging,²⁶ resting-state functional MR imaging connectivity,²⁷ and

diffusion-weighted imaging,²⁸ showed the absence of tissue changes in the visually hyperintense dentate nuclei on unenhanced T1-weighted images after cumulative doses of GBCA. These findings were in agreement with cellular viability data obtained with histologic studies.^{13,29} Thus, it seems that the gadolinium deposition observed in the brains of serially injected patients differs from that causing NSF in terms of clinical consequences.

What Matters to Patients

What matters to patients is still the main open question. Patients should be informed that there is no documented clinical risk related to gadolinium deposition in their brains and that there is substantial convergent agreement on this subject among international institutions such as the FDA,³⁰ European Medicines Agency (EMA),¹⁸ and American College of Radiology, together with the American Society of Neuroradiology,³¹ International Society for Magnetic Resonance in Medicine,³² and European Society for Magnetic Resonance in Medicine and Biology–Gadolinium Research & Education Committee.³³

Thus, by summarizing the content, interpreting the meaning of the recommendations offered by several authorities, and integrating these into clinical practice, we identified 4 major points: 1) The indication, feasibility, appropriateness, and necessity of GBCA to solve each clinical question must be investigated, controlled, and validated (including a risk-benefit analysis for each patient) by the on-site radiologist or neuroradiologist; 2) each patient should be fully informed on all relevant and updated information about GBCA safety by the on-site radiologist or neuroradiologist before undergoing the MR study; 3) GBCA should be used according to the national regulations on a local basis; and 4) as for the gadolinium deposition in the brain, there is no direct proof of a causal relationship with an impact on neurologic and neurocognitive functions.

While further research on the clinical consequences of gadolinium deposition should be promoted, it remains to be elucidated whether the presence of deposited gadolinium represents a vulnerable condition in patient groups with neurodegeneration either related to aging and/or progression of chronic diseases.

There is evidence of gadolinium deposition, with even higher concentrations, in human tissue beyond the brain, including bone,³⁴ skin,³⁵ and liver.³⁶ The clinical meaning of this deposition is still under scrutiny; however, no direct relationship of causality with severe adverse consequences has been reported to date. Moreover, an increased signal intensity of the anterior pituitary gland, not yet confirmed to be caused by tissue gadolinium deposition, was recently reported in patients who had undergone serial injections of gadodiamide.³⁷

Last, a constellation of symptoms self-reported by patients after exposure to GBCA was identified in 2016 under the suggested definition of gadolinium deposition disease (GDD).³⁸ The symptoms referred to as GDD included headache, brain fog, fatigue, bone pain, central torso pain, subcutaneous tissue thickening, and tightness of hand and foot with a gloves-and-socks pattern. In this respect, a recent study showed no statistically significant difference in incidence of GDD symptoms between gadodiamide (linear) and gadoterate meglumine (macrocytic).³⁹ Given the well-known difference in terms of deposition between linear and

macrocytic GBCA, this finding points to a different pathway between exposure to GBCA and reports of symptoms that some think should be attributed to gadolinium exposure.

CONCLUSIONS

Scientifically available information about the safety and stability constant of the compounds, together with clinical, functional, and structural data after serial GBCA injections, as well as technical development geared to dose reduction (or altogether elimination of GBCA if proved to be unnecessary in specific clinical scenarios), must be taken into account and integrated to provide an answer as to what matters most to patients.

Even if what really counts is whether retained gadolinium in the brain and body is harmful, and, to date, no proved causation with permanent severe adverse effects has been reported in patients, we should keep investigating the topic, and if the current standard practice can be outperformed using different strategies, we should definitely go for it.

Disclosures: Alex Rovira—UNRELATED: Board Membership: Bayer AG, Biogen, Novartis, Icometrix, Roche; Payment for Lectures Including Service on Speakers Bureaus: Sanofi Genzyme, Merck Serono, Teva Pharmaceutical Industries Ltd, Novartis, Roche, Biogen; Payment for Development of Educational Presentations, money was paid to defray expenses for travel, lodging and registration: Sanofi Genzyme, Merck Serono, Novartis, Roche, Biogen. Paul M. Parizel—Other Relationships: I have, in the past, participated as a speaker in symposia and courses that were cosponsored by the industry (Bracco, Guerbet, Schering, GE Healthcare), but not in the past 3 years, and never in relationship to the topic of this editorial.

REFERENCES

1. Parizel PM, Degryse HR, Gheuens J, et al. **Gadolinium-DOTA enhanced MR imaging of intracranial lesions.** *J Comput Assist Tomogr* 1989;13:378–85 CrossRef Medline
2. Aime S, Caravan P. **Biodistribution of gadolinium-based contrast agents, including gadolinium deposition.** *J Magn Reson Imaging* 2009;30:1259–67 CrossRef Medline
3. Knop RH, Frank JA, Dwyer AJ, et al. **Gadolinium cryptelates as MR contrast agents.** *J Comput Assist Tomogr* 1987;11:35–42 CrossRef Medline
4. Spinosa DJ, Kaufmann JA, Hartwell GD. **Gadolinium chelates in angiography and interventional radiology: a useful alternative to iodinated contrast media for angiography.** *Radiology* 2002;223:319–25 CrossRef Medline
5. Grobner T. **Gadolinium: a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis?** *Nephrol Dial Transplant* 2006;21:1104–08 CrossRef Medline
6. Cowper SE, Robin HS, Steinberg SM, et al. **Scleromyxoedema-like cutaneous diseases in renal-dialysis patients.** *Lancet* 2000;356:1000–01 CrossRef Medline
7. **FDA ALERT. Gadolinium-Based Contrast Agents for Magnetic Resonance Imaging Scans.** 2006. <https://www.ismrm.org/special/FDA%20gadolinium1206.pdf>. Accessed March 4, 2020
8. Kanda T, Ishii K, Kawaguchi H, et al. **High signal intensity in the dentate nucleus and globus pallidus on unenhanced T1-weighted MR images: relationship with increasing cumulative dose of a gadolinium-based contrast material.** *Radiology* 2014;270:834–41 CrossRef Medline
9. 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;50:470–72 CrossRef Medline
10. McDonald RJ, McDonald JS, Kallmes DF, et al. **Gadolinium deposition in human brain tissues after contrast-enhanced MR imaging**

- in adult patients without intracranial abnormalities. *Radiology* 2017;285:546–54 CrossRef Medline
11. Mallio CA, Ramalho J, Quattrocchi CC. **Impact of brain irradiation, chemotherapy, and presence of primary brain tumors on changes in signal intensity after exposure to gadolinium-based contrast agents.** *Radiology* 2019;290:575–76 CrossRef Medline
 12. Errante Y, Cirimele V, Mallio CA, et al. **Progressive increase of T1 signal intensity of the dentate nucleus on unenhanced magnetic resonance images is associated with cumulative doses of intravenously administered gadodiamide in patients with normal renal function, suggesting dechelation.** *Invest Radiol* 2014;49:685–90 CrossRef Medline
 13. Lohrke J, Frisk AL, Frenzel T, et al. **Histology and gadolinium distribution in the rodent brain after the administration of cumulative high doses of linear and macrocyclic gadolinium-based contrast agents.** *Invest Radiol* 2017;52:324–33 CrossRef Medline
 14. Frenzel T, Lengsfeld P, Schirmer H, et al. **Stability of gadolinium-based magnetic resonance imaging contrast agents in human serum at 37°C.** *Invest Radiol* 2008;43:817–28 CrossRef Medline
 15. Dekkers IA, Roos R, van der Molen AJ. **Gadolinium retention after administration of contrast agents based on linear chelators and the recommendations of the European Medicines Agency.** *Eur Radiol* 2018;28:1579–84 CrossRef Medline
 16. Bussi S, Coppo A, Botteron C, et al. **Differences in gadolinium retention after repeated injections of macrocyclic MR contrast agents to rats.** *J Magn Reson Imaging* 2018;47:746–52 CrossRef Medline
 17. Behzadi AH, Zhao Y, Farooq Z, et al. **Immediate allergic reactions to gadolinium-based contrast agents: a systematic review and meta-analysis.** *Radiology* 2018;286:471–82 CrossRef Medline
 18. European Medicines Agency. **EMA’s final opinion confirms restrictions on use of linear gadolinium agents in body scans (21 July 2017).** https://www.ema.europa.eu/en/documents/referral/gadolinium-article-31-referral-emas-final-opinion-confirms-restrictions-use-linear-gadolinium-agents_en-0.pdf. Accessed January 9, 2020
 19. Pharmaceuticals and Medical Devices Agency. **Report on the investigation results.** Published November 11, 2017. <https://www.pmda.go.jp/files/000221379.pdf>. Accessed January 9, 2020
 20. Shen Z, Wu A, Chen X. **Iron oxide nanoparticle-based contrast agents for magnetic resonance imaging.** *Mol Pharm* 2017;14:1352–64 CrossRef Medline
 21. Amukotuwa SA, Marks MP, Zaharchuk G, et al. **Arterial spin-labeling improves detection of intracranial dural arteriovenous fistulas with MRI.** *AJNR Am J Neuroradiol* 2018;39:669–77 CrossRef Medline
 22. Delgado AF, Delgado AF, De Luca F, et al. **Arterial spin-labeling in children with brain tumor: a meta-analysis.** *AJNR Am J Neuroradiol* 2018;39:1536–42 CrossRef Medline
 23. Gong E, Pauly JM, Wintermark M, et al. **Deep learning enables reduced gadolinium dose for contrast-enhanced brain MRI.** *J Magn Reson Imaging* 2018;48:330–40 CrossRef Medline
 24. Welk B, McArthur E, Morrow SA, et al. **Association between gadolinium contrast exposure and the risk of parkinsonism.** *JAMA* 2016;316:96–98 CrossRef Medline
 25. Vymazal J, Krámská L, Brožová H, et al. **Does serial administration of gadolinium-based contrast agents affect patient neurological and neuropsychological status? Fourteen-year follow-up of patients receiving more than fifty contrast administrations.** *J Magn Reson Imaging* 2019 Oct 30. [Epub ahead of print] CrossRef Medline
 26. Eisele P, Konstandin S, Szabo K, et al. **Sodium MRI of T1 high signal intensity in the dentate nucleus due to gadolinium deposition in multiple sclerosis.** *J Neuroimaging* 2017;27:372–75 CrossRef Medline
 27. Mallio CA, Piervincenzi C, Gianolio E, et al. **Absence of dentate nucleus resting-state functional connectivity changes in nonneurological patients with gadolinium-related hyperintensity on T1-weighted images.** *J Magn Reson Imaging* 2019;50:445–55 CrossRef Medline
 28. Eisele P, Szabo K, Ebert A, et al. **Diffusion-weighted imaging of the dentate nucleus after repeated application of gadolinium-based contrast agents in multiple sclerosis.** *Magn Reson Imaging* 2019;58:1–5 CrossRef Medline
 29. Fingerhut S, Sperling M, Holling M, et al. **Gadolinium-based contrast agents induce gadolinium deposits in cerebral vessel walls, while the neuropil is not affected: an autopsy study.** *Acta Neuropathol* 2018;136:127–38 CrossRef Medline
 30. **FDA warns that gadolinium-based contrast agents (GBCA) are retained in the body; requires new class warnings.** <https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-warns-gadolinium-based-contrast-agents-gbcas-are-retained-body>. Accessed January 9, 2020
 31. **ACR–ASNR Position Statement on the use of gadolinium contrast agents. Manual on Contrast Media Version 10.3.** https://www.acr.org/-/media/ACR/files/clinical-resources/contrast_media.pdf. Accessed January 9, 2020
 32. Gulani V, Calamante F, Shellock FG, et al; International Society for Magnetic Resonance in Medicine. **Gadolinium deposition in the brain: summary of evidence and recommendations.** *Lancet Neurol* 2017;16:564–70 CrossRef Medline
 33. Quattrocchi CC, Ramalho J, van der Molen AJ, et al; GREC, European Gadolinium Retention Evaluation Consortium and the ESNR, European Society of Neuroradiology. **Standardized assessment of the signal intensity increase on unenhanced T1-weighted images in the brain: the European Gadolinium Retention Evaluation Consortium (GREC) Task Force position statement.** *Eur Radiol* 2019;29:3959–67 CrossRef Medline
 34. Darrah TH, Prutsman-Pfeiffer JJ, Poreda RJ, et al. **Incorporation of excess gadolinium into human bone from medical contrast agents.** *Metallomics* 2009;1:479–88 CrossRef Medline
 35. Roberts DR, Lindhorst SM, Welsh CT, et al. **High levels of gadolinium deposition in the skin of a patient with normal renal function.** *Invest Radiol* 2016;51:280–89 CrossRef Medline
 36. Maximova N, Gregori M, Zennaro F, et al. **Hepatic gadolinium deposition and reversibility after contrast agent-enhanced MR imaging of pediatric hematopoietic stem cell transplant recipients.** *Radiology* 2016;281:418–26 CrossRef Medline
 37. Mallio CA, Lo Vullo G, Messina L, et al. **Increased T1 signal intensity of the anterior pituitary gland on unenhanced magnetic resonance images after chronic exposure to gadodiamide.** *Invest Radiol* 2020;55:25–29 CrossRef Medline
 38. Semelka RC, Ramalho J, Vakharia A, et al. **Gadolinium deposition disease: Initial description of a disease that has been around for a while.** *Magn Reson Imaging* 2016;34:1383–90 CrossRef Medline
 39. Parillo M, Sapienza M, Arpaia F, et al. **A structured survey on adverse events occurring within 24 hours after intravenous exposure to gadodiamide or gadoterate meglumine: a controlled prospective comparison study.** *Invest Radiol* 2019;54:191–97 CrossRef Medline