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REVIEW

Gadolinium deposition and the potential for toxicological sequelae – A literature review of issues surrounding gadolinium-based contrast agents

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Every year, approximately 30 million magnetic resonance imaging scans are enhanced with gadolinium-based contrast agents (GBCAs) worldwide. Although the development of nephrogenic systemic fibrosis in patients with renal impairment is well-documented, over recent years it has become apparent that exposure to GBCAs can potentially result in gadolinium deposition within human bone and brain tissue even in the presence of normal renal function. This review will address some of the controversies surrounding the safety of GBCA administration based on evidence from *in vivo* experiments, animal studies and clinical studies. We additionally evaluate the potential risk of toxicity from exposure to gadolinium in light of new guidance published by the US Food and Drug Administration and the European Medicines Agency, and discuss whether gadolinium deposition disease exists as a *new* diagnosis.

Introduction

Gadolinium-based contrast agents (GBCAs) have been widely used since 1988 to enhance the quality of magnetic resonance imaging (MRI) studies, and currently up to 30% of the 30 million MRI scans performed annually use GBCAs [1, 2]. Despite an overall excellent safety profile, following initial reports in 2006, it became apparent that GBCA administration was associated with the development of nephrogenic systemic fibrosis (NSF) in patients with severe renal impairment [3]. More recently, studies have shown that gadolinium deposits can potentially develop in neural tissue following exposure to GBCAs in those with normal underlying renal function [4–10]; this deposition has led to several groups reporting an association with a condition known by some as *gadolinium deposition disease* [11]. In light of these findings, guidance from the European Medicines Agency (EMA) published in 2017 recommended withdrawal of multiple GBCAs from clinical use [12]. This review will attempt to address some of the controversies surrounding the safety of GBCA administration, whether gadolinium deposition in those individuals with normal renal function is associated with a risk of toxicity, and whether gadolinium deposition disease exists as a *new* diagnosis.

Gadolinium-based contrast agents – History

The rare-earth metal, gadolinium, was discovered in 1880 by the Swiss chemist Jean Charles Galissard De Marignac, who named the element *α-yttrium*; it was later renamed in honour of chemist, Johann Gadolin, the first scientist to describe a rare-earth element. Gadolinium was initially used as an additive to iron- and chromium-based alloys to improve their

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resistance to oxidation and high temperatures [13] but discovery of its unique magnetic and neutron absorption properties led to the use of gadolinium in a wide range of other functions, including neutron capture cancer therapy [14], nuclear marine propulsion and the production of gadolinium yttrium garnets, which have microwave applications. The 1980s heralded the development of gadolinium chelates whereby a ligand is bonded to the gadolinium ion to improve its stability and reduce toxicity, with pentetic acid (DTPA) being the first chelating agent used in this way [15]. Other chelating ligands include DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid) and BOPTA ((9R,S)-2,5,8-Tris (carboxymethyl)-12-phenyl-11-oxa-2,5,8-triazadodecane-1,9-dicarboxylic acid).

Intravenous administration of free gadolinium (Gd^{3+}) ions during MRI shortens both the T1 and T2 relaxation times of water protons and thus increases signal intensity, allowing improved differentiation of tissues [16]. Gd^{3+} ions are of a similar size to calcium ions and competitively bind to numerous pharmacological targets, including voltage-gated calcium channels [17]. Gadolinium ions are therefore complexed with chelating ligands to prevent toxicity when used in contrast media [18]. In 1988, gadopentetic acid became the first MRI contrast agent to be approved in the USA for clinical use and, to date, gadolinium chelates remain the most commonly used MRI contrast agents [1].

Gadolinium-based contrast agents – Pharmacology

GBCAs are traditionally classified based on the molecular structure of the chelating ligand, the molecule that binds the gadolinium, and they can be considered to be either linear or macrocyclic. Linear ligands are elongated, flexible chains that wrap around the gadolinium ion whilst macrocyclic ligands form a cage-like structure that encloses the ion within a cavity [19]. Linear ligands are more prone to dechelation, whereby gadolinium unpairs from the chelating ligand and free Gd^{3+} enters the circulation and/or tissues, compared with macrocyclic ligands, which have lower dissociation constants and form highly stable complexes [20]. *In vitro* studies have shown that the kinetic stability of GBCAs varies considerably depending on the agent, with the nonionic linear agent, gadodiamide, demonstrating a dissociation half-life of approximately 35 s at pH 1.0, whilst the ionic macrocyclic agent, gadoterate, appears to take more than a month to dissociate under similar conditions; it is unclear how these dissociation times would translate to physiological pH [19]. GBCAs can be further categorized as *ionic* complexes, which dissolve into charged particles, or *nonionic* complexes, that remain neutral [19, 21–29] .

GBCAs are administered intravenously at doses ranging from 0.025 to 0.3 mmol kg^{-1} of the gadolinium chelate depending on the agent and the anatomical site being imaged [30]. Most clinically approved gadolinium chelates are primarily excreted via the renal system (Table 1), aside from gadoxetate, which undergoes hepatobiliary elimination and as a result is used in the evaluation of liver lesions. GBCAs typically have a terminal blood half-life in the range of 1–3 h in healthy adults with normal renal function and, following administration, the gadolinium chelate is distributed rapidly and equilibrates within the intravascular and interstitial compartments and may additionally diffuse or be taken up into intracellular spaces (renal and hepatic tissue) [30].

The binding of GBCAs to serum proteins results in greater enhancement of signal intensity. Gadobenate dimeglumine (linear) binds weakly and transiently to albumin, achieving binding rates of <10%, whilst gadofosveset is the only GBCA that undergoes significant protein binding *in vitro*, with albumin binding of >80% [31]. This GBCA contains a lipophilic biphenylcyclohexyl group that binds reversibly to albumin, allowing focused intravascular imaging [30, 32]. The binding to serum albumin enhances signal intensity by decreasing the T1 relaxation time of water for up to 4 h postinjection [33]. Production of gadofosveset was discontinued in 2011 for commercial reasons [34].

Numerous multicentre double-blinded randomized comparison studies have shown that blinded radiologists demonstrate a highly significant preference for gadobenate dimeglumine when evaluating central nervous system lesions, including brain tumours, compared with gadobutrol ($P < 0.0001$ [35], gadodiamide ($P < 0.0001$) [36] and gadopentetate dimeglumine ($P < 0.0001$ and $P < 0.001$) [37, 38]. Gadopentetate dimeglumine (linear) is typically the preferred contrast agent for direct magnetic resonance arthrography [39], whilst gadoxetate (linear) and gadobenate dimeglumine (linear) are often used in hepatobiliary imaging [40].

GBCAs are typically considered to be well-tolerated [1, 41], with the incidence of adverse drug reactions being considerably lower than for iodinated contrast media [42]. The most frequently reported adverse events include nausea and anxiety (0.039 and 0.034% respectively) [42], while the incidence of immediate hypersensitivity reactions, defined as the development of pruritus, urticarial or anaphylaxis within 1 h following GBCA administration has been estimated to be between 0.079% and 0.096% (data pooled from various GBCAs) [17, 43].

Gadolinium-induced NSF in patients with renal impairment

NSF, also known as nephrogenic fibrosing dermopathy, previously considered to be an acquired, idiopathic disease was initially linked to exposure to GBCAs in 2006 [3]. The condition is characterized by progressive thickening of the skin overlying the limbs and occasionally the trunk, with areas of hyperpigmentation [3]. The initial stages of NSF are commonly mistaken for the dermatological conditions scleroderma and scleromyxoedema, based on their similar features. The skin lesions become indurated and flexure contractures can eventually form, resulting in significant disability [44]. NSF additionally manifests with a spectrum of noncutaneous features, with fibrotic changes developing within multiple anatomical sites, including cardiac tissue, where the myocardium may be extensively replaced with dense, fibrous tissue [45, 46], and pleural tissue, with patients developing interstitial pulmonary fibrosis [45, 47]. Other affected sites reported in the literature include neural tissue [46], the gastrointestinal tract

Table 1

Properties of gadolinium-based contrast agents

Generic name	Trade name	Structure	Net charge	EMA risk class (risk of developing NSF)	Protein binding	Elimination route	Elimination half-life (h) [ref]	Plasma/serum clearance (ml/min kg^{-1}) [ref]	Distribution volume (ml kg^{-1}) [ref]
Gadoterate meglumine	Dotarem	Macrocyclic	Ionic	Low	No	Renal	2.0 ± 0.7 ♂ [21] 1.4 ± 0.2 ♀ [21]	1.64 ± 0.35 ♂ [21] 1.74 ± 0.12 ♀ [21]	211 ± 35 ♂ [21] 179 ± 26 ♀ [21]
Gadobutrol	Gadavist/ Gadovist	Macrocyclic	Nonionic	Low	No	Renal	1.8 [1.2, 6.6] [22]	1.50 [0.83–2.50] [22]	220 [100–420] [23]
Gadoteridol	ProHance	Macrocyclic	Nonionic	Low	No	Renal	1.6 ± 0.1 [24]	1.50 ± 0.35 [24]	204 ± 58 [24]
Gadobenate dimeglumine	MultiHance	Linear	Ionic	Medium	<10%	Renal Hepatobiliary (<4%)	1.2 ± 0.3 to 2.0 ± 0.6 [25]	1.55 ± 0.17 to 2.22 ± 4.5 [25]	170 ± 16 to 282 ± 79 [25]
Gadoxetate	Primovist/ Eovist	Linear	Ionic	Medium	10%	Renal (50%) Hepatobiliary (50%)	1.9 ± 0.2 to 3.1 ± 0.8 [26]	2.13 ± 0.16 to 2.72 ± 0.18 [26]	380 ± 50 to 550 ± 30 [26]
Gadofosveset	Ablavar/ Vasovist	Linear	Ionic	Medium	79.8–87.4%	Renal Hepatobiliary (5%)	16.3 ± 2.6 [105]	0.11 ± 0.02 [105]	148 ± 16 [105]
Gadopentetate dimeglumine	Magnevist	Linear	Ionic	High	No	Renal	1.6 ± 0.1 [106]	1.94 ± 0.28 [106]	266 ± 43 [106]
Gadodiamide	Omniscan	Linear	Nonionic	High	No	Renal	1.3 ± 0.3 [107]	1.80 [107]	200 ± 61 [107]
Gadoversetamide	OptiMARK	Linear	Nonionic	High	No	Renal	1.7 ± 0.3 [108]	1.20 ± 0.27 [108]	162 ± 25 [108]

Data are expressed as either mean ± standard deviation or median [interquartile range]
EMA, European Medicines Agency; NSF, nephrogenic systemic fibrosis

[48], skeletal muscle [49] and the testes [49]. The disease progresses rapidly over a course of months and is associated with increased mortality [50].

NSF develops exclusively in patients with renal impairment who have been exposed to GBCAs, with no reported cases developing in patients with an estimated glomerular filtration rate (eGFR) of >60 ml min^{-1} 1.73-m^{-2} and only two reported cases in cases with an eGFR of >30 ml min^{-1} 1.73-m^{-2} [51–53]. Although estimates vary, it appears that the risk of developing NSF may be anywhere between 0.26 and 8.8% [54, 55], depending on factors that increase the incidence of the condition, including multiple scans with GBCAs, the use of GBCAs at a dose higher than 0.1 mmol kg^{-1} and an eGFR < 15 ml min^{-1} 1.73-m^{-2} [56]. Importantly, NSF is more likely to develop following the use of linear, rather than macrocyclic agents and this will be discussed in greater detail below. The pathophysiological process that triggers the development of fibrotic changes remains unclear but exposure to GBCAs that have comparatively high dissociation rates are more likely to lead to NSF development, and patients with advanced chronic kidney disease, particularly those requiring renal replacement therapy, appear to be more susceptible [57]. GBCA clearance is delayed in patients with renal impairment, which results in greater dissociation of Gd^{3+} ions from the ligand chelate, leading to subsequent accumulation within tissues and organs [17]. Dermal thickening develops alongside accumulation of mucin and thick collagen bundles [46, 58], whilst increased numbers of macrophages, myofibroblasts and fibrocytes (fibroblast progenitors) are seen, indicating that gadolinium exerts an immunomodulatory action that induces fibrosis [58]. Recent *in vitro* work has shown that exposing mesenchymal stem cells to gadolinium chloride leads to increased signalling of the endothelin-1/endothelin receptor that modulates fibrosis and calcification [59] and upregulates proinflammatory/profibrotic cytokine and growth factor expression, possibly due to increased activation of toll-like receptors [58]. Reports suggest that the onset of NSF typically develops within 1–8 weeks of exposure to GBCAs [60].

Results from a large-scale study utilizing three major clinical databases showed that of 279 confirmed and nonconfounded cases of NSF, all involved the use of a linear GBCA and 73.5% had received a nonionic product [61]. Similarly, data published following a questionnaire to members of the European Society of Urogenital Radiology showed that all of the patients known to have NSF had been exposed to gadodiamide (a nonionic linear GBCA) in the weeks prior to onset of the condition, with further data from the USA indicating that that approximately 90% of patients with NSF had received gadodiamide [56]. Although there are isolated case reports of NSF developing following exposure to macrocyclic GBCAs [62], the overwhelming majority of cases occur with linear agents. The European Committee for Medicinal Products for Human Use have since reviewed the evidence regarding the risk of NSF development in patients with severe renal impairment following gadolinium exposure and the EMA reclassified the clinically approved GBCAs according to the risk of NSF [12] (Table 1). The US Food and Drug Administration (FDA), advises that the linear agents gadopentetate dimeglumine, gadodiamide and gadoversetamide are contraindicated in patients with severe kidney disease (eGFR <30 ml min^{-1} 1.73-m^{-2}) [51].

Gadolinium deposition in patients with normal renal function

Gadolinium deposition within bones

Every year, approximately 30 million contrast-enhanced MRI scans are conducted worldwide [1] and despite links between GBCA administration and the development of NSF being known for almost a decade, the contrast medium has historically been considered to have an excellent safety profile in patients who do not have severe renal impairment. However, gadolinium deposition within the long bones in rodents has been recognized for >25 years, with correlations identified between acid dissociation rates and gadolinium retention, which was attributed to presumed gadolinium dissociation from its chelates [63]. In 1992, Wedeking *et al*. [63] evaluated the *in vivo* tissue distributions of a range of GBCAs, including gadobenate dimeglumine (ionic, linear), gadodiamide (nonionic, linear), gadoterate meglumine (ionic, macrocyclic) and gadoteridol (nonionic, macrocyclic) using a murine model. The mice received a single intravenous injection of a radiolabelled GBCA dosed at 0.44 mmol kg^{-1} and tissue distributions were measured at multiple intervals ranging from 5 min to 14 days. The team showed that administration of GBCAs resulted in gadolinium deposits within the liver and femur of the mice, the linear agents resulting in a higher rate of deposition compared with the macrocyclic agents [63].

In 2004, it was subsequently shown via a series of *in vivo* experiments conducted using bone tissue from patients undergoing hip replacement surgery that gadolinium is retained within the femur in humans following administration of either 0.1 mmol kg^{-1} gadoteridol (a nonionic, macrocyclic agent) or 0.1 mmol kg^{-1} gadodiamide (a nonionic, linear agent) between 3–8 days before surgery [64] (Table 2). The bone samples from the gadoteridol group had an average of 0.466 μg gadolinium per g of bone, compared with 1.18 μg in the gadodiamide group. Gadolinium was undetectable in a control group, where bone samples were taken from patients who had not been exposed to GBCAs [64]. Whether the deposits represented free gadolinium ions or the gadolinium chelate was unclear. The same group subsequently compared exposure to gadodiamide with gadoteridol – use of the former resulted in approximately 2.5 times more gadolinium deposition in the first study and 4 times more in the latter, demonstrating that whilst both forms of GBCA can result in bone deposits, linear ligands, which are more prone to dechelation, are more likely to do so, potentially indicating that Gd^{3+} ions may become incorporated within bone [40, 64]. Of note, the renal function of the participants was not reported for either study. A subsequent study assessed levels of gadolinium present in bone from femoral heads and found that gadolinium concentrations were significantly elevated compared to control subjects who had not received GBCAs up to 8 years post-GBCA administration [65] (Table 2). Again, data regarding the renal function of the subjects were not presented.

Gadolinium deposition within brain tissue

In 2010, Xia *et al*. reported that insoluble deposits containing Gd associated with phosphorus and calcium were found in biopsies from human brain tumours in 28 patients who had

Table 2

Summary of studies involving human participants with gadolinium deposition

	Study design	Subject characteristics	Study findings
Gibby *et al.* 2004 [64]	Analysis of bone tissue obtained from patients undergoing a total hip arthroplasty with removal of the femoral head to assess for gadolinium deposition using inductivity coupled plasma atomic emission spectroscopy. Patients were dosed at 0.1 mmol kg^{-1} GBCA 3–8 days prior to surgery.	25 subjects, 10 of whom received gadodiamide, whilst eight received gadoteridol. Renal function of the subjects was not stated.	Gadolinium was detected at significantly higher levels in patients who had received GBCAs compared with the control subjects. Gadodiamide administration resulted in 2.5 times more gadolinium deposition than gadoteridol.
White *et al.* 2006 [40]	Analysis of bone tissue obtained from patients undergoing a total hip arthroplasty with removal of the femoral head to assess for gadolinium deposition. Patients were dosed at 0.1 mmol kg^{-1} GBCA 3–8 days prior to surgery.	27 subjects, 10 of whom received gadoteridol, whilst nine received gadodiamide. Renal function of the subjects was not stated.	Gadolinium was detected at significantly higher levels in patients who had received GBCAs compared with the control subjects. Gadodiamide administration resulted in 4 times more gadolinium deposition than gadoteridol.
Darrah *et al.* 2009 [65]	Analysis of bone tissue obtained from patients undergoing hip arthroplasty with removal of the femoral head to assess for gadolinium deposition. Dosage/frequency information was not available to the researchers in sufficient detail.	31 subjects (18 control subjects, six received gadodiamide, five received gadoteridol, two received an unknown GBCA and an additional four subjects are suspected to have received GBCA but medical records cannot confirm this). Renal function of the subjects was not stated.	Gadolinium was detected at significantly higher levels in patients who had received GBCAs compared with the control subjects. No difference was observed in bone gadolinium concentrations between those who had received gadodiamide and those with gadoteridol.
Xia *et al.* 2010 [4]	Retrospective study analysing brain tumour biopsies following at least one MRI scan enhanced with a GBCA using scanning electron microscopy/energy dispersive X-ray spectroscopy. Dose of gadolinium not stated.	28 subjects with brain tumours who had no evidence of severe renal disease.	Gadolinium deposits were found in highly vascular areas, frequently within the wall of blood vessels, and in association with calcifications.
Errante *et al.* 2014 [5]	Retrospective, observational study reviewing MR images. Patients were dosed at 0.1 mmol kg^{-1} GBCA.	38 subjects with multiple sclerosis and 37 with brain metastases who had undergone at least two gadodiamide administrations. All subjects had normal renal and hepatobiliary function.	Progressive increase in T1 signal intensity of the dentate nucleus after multiple GBCA administrations.
Kanda *et al.* 2014 [6]	Single centre, retrospective study reviewing MR images. Dosing information was not available.	35 subjects, 19 of whom were known to have received GBCAs. Among those who received GBCAs, 11 were known to have a tumour (not in the brain) and 16 were undergoing chemotherapy. All patients in the contrast group had eGFR >60 ml min^{-1} 1.73-m^{-2}.	Increased T1 signal intensity in the dentate nucleus and globus pallidus; signal intensity showed positive correlation with previous GBCA exposure.
Kanda *et al.* 2015 [10]	Single centre, retrospective study reviewing MR images. Dosing information was not available.	127 subjects, 74 of whom had brain metastases, 20 had a primary brain tumour, six had demyelination, and the remainder had conditions including cerebritis, meningitis, vasculitis, and cerebral infarction. 31 subjects had mild renal insufficiency.	Increased T1 signal intensity in the dentate nucleus was seen in patients who had undergone MR scanning with linear, but not macrocyclic, GBCAs.
McDonald *et al.* 2015 [68]	Single centre, retrospective study reviewing MR images and performing post-mortem analysis of neuronal tissues to measure gadolinium. Patients were dosed at 0.1 mmol kg^{-1} GBCA.	23 subjects, 13 of whom received GBCAs. Among those who received GBCAs, pathologies included: five with glioblastomas, four with cerebral metastases, one each with subependymoma, oligodendroglioma, pituitary adenoma and encephalitis. Seven of the patients who received GBCAs had CKD stages 2-3A.	A dose-dependent relationship between intravenous GBCA administration and neuronal tissue deposition, as well as MR T1 signal intensity changes was found.
Kanda *et al.* 2015 [8]	Single centre, post-mortem study. Inductively coupled plasma mass spectroscopy was used to measure gadolinium in formalin-fixed brain samples in patients who had undergone MR imaging. Patients were dosed at 0.1 mmol kg^{-1} GBCA.	10 subjects, five of whom received GBCAs. Among those who received GBCAs, pathologies included: malignant lymphoma, glioblastoma, maxillary carcinoma, brain infarction, and pneumonia. No subjects had CKD stage 3B-5.	Gadolinium was detected in all specimens in the GBCA group and, at lower levels, in several samples in the non GBCA participants (errors in sample preparation for 1 participant noted).
Murata *et al.* 2016 [9]	Single centre, post-mortem study. Multiple brain areas, including globus pallidus and dentate nucleus, as well as bone and skin, were	Nine subjects (five received gadoteridol, two gadobutrol, one gadobenate, one gadoxtetate). Nine control subjects. 10	Gadolinium deposition in brain and bone tissue occurs with macrocyclic and linear GBCAs. Deposition of gadolinium in cortical

(continues)

Table 2

(Continued)

	Study design	Subject characteristics	Study findings
	analysed using inductively coupled plasma mass spectrometry. Patients were dosed at 0.1 mmol kg^{-1} GBCA.	participants had known malignancy, whilst the others had underlying inflammatory conditions. All had normal renal function.	bone occurs at higher levels compared with brain tissue and shows a correlation between the two.
Stojanov *et al*. 2016 [70]	Single centre, retrospective study reviewing MR images. Patients were dosed at 0.1 mmol kg^{-1} GBCA.	58 subjects with relapsing–remitting multiple sclerosis. All subjects received gadobutrol and had normal renal function.	Increased T1 signal intensity was observed within the dentate nucleus and globus pallidus after multiple gadobutrol injections, with greater signal intensity increases where gadobutrol doses were given over a shorter period.
McDonald *et al*. 2017 [7]	Single centre, *postmortem* study. Inductively coupled plasma mass spectroscopy was used to measure gadolinium in brain samples in patients who had undergone MR imaging, whilst light microscopy was utilised to quantify and localise gadolinium deposition. Patients were dosed at 0.1 mmol kg^{-1} GBCA.	15 subjects, five of whom had received at least four gadodiamide administrations (all five had noncerebral malignancies and four of these had CKD stage 3–4).	A dose-dependent relationship between intravenous GBCA administration and neuronal tissue deposition was found, with deposits localised to the capillary endothelium and neuronal interstitium and, in two cases, within the nucleus of the cell.
McDonald *et al*. 2017 [69]	Single centre, retrospective, case–control study reviewing post-mortem brain tissues of paediatric patients. Patients were dosed at 0.1 mmol kg^{-1} GBCA.	Six paediatric subjects, three of whom had primary brain malignancies and had been exposed to gadodiamide. All subjects had normal renal function.	Intracranial gadolinium deposits were found in the dentate and deep grey nuclei in patients who had received GBCAs.
Lee *et al*. 2017 [73]	Single centre, retrospective study reviewing MR images. Detailed dosing information was not available.	385 subjects who had received gadoterate meglumine contrast, 143 of which had brain tumours and 201 had noncerebral malignancies. 34 patients had undergone whole brain radiotherapy. None of the subjects had severely impaired renal function (defined as estimated glomerular filtration rate, 45 ml min^{-1} 1.73-m^{-2}) or acute renal failure, but 28 had abnormal renal function.	Multiple repeated administrations of macrocyclic GBCAs were not associated with increased T1 signal intensity in deep brain nuclei in patients with normal renal function, whilst those with impaired renal function had increased signal intensity in the dentate nucleus.
Tibussek *et al*. 2017 [71]	Retrospective case–control study reviewing paediatric MRI brain scans. Patients were dosed at 0.1 mmol kg^{-1} GBCA.	24 paediatric subjects with brain tumours who had undergone at least nine GBCA administrations and 24 control subjects without intracranial pathologies. All patients had normal renal function.	Multiple administrations of GBCAs in children were not associated with increased T1 signal intensity in MRI brain scans.
Conte *et al*. 2017 [72]	Intraindividual comparative study. MRI scans were reviewed from participants who had undergone multiple administrations of gadoxetate sodium. Patients were dosed at 0.025 mmol kg^{-1} GBCA.	18 patients with stage III multiple melanoma who had normal renal function.	Multiple administrations of gadoxetate disodium were not associated with increased T1 signal intensity within the dentate nucleus or globus pallidus.

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GBCA, gadolinium-based contrast agent; MRI, magnetic resonance imaging

undergone at least one MRI scan with GBCA use, and were more likely to be found in biopsies from patients scanned with the linear agent, gadodiamide, rather than the macrocyclic agent, gabonenate dimeglumine [4] (Table 2).

Although hyperintense areas on unenhanced T1-weighted scans have previously been observed in the neural tissue of patients who had multiple sclerosis and those who had been treated with brain irradiation for several years [66, 67], this had been attributed to the pathophysiology of the underlying conditions rather than previous exposure to one or more GBCA. In 2014, the first report linking previous exposure to GBCAs with the detection of high signal intensity on subsequent unenhanced T1-weighted MRI brain scans images was published [6]. The study compared 19 patients who had received GBCAs (16 of whom had undergone chemotherapy) with control patients and observed increased T1 signal intensity in the dentate nucleus (the largest of the four pairs of deep cerebellar nuclei) and globus pallidus (a pair of nuclei that make up the basal ganglia). The signal intensity showed positive correlation with previous GBCA exposure, suggesting that GBCAs may be deposited within brain tissue following repeated exposures. All patients included in this retrospective study had received the linear agents gadopentetate dimeglumine or gadodiamide for MRIs as part of their standard care; these were the only agents used at that institute [6] (Table 2). Similarly, in another retrospective observational study, 38 patients with multiple sclerosis and 37 with brain metastases who had undergone multiple MRI scans utilizing intravenous gadodiamide (a linear GBCA) had dose-dependent signal intensity changes seen on subsequent unenhanced scans. Twenty-three of these 75 patients had undergone six or more contrast-enhanced MRI scans [5].

Several months later, results were published from a *postmortem* study comparing brain tissue samples from 13

deceased adult patients who underwent between four and 29 gadodiamide-enhanced MRI scans with 10 patients who had not received GBCAs [68]. None of the patients had significant renal or hepatic impairment and all had provided *antemortem* consent. Of note, the GBCA cohort consisted primarily of patients with cerebral malignancies, whilst the non-GBCA cohort underwent MRI for a range of conditions, including dementia, transient ischaemic attacks and seizures. Tissue samples were harvested from the posterior fossa (dentate nucleus and pons) and basal ganglia (globus pallidus and thalamus) and analysed using inductively coupled plasma mass spectrometry, in addition to transmission electron and light microscopy techniques. The study identified that the brain tissue of patients who had received GBCAs contained 0.1–58.8 μg of gadolinium per g of tissue, compared with undetectable levels of gadolinium in the control group, although it is not clear whether this was chelated or free gadolinium. The researchers also showed that there were dose-dependent relationships between the number of scans that a patient had undergone and the amount of gadolinium deposition present. Additionally, there were positive correlations between the number of GBCA exposure events and the observed MRI signal intensity changes, confirming the hypothesis that gadolinium deposits may be present in the brain after GBCA-enhanced MRI scans and that these changes can be seen as areas of high signal intensity on unenhanced MRI brain scans [68]. The same research group reported similar findings in another cohort of 15 adult patients, five of whom had been exposed to the nonionic linear agent, gadodiamide on 4–18 occasions [7]. They again reported a dose-dependent relationship between intravenous GBCA administration and deposition within the globus pallidus and dentate nucleus, with deposits localized to the capillary endothelium and neuronal interstitium and, in two cases, within the nucleus of the cell. Of note, all five GBCA-exposed patients had noncerebral malignancies and four of these had impaired renal function, with eGFRs ranging from 24 to 57 ml min^{-1} 1.73-m^{-2} [7]. This group has also undertaken a study in six paediatric subjects, three of whom had primary brain malignancies and had been exposed to gadodiamide [69]; gadolinium deposits were found in the dentate and deep grey nuclei in each of the GBCA-exposed children, all of whom had an eGFR >80 ml min^{-1} 1.73-m^{-2} [69].

A study involving 58 patients with relapsing–remitting multiple sclerosis, all of whom had normal renal function, identified increasing T1-weighted signal intensity within the dentate nucleus and globus pallidus following four to six administrations of gadobutrol, a macrocyclic agent [70], while a small study by Murata *et al*. [9] assessing *postmortem* brain specimens from nine participants with normal renal function who had received gadoteridol, gadobutrol, gadobenate or gadoxtetate showed that gadolinium deposition can occur in brain and bone tissue with both macrocyclic and linear agents. Of note, seven of the nine participants had malignancies whilst the remaining two had inflammatory conditions [9] (Table 2). Numerous research groups have since confirmed these findings of increased T1 signal intensity within the brains of patients who have been exposed to GBCAs from both linear and macrocyclic groups [70–72]. Conversely, a study reviewing MRI scans from 385 patients who had received multiple repeated administrations (from 2 to 52) of the macrocyclic GBCA, gadoterate meglumine found no associated increase in T1 signal intensity in deep brain nuclei in subjects who had normal renal function [73] (Table 2).

Stability

In 2008, it was shown that when various GBCAs were incubated with human serum at 37°C, pH 7.4 at a concentration of 1 mmol l^{-1} for 15 days, which is comparable to the concentrations achieved with use of GBCAs in MRI scans, the macrocyclic agents (gadobutrol, gadoteridol and gadoterate meglumine) remained stable, whilst free Gd^{3+} release occurred with the linear GBCAs [74, 75]. Approximately 2% of the gadolinium dissociated from the ionic linear GBCAs (gadopentetate dimeglumine, gadobenate dimeglumine, gadoxetate and gadofosveset) and 20% of the nonionic linear GBCAs (gadodiamide and gadoversetamide), confirming the low dechelation rate of macrocyclic agents and the comparatively reduced stability of nonionic complexes compared with ionic ones [75]. Interestingly, both the ionic and nonionic macrocyclic agents remained stable, the ionic linear GBCAs demonstrated minimal dissociation, but the ionic and nonlinear GBCAs showed significant levels of dissociation and therefore there is a potentially greater risk of gadolinium deposition with the use of agents in this group.

Mechanistic studies investigating gadolinium deposition

Although gadolinium has been identified in postmortem brain tissue following GBCA exposure, none of the studies to date have determined whether this is free or chelated gadolinium, and there is no evidence at present that the latter would lead to toxicity even if it were deposited in brain tissue. Additionally, no link has been reported in the medical literature between GBCA exposure (with or without evidence of retention of gadolinium within the neural tissues) and symptoms indicative of calcium channel blockade, which would be expected if circulating free Gd^{3+} ions, rather than chelated gadolinium, were present. Studies have utilized animal models to confirm that Gd^{3+} competes with Ca^{2+} to bind with a variety of biological receptors, with competitive antagonism between the two demonstrated using multiple targets, including porcine pancreatic phospholipase A_2 [76] and bovine chromaffin cells [77].

Recent murine studies have shown that GBCA administration in renally-impaired rats results in *in vivo* dechelation over a period of 11 days when gadodiamide (nonionic, linear) is administered; however, *in vivo* dechelation was not seen in this model with gadoterate meglumine (ionic, macrocyclic) administration [78]. Furthermore, when very high doses (13.2 mmol kg^{-1} over 8 weeks) were given to healthy rats, the linear agent, gadodiamide but not gadoteridol (nonionic, macrocyclic) yielded insoluble gadolinium-containing species, which is likely to represent dechelated gadolinium [79]. Similarly, rats receiving 10 daily injections of 2.5 mmol kg^{-1} of either GBCAs or saline developed insoluble gadolinium deposits in the brain when linear agents (gadodiamine, gadopentetate dimeglumine and gadobenate dimeglumine) were given, but were not present with macrocyclic agents (gadobutrol and gadoterate meglumine) or

saline [74]. Whether these findings would have been present with fewer injections is not clear. Numerous authors have postulated that these findings occur due to transmetallation of unstable GBCA complexes, whereby Gd^{3+} undergoes replacement with cations, such as copper, zinc, iron and calcium, and free gadolinium ions subsequently bind to endogenous anions, such as phosphate and carbonate, forming insoluble deposits within tissues [19, 40, 80]. In keeping with this theory, Corot *et al*. have shown that linear, but not macrocyclic GBCAs, were capable of inhibiting zinc-dependent angiotensin-converting enzyme activity in rat and rabbit models [81].

In vitro studies have explored the potential mechanisms by which NSF develops. Human monocyte-derived macrophages that were incubated with the linear agent, gadodiamide (50 mmol l^{-1}), showed increased gene expression, as well as increased 'nuclear factor kappa-light-chain-enhancer of activated B cells' activity [82]. This is a transcription factor that plays a critical role in the induction of the inflammatory response and chemokine production, and also regulates expression of the cyclo-oxygenase-2 enzyme [83]. An additional study where human dermal fibroblasts were incubated with GBCA-treated monocyte culture supernatants showed a significant increase in production of types I and III collagen, fibronectin and α-smooth muscle actin expression in normal dermal fibroblasts [84]. Furthermore, there was increased expression of the proinflammatory cytokine interleukin-6 [84]. These results indicate that GBCAs may promote the development of a proinflammatory, and subsequently profibrotic, state.

All clinical studies to date that confirm gadolinium deposition within brain tissue, either by MRI or analysis of *postmortem* samples, have involved patients with a history of neoplastic disease [6], including those with brain metastases; central nervous system disorders, such as multiple sclerosis [5]; or systemic inflammatory conditions (Table 2). All of these conditions can potentially be associated with inflammation of cerebral tissues, structural brain abnormalities and/or disruption of the blood–brain barrier. Although mechanisms for blood–brain barrier or cerebrospinal fluid barrier disruption may vary, potential causes include the development of intravascular microthrombi and subsequent cerebral ischaemia, and endothelial activation with increased expression of proinflammatory cytokines [85]. There have been no *in* vitro, animal or human studies which have investigated whether patients with conditions associated with disruption of the blood–brain barrier or inflammatory changes within the brain may be more vulnerable to developing deposition of gadolinium following GBCA exposure compared with patients who do not have pre-existing central nervous system or systemic inflammatory disease (s).

Animal studies

Over recent years, animal studies have been conducted to elucidate the mechanisms of gadolinium deposition and to explore its potential clinical significance. Studies involving murine and canine models have shown that high-level dosing (≥2 mmol kg^{-1} in mice and ≥0.3 mmol kg^{-1} in dogs), as well as repeated dosing (between 2 and 31 times), of the nonionic, macrocyclic GBCA, gadobutrol, causes vacuolization of renal tubular epithelium without any significant effect on renal function [86]. As with humans, increased T1 weighted signal intensities develop in deep cerebellar nuclei following administration of GBCAs in rats, although these changes have been repeatedly seen with linear GBCAs, but not with macrocylic agents for which no effect was observed [87, 88].

Further data published in 2017 showed that rats who received extremely high doses of macrocyclic GBCAs (20 administrations of 0.6 mmol kg^{-1} over 5 weeks giving a total dose of 12 mmol kg^{-1}; humans are typically dosed at around 0.1 mmol kg^{-1} per single GBCA MRI scan, although gadoxetate disodium is dosed at 0.025 mmol kg^{-1}) showed no measurable retention in their skin, blood or liver after 28 days, but developed gadolinium deposits in their cerebrum, cerebellum, kidneys and femur [89]. Of note, administration of the linear GBCA, gadodiamide, was associated with histological skin lesions in rats with impaired renal function, whilst the macrocyclic GBCA, gadoterate meglumine, was not [78]. Additionally, a study where healthy rats received high doses of six GBCAs, four of which were linear and two macrocyclic, showed that only those exposed to gadodiamide (nonionic, linear) developed macroscopic and histological skin changes that bear resemblance to the lesions present in NSF patients [90].

A more recent study has shown that high-dose (1.8 mmol kg^{-1}) administration of six of the nine GBCAs that have been in clinical use (linear agents – gadodiamide, gadopentetate dimeglumine, gadobenate dimeglumine – and macrocyclic agents – gadoterate meglumine, gadobutrol and gadoteridol) to rats results in GBCA infiltration and distribution in the cerebrospinal fluid (CSF), as demonstrated by fluid-attenuated MRI and gadolinium measurements in CSF, blood and brain tissue samples using inductively coupled plasma mass spectrometry [91]. All of the studied agents crossed the blood–CSF barrier, although they were subsequently cleared within 24 h, regardless of the GBCA structure and physicochemical properties [91], indicating a possible mechanism by which neural GBCA deposition occurs. Whether GBCAs can cross the blood-CSF or blood–brain barriers in humans remains unclear as there has been little research into mechanisms by which GBCAs enter neural tissue. Analysis of *postmortem* samples of the dentate nucleus and globus pallidus from patients who had received gadodiamide found that gadolinium deposition was primarily limited to the capillary endothelium and neuronal interstitium and, in only two cases, within the nucleus of the cell [7].

Data from murine studies confirm that exposure to rare-earth metals, typically demonstrated with lanthanum, results in significant neurotoxic effects during neurodevelopment [92], possibly via the ions competitively binding to calcium channels within hippocampal cells. This may result in mitochondrial dysfunction with gestational and early-age exposure to La^{3+} ions, causing impaired spatial learning and memory in young rats [93]. GBCAs have been shown to cross the placenta in nonhuman primates, with juvenile macaques having low levels of up to 0.000025% of the injected dose of gadolinium present in multiple tissues, particularly in the femur, but also in the liver following *in utero* exposure to via placental MRI after intravenous gadoteridol (macrocyclic) administration on gestational days 85 and 135 [94]. Whether this has implications for human pregnancies is unclear.

McDonald *et al*. commented in 2017 that paediatric brains are more susceptible than adult brains to the neurotoxic effects of heavy metal exposure and that similar effects could develop following exposure to rare earth elements, such as gadolinium, and that until further research has been carried out, caution should be exercised when considering whether GBCA administration is required in younger patients [69]. There are, however, a wide variety of indications for GBCA use in paediatric patients, including the evaluation of congenital heart disease, vascular tumours and malformations, and congenital central nervous system abnormalities and there is no definitive evidence that exposure to GBCAs, and potential gadolinium deposition, is harmful. At present, only gadobutrol (macrocyclic) and gadoterate meglumine (macrocyclic) are licensed by the FDA for use in patients younger than 2 years, whilst gadopentetate (linear), gadodiamide (linear), gadobenate dimeglumine (macrocyclic) and gadoteridol (macrocyclic) have been approved for the use in children older than 2 years and these agents are thus prescribed for off-label indications in many paediatric cases [95].

What is the clinical significance of gadolinium deposition?

Following the identification of potential gadolinium deposition following GBCA administration, there has been interest amongst the medical community and in the lay press in whether clinical sequelae may result when this occurs. The largest study published to date to investigate possible clinical manifestations of presumed gadolinium deposition identified 42 patients who reported long-term symptoms beyond 3 months post-GBCA administration, including central (n = 15, 36%) and peripheral pain (n = 26, 62%), headache (n = 28, 67%), bone pain (n = 26, 62%), skin changes (n = 22, 52%), and clouded mentation (n = 29, 69%) [11]. However, there was significant bias in the recruitment of study subjects, no control group recruited, and limited clinical detail provided in the paper. Participants were recruited from online support groups where subjects had self-identified as having *gadolinium toxicity* without relevant medical records being available directly from medical institutions; data were not reported on renal function, results of investigations, and physician assessments or diagnoses. It is therefore difficult to be able to determine the clinical significance of this study and whether or not gadolinium played a role in the symptoms reported to be present.

In view of the fact that gadolinium deposition has been shown to primarily occur in the dentate nucleus and globus pallidus, it is likely that if this results in neurological/clinical sequalae, the features present would relate to dysfunction of these structures and include movement disorders; whereas nonspecific, sensory symptoms, including sharp or burning pain that was typically present in a glove and stocking distribution, and generalized bone and joint pain appear to prevail in the report. No studies to date have assessed whether peripheral nerve damage occurs following gadolinium exposure. Further details regarding the bone pain that patients complained of are not available and thus whether this could be a consequence of gadolinium deposition within bones remains unclear. The patients in this study also reported skin changes ranging from *discolouration* to *thickening of skin over the limbs*; but the limited clinical detail and context provided limits interpretation of these reported skin changes [11]. Of note, human bone turnover rates are typically around 5–15% in healthy adults (with increased rates in pregnant, lactating and postmenopausal women), and thus if gadolinium were to be deposited within bone, either in the form of a chelate or as free ions, there remains the potential that it could re-enter the circulation following bone resorption and remodelling over later years [65] but no studies have yet been performed to assess this risk.

Low-level background environmental contact to heavy metals typically results in detectable blood and urine concentrations of arsenic [96], lead [97], mercury [98], cadmium [99] and other heavy metals in healthy individuals who have not had significant additional exposure to these metals. Although several laboratories quote expected concentrations of gadolinium in urine and blood, to date no data have been published in the literature to establish a reference range for gadolinium concentrations in healthy individuals who have not had exposure to a GBCA [100, 101]. Interpretation of blood and urine concentrations in patients who are concerned regarding potential GBCA-induced symptoms is therefore challenging and there is a need for studies to establish a reference range for gadolinium in those who have not had exposure to a GBCA.

Current recommendations

Guidance from the FDA, published in May 2017, stated that there is no evidence that gadolinium retention from any of the GBCAs, including those associated with higher retention of gadolinium, is harmful, and thus their use, where clinically indicated, should not be restricted [102]. This was followed up in late December 2017 with further guidance stating that linear GBCAs result in more retention and retention for a longer time than macrocyclic GBCAs, and thus health care professionals should consider the retention characteristics of each agent when choosing a GBCA for patients who may be at higher risk for gadolinium retention, and aim to minimize repeated GBCA imaging studies when possible but do not avoid or defer necessary GBCA MRI scans [103].

In July 2017, the EMA recommended an EU-wide suspension of all commercially available linear GBCAs, aside from gadoxetate and gadobenate dimeglumine, which are taken up in the liver and thus "meet an important diagnostic need" [12]. Subsequently, in December 2017, the UK Medicines and Healthcare products Regulatory Agency (MHRA) issued a recommendation that licenses be suspended for the linear agents, gadodiamide and intravenous gadopentetic acid (although intra-articular use of the latter remains authorized), whilst the use of gadobenate dimeglumine and gadoxetate will be limited to liver imaging with specific contrast requirements [104]. The MHRA went on to state that GBCAs should only be used "when diagnostic information is essential" and would not be available with an unenhanced scan, and at the lowest possible effective dose [104].

Following the consistent reports of gadolinium deposition within the femur, dentate nucleus and globus pallidus associated with linear GBCAs in the aforementioned studies, it appears prudent that the EMA and FDA have now limited

the use of linear GBCAs in clinical practice until further information is available regarding gadolinium retention. As many of these studies, particularly the earlier ones, were conducted using linear agents, such as gadodiamide, it remains unclear whether switching to macrocyclic agents will limit the risk of gadolinium deposition.

Future research

It has yet to be established whether gadolinium deposition, possibly via dechelation, can result in a spectrum of clinical sequelae, which may range from subtle skin changes, as self-reported by subjects from online support groups, to NSF in patients with severe renal impairment. However, it is important to note that there are no reports in the medical literature of proven associations between gadolinium deposition and clinical signs and symptoms in patients with normal renal function.

Whilst dechelation has not been demonstrated as part of the mechanism for neural gadolinium deposition, the vast majority of the clinical studies where deposition has been identified have primarily been conducted in patients who had received linear agents (Table 2), which are known to have lower dissociation thresholds. Furthermore, most linear agents are currently being removed from clinical use in Europe and thus the relevance of these studies in future practice is unclear [12, 104].

As mentioned throughout this review, gadolinium deposition in neural tissues has solely been established in patients with inflammatory, infective, or malignant disease. Further studies are required to determine whether healthy subjents receiving GBCAs, particularly the macrocyclic agents in current clinical use are associated with gadolinium deposition, thus establishing whether systemic inflammation or structural damage to the blood–brain barrier contributes to retention of gadolinium within brain tissue and to assess the potential risk for specific groups of patients. To date, no healthy volunteer studies have been undertaken assessing the potential for gadolinium deposition within the brain, skin or bones. In addition, both mechanistic and cohort studies are required to elucidate the mechanisms by which gadolinium deposits within human tissue, and whether this leads to clinically significant sequelae.

Conclusion

GBCAs are essential components of the MRI scanning process and allow accurate diagnosis and delineation of a multitude of pathologies that may otherwise go undetected. They have an excellent safety profile, particularly now that physicians are able to identify patients who may be at particular risk of developing adverse effects, such as NSF. Current data show that there is a risk of neural tissue retention with all gadolinium-based agents, although greater gadolinium deposition occurs when less stable GBCAs are used, many of which have been removed from routine clinical use in recent years. Whether this can result in clinical consequences has yet to be fully established but no well-designed studies have produced evidence that patients have developed neurological or systemic illness following GBCA administration. There is a need for further studies to determine the normal range for gadolinium in those who have not been exposed to GBCA; to investigate whether GBCA administration in those with no underlying inflammatory, infective, or malignant diseases associated with gadolinium deposition; and to determine whether gadolinium deposition is associated with clinically significant sequelae. In the meantime, medical professionals should continue to evaluate the pharmacokinetics and pharmacodynamics of individual GBCAs when choosing the most appropriate contrast media for individual patients and aim to adhere to current recommendations regarding the use of GBCAs.

Competing Interests

There are no competing interests to declare.

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