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Is it safe to use gadolinium-based contrast agents in MRI?

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Abstract

Gadolinium-based contrast agents have greatly expanded the capability of magnetic resonance imaging and have been used extensively in neuroradiology over the past 30 years. When initially developed they were thought to be relatively harmless; it was later discovered they are associated with nephrogenic systemic fibrosis and should be used with caution in certain patient groups, especially those with renal failure. Lately it has been found that the use of these contrast agents may result in deposition of gadolinium in the brain even in patients with an intact blood-brain barrier. While this has not been shown to be associated with any clinical effects, a precautionary approach has been advised by the regulatory authorities. Here we review the development of the gadolinium contrast agents, their use and the advice related to this new information.

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Introduction

Magnetic resonance imaging (MRI) was first performed on a human in 1977 to produce a cross-sectional image of the thorax.[1] Since then MRI has steadily improved with regards to image quality and acquisition times and is now an essential tool in a variety of diagnostic pathways. In England alone over 3.08 million MRI scans were performed between 2015 and 2016.[2]

Image contrast in MRI is created by the differences in proton relaxation times. While it was noted that in most cases the differences between the relaxation times of different tissues and those between normal tissue and pathological lesions is usually large enough to allow good contrast, investigators noticed there were situations where this contrast was not high enough to allow proper discrimination. These differences in relaxation times can be amplified by paramagnetic ions, with gadolinium being the most useful relaxation agent.[3]

Gadolinium is a rare-earth metal of the lanthanide series and is named after Finnish chemist Johan Gadolin, who discovered the mineral gadolinite in 1787. It is present in the earth surface at an amount of around 6.2 mg/kg, making it one of the more abundant rare metals (more abundant than uranium). Its ion (Gd^{3+}) possesses seven unpaired electrons, allowing it to create a high magnetic moment that is effective at enhancing proton relaxation. The free ion is also extremely toxic[4] mostly because of its ability to bind with calcium-ion channels, thus being quite toxic to myocytes and neurons.[5] Chelation improves its water solubility and its toxicity is reduced by a factor of 100.[6]

The first gadolinium-based contrast agent (GBCA) was gadolinium diethylenetriamine-pentaacetic acid which demonstrated good stability, tolerance and over 90% urinary excretion.[7] It was first used in human volunteers on the 10 November 1983, where it demonstrated uniform enhancement of the bladder.[8] In 1984, gadolinium diethylenetriamine-pentaacetic acid was used to characterise an abscess in a dog's brain,[9] demonstrating the diagnostic potential of gadolinium agents in neuroradiology. Over the next 20 years, 200 million patients have had GBCAs administered;[10] their effect has been nothing short of revolutionary in the field of radiology.

The general indications of GBCAs in neuroradiology include lesion identification (e.g. lesions in the cerebellopontine angle and sellar/parasellar regions, metastasis and demyelinating lesions) and characterisation (e.g. differentiating tumour from infection or inflammation, characterising the perfusion and/or permeability of a lesion).

Gadolinium-based contrast agents

The classification of GBCAs is determined by the compounds that are chelated to the gadolinium ion. Gadolinium contrast agents are subdivided into two groups: linear or macrocyclic depending on whether ligands are derived from a linear or a macrocyclic amine. These are each further subdivided into

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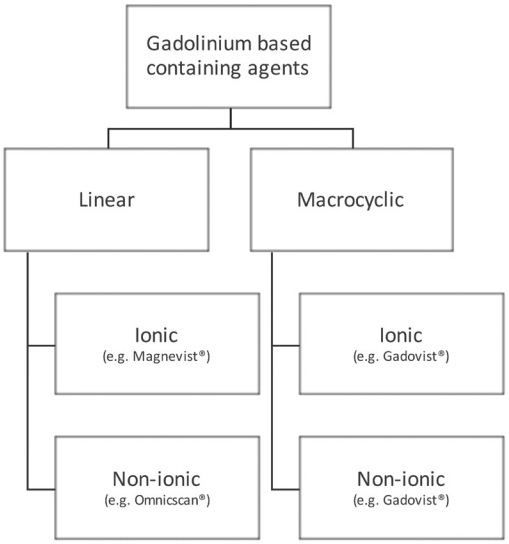
ionic and non-ionic (Figure 1). There are currently nine GBCAs on the market; six demonstrate extracellular fluid distribution while the remaining three are so-called organ-specific agents.

In cyclic agents, the gadolinium ion is cocooned in a circular structure which in general makes them more kinetically stable and inert than their linear counterparts.[5] The amount of free Gd^{3+} ions released in incubated human serum is higher in linear agents when compared to macrocyclic agents.[11] All GBCAs are administered intravenously, usually at a dose of 0.1 mmol Gd/kg. They demonstrate bi-exponential plasma kinetics (distribution followed by elimination). Being hydrophilic they are mostly eliminated via the renal route, although some demonstrate some hepatic elimination. In patients with normal renal function the terminal half-life is 1.5 hours and in patients with moderately impaired renal function this may increase to up to 8 hours.[12]

Figure 1 Classification of available gadolinium-based contrast agents



Contrast characteristics

A contrast agent is a diagnostic aid used to enhance or create the required contrast in an image between the organ, vessel or tract in which it is present and the surrounding tissues. It is important to note that contrast agents are not intended to have any pharmacological activity. The chelated gadolinium ion shortens what is known as T1 relaxation time, producing a signal. Since gadolinium has a higher atomic number than that of iodine (64 vs 53), it absorbs more X-rays. As such, gadolinium contrast agents were occasionally used for patients who were allergic to iodinated contrast agents.[13–15] This practice was discontinued when it was discovered that gadolinium was associated with nephrogenic systemic fibrosis.

Normal enhancement in the brain

Enhancement of the central nervous system can be subdivided into vascular and extravascular (or interstitial) enhancement. Vascular enhancement is related to blood flow or blood volume whereas interstitial enhancement is dependent on the permeability of the blood brain barrier. The blood brain barrier can be disrupted by a wide range of pathologies such as inflammation, ischaemia or abnormal angiogenesis.[16] It is important to know what areas normally enhance in the brain so as not to be mistaken as pathology. These are structures that reside outside the blood brain barrier and include the pineal gland, choroid plexus, cavernous sinuses, anterior pituitary and dura mater. There are also pathologies that do not enhance in areas that usually enhance such as certain pituitary macroadenomas.

Nephrogenic systemic fibrosis

Although rare, nephrogenic systemic fibrosis is a life-threatening disease that has been associated with GBCAs administered to patients with renal impairment. While the first cases were reported in 1997,[17] it was only in 2006 that the condition was being associated with exposure to gadolinium.[18] At the time this went against the widely-held notion that gadolinium contrast agents were safe in patients in renal failure, in whom iodine-based contrast agents were contraindicated. After further reports and studies[19,20] the European Medicines Authority[21] recognised the link between nephrogenic systemic fibrosis and gadolinium and recommended that high risk gadolinium contrast agents (gadoversetamide, gadodiamide and gadopentetic acid) should be avoided in patients with severe renal failure, while medium and low risk agents could be used in this patient group but only at the minimum recommended dose. In 2007 the US Food and Drug Administration (FDA) issued similar warnings but did not distinguish between high and low risk gadolinium contrast agents at the time.[22] It is important to note that the majority of cases of nephrogenic systemic fibrosis were patients who had been exposed to linear GBCAs.[23]

Gadolinium deposition in the brain

In 2009 a study had associated T1 hyperintensity of the dentate nucleus of the cerebellum with secondary progressive multiple sclerosis.[24] The dentate nucleus is usually of low signal on T1-weighted MRI images and does not normally enhance with contrast (Figure 2). At first this was thought to demonstrate grey matter damage,[24,25] in a disease that mainly affects only white matter. This finding was also discovered in patients who had previously undergone brain irradiation.[26]

In 2014, research groups started noticing this finding was more prevalent in patients who had undergone multiple gadolinium-enhanced MRI scans. They also noted that the signal intensity increased with the growing number of exposures to gadolinium contrast agents.[27,28] In the study by Kanda et al.[27] there were no patients diagnosed with multiple sclerosis and patients were also found to have a high T1-signal in the globus pallidus, one of the basal ganglia. The relation of this finding with the severity of multiple sclerosis and brain irradiation was actually a confounding factor. Over the next three years, other studies have come to similar conclusions.[28–31] While it was already known that disruption

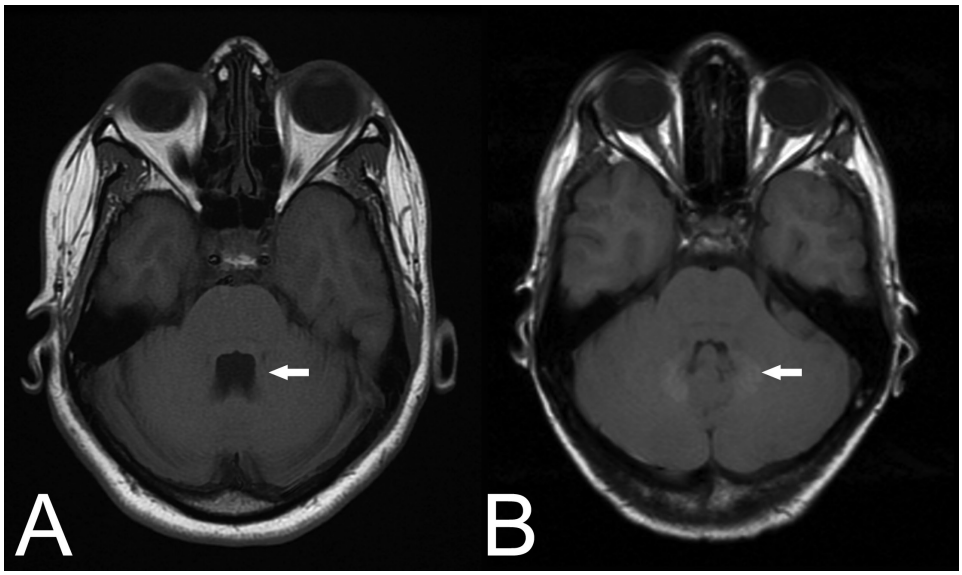


Figure 2 A: Normal T1-weighted axial scan through the posterior fossa demonstrating low signal in the dentate nucleus. B: T1-weighted non-contrast axial scan demonstrating high signal of the dentate nucleus

of the blood brain barrier by tumours can cause retention of GBCAs in tissues surrounding them,[32,33] this phenomenon was occurring in patients with an undisrupted blood brain barrier and a normal renal function.[34] Later it was discovered that this phenomenon was more likely to occur with linear rather than macrocyclic GBCAs.[31,35,36] This could be due to the different kinetic stabilities between linear and macrocyclic agents.[37,38] However, a study evaluating the deposition of gadolinium in brain and bone post mortem in nine patients with normal renal function showed deposition of gadolinium in the globus pallidus and the dentate nucleus irrespective of whether they had been exposed to linear or cyclic agents.(39) More recently it was highlighted that the high signal intensity in the dentate nucleus decreases after switching from a linear to a macrocyclic GBCA, suggesting that this phenomenon is actually reversible.[40]

One of the main questions is whether there are clinical manifestations of this imaging phenotype. More research is needed in the area as the effects are not clear. The dentate nucleus is involved in executive and affective functions of the brain related to attention, memory and reasoning.[41] It has been postulated that damage to the globus pallidus may lead to parkinsonian symptoms. However a retrospective study showed no correlation between gadolinium exposure and parkinsonism.[42]

Effect on clinical practice

In 2015, after the initial reports of gadolinium deposition within the brain, the FDA advised review of protocols for administration of GBCAs while the research was being evaluated in order to limit exposure of the brain to gadolinium.[43] In the meantime the FDA suggested that administration of GBCAs should only be used in clinical situations if further information provided by the contrast was necessary and to re-evaluate the requirement of repeated contrast-enhanced MRI in certain clinical pathways. The European Medicines Agency also issued a similar statement[44] stating that it was currently reviewing the evidence. There have already been some concerns that deposition of gadolinium could be linked with certain pathologies such as Alzheimer's disease. However, at present, there is no evidence to prove this.[45] Some have proposed renaming the systemic deposition of gadolinium in bone, brain and skin as gadolinium deposition disease in those patients who develop symptoms hours to two months after administration of a GBCA.[46] Further research is required to ascertain the direct or indirect causality of this process.

Conclusion

There is no doubt that GBCAs can cross the blood brain barrier and deposit in the brain. The difference to the discovery of gadolinium being linked to nephrogenic systemic fibrosis is that to date there are no clinical signs or symptoms that have been linked with the imaging findings; therefore a precautionary proactive approach rather than a reactive approach has been suggested. It appears that this phenomenon occurs mostly with linear GBCAs, even in patients with a normal renal function and may be reversible. (40) Although most of the evidence emerged from single centres and is retrospective in nature, the results cannot be ignored. It is important to note that GBCAs are an essential tool in the field of neuroradiology and, with the necessary precautions, the benefits they provide outweigh the risks. More research is required to address the impact that this finding will have on the patients' clinical pathways.

References

1 Damadian R, Minkoff L, Goldsmith M et al. Field focusing nuclear magnetic resonance (FONAR): visualization of a tumor in a live animal. *Science* 1976; 194: 1430–2.
2 NHS England. Diagnostic Imaging Dataset Annual Statistical Release 2015/16. 2016. https://www.england.nhs.uk/statistics/wp-content/uploads/sites/2/2015/08/Annual-Statistical-Release-2015-16-DID-PDF-1.5MB.pdf (accessed 27/4/17).
3 Mendonça-Dias MH, Gaggelli E, Lauterbur PC. Paramagnetic contrast agents in nuclear magnetic resonance medical imaging. *Semin Nucl Med* 1983; 13: 364–76.
4 Tweedle MF, Hagan JJ, Kumar K et al. Reaction of gadolinium chelates with endogenously available ions. *Magn Reson Imaging* 1991; 9: 409–15.
5 Sherry AD, Caravan P, Lenkinski RE. Primer on gadolinium chemistry. *J Magn Reson Imaging* 2009; 30: 1240–8.
6 Penfield JG, Reilly RF. What nephrologists need to know about gadolinium. *Nat Clin Pract Nephrol* 2007; 3: 654–68.
7 Weinmann HJ, Brasch RC, Press WR et al. Characteristics of gadolinium-DTPA complex: a potential NMR contrast agent. *AJR Am J Roentgenol* 1984; 142: 619–24.
8 Laniado M, Weinmann HJ, Schörner W et al. First use of GdDTPA/dimeglumine in man. *Physiol Chem Phys Med NMR* 1984; 16: 157–65.
9 Runge VM, Clanton JA, Price AC et al. Dyke Award. Evaluation of contrast-enhanced MR imaging in a brain-abscess model. *AJNR Am J Neuroradiol* 1985; 6: 139–47.
10 Thomsen HS. Nephrogenic systemic fibrosis: a serious late adverse reaction to gadodiamide. *Eur Radiol* 2006; 16: 2619–21.
11 Frenzel T, Lengsfeld P, Schirmer H et al. Stability of gadolinium-based magnetic resonance imaging contrast agents in human serum at 37 degrees C. *Invest Radiol* 2008; 43: 817–28.
12 Aime S, Caravan P. Biodistribution of gadolinium-based contrast agents, including gadolinium deposition. *J Magn Reson Imaging* 2009; 30: 1259–67.
13 Bloem JL, Wondergem J. Gd-DTPA as a contrast agent in CT. *Radiology* 1989; 171: 578–9.
14 Quinn AD, O'Hare NJ, Wallis FJ et al. Gd-DTPA: an alternative contrast medium for CT. J Comput Assist Tomogr 1994; 18: 634–6.
15 Gierada DS, Bae KT. Gadolinium as a CT contrast agent: assessment in a porcine model. *Radiology* 1999; 210: 829–34.
16 Smirniotopoulos JG, Murphy FM, Rushing EJ et al. Patterns of contrast enhancement in the brain and meninges. *Radiographics* 2007; 27: 525–51.
17 Cowper SE, Robin HS, Steinberg SM et al. Scleromyxoedema-like cutaneous diseases in renal-dialysis patients. *Lancet* 2000; 356: 1000–1.
18 Grobner T. Gadolinium – a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis? *Nephrol Dial Transplant* 2006; 21: 1104–8.
19 Marckmann P. An epidemic outbreak of nephrogenic systemic fibrosis in a Danish hospital. *Eur J Radiol* 2008; 66: 187–90.
20 Bennett CL, Qureshi ZP, Sartor AO et al. Gadolinium-induced nephrogenic systemic fibrosis: the rise and fall of an iatrogenic disease. *Clin Kid J* 2012; 5: 82–8.
21 European Medicines Agency. *Questions and answers on the review of gadolinium-containing contrast agents.* http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/gadolinium_31/WC500015635.pdf (accessed 23/11/16).
22 *FDA Requests Boxed Warning for Contrast Agents Used to Improve MRI Images*. https://www.itnonline.com/content/fda-requests-boxed-warning-contrast-agents-used-improve-mri-images (accessed 28/8/17).
23 Bardin T, Richette P. Nephrogenic systemic fibrosis. *Curr Opin Rheumatol* 2010; 22: 54–8.
24 Roccatagliata L, Vuolo L, Bonzano L et al. Multiple sclerosis: hyperintense dentate nucleus on unenhanced T1-weighted MR images is associated with the secondary progressive subtype. *Radiology* 2009; 251: 503–10.
25 Absinta M, Rocca MA, Filippi M. Dentate nucleus T1 hyperintensity in multiple sclerosis. *AJNR Am J Neuroradiol* 2011; 32: E120–E121.
26 Kasahara S, Miki Y, Kanagaki M et al. Hyperintense dentate nucleus on unenhanced T1-weighted MR images is associated with a history of brain irradiation. *Radiology* 2011; 258: 222–8.
27 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.
28 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.
29 McDonald RJ, McDonald JS, Kallmes DF et al. Intracranial gadolinium deposition after contrast-enhanced MR imaging. *Radiology* 2015; 275: 772–82.
30 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: 470–2.
31 Kanda T, Osawa M, Oba H et al. High signal intensity in dentate nucleus on unenhanced T1-weighted MR images: association with linear versus macrocyclic gadolinium chelate administration. *Radiology* 2015; 275: 803–9.
32 Essig M, Weber M-A, Tengg-Kobligk von H et al. Contrast-enhanced magnetic resonance imaging of central nervous system tumors: agents, mechanisms, and applications. *Top Magn Reson Imaging* 2006; 17: 89–106.
33 Xia D, Davis RL, Crawford JA et al. Gadolinium released from MR contrast agents is deposited in brain tumors: in situ demonstration using scanning electron microscopy with energy dispersive X-ray spectroscopy. *Acta Radiol* 2010; 51: 1126–36.
34 Kanda T, Fukusato T, Matsuda M et al. Gadolinium-based contrast agent accumulates in the brain even in subjects without severe renal dysfunction: evaluation of autopsy brain specimens with inductively coupled plasma mass spectroscopy. *Radiology* 2015; 276: 228–32.
35 Radbruch A, Weberling LD, Kieslich PJ et al. Gadolinium retention in the dentate nucleus and globus pallidus is dependent on the class of contrast agent. *Radiology* 2015; 275: 783–91.
36 Cao Y, Huang DQ, Shih G et al. Signal change in the dentate nucleus on T1-weighted MR images after multiple administrations of gadopentetate dimeglumine versus gadobutrol. American Journal of Roentgenology. *AJR Am J Roentgenol* 2016; 206: 414–9.
37 Ramalho J, Semelka RC, Ramalho M et al. Gadolinium-based contrast agent accumulation and toxicity: an update. *AJNR Am J Neuroradiol* 2016; 37: 1192–8.
38 Huckle JE, Altun E, Jay M, Semelka RC. Gadolinium deposition in humans. *Invest Radiol* 2016; 51: 236–40.
39 Murata N, Murata K, Gonzalez-Cuyar LF et al. Gadolinium tissue deposition in brain and bone. *Magn Reson Imaging* 2016; 34: 1359–65.
40 Radbruch A, Weberling LD, Kieslich PJ 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.
41 Habas C. Functional imaging of the deep cerebellar nuclei: a review. *Cerebellum* 2009; 9: 22–8.
42 Welk B, McArthur E, Morrow SA et al. Association Between Gadolinium Contrast Exposure and the Risk of Parkinsonism. *JAMA* 2016; 316: 96–3.
43 US Food and Drug Administration. *FDA evaluating the risk of brain deposits with repeated use of gadolinium-based contrast agents for magnetic resonance imaging (MRI).* http://www.fda.gov/Drugs/DrugSafety/ucm455386.htm#collapseOne (accessed 21/12/16).
44 European Medicines Agency. *EMA reviewing gadolinium contrast agents used in MRI scans.* http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/gadolinium_contrast_agents_31/Procedure_started/WC500203487.pdf (accessed 21/12/16).
45 Ward P. *Danger of 'gadolinium phobia' looms in Europe*. March 2016. http://www.auntminnie.com/index.aspx?sec=rca&sub=ecr_2016&pag=dis&itemid=113623 (accessed 21/12/16).
46 Semelka RC, Ramalho M, AlObaidy M et al. Gadolinium in humans: a family of disorders. *AJR Am J Roentgenol* 2016; 207: 229–33.