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MINISYMPOSIUM: QUALITY AND SAFETY

Gadolinium-based contrast agents — review of recent literature on magnetic resonance imaging signal intensity changes and tissue deposits, with emphasis on pediatric patients

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Abstract

Gadolinium has been used as a base for contrast agents in MRI for the last three decades. Numerous studies over the last 4 years have reported increased signal intensity in deep brain nuclei in non-contrast MRI images following gadolinium-based contrast agent (GBCA) administration. Pathology studies performed on adults and children, and rodent necropsy studies have also shown gadolinium deposition in brain and other tissues after GBCA administration. The purpose of this review was to summarize and discuss the knowledge gained from these reports and the relevance for imaging pediatric patients.

Keywords Brain · Children · Deposition · Gadolinium · Gadolinium-based contrast agents · Magnetic resonance imaging · T1 signal

Introduction

Gadolinium (Gd) is a highly paramagnetic lanthanide-series heavy metal used as a base for intravenous contrast agents in MRI. While the free gadolinium ion (Gd3+) itself is intrinsically toxic [1, 2], gadolinium-based contrast agents (GBCAs) contain organic ligands that bind Gd3+ to form stable molecular complexes that can be administered intravenously and then subsequently excreted from the body [3, 4]. The seven GBCAs on the market differ by the configuration of their chelating agents, which can be either linear or macrocyclic, and are further subdivided as ionic or nonionic [1, 3, 4] (Table 1). Macrocyclic GBCAs have higher structural stability than linear agents, and ionic agents tend to bind Gd3+ more tightly than nonionic agents [1, 4, 5].

The first GBCA to be approved by the United States Food and Drug Administration (FDA) in 1988 was Magnevist (gadopentetate dimeglumine; Bayer, Leverkusen, Germany), a linear ionic agent. Overall, GBCAs have been considered safe during the last three decades of their clinical use [2, 6]. In fact, during the first 15 years after their introduction, contrast-enhanced MRI was considered safer than CT for imaging children with impaired renal function because of a perceived risk of iodine contrast-induced nephropathy. However in 2006 an association between GBCAs and nephrogenic systemic fibrosis (NSF) was reported [7, 8].

Further research into the association of gadolinium exposure and development of NSF revealed that nearly all cases of NSF occurred following administration of linear GBCAs in patients with renal impairment. This led to a series of practice guidelines limiting use of GBCAs in patients with renal impairment [9], as well as a general shift toward use of macrocyclic agents [3]. Still, GBCAs continued to be used in patients with normal renal function without concern for adverse effects. Literature regarding gadolinium retention in the body was sparse and did not gain significant attention from the medical community until 4 years ago.

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Table 1 Gadolinium-based contrast agents currently available for clinical use

Trade name	Generic name	Chemical nomenclature	Manufacturer	Geometry	Charge	Excretion
Omniscan	Gadodiamide	Gd-DTPA-BMA	GE Healthcare, Waukesha, WI	Linear	Nonionic	Renal
Magnevist	Gadopentetate dimeglumine	Gd-DTPA	Bayer, Leverkusen, Germany	Linear	Ionic	Renal
MultiHance	Gadobenate dimeglumine	Gd-BOPTA	Bracco, Milan, Italy	Linear	Ionic	Renal
Eovist	Gadoxetate disodium	Gd-EOB-DTPA	Bayer, Leverkusen, Germany	Linear	Ionic	Hepatobiliary >> Renal
ProHance	Gadoteridol	Gd-HP-DO3A	Bracco, Milan, Italy	Macrocyclic	Nonionic	Renal
Gadovist	Gadobutrol	Gd-BT-DO3A	Bayer, Leverkusen, Germany	Macrocyclic	Nonionic	Renal
Dotarem	Gadoterate meglumine	Gd-DOTA	Guerbet, Villepinte, France	Macrocyclic	Ionic	Renal

In 2014, Kanda et al. [10] reported a new observation of increased T1 signal intensity in the globi pallidi and the dentate nuclei on non-contrast brain MRI examinations of patients who had previously received multiple doses of GBCAs. In their discussion, the authors highlighted two older articles that reported on gadolinium deposition after GBCA administration: one described bone deposition in patients who had undergone contrast-enhanced MRI before hip replacement (specimens included resected femoral heads) [11], while the other described retention in mice (specimens included liver) [12]. Kanda's report received wide attention from the medical community and led to a broad effort to further investigate the mechanism and clinical relevance of gadolinium retention in otherwise healthy patients. Our specific purpose in this article was to review the abundant recent literature on gadolinium retention and to summarize the knowledge that has been gained from these reports.

Studies reporting high T1 signal intensity in the brain

The breakthrough article by Kanda et al. [10] was the first study that demonstrated signal changes occurring in the brain parenchyma of patients who previously received GBCAs. This article led to extensive research on GBCAs over the last 4 years, evaluating different agents and their effect on T1 signal on unenhanced MR studies on various regions in the brain in a variety of patient cohorts, including adults and children, groups with normal versus impaired renal function, and groups with diseases such as multiple sclerosis that might affect the integrity of the blood–brain barrier. In this section we discuss reports on signal changes in the brain parenchyma of adults who received GBCAs (Table 2; [10, 13–29]).

Prior intravenous (IV) administration of the linear ionic agent Magnevist and the linear nonionic agent Omniscan (gadodiamide) in patients with normal renal function was associated with increase in T1 signal intensity in the dentate nuclei and globi pallidi in two studies, with linear correlation between the administered dose and the signal intensity that persisted for several years following at least five administrations [10, 13]. A study by Zhang et al. [14] demonstrated that following multiple (39–59) administrations of both these GBCAs, there was increased signal in other regions of the brain, as well, including the posterior thalamus, substantia nigra, red nucleus, cerebellar peduncles and colliculi.

Other studies have evaluated the linear ionic agent MultiHance (gadobenate dimeglumine). One study by Weberling et al. [15] on 50 patients who received at least five administrations of MultiHance demonstrated increased signal in the dentate nuclei. They compared their results to published literature and found no significant difference between the dentate nuclei T1 signal intensity changes in comparison to changes observed after administrations of Magnevist, also a linear ionic agent. However there was a statistically significant higher dentate nucleus/pons signal intensity ratio associated with exposure to MultiHance as compared to Dotarem (gadoterate meglumine), a macrocyclic ionic agent. On the other hand, a study by Ramalho et al. [16] from about the same time on 69 patients, of whom 23 received the linear nonionic agent Omniscan and 46 received the linear ionic agent MultiHance (3–11 doses in each group), found that when the T1 signal intensity was compared between the last and first administrations there was a statistically significant increase in the globi pallidi and dentate nuclei signal intensity in the Omniscan group. They also reported a trend toward a significant increase in the dentate nuclei signal intensity but no increased signal intensity in the globi pallidi in the MultiHance group [16].

To the best of our knowledge, only one study, by Conte et al. [17], evaluated Eovist (gadoxetate disodium), a linear ionic liver-specific GBCA with up to 50% hepatobiliary excretion in the normal liver. This study analyzed a small sample of 18 patients with melanoma who received 2–18 doses of Eovist and had MR imaging of their brain and abdomen. The authors found a trend (P=0.09) toward increased globi pallidi signal intensity between the last and first

Table 2 Studies reporting T1 signal intensity changes following administration of gadolinium-based contrast agents (GBCAs) in adults

Author	Year	GBCA	GBCA description	Number of patients	Number of GBCA doses	T1 signal intensity increase[a]
Kanda et al. [10]	2014	Omniscan Magnevist	Linear, nonionic Linear, ionic	19	6–12	Yes (analyzed together)
Errante et al. [13]	2014	Omniscan	Linear, nonionic	75	1->6	Yes
Zhang et al. [14]	2017	Omniscan Magnevist MultiHance	Linear, nonionic Linear, ionic Linear, ionic	13	39–59	Yes (analyzed together)
Weberling et al. [15]	2015	MultiHance	Linear, ionic	50	5–15	Yes
Ramalho et al. [16]	2015	Omniscan	Linear, nonionic	23	3–11	Yes
		MultiHance	Linear, ionic	46	3–11	No
Conte et al. [17]	2017	Eovist	Linear, ionic	18	2–18	No
Kanda et al. [18]	2015	Magnevist	Linear, ionic	23	1–11	Yes
		ProHance	Macrocyclic, nonionic	36	1–15	No
			Both linear and macrocyclic agents received	14	5–8	Yes –Attributed to linear agent
Radbruch et al. [19]	2015	MultiHance	Linear, ionic	50	>5	Yes
		Dotarem	Macrocyclic, ionic	50	>5	No
Cao et al. [20]	2016	Magnevist	Linear, ionic	25	6–23	Yes
		Gadovist	Macrocyclic, nonionic	25	6–16	No
Bae et al. [21]	2017	Omniscan Magnevist	Linear, nonionic Linear, ionic	6	15–30	Yes
		Gadovist Dotarem	Macrocyclic, nonionic Macrocyclic, ionic	44	14–51	No
			Both linear and macrocyclic agents received	72	12–65	Yes – Attributed to linear agent
Radbruch et al. [22]	2015	Gadovist	Macrocyclic, nonionic	30	5–19	No
Langner et al. [23]	2017	Gadovist	Macrocyclic, nonionic	217	1–8	No
Kromrey et al. [24]	2017	Gadovist	Macrocyclic, nonionic	271	>=1	No
Lee et al. [25]	2017	Dotarem	Macrocyclic, ionic	385	2–52	No, with normal renal function
Bjørnerud et al. [26]	2017	Gadovist	Macrocyclic, nonionic	17	10–44	Yes, in high-grade glioma patients
Forslin et al. [27]	2017	Omniscan Magnevist Dotarem	Linear, nonionic Linear, ionic Macrocyclic, ionic	23	3–12	Yes – MS patients. Most received linear agents
Stojanov et al. [28]	2016	Gadovist	Macrocyclic, nonionic	58	4–6	Yes – MS patients
Splendiani et al. [29]	2018	Dotarem	Macrocyclic, ionic	81	4–11	Yes – MS patients
		Gadovist	Macrocyclic, nonionic	77	5–14	Yes – MS patients

[a] T1 signal intensity increase in the brain on unenhanced MR images

MS multiple sclerosis

administrations but no significant difference in the dentate nuclei signal intensities.

Several studies comparing T1 signal intensities after multiple administrations of the linear agents Magnevist and Omniscan to the macrocyclic agents Dotarem, Gadovist (gadobutrol) and ProHance (gadoteridol) demonstrated increased signal intensity in the globi pallidi and dentate nuclei following administration of the linear agents, but no increase in signal intensity was found following administration of macrocyclic agents [18–21]. In one of these studies, Bae et al. [21] evaluated 122 patients and demonstrated that even following multiple (between 15 and 65) administrations of either linear (Magnevist, Omniscan) or macrocyclic (Gadovist, Dotarem) agents, there was no increased signal intensity associated with

the macrocyclic agents, but there was a significant increase in signal intensity in the globi pallidi and dentate nuclei following administration of linear agents.

Other studies evaluated T1 signals in patients who received only macrocyclic agents. Two studies, one by Radbruch et al. [22] on 30 patients and one by Langner et al. [23] on 217 patients, evaluated T1 signal intensities in brains of patients who received at least five doses of Gadovist, a macrocyclic nonionic agent, and found no increased parenchymal signal. A study by Kromrey et al. [24] evaluated 271 healthy volunteers 5 years after a single 1.5-fold dose (1.5 mmol/kg) administration of Gadovist and found no increased signal intensity in the globi pallidi or dentate nuclei. In one study by Lee at al. [25], who evaluated 385 patients who received 2–52 doses of Dotarem, the majority of patients showed no T1 signal change between the first and last scans; in 28 with mildly impaired renal function, with glomerular filtration rate (GFR) ranging 45–60 mL/min, there was increased signal intensity in the dentate nuclei but not in the globi pallidi. Nevertheless a study by Bjørnerud et al. [26] demonstrated increased T1 signal intensity in the dentate nuclei in 17 patients following multiple administrations (10–44) of Gadovist. However all of the patients in this study were diagnosed with a high-grade glioma, which might alter the blood–brain barrier by itself or secondary to radiation therapy.

Several studies were performed on patients with multiple sclerosis and found increased signal in the dentate nuclei and globi pallidi after multiple administrations of both linear and macrocyclic agents [27–29]. One study by Forslin et al. [27] found an association between increased T1 signal in the dentate nuclei and globi pallidi, and lower verbal fluency scores; this association remained significant after corrections for several aspects of multiple sclerosis disease severity.

In summary, there is clearly increased T1 signal intensity in the globi pallidi and dentate nuclei following multiple administrations of linear GBCAs; this finding is dose-dependent and is more significant with linear nonionic versus ionic agents, likely secondary to the higher overall kinetic stability of the latter in physiological conditions. Many studies demonstrated no increased T1 signal following multiple administrations of all three macrocyclic GBCAs that are on the market in subjects with normal renal function and intact blood–brain barrier. Studies that demonstrated increased T1 signal intensity in association with macrocyclic GBCAs were performed either on patients with disorders affecting the integrity of the blood–brain barrier (e.g., multiple sclerosis and high-grade gliomas) or on patients with renal function impairment. Nonetheless evaluation of signal intensities is probably not a sensitive method for detecting gadolinium deposits in tissues. Consequently tissue biopsy and autopsy studies were performed, as well, and are discussed in the following section.

Tissue biopsy and autopsy studies

In 2004 Gibby et al. [30] and in 2006 White et al. [11] reported deposition of gadolinium in femoral bone tissue excised during hip replacement surgeries in patients who underwent MRI examinations with IV GBCA several days prior to the surgery. They compared the linear nonionic agent Omniscan and the macrocyclic nonionic agent ProHance and found that gadolinium was retained in the bones with both agents, with 2.5- to 4-fold higher intraosseous concentrations associated with Omniscan as compared to ProHance. Another study, by Darrah et al. [31], that also evaluated femoral samples found retention of gadolinium 8 years following IV administration of either Omniscan or ProHance, with no significant difference in the concentration of gadolinium between the agents. They also found higher concentrations of GBCA in trabecular bone than in cortical bone, and lower concentrations in patients with osteoporosis or fractures in contrast to patients with osteoarthritis, and they concluded that gadolinium might be released from the bone in the context of demineralization. In 2010, a study by Xia et al. [32] demonstrated gadolinium deposits in biopsied brain tumors, with higher concentration in specimens from patients who received the linear nonionic agent Omniscan when compared to MultiHance, a linear ionic agent. The authors concluded that this deposition occurs secondary to loss of the integrity of the blood–brain barrier, and is lower with MultiHance because of its greater chemical stability. In 2011, a study by Christensen et al. [33] demonstrated gadolinium deposition in the skin biopsied from patients with NSF.

After the breakthrough article by Kanda et al. [10] in 2014, several published autopsy studies strengthened the recognition of gadolinium deposits in brain and other tissues in healthy subjects with normal renal function and intact blood–brain barrier. The first known autopsy study that followed Kanda's article was by McDonald et al. [34]. They analyzed brain tissues from autopsies of 13 subjects with normal renal function who received 1–29 administrations of Omniscan, with a wide range of timing between the last contrast administration and death, ranging from several days to years [34]. They found gadolinium deposits in capillary endothelium and neural interstitium in a dose-dependent relationship that correlated with T1 signal intensities on pre-contrast MRI scans [34]. They concluded that "intravenous GBCA exposure is associated with neuronal tissue deposition in the setting of relatively normal renal function" [34]. Shortly after, another autopsy study by Kanda et al. [35] evaluated brain tissue of five subjects who had received the linear ionic agent Magnevist alone or in combination with other GBCAs, and found brain deposits with the highest concentrations in the globi pallidi and dentate nuclei. Another autopsy study by McDonald et al. [36] found deposits in brains of five patients with no known blood–brain barrier abnormalities after 4–18 doses of Omniscan, with higher concentrations in the globi

pallidi as compared to the dentate nuclei. Tissue localization performed with transmission electron microscopy showed gadolinium deposits present in the endothelial wall and neuronal interstitium but also in neuronal nuclei [36]. However they found no evidence of gadolinium-mediated histological changes to suggest a toxic effect.

A study by Murrata et al. [37] evaluated brain, skin and bone tissues from autopsies in nine subjects who received either macrocyclic agents (ProHance and Gadovist) or linear ionic agents (MultiHance and Eovist). Interestingly, they found the highest concentrations in two patients who had received Gadovist (of which one died several days after the administration with multi-organ failure). They also found that bone concentrations were 23-fold higher than brain concentrations. Low concentrations of gadolinium were found in the skin in three of the autopsies from whom the skin was sampled. These patients had received either MultiHance or ProHance [37].

In summary, gadolinium deposits in the brain, bone, skin and liver and possibly other tissues as well. Brain, bone and skin depositions were demonstrated with both linear and macrocyclic agents. The concentrations in osseous tissues are significantly higher than those in the brain, which might be explained by the similarity of the gadolinium ion to ionic calcium [3]. Autopsy studies show that gadolinium retention in the brain occurs independent of renal function and blood–brain barrier integrity. The concentrations of retained gadolinium are cumulative, proportionally related to the administered doses, and small concentrations of gadolinium appear to persist for years.

Gadolinium-based contrast agents in pediatric patients

Like in adults, GBCAs are frequently employed in pediatric patients for characterizing and staging tumors, evaluating inflammatory and infectious processes, and assessing vascular structures, and GBCAs are used in approximately 40% of the total number of MRI examinations performed annually in children in the United States [38].

Despite being safely used in pediatric patients since their introduction in clinical practice in the late 1980s [39–44], GBCAs are often an off-label indication, although well supported by clinical standard of care [45, 46]. NSF has been reported in few pediatric patients, all 8 years or older, despite the known renal functional immaturity characteristic for children younger than 2 years [46, 47].

With the new safety concerns regarding gadolinium retention, multiple studies documenting signal changes in pediatric brain structures after the use of GBCAs have been published, following the trend and overall mirroring the findings described in adults (Table 3; [46, 48–56]).

Two initial case reports by Miller et al. [48] and Roberts and Holden [49] described increased T1 signal intensity on unenhanced MR images in the dentate nuclei and globi pallidi after 35 and 6 doses, respectively, of the linear ionic agent Magnevist. This same agent was further evaluated in several subsequent studies, documenting dose-dependent increases in T1 signal intensity in the dentate nuclei [46] and in the dentate nuclei and globi pallidi [50]. Statistically significant increase in dentate nucleus/pons signal intensity ratio after 12 or more doses of Magnevist as well as the linear nonionic agent Omniscan was described by Kasper et al. [51]. Interestingly, in one study, by Flood et al. [52], no significant T1 signal change was found in the globi pallidi despite the dose-dependent T1-weighted hyperintensity changes in the dentate nuclei documented in this series of patients after exposure to Magnevist.

Another linear ionic agent, MultiHance, however, did not show any statistically significant differences in mean signal intensity in the dentate nuclei, globi pallidi, pons or thalami after 5–15 doses of GBCA versus age- and weight-matched gadolinium-naïve controls [53]. Possible explanations for these results, which appear to contradict prior studies of linear ionic agents, include a different patient population with no neurological abnormalities, as well as the presence of the aromatic substituent component in the gadobenate dimeglumine (MultiHance) molecule, which might influence the elimination profile by increasing the kinetic inertia [5].

Serial injections of macrocyclic agents, both ionic and non-ionic, were not found to cause MR signal changes in deep brain nuclei, or signal intensity ratios (dentate nucleus/pons, globus pallidus/thalamus) differences between patient cohorts and matched controls [54], and between first and last GBCA administration in several studies on pediatric patients [51, 55]. However a study by Rossi Espagnet et al. [56] found increased signal intensity ratios of globus pallidus/thalamus and dentate nucleus/pons after >6 serial administrations of the macrocyclic ionic agent Dotarem, with no visible T1 hyperintensity. Controversies following the publication of this study [57, 58] emphasized that in all the published studies, there was no clear explanation of the origin of the T1 hyperintensity present in brain structures, either visible or demonstrated by measurements of signal intensity changes. Soon after, a study by Tamrazi et al. [59] in 2017 showed that associated conditions also appear to play a role in signal changes in the deep brain nuclei. Brain radiation appeared to cause increased signal intensity in the dentate nuclei, independent of GBCA administration, at less than 10 doses of Magnevist, while primary brain tumors were associated with an increase of signal intensity in the globi pallidi [59].

In summary, several studies on pediatric patients showed T1 signal hyperintensity in deep brain nuclei after exposure to linear GBCAs, suggestive of gadolinium deposition. On the

Table 3 Studies reporting T1 signal intensity changes following administration of gadolinium-based contrast agents (GBCAs) in pediatric patients

Authors	Year	GBCA	GBCA description	Number of patients	Number of GBCA doses	T1 signal intensity increase[a]
Miller et al. [48]	2015	Magnevist	Linear ionic	1	35	Yes
Roberts & Holden [49]	2016	Magnevist	Linear ionic	1	6	Yes
Roberts et al. [46]	2016	Magnevist	Linear ionic	16	4–16	Yes
Hu et al. [50]	2016	Magnevist	Linear ionic	21	5–37	Yes
Kasper et al. [51]	2018	Omniscan Magnevist	Linear nonionic Linear ionic	16	>12	Yes
		Dotarem Gadovist	Macrocyclic ionic Macrocyclic nonionic	54	>12	No
Flood et al. [52]	2017	Magnevist	Linear ionic	46	>3	Yes
Schneider et al. [53]	2017	MultiHance	Linear ionic	34	5–15	No
Radbruch et al. [54]	2017	Dotarem	Macrocyclic ionic	41	5–23	No
Tibussek et al. [55]	2017	ProHance	Macrocyclic nonionic	3	10–18	No
		ProHance Dotarem	Macrocyclic ionic	21	9–24	No
Rossi Espagnet et al. [56]	2017	Dotarem	Macrocyclic ionic	50	6–18	Yes

[a] T1 signal intensity increase in the brain on unenhanced MRI images

other hand, no significant differences in T1 signal intensities of these brain areas could be documented after administration of macrocyclic agents in three studies, with a single paper showing an increased signal intensity ratio without visible T1 hyperintensity. This favors the conclusion that macrocyclic GBCAs are less likely to deposit in the body and are therefore safer for use. As a consequence, most pediatric practices switched or were planning to switch to macrocyclic agents according to a survey of the pediatric providers in North America published in 2017 [60].

The first pathology studies in pediatric patients were published in 2016–2017, documenting gadolinium presence in brain and liver tissue samples. A study by Maximova at al. [61] evaluated liver tissue biopsied from 21 children following allogeneic bone marrow transplant; these children had 1–6 prior administrations of a macrocyclic agent, and 8 of them also received deferoxamine for chelation of iron overload. Liver gadolinium deposits were found in all children, with linear correlation between the concentration and the administered dosage [61]. Nevertheless there were significantly lower concentrations of gadolinium in the children who received the chelating agent deferoxamine [61].

In 2017, Roberts et al. [62] published a case report documenting a distribution map of gadolinium deposits after four linear GBCA doses, using laser ablation inductively coupled plasma mass spectroscopy, in a 17-year-old decedent. The highest levels of gadolinium were found in the dentate nuclei and cerebellar cortex. Interestingly, despite the heavy gadolinium load in the dentate nuclei, there was no corresponding T1 hyperintensity on unenhanced MRI [62]. This was followed by a study from McDonald et al. [38] that confirmed gadolinium brain deposition in three pediatric decedents with normal renal function who underwent multiple MR examinations with the linear nonionic agent Omniscan.

In summary, gadolinium deposition has been demonstrated pathologically in pediatric brain and liver tissue after both linear and macrocyclic GBCA exposure, replicating the findings in adults.

Rodent studies

Several rodent studies assessing gadolinium deposition have been performed since 2014 [63–66], although gadolinium dissociation in vivo in rats was first shown in 1992 by Wedeking et al. [67] without eliciting much attention from the medical community at that time.

In recent studies, multiple IV injections of linear or macrocyclic agents were administered to rodents over a period of several days to several weeks, followed by necropsies. In some cases, MRI brain examinations were performed prior to the necropsy. All studies that compared linear to macrocyclic agents found significantly higher concentrations of deposited gadolinium associated with linear GBCAs when compared to macrocyclic GBCAs.

An article by McDonald et al. [63] demonstrated that the concentration of gadolinium in all examined rat tissues was 2- to 4-fold higher with linear agents than with macrocyclic agents. Furthermore they found that concentrations in visceral organs, including the liver, spleen and kidneys, were 100 times higher than in the brain.

Two articles, one by Gianolio et al. [64] and the other by Frenzel et al. [65], found that the deposited gadolinium in the cases of linear agents consists largely of insoluble

macromolecules, which are different chemically from the chelated ion form. The Frenzel group also reported that most of the deposited gadolinium in the rats injected with macrocyclic GBCAs consisted of low molecular weight soluble form, which is similar chemically to the injected GBCA [65].

A study by Kartamihardja et al. [66] reported that there was a significantly higher clearance rate of macrocyclic agents from various parts of the brain when compared to linear agents. They evaluated the concentration of gadolinium in brain tissues after 3 days from the final administration and found it to be 2- to 5-fold higher with linear than with macrocyclic agents. However when they evaluated a different group of rats that were sacrificed 45 days after the final administration of GBCA, they demonstrated this difference to be substantially higher — 15–75 times higher gadolinium concentrations were found in the brains of rats injected with linear agents than in those injected with macrocyclic agents [66]. Moreover there was significant clearance of macrocyclic agents in rats with renal failure but no significant clearance of linear agents [66].

A recent study by Bussi et al. [68] compared the three macrocyclic agents Dotarem, ProHance and Gadovist in rats that were sacrificed 28 days following multiple administrations of one of these GBCAs. The authors found significantly lower concentrations of gadolinium in rats injected with Dotarem when compared to the other two agents, in the cerebrum, cerebellum, femur and renal tissues.

In summary, gadolinium retention occurs in rats' abdominal viscera at substantially (hundreds-fold) higher concentrations than in the brain. There is evidence of a chemical change of GBCAs' molecules that occurs in vivo at a considerably higher rate with linear agents secondary to their relative chemical instability. This seems to prevent clearance of gadolinium from the body. At the same time, there is evidence that clearance of gadolinium from the body continues to occur over time with macrocyclic agents because of their chemical stability, which allows them to remain in their chelated form for longer periods. Furthermore there are differences between macrocyclic agents that are related to their chemical stability, with a higher clearance rate of Dotarem, which is ionic and hence more stable than ProHance and Gadovist.

Discussion

While numerous studies demonstrated no brain signal changes in association with macrocyclic GBCAs, tissue, human autopsy and rodent necropsy studies demonstrated that these agents do indeed deposit in brain and other tissues. The evidence suggests that all GBCAs are incompletely cleared from the body and that small amounts are retained in the brain, bones and other tissues of healthy subjects with normal renal function and intact blood–brain barrier. The concentrations of tissue gadolinium deposits are cumulative and are dependent on the chemical stability of the agent. Deposition rates are higher in patients with impaired renal function, which has also been demonstrated in experimental rodent studies. Brain deposition is probably more significant in patients with diseases affecting the integrity of the blood–brain barrier. However, even in healthy subjects gadolinium concentrations are significantly higher in tissues other than neuronal tissue, particularly the skeleton, which might become a reservoir of gadolinium from which it could be released when there is increased bone turnover [31]. This is not surprising because the free gadolinium ion bears chemical similarity to ionic calcium and other metals that might substitute for calcium and deposit in bone tissue [3, 69]. This raises the question whether gadolinium toxicity manifested with NSF or with other clinical presentations occurs in patients long after the GBCA administration. This is conceivable in certain clinical scenarios, leading to osteoporosis and increased bone turnover with subsequent release of gadolinium deposited in the bones [70], particularly in association with renal failure that would delay the clearance of this released gadolinium.

We are aware of no study to date that has delineated the exact chemical structure of gadolinium deposits in human or animal tissues. Specifically, it is not clear whether the deposited gadolinium is the highly toxic free gadolinium ion, it remains bound to its chelating molecule, or it is otherwise bound to competitor ligands. Current methods of gadolinium detection in tissue including inductively coupled plasma mass spectroscopy, while being highly sensitive, can only detect elemental gadolinium because the analyzed tissue is usually destroyed in the process [71]. As a result, most of the studies measured total concentration of gadolinium in tissue, without delineating the chemical form (i.e. chelated versus non-chelated). However, from rat studies [64, 65] we have learned that an in vivo chemical change occurs in the majority of deposited molecules of linear agents after a relatively short time. While this is indicative of de-chelation, it does not necessarily mean that free gadolinium ions are released. Nevertheless, this chemical change does not occur with macrocyclic agents in the short term. Because rodent studies have all been relatively short in duration, there is no current information with regard to the molecular structure of retained gadolinium in the long term. Of note, no definite histological evidence of cytotoxic effects of gadolinium deposits have been proved [63].

To the best of our knowledge, although the term "gadolinium deposition disease" was introduced [72], there are no scientifically proven clinical long-term adverse effects from GBCAs in subjects with normal renal function. A recent study by Robert J. McDonald, MD, presented at the 103rd Scientific Assembly and Annual Meeting of the Radiological Society of North America (RSNA 2017), did not identify any significant association between GBCA exposure and cognitive decline, dementia, diminished neuropsychological or motor

performance [73]. Although there is not sufficient knowledge regarding the long-term effects, gadolinium deposition raises a potentially greater concern in childhood when tremendous brain development and rapid skeletal growth occur. In pediatric patients, we have witnessed a significant increase in contrast-enhanced MR imaging over the last decade in an attempt to avoid ionizing radiation, an effort that gained momentum around the year 2007 when the "Image Gently" campaign was launched [74, 75]. Long-term, large cohort studies would be required to determine the safety of GBCAs in children.

Because long-term effects of GBCAs are not known, they should be administered with caution and with the lowest dose necessary to answer the clinical question, and each case should be evaluated and protocoled individually. In some cases, radiologists need to review pre-contrast images in real time while the child is being scanned to determine the necessity a GBCA, rather than protocoling a study based on the clinical indication alone. For example, when assessing for osteomyelitis, if the initial T1- and T2-weighted images do not demonstrate abnormal bone marrow signal, osteomyelitis can be safely excluded without using GBCAs. Macrocyclic agents are preferred over linear agents when possible. The radiologist should always evaluate whether the administration of gadolinium would add value, especially in neonates in whom glomerular filtration rate is inherently lower, as well as in children who are typically exposed to multiple GBCA administrations (e.g., those with optic pathway gliomas, tuberous sclerosis). A recent study by Maloney et al. [76] demonstrated that changes in the pattern of enhancement in pediatric patients with optic pathway gliomas did not cause a change in management, and as such, GBCA administration might not be needed for follow-up in these pediatric patients who often undergo a significant number of MRI examinations during their lifetime. Future considerations might include alternatives to GBCAs and administration of chelating agents such as deferoxamine following GBCA injection because it was shown in at least one study to decrease gadolinium retention in the liver [61].

Conclusion

Intravenous administration of GBCAs of all classes leads to gadolinium deposition in the body in small amounts, in healthy children and adults. While no clinical long-term adverse effects have been proved, further investigation is required. In the meantime, GBCAs should be administered with caution, particularly in children, who are expected to live long after the administration and in whom organs are still developing.

Compliance with ethical standards

Conflicts of interest None

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