Archives of Radiology
ISSN: 2638-521X
Volume 1, Issue 2, 2018, PP: 4-10

Gadolinium (III)-Based Contrast Agents, Gadolinium Deposition in Tissues and the Clinical Significance: A Review

Gregory M Armstrong, Avinash Kumar Kanodia, Gillian Duncan, Thiru Sudarshan, Robert Foster

Department of Radiology, Ninewells Hospital, Dundee, UK.
avinash.kanodia@nhs.net

***Corresponding Author:** Dr. AK Kanodia, Consultant Radiologist, Ninewells Hospital, Dundee, UK.*

Abstract

Gadolinium based contrast agents (GBCA) have been used for several decades for MR imaging. These have generally been considered safe. In the past, some of these were found to be associated with nephrogenic systemic fibrosis in patients with impaired renal function, that were eventually discarded. More recently, there has been an ongoing debate due to evidence of gadolinium deposition in the brain, bones and other tissues in people with normal renal function. The linear gadolinium-based contrast agents have been particularly found to be associated with this phenomena. The clinical significance of gadolinium deposition is not entirely certain and remains a matter of debate, particularly since macrocyclic are increasingly being preferred over linear regions. Different regulatory agencies are looking into evidence and whether use of gadolinium based contrast agents needs to be restricted for clinical use.

The current article is intended to serve as a review of the literature about GBCAs, review of relevant studies and potential clinical implications regarding use of these agents.

Keywords: *Gadolinium deposition, macrocyclic agents, linear agents*

Introduction

Gadolinium is a lanthanide-series, trivalent rare earth metal with paramagnetic properties, which has seen use in magnetic resonance imaging (MRI) as a contrast agent for three decades. Through magnetic interactions with adjacent protons, gadolinium permits improved contrast in the tissues in which it accumulates. While toxic in its free, aqueous ion form, gadolinium was long thought to be rendered non-toxic in complex with organic carrier ligands. Indeed, thus chelated, its toxicity was shown to be comparable to iodinated X-ray contrast agents. Some 20 years ago, however, the first reports of rare – but serious – adverse, scleroderma-like reactions to these contrast agents began to emerge in patients with impaired renal function, which was termed nephrogenic systemic fibrosis (NSF). Per subsequently established guidelines, careful evaluation of kidney function prior to administration of gadolinium contrast agents (in line with guidelines for X-ray contrast agent use) all but eliminated the incidence of NSF.

The last few years have seen gadolinium once again subject to scrutiny, following reports of gadolinium deposition in the brain, bone and other tissues in persons with normal kidney function. The clinical significance of this gadolinium accumulation, however, is still largely unclear. Gadolinium-based contrast agents, gadolinium deposition and so-called gadolinium deposition disease will be discussed herein.

MRI and Gadolinium(III)-Based Contrast Agents

Using radiofrequency (RF) pulses of an appropriate frequency to excite protons' (particularly those in

water and fat) nuclear spin energy transitions, MRI permits the measurement of the RF signal emitted by these protons as they relax back into equilibrium with strong magnetic field gradients, and allows their localisation in space. Paramagnetic metal ions such as gadolinium(III) (Gd^{3+}) produce oscillating magnetic fields via thermally driven motion, and thereby increase the rate of decay in the polarisation of nearby protons in the magnetic field; this shortens the so-called T_1 (or "spin-lattice relaxation") relaxation time, and increases the signal detected on T_1-weighted MRI sequences where Gd^{3+} is present.

Gadolinium(III)-based contrast agents (GBCAs) are organic carrier molecules which chelate Gd^{3+}, significantly reducing their toxicity (1). Most commonly used in MR angiography studies and in the investigation of brain tumour enhancement, GBCAs have been in use for 30 years, and used in contrast-enhanced MRI studies of well over 100 million patients (2). Indeed, in 2016, some 30 – 45% of all MRI studies performed used GBCAs (3).

The European Medicines Agency (EMA) classifies GBCAs according to their charge (ionic or non-ionic) and their geometry (linear or macrocyclic). Macrocyclic GBCAs enclose Gd^{3+} ions in "claw"-like structures, exhibiting markedly lower dissociation constants than their linear (and earlier-developed) counterparts (4). Because the toxic effects of gadolinium are believed to arise from its competition with Ca^{2+} cations (1) in its free, aqueous form, GBCAs with lower dissociation constants (*i.e.* those which least allow dissociation of free Gd^{3+}) are classed as low-risk. Linear GBCAs are distributed across intermediate- and high-risk classes, depending on whether they are ionic (and therefore less able to cross the blood-brain barrier; intermediate risk) or non-ionic (more likely to cross; high risk).

Low-risk, macrocyclic GBCAs include Dotarem (gadoterate meglumine), Gadovist (gadobutrol) and ProHance (gadoteridol). Intermediate-risk, linear, ionic GBCAs include Magnevist (gadopentetate dimeglumine), MultiHance (gadobenate dimeglumine) and Primovist (gadoxetate disodium). Highest risk are those non-ionic linear GBCAs such as Omniscan (gadodiamide) and OptiMARK (gadoversetamide).

The utility of GBCAs in investigating brain tumour enhancement was based on the observation that ordinarily, due to their hydrophobicity, GBCAs do not cross the blood-brain barrier; areas of T_1-weighted signal enhancement therefore indicated GBCA leak into brain tissue, due to tumour-induced degradation of the blood-brain barrier. Under such circumstances, these contrast-enhancing lesions should only remain hyperintense for 30 minutes (5).

Even in patients with normal kidney function, however, evidence began to emerge that gadolinium could be retained after GBCA exposure, even many years later. It is now understood that over time, GBCAs are able to pass even competent, intact blood-brain barriers, via a variety of proposed mechanisms, such as specific metal transporters, transmetallation (*i.e.* substitution of Gd^{3+} by other metal and metalloid ions, such as Zn^{2+}, Cu^{2+} and Ca^{2+}), interactions with the glymphatic system and/or perivascular spaces (3,6). This gadolinium accumulation is reflected by changes in unenhanced T_1-weighted brain MRI appearances.

Gadolinium Deposition in the Brain

Evidence of gadolinium deposition and long-term retention in the brain was first shown retrospectively, in a study by Kanda *et al.* in 2013, wherein they found persistent T_1 shortening in deep grey matter structures – specifically the globus pallidus (GP) of the basal ganglia and the dentate nuclei (DN) of the cerebellum – associated with exposure to linear GBCAs (7). Nineteen patients with brain tumours, each of whom had undergone at least 6 examinations with linear GBCAs such as Magnevist/gadopentate dimeglumine and/or Omniscan/gadodiamide, were compared with 16 control patients, who had each undergone at least 6 unenhanced MRI studies. Kanda *et al.* found that only those patients who had been exposed to linear GBCAs showed T_1 shortening in their deep grey matter nuclei on MRI, with increased DN to pons (DNP) and GP to thalamus (GPT) ratios of signal intensity on T_1-weighted sequences. Moreover, this increase in T_1-weighted signal intensity correlated to the patients' administered dose.

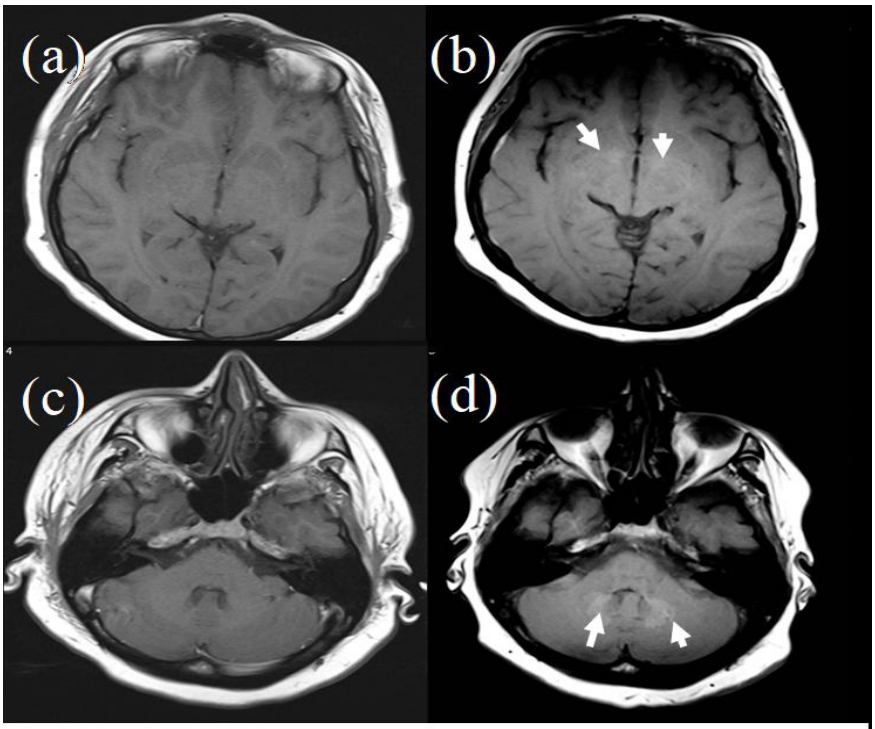

Figure 1: MRI T1-weighted images of a patient. (a) and (c) represent initial images and (b) and (d) after several contrast enhanced studies. Arrows in (b) and (d) show high T1 signal in globi pallidi and dentate nuclei respectively, attributed to Gadolinium deposition. Case courtesy of Prof Alan Coulthard, Radiopaedia.org, rID: 38904. Modified from original images (50).

Later studies demonstrated increased DNP T_1w signal intensity after Omniscan/gadodiamide exposure in patients with relapsing-remitting multiple sclerosis (8) and in patients with meningiomas (9). The relationship was, again, dose-dependent – even in those patients who had undergone fewer than 6 GBCA-enhanced MRI studies.

Across numerous studies, the dentate nuclei were consistently found to be the principal site of T_1-weighted signal intensity increase in response to GBCA administration (7,10–14). The dentate nuclei are adjacent to the choroid plexus of the fourth ventricle, thought to be involved in heavy metal/metalloid ion sequestration (15), which may in part explain the preferential gadolinium deposition therein; but the dentate nuclei are themselves a preferential site of metallic ion and calcium accumulation (16,17). In any event, with increasing linear GBCA exposure, other structures begin to show deposition of gadolinium as well, as shown by Zhang *et al.* (2016): thirteen patients, each of whom had undergone at least 35 linear-GBCA-enhanced MRI studies, were investigated and found to have increased T_1-weighted signal intensity in not only the DN and GP, but also in the superior cerebellar peduncle, the superior and inferior colliculi, the red nucleus, the thalamus and the substantia nigra (18). These structures are also believed to be involved in metal and metalloid ion sequestration (19).

GBCA structure appears to be an important factor in determining gadolinium retention in the brain, with T_1 shortening in the dentate nuclei seen after exposure to Magnevist/gadopentate dimeglumine (a linear GBCA), but not after exposure to ProHance/gadoteridol (a macrocyclic GBCA) (10). Numerous subsequent studies bore out this observation, with dose-dependent increases in T_1-weighted DN signal intensity observed only with exposure to linear GBCAs; not to macrocyclic GBCAs (14,20–22). Indeed, whether by conventional methods (20,23) or newer, relaxometry-based methods (24), no evidence for T_1 shortening with exposure to macrocyclic GBCAs could be found. Investigating gadolinium-retention-induced

susceptibility changes in the DN by quantitative susceptibility mapping (QSM) also revealed higher values in patients exposed to linear GBCAs than in patients who had not (25); patients who had been exposed only to macrocyclic GBCAs were found to have susceptibility values in their DN similar to those of the unexposed, control group.

These data are entirely consistent with the hypothesis that gadolinium brain deposition is related to the propensity of gadolinium to dissociate from its chelating carrier molecule (26), where linear GBCAs far more readily release Gd^{3+} from complex than do macrocyclic GBCAs.

While gadolinium deposition in the brain undoubtedly gives rise to T_1-weighted signal intensity changes, there may be certain conditions which show the same (or similar) MRI changes in the absence of gadolinium deposition; such mimics include Wilson's disease, post-radiotherapy changes and hepatic encephalopathy (27). QSM-based MRI studies may help to discriminate susceptibility changes arising from calcification from those arising from paramagnetic metals (*e.g.* gadolinium) (28).

Unsurprisingly, studies employing autopsy findings of gadolinium brain deposition have been far fewer than those employing unenhanced MRI studies; nevertheless, what few have been published show similar results. Kanda *et al.* (2015) describe, in 5 persons who had undergone more than 2 administrations of Magnevist/gadopentate dimeglumine and/or Omniscan/gadodiamide, gadolinium deposition in the DN and GP, and to a lesser extent, in cerebellar white matter tracts, and the cortex and white matter tracts of the frontal lobe (29). In control subjects, no gadolinium was found deposited in any structures of the brain.

Gadolinium deposition has been investigated in several studies using rat models, the results of which largely recapitulate the observations made in human subjects: gadolinium deposition is dose-dependent, highest with linear GBCAs, absent with macrocyclic GBCAs, and preferentially occurs in deep grey matter structures homologous to those in the human brain. Comparing the administration of various linear GBCAs (Omniscan/gadodiamide, MultiHance/gadobenate dimeglumine and Magnevist/gadopentate dimeglumine) with the administration of either Dotarem/gadoterate meglumine or of saline vehicle control in rats resulted in increased T_1-weighted signal intensity in the deep cerebellar nuclei (DCN), which was highest with Omniscan/gadodiamide, and absent with Dotarem/gadoterate meglumine (30,31). Those rats exposed to linear GBCAs were found to have gadolinium deposition in the brains on post-mortem dissection, whereas those exposed to Dotarem/gadoterate meglumine and vehicle control were not. Another similar study demonstrated an increased DCN to pons signal intensity ratio in rats on T_1-weighted sequences in response to linear GBCAs, which was not demonstrated in response to macrocyclic GBCAs or saline control (32). Again, among the linear GBCAs tested, the MRI changes were most pronounced with Omniscan/gadodiamide.

Gadolinium Deposition in Bone and Other Tissues

The bone is another major site of gadolinium accumulation (33) via its exchange for Ca^{2+}, and as such, has been hypothesised to act as a significant reservoir of gadolinium with respect to its persistence elsewhere in the body (34). Even in persons with normal kidney function, 0.25 – 1% of injected gadolinium may dissociate from its ligand and deposit in bone (35). In consequence, bone measures of gadolinium have been proposed as a potentially useful proxy for brain gadolinium levels (36), especially since MRI studies may underrepresent "true" gadolinium concentrations (since some gadolinium in the brain is likely to exist in an insoluble, and therefore magnetically inert, form).

One means of investigating concentrations of gadolinium in bone is made possible by examining resected femoral heads from patients following total hip arthroplasty. In two such studies, using femoral heads resected from patients 3 to 8 days after they had been exposed to either the linear GBCA Omniscan/gadodiamide or the macrocyclic GBCA ProHance/gadoteridol, gadolinium concentrations were found to be 2.5 – 4 times higher in those patients who had received Omniscan/gadodiamide (37,38). Even up to 8 years after GBCA exposure, high levels of gadolinium have been found in resected femoral heads (35).

Skin, too, appears to be subject to gadolinium accumulation after exposure to GBCAs, with gadolinium having been demonstrated at autopsy in subjects with normal renal function (36). While concentrations were found to be higher following

linear GBCA exposure, gadolinium was also detected after exposure to macrocyclic GBCAs. In rat models, gadolinium deposition has also been shown (39,40), and has been found to be higher following linear GBCA exposure than following macrocyclic GBCAs (41).

Clinical Significance of Gadolinium Deposition and Gadolinium Deposition Disease

Aside from acute and anaphylactoid adverse reactions to GBCAs, which are rare (0.08 – 0.12%) (42,43), and apart from nephrogenic systemic fibrosis, which has all but disappeared following changes to guidelines requiring careful evaluation of GFR prior to GBCA administration (44), there are very few recognised clinical features of gadolinium deposition. No association has been found, for example, between gadolinium exposure and Parkinsonism (45,46), despite evidence of accumulation in the basal nuclei – including the substantia nigra, specifically, at higher doses (18).

Nevertheless, since 2014, there have been sporadic reports of what has been tentatively termed gadolinium deposition disease (GDD) (47,48) in patients with normal renal function, whose symptoms cannot be explained by other/subsequent diseases and in whom gadolinium has been demonstrated (either in urine, hair or saphenous veins) (48,49). The symptoms allegedly attributed to GDD are myriad, but include tightness and/or pain in the limbs (especially distally), tightness and/or pain in the central torso and/or generalised pain, bone pain, and general confusion/impaired cognition (47,48). Symptoms have been reported hours to months after exposure, but the majority have been described as occurring within the first month; those who described distal limb pain felt that this persisted beyond the other symptoms (48). Unusually, however, these symptoms have been reported for all GBCAs, regardless of structure, with the sole exception of Dotarem/gadoterate meglumine, and have been reported even after only one exposure (48,49); features which do not correlate well with the current understanding of dose- and structure-/class-dependent gadolinium in the body. That all the symptoms have been self-reported (by only 42 patients), collected by anonymous survey, involved no control group, and gathered at one research centre significantly hamper the meaningful interpretation of these data. A much more rigorous evaluation of the incidence of (presumed) GDD is doubtless warranted, but no evidence at present time yet suggests a reasonable link between these symptoms and GBCAs.

The repercussions of the phenomenon of Gadolinium deposition without definite evidence of adverse clinical outcomes are unclear, more particularly in context of macrocyclic agents. Currently, there is an ongoing debate whether GBCAs should be restricted in use or more stringent guidelines be produced. Various agencies and government bodies are looking into it and while there are no current guidelines that overtly restrict their use, it is likely that more specific guidelines will be produced particularly if more evidence emerges for any adverse clinical outcomes. In the meanwhile, it will be prudent if some self restraint be imposed with judicious use of these agents and limiting the use in context of both the dosage and frequency of such examinations.

Conclusions

Gadolinium-based contrast agents are an invaluable tool in conjunction with MR imaging, and, despite rare (though serious) adverse reactions in the form of anaphylactoid reactions and nephrogenic systemic fibrosis, have an excellent safety record. Recent years have seen a sizeable body of literature emerge concerning gadolinium deposition in the brain (and other tissues) and the MRI changes which accompany it, but no significant evidence yet exists in support of any associated clinical features. Moreover, what little gadolinium deposition which has been demonstrated seems to be obviated by favouring macrocyclic contrast agents over earlier, linear chelates. Further work is wanted to evaluate so-called gadolinium deposition disease, but at present, there seems to be little cause for concern. It will be prudent, however, that these agents be used judiciously and excessive use be avoided since the research is still ongoing and criteria for their optimum use are still evolving.

References

[1] Sherry AD, Caravan P, Lenkinski RE. Primer on gadolinium chemistry. J Magn Reson Imaging. 2009 Dec 1;30(6):1240–8.

[2] Hao D, Ai T, Goerner F, Hu X, Runge VM, Tweedle M. MRI contrast agents: Basic chemistry and safety. J Magn Reson Imaging. 2012 Nov 1;36(5):1060–71.

[3] Kanal E. Gadolinium based contrast agents (GBCA): Safety overview after 3 decades of clinical experience. Magn Reson Imaging. 2016 Dec 1;34(10):1341–5.

[4] Rogosnitzky M, Branch S. Gadolinium-based contrast agent toxicity: a review of known and proposed mechanisms. BioMetals. 2016 Jun 1;29(3):365–76.

[5] Tien RD, Brasch RC, Jackson DE, Dillon WP. Cerebral Erdheim-Chester disease: persistent enhancement with Gd-DTPA on MR images. Radiology. 1989 Sep 1;172(3):791–2.

[6] Kanda T, Nakai Y, Oba H, Toyoda K, Kitajima K, Furui S. Gadolinium deposition in the brain. Magn Reson Imaging. 2016 Dec 1;34(10):1346–50.

[7] 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. 2013 Dec 7;270(3):834–41.

[8] 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 Oct;49(10):685.

[9] Quattrocchi CC, Mallio CA, Errante Y, Cirimele V, Carideo L, Ax A, 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 Jul;50(7):470.

[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 Jan 27;275(3):803–9.

[11] 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. Am J Roentgenol. 2015 Dec 23;206(2):414–9.

[12] Adin ME, Kleinberg L, Vaidya D, Zan E, Mirbagheri S, Yousem DM. Hyperintense Dentate Nuclei on T1-Weighted MRI: Relation to Repeat Gadolinium Administration. Am J Neuroradiol. 2015 Oct 1;36(10):1859–65.

[13] Hu HH, Pokorney A, Towbin RB, Miller JH. Increased signal intensities in the dentate nucleus and globus pallidus on unenhanced T1-weighted images: evidence in children undergoing multiple gadolinium MRI exams. Pediatr Radiol. 2016 Oct 1;46(11):1590–8.

[14] 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 Nov 1;51(11):683–90.

[15] Zheng W. Toxicology of Choroid Plexus: Special Reference to Metal-Induced Neurotoxicities. Microsc Res Tech. 2001 Jan 1;52(1):89–103.

[16] Popescu BFG, Robinson CA, Rajput A, Rajput AH, Harder SL, Nichol H. Iron, Copper, and Zinc Distribution of the Cerebellum. The Cerebellum. 2009 Jun 1;8(2):74–9.

[17] Ward RJ, Zucca FA, Duyn JH, Crichton RR, Zecca L. The role of iron in brain ageing and neurodegenerative disorders. Lancet Neurol. 2014 Oct;13(10):1045–60.

[18] 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. 2016 Aug 11;282(2):516–25.

[19] Kanda T, Oba H, Toyoda K, Kitajima K, Furui S. Brain gadolinium deposition after administration of gadolinium-based contrast agents. Jpn J Radiol. 2016 Jan 1;34(1):3–9.

[20] 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. 2016 Dec 7;282(3):699–707.

[21] 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 Apr 6;275(3):783–91.

[22] 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 Dec;50(12):805–10.

[23] Eisele P, Alonso A, Szabo K, Ebert A, Ong M, Schoenberg SO, et al. Lack of increased signal intensity in the dentate nucleus after repeated administration of a macrocyclic contrast agent in multiple sclerosis. Medicine (Baltimore) [Internet]. 2016 Sep 30;95(39). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5265887/

[24] Tedeschi E, Cocozza S, Borrelli P, Ugga L, Morra VB, Palma G. Longitudinal Assessment of Dentate Nuclei Relaxometry during Massive Gadobutrol Exposure. Magn Reson Med Sci. 2018;17(1):100–4.

[25] 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 May 1;45(5):1352–8.

[26] Kanal E, Tweedle MF. Residual or Retained Gadolinium: Practical Implications for Radiologists and Our Patients. Radiology. 2015 May 5;275(3):630–4.

[27] Ginat DT, Meyers SP. Intracranial Lesions with High Signal Intensity on T1-weighted MR Images: Differential Diagnosis. RadioGraphics. 2012 Mar 1;32(2):499–516.

[28] Chen W, Zhu W, Kovanlikaya Ii, Kovanlikaya A, Liu T, Wang S, et al. Intracranial Calcifications and Hemorrhages: Characterization with Quantitative Susceptibility Mapping. Radiology. 2013 Oct 28;270(2):496–505.

[29] 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 May 5;276(1):228–32.

[30] Robert P, Lehericy S, Grand S, Violas X, Fretellier N, Idée J-M, 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 Aug;50(8):473.

[31] Robert P, Violas X, Grand S, Lehericy S, Idée J-M, Ballet S, et al. Linear Gadolinium-Based Contrast Agents Are Associated With Brain Gadolinium Retention in Healthy Rats. Invest Radiol. 2016 Feb;51(2):73.

[32] 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 Feb;51(2):83.

[33] Tweedle MF, Wedeking P, Kumar K. Biodistribution of radiolabeled, formulated gadopentetate, gadoteridol, gadoterate, and gadodiamide in mice and rats. Invest Radiol. 1995 Jun;30(6):372–80.

[34] Hirano S, Suzuki KT. Exposure, metabolism, and toxicity of rare earths and related compounds. Environ Health Perspect. 1996 Mar;104(Suppl 1):85–95.

[35] Darrah TH, Prutsman-Pfeiffer JJ, Poreda RJ, Campbell ME, Hauschka PV, Hannigan RE. Incorporation of excess gadolinium into human bone from medical contrast agents. Metallomics. 2009 Nov 1;1(6):479–88.

[36] 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 Jul;51(7):447.

[37] Gibby WA, Gibby KA, Gibby WA. Comparison of Gd Dtpa-bma (omniscan) versus Gd Hp-do3a (prohance) Retention in Human Bone Tissue by Inductively Coupled Plasma Atomic Emission Spectroscopy. Invest Radiol. 2004 Mar 1;39(3):138–42.

[38] 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 Mar 1;41(3):272–8.

[39] Bussi S, Fouillet X, Morisetti A. Toxicological assessment of gadolinium release from contrast media. Exp Toxicol Pathol. 2007 Apr 26;58(5):323–30.

[40] Sieber MA, Lengsfeld P, Frenzel T, Golfier S, Schmitt-Willich H, Siegmund F, et al. Preclinical investigation to compare different gadolinium-based contrast agents regarding their propensity to release gadolinium in vivo and to trigger nephrogenic systemic fibrosis-like lesions. Eur Radiol. 2008 Oct 1;18(10):2164–73.

[41] Wáng Y-XJ, Schroeder J, Siegmund H, Idée J-M, Fretellier N, Jestin-Mayer G, et al. Total gadolinium tissue deposition and skin structural findings following the administration of structurally different gadolinium chelates in healthy and ovariectomized female rats. Quant Imaging Med Surg. 2015 Jul 13;5(4):534–45.

[42] Jung J-W, Kang H-R, Kim M-H, Lee W, Min K-U, Han M-H, et al. Immediate Hypersensitivity Reaction to Gadolinium-based MR Contrast Media. Radiology. 2012 Aug 1;264(2):414–22.

[43] Bruder O, Schneider S, Pilz G, van Rossum AC, Schwitter J, Nothnagel D, et al. 2015 Update on Acute Adverse Reactions to Gadolinium based Contrast Agents in Cardiovascular MR. Large Multi-National and Multi-Ethnical Population Experience With 37788 Patients From the EuroCMR Registry. J Cardiovasc Magn Reson. 2015 Jul 14;17:58.

[44] Thomsen HS, Morcos SK, Almén T, Bellin M-F, Bertolotto M, Bongartz G, et al. Nephrogenic systemic fibrosis and gadolinium-based contrast media: updated ESUR Contrast Medium Safety Committee guidelines. Eur Radiol. 2013 Feb 1;23(2):307–18.

[45] Balint B, Bhatia KP. T1-weighted basal ganglia hyperintensities due to gadolinium deposition – a cautionary note. Parkinsonism Relat Disord. 2016 Nov 1;32:135–6.

[46] 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 Jul 5;316(1):96–8.

[47] Semelka RC, Ramalho M, AlObaidy M, Ramalho J. Gadolinium in Humans: A Family of Disorders. Am J Roentgenol. 2016 May 25;207(2):229–33.

[48] Semelka RC, Ramalho J, Vakharia A, AlObaidy M, Burke LM, Jay M, et al. Gadolinium deposition disease: Initial description of a disease that has been around for a while. Magn Reson Imaging. 2016;34(10):1383–90.

[49] Semelka RC, Commander CW, Jay M, Burke LMB, Ramalho M. Presumed Gadolinium Toxicity in Subjects With Normal Renal Function: A Report of 4 Cases. Invest Radiol. 2016;51(10):661–5.

[50] https://radiopaedia.org/cases/gadolinium-retention-in-the-brain. *Case courtesy of Prof Alan Coulthard, Radiopaedia.org, rID: 38904*

Citation: **Gregory M Armstrong, Avinash Kumar Kanodia, Gillian Duncan, Thiru Sudarshan, Robert Foster.** *Gadolinium (III)-Based Contrast Agents, Gadolinium Deposition in Tissues and the Clinical Significance: A Review. Archives of Radiology. 2018; 1(2): 4-11.*