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REVIEW ARTICLE

Distribution and chemical forms of gadolinium in the brain: a review

[1]TOMONORI KANDA, MD, PhD, [1,2]YUDAI NAKAI, MD, [1,2]AKIFUMI HAGIWARA, MD, [2,3]HIROSHI OBA, MD, PhD, [2,3]KEIKO TOYODA, MD, PhD and [3]SHIGERU FURUI, MD, PhD

[1]Department of Radiology, Kobe University School of Medicine, Hyogo, Japan
[2]Department of Radiology, Graduate School of Medicine, University of Tokyo, Tokyo, Japan
[3]Department of Radiology, Teikyo University School of Medicine, Tokyo, Japan

Address correspondence to: Dr Tomonori Kanda
E-mail: *k_a@hotmail.co.jp*

ABSTRACT

In the 3 years since residual gadolinium-based contrast agent (GBCA) in the brain was first reported, much has been learned about its accumulation, including the pathway of GBCA entry into the brain, the brain distribution of GBCA and its excretion. Here we review recent progress in understanding the routes of gadolinium deposition in brain structures.

INTRODUCTION

Gadolinium is a heavy metal and it is toxic to humans. Once it has entered the body, most of it is retained. In its major use as the contrast agent in MRI procedures, it is administered in chelated form. The chelation of gadolinium protects the body from the toxicity and allows rapid elimination of the metal. In fact, gadolinium-based contrast agents (GBCAs) have been safely used for over 25 years, except for rare cases of nephrogenic systemic fibrosis and acute allergic reactions.[1]

However, in 2013, our group reported the detection of gadolinium deposition in the brain, which led to a reconsideration of the safety of GBCA.[2] Following GBCA administration, the gadolinium component persists in the human brain long enough to raise concern about its toxicity. Among the many researchers who have further investigated this phenomenon are Errante[3] and Adin,[4] who evaluated the association between a history of GBCA administration and the high signal intensity of the dentate nucleus on the MRI scans of these patients. Their results paralleled our own. Finally, gadolinium deposition in the human brain was confirmed in autopsy specimens.[5–7] In the following, we review recent progress in studies of gadolinium deposition in the brain.

The basic chemistry of GBCAs

Commercially available GBCAs are divided into linear chelated and macro-cyclic chelated GBCAs. Linear GBCAs are relatively unstable compared with macrocyclic GBCAs. Both the thermodynamic and the kinetic stability of GBCAs have been evaluated *in vitro*, but there is no good indicator of their *in vivo* stability.[8,9]

Our group demonstrated the high signal intensity in the dentate nucleus and globus pallidus on T_1 weighted imaging (T1WI) and its correlation with the number of previous linear GBCA administrations. With a history of more than five linear GBCA administrations, high signal intensity appears in the dentate nucleus and globus pallidus.[2] To determine whether GBCA stability correlates with the high signal intensity of these brain structures, we evaluated 127 patients who had undergone contrast-enhanced MRI. Nine patients had a hyperintense dentate nucleus. The high signal intensity correlated with past administration of the gadopentetate dimeglumine (linear GBCA) but not with that of the gadoteridol ([10] Radbruch et al evaluated 50 patients (linear group) with a history of at least 6 (mean 7.06) linear GBCA (gadopentetate dimeglumine) injections and 50 patients (macrocyclic group) with a history of at least 6 (mean 7.32) injections of macrocyclic GBCAs (gadoterate meglumine) for contrast-enhanced MRI. The signal intensities of the dentate nucleus and globus pallidus were significantly increased in the linear but not the macrocyclic group.[11] These results convinced most radiologists that repeated linear, but not macrocyclic GBCA administration increased the signal intensity in the dentate nucleus. In their study of patients with high-dose macrocyclic GBCA administration, Radbruch et al evaluated 33 patients who had received at least 20 macrocyclic GBCA

injections and found no change in the signal intensity of the dentate nucleus.[12] These data suggest that macrocyclic GBCAs, even at high doses, are unlikely to result in a high signal intensity of the dentate nucleus.

An exception was reported by Stojanov, et al[13] in a study of 58 patients with 4 to 6 macrocylic GBCA (gadobutrol) administrations. Increased signal intensities of the dentate nucleus and globus pallidus based on region-of-interest analysis were detected; however, in our opinion, the areas shown in their published figures do not exhibit obvious high intensity. Moreover, gadobutrol is of relatively low thermodynamic stability, but of high kinetic stability.[1] Thus, doubts arose regarding the result of Stojanov et al[13] and attempts were made to replicate their study.[14] Radbruch et al analysed the MRI scans of 30 patients administered gadobutrol for a mean 7.3 times and found no change in signal intensity even though the amount of GBCA administered to the patients in their series was higher than in Stojanov's study.[15] Cao et al also assessed 25 patients administered gadobutrol for a mean 7.8 times and concluded that the repeated administration of gadobutrol does not cause a signal intensity change in the dentate nucleus.[16] It is therefore now widely held that repeated linear, but not but macrocyclic GBCA administration causes a signal change in the dentate nucleus on MRI. Further support for this finding comes from in studies in rats.[17,18]

In addition, linear GBCAs also differ in their stability. Ramalho et al compared the brain MRI scans of 23 patients who previously received an average of five gadodiamide (linear GBCA) administrations and 46 patients who previously received an average of 4.6 administrations of gadobenate dimeglumine (linear GBCA). High signal intensity in the dentate nucleus was observed only in the gadodiamide administration group, indicating that it leads to greater gadolinium accumulation in the brain than is the case with gadodiamide.[19] Weberling, et al compared the brain MRI scans of 50 patients with an average of 7.7 previous gadobenate dimeglumine (linear GBCA) administrations, 50 patients with an average of 6.3 previous gadopentetate dimeglumine (linear GBCA) administrations and 50 patients with an average of 6.1 previous gadoterate meglumine (macrocyclic GBCAs) administrations. The signal intensity of the dentate nucleus in the gadobenate dimeglumine group was lower than that in the gadopentetate dimeglumine group, but higher than that in the gadoterate meglumine group.[20] These results indicated that administration of the linear GBCA gadobenate dimeglumine causes a high signal intensity in the dentate nucleus but of a smaller magnitude than associated with other linear GBCAs.

Gadoxetic acid is a hepato-specific linear GBCA partially excreted by the liver. The amount of gadolinium in a standard clinical dose of gadoxetic acid is only a quarter of that in other GBCAs. However, Kahn, et al reported a high signal intensity of the dentate nucleus in patients with >10 gadoxetic acid administrations (the dose of gadoxetic acid was not reported).[21]

Brain distribution of gadolinium

In our first report, we evaluated brain gadolinium deposition on MRI scans. The results showed a correlation between the signal intensity of the dentate nucleus, and, to a lesser extent, that of the globus pallidus, and the accumulated GBCA dose. In that study, patients had been administered a GBCA 0–30 times.[2] McDonald et al evaluated the signal intensity change of the pulvinar and pons in addition to that of the dentate nucleus and globus pallidus in 13 patients with at least 4 GBCA administrations. The signal intensity of all brain structures correlated with the amount of past GBCA administration. The authors confirmed their findings in autopsy specimens, as the gadolinium concentration in the same regions correlated with the dose of past GBCA administration.[5] Our group evaluated five cadavers with previous GBCA administration.[6] Gadolinium accumulation was detected in the dentate nucleus, globus pallidus, cerebellar white matter, frontal lobe white matter and frontal lobe cortical matter from the autopsy specimens. A higher signal intensity in the dentate nucleus and globus pallidus than in the other brain regions that were examined was again seen in patients with repeat GBCA administrations.

However, in our study,[6] gadolinium was also detected in the brains of patients with no history of GBCA administration. Since gadolinium does not exist in nature, its source is unclear. Thus, the signal has been suggested to be an artefact (noise) of inductively coupled plasma mass spectrometry (ICP-MS), to indicate an unknown history of GBCA administration, or evidence of gadolinium contamination during the experiment. It may also be that gadolinium levels are gradually increasing in the environment due to the use of GBCAs in MRI and their wastewater discharge,[22,23] such that the human body accumulates gadolinium from environmental sources.

The high signal intensity associated with repeated GBCA administration is not limited to the dentate nucleus and globus pallidus but may also occur in other parts of the brain. Zhang et al evaluated 13 patients with at least 35 administrations of linear GBCAs. They reported T_1 shortening in the dentate nucleus (100%), globus pallidus (100%), substantia nigra (100%), thalamus pulvinar (92%), red nucleus (77%), colliculi (77%), superior cerebellar peduncle (54%), caudate nucleus (31%), whole thalamus (23%) and putamen (15%).[24] Although described in a case report, high signal intensity was also recognized in the calcarine sulcus, pre-central gyri, and post-central gyri in the brain MRI scan of a patient who received GBCA at least 86 times.[25] Since these tissues accumulate less gadolinium than the cerebellar dentate nucleus, a signal difference with the surrounding tissues will not be detected unless a large amount of contrast medium is administered.

Washout

In our initial report, we postulated that GBCA accumulation, while long-lasting, is not permanent, based on a graph of GBCA administration frequency *vs* signal ratio, which showed that the rise in the latter decreases in patients with a larger number of contrast administrations.[2] In the study that measured the gadolinium concentration in autopsied brain tissue, there was a trend

in which the longer the period from GBCA administration to death, the lower the gadolinium concentration in the brain.[6,7] Radbruch et al reported a decrease in the signal ratio following the administration of a macrocyclic GBCA to a patient with a signal rise due to linear GBCA administration. This finding suggested that gadolinium washout from the brain following macrocyclic GBCA administration is greater than gadolinium accumulation due to linear GBCA administration.[26]

In a study from the GE Global Research Center, linear GBCA was administered to healthy rats 20 times (total: 12 mmol kg^{-1}), and the gadolinium remaining in rat brain then measured 1 and 20 weeks later. The gadolinium concentration in the rat brain at 20 weeks was 50% less than that at 1 week after GBCA administration, consistent with a gadolinium washout mechanism.[27] In this study, it was unclear whether the decreased gadolinium was of the chelated or de-chelated form. The chemical form of residual gadolinium in the rat brain was the focus of another study. In another report from Frenzel, of Bayer AG, the gadolinium concentration in the blood, cerebrospinal fluid (CSF), and brain of rats was evaluated 4.5 and 24 h after intravenous GBCA administration. Saline, a linear GBCA, or a macrocyclic GBCA was administered 10 times, after which the gadolinium concentration in the brain tissue of rats was measured after 3 days and after 24 days, distinguishing between water-soluble and water-insoluble forms. The concentration of water-soluble gadolinium in rat brain did not differ with respect to linear *vs* macrocyclic GBCA administration and was lower after 24 days than after 3 days, regardless of the type of GBCA. Water-insoluble gadolinium is observed in the rat brain only after the administration of linear GBCA, and its concentration in brain structures does not change between 3 and 24 days.[28] These results suggest that, after GBCA administration, only the fraction of gadolinium that becomes water-insoluble, due to chelate detachment, persists in the brain and is then gradually excreted. The fraction of gadolinium excreted from the brain remains to be determined.

Glymphatic system

How gadolinium-based contrast agents enter the brain is unclear. In the transport of metals that are essential elements required for normal function,[29] metal transporters are involved, but these sometimes malfunction and recognize other metals.[30,31] The globus pallidus and cerebellar dentate nucleus, that is, the structures of high signal intensity on T1WI images in patients with repeat GBCA administration, are sites where metals such as iron are deposited.[32,33] Although we initially hypothesized that gadolinium passes through the blood–brain barrier (BBB) via a metal transporter, the mechanism seems to be more complicated.

Takeda et al administered a tracer metal ($^{65}ZnCl_2$ or $^{54}MnCl_2$) intravenously to rats and evaluated its pathway in the brain. Both $^{65}ZnCl_2$ and $^{54}MnCl_2$ first accumulated in the CSF and then entered the brain, where they were redistributed.[34] Aoki et al administered manganese to the rat intravenously and then performed brain MRI 2 h, 1, 4 and 14 days later. Manganese was detected only in the CSF 2 h after the infusion but then spread throughout the brain.[35] These results indicated that metals in the brain are mainly transported from the CSF rather than entering by crossing the blood–brain barrier.

Iliff et al showed that most of the CSF enters the brain interstitium from around the penetrating branch artery and is excreted from around the cerebral vein to the lymphatic vessels of the neck. They also showed that low-molecular weight molecules enter the brain via the CSF flow and are then excreted into the lymphatic vessels.[36] Commercially available GBCAs injected into the intrathecal space of the rat brain are also transported into the brain by this pathway.[37] In 2015, Louveau et al[38] and Aspelund et al[39] established the presence of lymphatic vessels in the brain. They named this CSF flow pathway the glymphatic system.[40]

GBCA transfer from the CSF to the brain occurs not only in rats but also in humans. Eide et al performed brain MRI 1 and 4.5 h after the administration of GBCAs into the intrathecal space of patients with intracranial hypotension and suspected spontaneous CSF leakage. On T1WI MRI, the brain signal after GBCA administration gradually increased, coinciding with GBCA transfer from the CSF to the brain.[41] In the study by Öner et al, 6 patients who received between 0.5 and 1 ml of linear GBCAs (gadopentetate dimeglumin) via injection into the intrathecal space 2–12 years earlier were examined by brain MRI. These patients without a history of GBCA intravenous administration nonetheless had high signal intensity in the dentate nucleus and globus pallidus,[42] which suggests that the gadolinium contrast agent migrated from the CSF into the brain, accumulating in brain structures.

While GBCA in the CSF is transported through the glymphatic system into the brain, the mechanism by which GBCA in the blood is transported to the CSF is unclear. GBCA administered to a patient undergoing dialysis is detected in the CSF by MRI performed several days after GBCA administration.[43] Naganawa et al evaluated brain MRI scans performed 4 h after intravenous GBCA administration in 27 patients with near normal renal function. The signal intensities of the subarachnoid and perivascular spaces on the contrast-enhanced FLAIR images were significantly higher than those before GBCA administration, indicating that GBCA is also transferred to the CSF even in patients with near normal kidney function.[44]

In another report from Jost, of Bayer AG, the gadolinium concentration in the blood, CSF, and brain of rats was evaluated 4.5 and 24 h after intravenous GBCA administration. At 4.5 h, the gadolinium concentration was higher in the CSF than in the blood. At 24 h, the concentration was higher in the brain than in the blood and CSF. In the cerebellum and brain stem, however, the gadolinium concentration did not change regardless of whether linear or macrocyclic GBCA was used.[45]

Since long-term gadolinium deposition in the brain is greater with linear than with macrocyclic GBCAs, the deposits are probably made up mostly of the de-chelated form. The chelated form of gadolinium is transported in the brain via the glymphatic system; some of it is then released from the chelate and remains in the brain. In the study of GE Global Research Center, the gadolinium concentration in rats after linear GBCA administration

decreased by about 50% between 1 and 20 weeks.[27] The chelated form of gadolinium is probably excreted from the brain tissue within several weeks. The de-chelated form may be transported, via metal transporters, axonal transport, or another yet to be determined mechanism, to specific parts of the brain and accumulate there for longer periods of time.

MRI sequences

Most of the studies that examined the high signal intensity in the dentate nucleus on MRI were retrospective, based on spin echo T1WI,[2,5,11] T1FLAIR,[4] or magnetization prepared rapid acquisition of gradient echo sequence (MPRAGE)[46] images. However, gadolinium depositions in the dentate nucleus and globus pallidus are very small,[5–7] such that the detection limit must be taken into account in MRI evaluations. We reported that spin echo T1WI has a higher sensitivity than T1FLAIR images in the detection of the hyperintense signal of the dentate nucleus.[47] Ramalho et al evaluated the spin echo T1WI and MPRAGE images of 18 patients who underwent at least three linear GBCA administrations. Rather than comparing the detectability of the high signal intensity in the dentate nucleus by these two imaging methods, they examined the agreement between the visual and quantitative evaluations and reported that better results were obtained with the MPRAGE sequences.[46]

Recent studies have been aimed at the more accurate evaluation of gadolinium deposits in the brain using MRI. Tedeschi et al measured the R1 ($1/T_1$) and R2* ($1/T_2$*) of the dentate nucleus in the scans of 74 multiple sclerosis patients with an average of 6 GBCA administrations. The R1 correlated with the number of previous GBCA administrations, but the R2* correlated only with patient age.[48] This result indicated that the high signal intensity of the cerebellar dentate nucleus reflects gadolinium rather than iron deposition, as the latter changes R2*. Hinoda et al used quantitative susceptibility mapping to evaluate 48 patients with an average of 9.5 GBCA administrations (contrast group) and 48 patients never administered GBCA (non-contrast group). Significantly higher magnetic susceptibility was determined in the contrast group than in the non-contrast group, and signal intensity was also significantly higher on the T1WI images of the former.[49] Kuno et al measured the T_1 and T_2 of the whole brain in 9 patients with between 1 and 8 previous GBCA administrations (contrast group) and 26 patients who never had been administered GBCA (non-contrast group). The T_1 value of the gray matter was significantly lower in the contrast group than in the non-contrast group, but the difference in the white matter of the 2 groups was not significant. The T_2 value of the whole brain did not differ between these groups, but it did correlate with the number of previous GBCA administrations. Although their study showed that gadolinium deposition occurs in the whole brain, many of their results were not statistically significant because of the small number of patients and limited number of previous GBCA administrations.[50] Further studies are needed to determine whether T_1 and T_2 maps are useful in the quantification of gadolinium deposition.

Safety

Gadolinium deposition in the brain was first reported roughly 3 years ago. Initially, concern was raised regarding gadolinium toxicity in humans,[1] but thus far only a skin rash is evidence of past GBCA administration[51,52] as there have been no reports clearly demonstrating brain toxicity. McDonald et al evaluated the brain tissue collected during the autopsy of patients each administered a total of 420 ml of gadodiamide (linear GBCA) over his or her lifetime but did not find pathological degeneration of brain tissue related to gadolinium deposition. Welk et al evaluated nearly 100,000 patients administered GBCA but found no association with Parkinson's symptoms.[53] Thus, the development of severe symptoms due to gadolinium deposition in the brain subsequent to GBCA administration seems to be low.

In March 2017, the European Medicines Agency's Pharmacovigilance and Risk Assessment Committee[54] proposed to discontinue the marketing of linear GBCAs, except for liver-specific GBCAs. In Europe, the use of linear GBCAs will probably decline. However, in April, the American College of Radiology[55] and the U.S. Food and Drug Administration[56] announced that there is no evidence to date that gadolinium accumulation in the brain is harmful to the human body, and there is no need to restrict its usage.

CONCLUSION

Much has been learned in the past 3 years about the mechanism of gadolinium accumulation in the brain following GBCA administration. Gadolinium retention in the brain is greater with linear than with macrocyclic GBCA. Gadolinium accumulation in the brain seems to involve the glymphatic system, the focus of continuing research.

REFERENCES

1. Kanda T, Oba H, Toyoda K, Kitajima K, Furui S. Brain gadolinium deposition after administration of gadolinium-based contrast agents. *Jpn J Radiol* 2016; **34**: 3–9. doi: https://doi.org/10.1007/s11604-015-0503-5
2. Kanda T, Ishii K, Kawaguchi H, Kitajima K, Takenaka D. High signal intensity in the dentate nucleus and globus pallidus on unenhanced T1-weighted MR images: relationship with increasing cumulative dose of a gadolinium-based contrast material. *Radiology* 2014; **270**: 834–41. doi: https://doi.org/10.1148/radiol.13131669
3. 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**: 685–90. doi: https://doi.org/10.1097/RLI.0000000000000072
4. Adin ME, Kleinberg L, Vaidya D, Zan E, Mirbagheri S, Yousem DM. Hyperintense dentate nuclei on T1-weighted MRI: relation to repeat gadolinium administration. *AJNR Am J Neuroradiol* 2015; **36**: 1859–65. doi: https://doi.org/10.3174/ajnr.A4378
5. McDonald RJ, McDonald JS, Kallmes DF, Jentoft ME, Murray DL, Thielen KR, et al. Intracranial gadolinium deposition after

contrast-enhanced MR imaging. *Radiology* 2015; **275**: 772–82. doi: https://doi.org/10.1148/radiol.15150025

6. Kanda T, Fukusato T, Matsuda M, Toyoda K, Oba H, Kotoku J, et al. Gadolinium-based contrast agent accumulates in the brain even in subjects without severe renal dysfunction: evaluation of autopsy brain specimens with inductively coupled plasma mass spectroscopy. *Radiology* 2015; **276**: 228–32. doi: https://doi.org/10.1148/radiol.2015142690
7. Murata N, Gonzalez-Cuyar LF, Murata K, Fligner C, Dills R, Hippe D, 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**: 447–53. doi: https://doi.org/10.1097/RLI.0000000000000252
8. Hao D, Ai T, Goerner F, Hu X, Runge VM, Tweedle M. MRI contrast agents: basic chemistry and safety. *J Magn Reson Imaging* 2012; **36**: 1060–71. doi: https://doi.org/10.1002/jmri.23725
9. Idée JM, Port M, Robic C, Medina C, Sabatou M, Corot C. Role of thermodynamic and kinetic parameters in gadolinium chelate stability. *J Magn Reson Imaging* 2009; **30**: 1249–58. doi: https://doi.org/10.1002/jmri.21967
10. Kanda T, Osawa M, Oba H, Toyoda K, Kotoku J, Haruyama T, 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**: 803–9. doi: https://doi.org/10.1148/radiol.14140364
11. Radbruch A, Weberling LD, Kieslich PJ, Eidel O, Burth S, Kickingereder P, et al. Gadolinium retention in the dentate nucleus and globus pallidus is dependent on the class of contrast agent. *Radiology* 2015; **275**: 783–91. doi: https://doi.org/10.1148/radiol.2015150337
12. Radbruch A, Haase R, Kieslich PJ, Weberling LD, Kickingereder P, Wick W, 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**: 699–707. doi: https://doi.org/10.1148/radiol.2016162241
13. 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**: 807–15. doi: https://doi.org/10.1007/s00330-015-3879-9
14. 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? *Eur Radiol* 2016; **26**: 816–7. doi: https://doi.org/10.1007/s00330-015-4019-2
15. Radbruch A, Weberling LD, Kieslich PJ, Hepp J, Kickingereder P, Wick W, 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**: 805–10. doi: https://doi.org/10.1097/RLI.0000000000000227
16. 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**: 414–9. doi: https://doi.org/10.2214/AJR.15.15327
17. Jost G, Lenhard DC, Sieber MA, Lohrke J, Frenzel T, Pietsch H. Signal increase on unenhanced T1-weighted images in the rat brain after repeated, extended doses of gadolinium-based contrast agents: comparison of linear and macrocyclic agents. *Invest Radiol* 2016; **51**: 83–9. doi: https://doi.org/10.1097/RLI.0000000000000242
18. Robert P, Lehericy S, Grand S, Violas X, Fretellier N, Idée JM, 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**: 473–80. doi: https://doi.org/10.1097/RLI.0000000000000181
19. Ramalho J, Castillo M, AlObaidy M, Nunes RH, Ramalho M, Dale BM, 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**: 836–44. doi: https://doi.org/10.1148/radiol.2015150872
20. Weberling LD, Kieslich PJ, Kickingereder P, Wick W, Bendszus M, Schlemmer HP, et al. Increased signal intensity in the dentate nucleus on unenhanced T1-weighted images after gadobenate dimeglumine administration. *Invest Radiol* 2015; **50**: 743–8. doi: https://doi.org/10.1097/RLI.0000000000000206
21. Kahn J, Posch H, Steffen IG, Geisel D, Bauknecht C, Liebig T, 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**: 708–16. doi: https://doi.org/10.1148/radiol.2016162535
22. Nozaki Y, Lerche D, Alibo DS, Tsutsumi M. Dissolved indium and rare earth elements in three Japanese rivers and Tokyo Bay: evidence for anthropogenic Gd and In. *Geochim Cosmochim Acta* 2000; **2364**: 3975–82. doi: https://doi.org/10.1016/S0016-7037(00)00472-5
23. Hatje V, Bruland KW, Flegal AR. Increases in anthropogenic gadolinium anomalies and rare earth element concentrations in San Francisco Bay over a 20 year record. *Environ Sci Technol* 2016; **50**: 4159–68. doi: https://doi.org/10.1021/acs.est.5b04322
24. Zhang Y, Cao Y, Shih GL, Hecht EM, Prince MR. Extent of signal hyperintensity on unenhanced T1-weighted brain MR images after more than 35 administrations of linear gadolinium-based contrast agents. *Radiology* 2017; **282**: 516–25. doi: https://doi.org/10.1148/radiol.2016152864
25. Khant ZA, Hirai T, Kadota Y, Masuda R, Yano T, Azuma M, et al. T1 shortening in the cerebral cortex after multiple administrations of gadolinium-based contrast agents. *Magn Reson Med Sci* 2017; **16**: 84–6. doi: https://doi.org/10.2463/mrms.mp.2016-0054
26. Radbruch A, Weberling LD, Kieslich PJ, Hepp J, Kickingereder P, Wick W, et al. Intraindividual analysis of signal intensity changes in the dentate nucleus after consecutive serial applications of linear and macrocyclic gadolinium-based contrast agents. *Invest Radiol* 2016; **51**: 683–90. doi: https://doi.org/10.1097/RLI.0000000000000308
27. Smith AP, Marino M, Roberts J, Crowder JM, Castle J, Lowery L, 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**: 743–51. doi: https://doi.org/10.1148/radiol.2016160905
28. Frenzel T, Apte C, Jost G, Schöckel L, Lohrke J, Pietsch H. Quantification and assessment of the chemical form of residual gadolinium in the brain after repeated administration of gadolinium-based contrast agents: comparative study in rats. *Invest Radiol* 2017; **52**: 396–404. doi: https://doi.org/10.1097/RLI.0000000000000352

29. Kanda T, Nakai Y, Aoki S, Oba H, Toyoda K, Kitajima K, et al. Contribution of metals to brain MR signal intensity: review articles. *Jpn J Radiol* 2016; **34**: 258–66. doi: https://doi.org/10.1007/s11604-016-0532-8
30. Bressler JP, Olivi L, Cheong JH, Kim Y, Maerten A, Bannon D. Metal transporters in intestine and brain: their involvement in metal-associated neurotoxicities. *Hum Exp Toxicol* 2007; **26**: 221–9. doi: https://doi.org/10.1177/0960327107070573
31. Fitsanakis VA, Zhang N, Garcia S, Aschner M. Manganese (Mn) and iron (Fe): interdependency of transport and regulation. *Neurotox Res* 2010; **18**: 124–31. doi: https://doi.org/10.1007/s12640-009-9130-1
32. Popescu BF, Robinson CA, Rajput A, Rajput AH, Harder SL, Nichol H. Iron, copper, and zinc distribution of the cerebellum. *Cerebellum* 2009; **8**: 74–9. doi: https://doi.org/10.1007/s12311-008-0091-3
33. Popescu BF, Nichol H. Mapping brain metals to evaluate therapies for neurodegenerative disease. *CNS Neurosci Ther* 2011; **17**: 256–68. doi: https://doi.org/10.1111/j.1755-5949.2010.00149.x
34. Takeda A, Akiyama T, Sawashita J, Okada S. Brain uptake of trace metals, zinc and manganese, in rats. *Brain Res* 1994; **640**: 341–4. doi: https://doi.org/10.1016/0006-8993(94)91891-0
35. Aoki I, Wu YJ, Silva AC, Lynch RM, Koretsky AP. In vivo detection of neuroarchitecture in the rodent brain using manganese-enhanced MRI. *Neuroimage* 2004; **22**: 1046–59. doi: https://doi.org/10.1016/j.neuroimage.2004.03.031
36. Iliff JJ, Wang M, Liao Y, Plogg BA, Peng W, Gundersen GA, et al. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β. *Sci Transl Med* 2012; **4**: 147ra111. doi: https://doi.org/10.1126/scitranslmed.3003748
37. Iliff JJ, Lee H, Yu M, Feng T, Logan J, Nedergaard M, et al. Brain-wide pathway for waste clearance captured by contrast-enhanced MRI. *J Clin Invest* 2013; **123**: 1299–309. doi: https://doi.org/10.1172/JCI67677
38. Louveau A, Smirnov I, Keyes TJ, Eccles JD, Rouhani SJ, Peske JD, et al. Structural and functional features of central nervous system lymphatic vessels. *Nature* 2015; **523**: 337–41. doi: https://doi.org/10.1038/nature14432
39. Aspelund A, Antila S, Proulx ST, Karlsen TV, Karaman S, Detmar M, et al. A dural lymphatic vascular system that drains brain interstitial fluid and macromolecules. *J Exp Med* 2015; **212**: 991–9. doi: https://doi.org/10.1084/jem.20142290
40. Iliff JJ, Goldman SA, Nedergaard M. Implications of the discovery of brain lymphatic pathways. *Lancet Neurol* 2015; **14**: 977–9. doi: https://doi.org/10.1016/S1474-4422(15)00221-5
41. Eide PK, Ringstad G. MRI with intrathecal MRI gadolinium contrast medium administration: a possible method to assess glymphatic function in human brain. *Acta Radiol Open* 2015; **4**: 205846011560963. doi: https://doi.org/10.1177/2058460115609635
42. Öner AY, Barutcu B, Aykol Ş, Tali ET. Intrathecal contrast-enhanced magnetic resonance imaging-related brain signal changes: residual gadolinium deposition? *Invest Radiol* 2017; **52**: 195–7. doi: https://doi.org/10.1097/RLI.0000000000000327
43. Rai AT, Hogg JP. Persistence of gadolinium in CSF: a diagnostic pitfall in patients with end-stage renal disease. *AJNR Am J Neuroradiol* 2001; **22**: 1357–61.
44. Naganawa S, Nakane T, Kawai H, Taoka T. Gd-based contrast enhancement of the perivascular spaces in the basal ganglia. *Magn Reson Med Sci* 2017; **16**: 61–5. doi: https://doi.org/10.2463/mrms.mp.2016-0039
45. Jost G, Frenzel T, Lohrke J, Lenhard DC, Naganawa S, Pietsch H. Penetration and distribution of gadolinium-based contrast agents into the cerebrospinal fluid in healthy rats: a potential pathway of entry into the brain tissue. *Eur Radiol* 2017; **27**: 2877–85. doi: https://doi.org/10.1007/s00330-016-4654-2
46. 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**: 1427–31. doi: https://doi.org/10.3174/ajnr.A4757
47. Kanda T, Oba H, Toyoda K, Furui S. Recent advances in understanding Gadolinium Retention in the brain. *AJNR Am J Neuroradiol* 2016; **37**: E1–. doi: https://doi.org/10.3174/ajnr.A4586
48. Tedeschi E, Palma G, Canna A, Cocozza S, Russo C, Borrelli P, et al. In vivo dentate nucleus MRI relaxometry correlates with previous administration of gadolinium-based contrast agents. *Eur Radiol* 2016; **26**: 4577–84. doi: https://doi.org/10.1007/s00330-016-4245-2
49. Hinoda T, Fushimi Y, Okada T, Arakawa Y, Liu C, Yamamoto A, et al. Quantitative assessment of gadolinium deposition in dentate nucleus using quantitative susceptibility mapping. *J Magn Reson Imaging* 2017; **45**: 1352–8. doi: https://doi.org/10.1002/jmri.25490
50. Kuno H, Jara H, Buch K, Qureshi MM, Chapman MN, Sakai O. Global and regional brain assessment with quantitative MR imaging in patients with prior exposure to linear gadolinium-based contrast agents. *Radiology* 2017; **283**: 195–204. doi: https://doi.org/10.1148/radiol.2016160674
51. Gathings RM, Reddy R, Santa Cruz D, Brodell RT. Gadolinium-associated plaques: a new, distinctive clinical entity. *JAMA Dermatol* 2015; **151**: 316–9. doi: https://doi.org/10.1001/jamadermatol.2014.2660
52. Semelka RC, Commander CW, Jay M, Burke LM, Ramalho M. Presumed gadolinium toxicity in subjects with Normal Renal function: a report of 4 cases. *Invest Radiol* 2016; **51**: 661–5. doi: https://doi.org/10.1097/RLI.0000000000000318
53. Welk B, McArthur E, Morrow SA, MacDonald P, Hayward J, Leung A, et al. Association between gadolinium contrast exposure and the risk of parkinsonism. *JAMA* 2016; **316**: 96–8. doi: https://doi.org/10.1001/jama.2016.8096
54. European Medicines Agency. PRAC concludes assessment of gadolinium agents used in body scans and recommends regulatory actions, including suspension for some marketing authorisations. 2002; [updated 2017 March 10; cited 2017 March 10]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2017/03/news_detail_002708.js...
55. American College of Radiology. ACR response to the European PRAC recommendations. 2017; [updated 2017 Apr 4; cited 2017 Apr 4]. Available from: https://www.acr.org/About-Us/Media-Center/Press-Releases/2017-Press-Releases/20170404-ACR-Response-t...
56. US Food and Drug Administration. FDA identifies no harmful effects to date with brain retention of gadolinium-based contrast agents for MRIs; review to continue. 2015; [updated 2017 May 22; cited 2015 Jul 27]. Available from: https://www.fda.gov/Drugs/DrugSafety/ucm559007.htm